ANNALS OF ONCOLOGY

ISSN 0923-7534 (print)
ISSN 1569-8041 (online)

Volume 29 Supplement 5 2018

ESMO 20th World Congress on Gastrointestinal Cancer, 20-23 June 2018, Barcelona, Spain

Guest Editors: ESMO 20th World Congress on Gastrointestinal Cancer Scientific Committee

OXFORD
UNIVERSITY PRESS

Japanese Society of Medical Oncology
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Annals of Oncology

Abstract Book

ESMO 20th World Congress on Gastrointestinal Cancer

Barcelona, Spain
20–23 June 2018

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Annals of Oncology

Official Journal of the European Society for Medical Oncology and the Japanese Society of Medical Oncology

Editorial office: Paola Minotti Bernasconi, Giovannella Porcu, Annals of Oncology, Via Luigi Taddei 4, CH-6962 Viganello-Lugano, Switzerland

Annals of Oncology is covered in C.A.B. International, Current Clinical Cancer, Current Contents/Clinical Medicine®, Current Contents/Life Sciences, Elsevier BIOBASE/Current Awareness in Biological Sciences, EMBASE/Excerpta Medica, IBIDS, Index Medicus/MEDLINE, The International Monitor in Oncology, Medical Documentation Service, Science Citation Index® and Science Citation Index Expanded.

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DOI: For information about DOIs and to resolve them, please visit http://www.doi.org

Methods of payment. (i) Cheque (payable to Oxford University Press, to Oxford University Press, Cashiers Office, Great Clarendon Street, Oxford OX2 6DP, UK) in GB£ Sterling (drawn on a UK bank), US$ Dollars (drawn on a US bank), or EU€ Euros. (ii) Bank transfer to Barclays Bank Plc, Oxford Group Office, Oxford (bank sort code 20-65-18) (UK), overseas only Swift code BARC GB 22 (GB£ Sterling to account no. 70299332, IBAN GB89BARC20651870299332; US$ Dollars to account no. 66014600, IBAN GB27BARC20651866014600; EU€ Euros to account no. 78923655, IBAN GB16BARC20651878923655). (iii) Credit card (Mastercard, Visa, Switch or American Express).

Annals of Oncology (ISSN 0923-7534) is published monthly by Oxford University Press, Oxford, UK and distributed in the USA by UKP Worldwide, 3390 Rand Road, South Plainfield, NJ 07080. Periodicals postage paid at Rahway, NJ. POSTMASTER: Send address changes to *Annals of Oncology*, Oxford University Press, C/O 3390 Rand Road, South Plainfield, NJ 07080.

Subscription records are maintained at Oxford University Press, Oxford, UK.

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Typeset by Cenveo Publisher Services, Bangalore, India.
Printed by Bell and Bain Ltd., Glasgow, UK.

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Annals of Oncology

Official Journal of the European Society for Medical Oncology

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Annals of Oncology 29 (Supplement 5): v1–v91, 2018
doi:10.1093/annonc/mdy151

POSTERS

P – 001 Factors influencing late presentation for health care among men with cancer esophagus attending Hospice Africa Uganda (HAU)

N Bandese
Hospice Africa Uganda, Kampala, Uganda

Introduction: Late presentation for health care among patients with Cancer Esophagus is a major problem in Uganda. Cancer of Esophagus is one of the curable cancers if caught in its early stages. World Health Organization (2010) reports that esophageal cancer is the second most common cancer among men and was responsible for over 25000 deaths in 2010, approximately 80% occurred in developing countries. It was projected that it will increase by 25% over the next 10 years if nothing is done like putting prevention measures of adequate screening and treatment into place.

Methods: A recording tape was used to store all the discussions for flexibility. The recorded material was first transcribed from local language then translated into English. Different themes were identified and then coding was done to come up with clear relations to the topic.

Results: The results were also presented to Hospice Africa Uganda and Mbarara regional referral hospital management for proper planning. The 60% of the patient had no transport neither finicial support to access or report at the health facilities. The 40% of these patient had financial support but did not have time to visit the health workers.

Conclusion: In conclusion, the themes realized which contributed to the late presentation for health care, could be grouped under three main factors: Socio-economic factors, Health system factors and Patient and community factors. These factors are interdependent. These need to be addressed by the responsible personnel in order to realize a change for the better in the health seeking mannerisms of patients.

P – 002 A novel patient derived orthotopic xenograft model of gastro-esophageal junction cancer: Key platform for translational discoveries

O Veeranki, Z Tong, A Mejia, R Katkhuda, B Mino, J Canales, A Garcia, W Lang, R Bassett, J Ajani, J Wu, S Kopetz, M Blum, W Hofstetter, C Kingsley, W Norton, D Maru
UT MD Anderson Cancer Center, Houston, Texas, USA

Introduction: Mouse models of gastroesophageal junction (GEJ) cancer strive to recapitulate the intratumoral heterogeneity and cellular crosstalk within patient tumors to improve clinical translation. GEJ cancers remain to be a therapeutic challenge due to a lack of reliable mouse model for preclinical drug testing.

Methods: A novel patient derived tumor orthotopic xenograft (PDOX) was established from GEJ cancer via transabdominal surgical implantation in athymic and NSG-SCID mice. Patient tumor was compared to subcutaneously implanted patient derived tumor xenograft (PDX) and PDOX by H&E, IHC, and next generation sequencing (T200.1 panel). Drug efficacy studies of CDK9 inhibitors with and without radiotherapy are being performed.

Results: Mechanical abrasion of mouse GEJ prior to surgical implantation of patient derived tumor in situ promotes tumor engraftment. Complete PDOX engraftment was observed with rapid intra and extra luminal tumor growth as evidenced by serial Magnetic Resonance Imaging. Patient derived stroma co-engrafts with tumor cells in GEJ-PDOX. PDOXs contain fibroblasts, immune and inflammatory cells, vascular and lymphatic vessels. Stromal hallmarks of aggressive GEJs are recapitulated in GEJ-PDOX mouse model. PDOXs demonstrates tumor invasion into vasculature. GEJ-PDOXs is a clinically relevant model for metastases and immunological studies.

Conclusion: Murine models have been instrumental in advancing our understanding of gastroesophageal cancers. However, these models have limited applications in tumor microenvironment, immune oncology and metastatic studies. A GEJ-PDOX model exhibits remarkable fidelity to human disease and captures the precise tissue microenvironment present within the local GEJ architecture facilitating it as a novel tool in translating findings from such studies. This model can be applied to address importance of tumor microenvironment in metastatic and immunological studies, and to develop novel therapeutic approaches for the treatment of GEJ cancer.

P – 003 Targeted-sequencing and comprehensive molecular profiling of gastric signet ring cell carcinoma

J Wei[1], N Wu[1], Y Wang[2], B Xu[2], Y Yang[1], J Du[1], L Yu[1], Z Zou[1], Y Shao[3], S Zhu[4], B Liu[5]
[1]The Comprehensive Cancer Center of Drum-Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China, [2]The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China, [3]Nanjing Shihe Gene Bio-Technology Co., Ltd., Nanjing, China, [4]The Beijing Genomics Institute, ShenZhen, China, [5]The Comprehensive Cancer Center of Drum-Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China

Introduction: Gastric cancer is a heterogeneous disease with various molecular subtypes. Signet ring cell carcinoma is characterized by a highly malignant phenotype of gastric cancer with no known effective molecularly targeted therapies. The limited knowledge of the molecular mechanisms underlying signet ring cell carcinoma hinders the development of therapeutic strategies.

Methods: We performed a targeted sequencing panel focusing on 416 genes in 70 gastric signet ring cell carcinoma (SRCC) tumor-normal pairs, for integrative genomic analysis. This gene panel is composed of 416 cancer-related genes which can test a wide range of genetic abnormalities including point mutations, fusions, insertions, deletions and amplifications. Furthermore, this panel covers all currently available molecular-targeted & chemotherapy drugs, and ongoing clinical trials.

Results: We identified previously well-known oncogenes and tumor suppressor genes mutation, including chromatin remodeling genes CDH1 (17%), ARID1A (9%), BRCA1 (6%), CHD4 (6%), SMARCA4 (4%), TP53 (27%) dysregulation, activation of receptor tyrosine kinases genes ERBB3 (9%), PIK3CA (7%), PTEN (6%), MTOR (4%), ERBB2 (4%), ERBB4 (3%), FGFR2 (3%), FGFR4 (3%), stem cell pathways genes TGFBR2 (6%), APC (3%), and others. Meanwhile, we observed new significantly mutated genes in SRCC. Specifically, gene PKHD1 (16%), MED12 (16%), STAG2 (10%), KDR (10%), ATRX (9%) were frequently mutated in SRCC tumor samples. However, RHOA mutation was detected only in 4% tumor samples. For DNA copy number profiling, genes including NOTCH1 (16%), FLT4 (9%), CCND1 (7%), HNF1A (6%), CDKN2A (6%), CDKN2B (6%) and RECQL4 (6%), were frequently altered in SRCC.

Conclusion: Our genomic landscape revealed SRCC was a distinct entity which harboring different mutational profile to other gastric cancers. Our results may provide potential target for genome-guided personalized therapy in SRCC.

P – 004 MicroRNAs and CDH1 regulation in intestinal-type gastric cancer

C Molinari[1], T Rossi[2], R Abou Khouzam[3], G Ranzani[3], G Tedaldi[2], P Ulivi[4], P Morgagni[5], L Saragoni[5], M Monti[2], D Calistri[6]
[1]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [2]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [3]University of Pavia, Pavia, Italy, [4]Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [5]Morgagni-Pierantoni Hospital, Forli, Italy, [6]Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Meldola, Italy

Introduction: Gastric cancer (GC) remains a major source of cancer morbidity and mortality worldwide. The most commonly accepted histologic classification of this disease separates it into two main subtypes: intestinal (IGC) and diffuse (DGC). The cadherin family is a cell adhesion-related protein family largely implicated in carcinogenesis of both histotypes, with the best-known member being E-cadherin. This calcium-dependent transmembrane adhesion protein is encoded by CDH1 tumor suppressor gene. While complete loss of E-cadherin is predominant in DGC, more subtle factors can be involved in its modulation in IGC, in which some level of protein is often retained. Such factors include miRNAs that play a role in gene expression dosage either directly by interacting with the CDH1 transcript, or indirectly by acting on genes that are part of its regulatory network. Aim of the study was to evaluate the levels of specific miRNAs involved in the regulation of CDH1 expression in IGC.

Methods: Fresh-frozen paired normal and cancer tissue samples were obtained from 40 patients diagnosed with IGC. An in silico and literature based approach was performed to determine the miRNAs most likely targeting CDH1 in GC. In case of an indirect effect on CDH1, the direct miRNA targets were noted. Expression analysis was carried out by using a custom-made RT pool containing primers for the miRNAs of interest and the TaqMan microRNA RT Kit. This was followed by qPCR reactions in miRNA custom-made 96-well plates and quantification by the 2-ΔCt method with RNU6 as a

reference. CDH1 expression levels were quantified by two step reverse transcription dPCR with GAPDH as an endogenous control.

Results: The combined in silico and literature-search based approach gave rise to a list of 14 miRNAs possibly involved in the regulation of CDH1 expression in GC (miR-506, miR-217, miR-199a, miR-153, miR-544a, miR-34c, miR-141, miR-429, miR-101, miR-200a, miR-200b, miR-200c, miR-26b, miR-23a). Tumor and normal paired samples from 17 patients have been analyzed so far. At the end of the qPCR reactions, 8 miRNAs could be successfully quantified (miR-141, miR-429, miR-200a, miR-200b, miR-200c, miR-101, miR-26b and miR-23a); among those miR-101 ($p = 0.00236$) and miR-26b ($p = 0.001623$) were found to be significantly lower in tumors compared to normal tissue, while miR-200c showed borderline significance ($p = 0.05373$). With respect to CDH1, it was similarly found to be significantly less in tumor than normal tissue ($p = 0.01$). Meanwhile, no significant correlations were found between miRNAs and CDH1 expression levels.

Conclusion: Based on our preliminary results both miR-26 and miR-101 seem to contribute to IGC carcinogenesis. To further investigate whether they act by perturbing E-cadherin-mediated signaling and cell-cell adhesion we are planning to analyze a bigger case series.

P – 005 Retrospective analysis of the frequency of the ALK translocation obtained by immunohistochemistry in gastric adenocarcinomas in a single Costa Rican hospital

L Corrales-Rodriguez[1], J Porras[1], M Araya[1], A van der Laat[2], P Khanna[3], M Juárez[1]

[1]Hospital San Juan de Dios, San José, Costa Rica, [2]Centro de Investigación y Manejo del Cancer/CCSS, San José, Costa Rica, [3]Centro de Investigación y Manejo del Cáncer, San José, Costa Rica

Introduction: Gastric cancer is now the fourth most common malignancy worldwide, and the second cause of mortality, with 738,000 deaths per year (10% of cancer deaths). This tumour encompasses a heterogeneous collection of histologic, anatomic, epidemiologic subtypes associated with a variety of known and unknown environmental and genetic factors. Numerous receptors such as mesenchymal epithelial transition (MET) receptor, epidermal growth factor receptor (EGFR), fibroblastic growth factor receptor (FGFR) and human epidermal growth factor receptor 2 (HER 2) have been shown potential to target specific pathways for tumour cell growth. Hence, more active searching of novel targets in gastric cancer is essential. The anaplastic lymphoma kinase (ALK) tyrosine kinase receptor has emerged recently as a potentially relevant biomarker and therapeutic target. The EML4-alk translocation has been analyzed in other types of cancer. The frequency of this translocation in gastric cancer has not been widely evaluated.

Methods: This study is designed to obtain the frequency of the ALK translocation obtained by positivity of the Ventana® ALK (D5F5) CDx immunohistochemistry assay in all patients with gastric adenocarcinoma. All patients with a gastric adenocarcinoma diagnosed from 2010 to 2015 at Hospital San Juan de Dios were evaluated for biopsy analysis. Epidemiologic data was obtained and various factors were analysed. Inclusion criteria for the study included patients 18 years of age or older, diagnosis with a proven biopsy of gastric adenocarcinoma, and sufficient tumor sample to perform the ALK translocation analysis using Ventana immunohistochemistry. Exclusion criteria included non- sufficient biopsy sample and incomplete medical records. Ethical Committee approval was obtained.

Results: A total of 485 gastric adenocarcinoma biopsy reports were obtained between 2010 and 2015 rom the Pathology Department at Hospital San Juan de Dios. Of these, complete information and adequate biopsy samples were able to be obtained in 272 patients. The ALK positivity was obtained in 12 patients (4.4%). The median age of diagnosis was 83.5 years old, and most likely to harbour a poorly differentiated tumor (45.5%). Negative patients had a median age at diagnosis of 72.6% and 32% had a poorly differentiated tumor. There was no difference in terms of gender (63% in both groups were male) and tumor site (62% vs 64% had an antral tumor).

Conclusion: Our findings suggested that some patients with gastric adenocarcinoma may harbour an ALK translocation diagnosed by the Ventana® ALK (D5F5) CDx Assay. Patients were more likely to be older than the general population with poorly differentiated tumors. This finding could provide another potentially relevant biomarker and therapeutic target in the management of gastric adenocarcinomas.

P – 006 Personalization of treatment for patients with stomach cancer using molecular genetic markers

I Bykov[1], M Mikerova[1], M Nemtsova[2], T Kchorobryh[2]

[1]Sechenov University, Moscow, Russian Federation, [2]First Moscow Medical University, Moscow, Russian Federation

Introduction: Surgical treatment is the most effective method of treatment of gastric cancer, however this method gives good results only at early stage of the disease. One way to improve the results of a gastric cancer patient's treatment is the strategy of personalization based on implication of gastric cancer molecular genetic markers.

Methods: The research was conducted in the Clinic of faculty surgery of N.N. Burdenko of Sechenov University. The study period ran from 2006 through 2017. Participants included 156 patients – 106 patients with gastric cancer (group of the research) and 50 patients with cholelithiasis (control). All 106 patients with cancer of the stomach underwent standard examination which included laboratory and instrumental (electrocardiography, external respiration function testing, ultrasonography of abdominal organs, esophagogastroduodenoscopy, X-ray examination, multislice computed tomography of organs of the thorax and abdominal cavity with intravenous contrasting) methods and consultations of profile experts. For the study, biopsies were performed during esophagogastroduodenoscopy, and samples for histological and cytological examination were taken. Samples of 53 patients received at biopsy were examined on molecular genetic markers. All 50 patients from the cholelithiasis group underwent preoperative examination including the esophagogastroduodenoscopy with biopsy, and molecular genetic markers were analyzed. All 106 patients with gastric cancer underwent surgical treatment: gastrectomy – 42 patients (40%) or resections – 64 patients (60%) with a lymph node dissection D1 – 9 patients (8%), D2 – 85 patients (87%), D3 – 13 patients (12%). In all the cases tumor cells were found in the samples, taken from a tumor. In all biopsy samples from edges of a resection tumor cells were found to be absent, atrophic gastritis in combination with an intestinal metaplasia and/or a dysplasia of various degree was found. Results of a postoperative histological examination of the stages of neoplastic process showed the following: T1N0M0 – 16 (15%), T1N1M0-T2N0M0 – 20 (18,9%), T1N2M0-T3N0M0 – 26 (24,6%), T2N2M0-T4N0M0 – 20 (18,9%), T3N2M0-T4N1M0 – 10 (9,4%%), T4N2M0-T4N2M1 – 14 (13,2%). High-grade differentiated adenocarcinoma was found in 16 cases (15%), moderately differentiated adenocarcinoma – 34 (32%), low-grade differentiated adenocarcinoma - 32 (30,2%), signet ring cell carcinoma – 22 (20,8%), undifferentiated cancer – 2 (2%). Cholecystectomia was performed in all 50 patients from group of comparison. In all biopsy samples from patients with cholelithiasis tumor cells were found to be absent, and atrophic gastritis without intestinal metaplasia and epithelial dysplasia were found.

Results: The methylation of genes *RASSF1A, MLH1*, the expression of genes of *MMP7, hTERT, BIRC5* and telomerase activity in combination with other methods of examination can be used for diagnostics of gastric carcinoma at early stages ($p < 0,01$). High level of *CDH1, N33, DAPK* methylation in morphologically normal tissue, boundary with tumoral, indicates high probability of involvement of this tissue in pretumor transformation ($p < 0,01$) that needs additional control for patients in the postoperative period with the aim of early diagnostics of a recurrence of the disease. The samples received endoscopically could be used for presurgical evaluation of gastric cancer molecular genetic markers ($p < 0,01$).

Conclusion: In our research we showed the possibility of introducing a system of molecular markers in clinical practice. The methylation of genes *RASSF1A, MLH1*, the expression of genes of *MMP7, hTERT, BIRC5* and telomerase activity helps to improve diagnostics of a gastric carcinoma and to concretize tactics of management with a patient.
As we continue our search for markers, it has to include evaluation of methylation genes CDH1, N33, RUNX3 as recurrence disease predictors. Also, the search for predictors of effective use of 5-fluorouracil and platinum based chemotherapeutic schemes continues. By preliminary estimate definition of polymorphic options of a gene TYMS (R2/R3, G>C, del 6 bp) and TP53 (Arg>Pro, ins 16 bp) is capable to influence individual choice of chemotherapy regimen.

P – 007 Neoadjuvant FLOT: Real world toxicity from a specialist UK centre

Z Kordatou[1], G Papaxoinis[2], T Waddell[1], V Owen-Holt[1], J Weaver[1], R Hubner[1], W Mansoor[1]

[1]The Christie NHS Foundation Trust, Manchester, UK, [2]Laiko General Hospital, Athina, Greece

Introduction: Perioperative FLOT (5FU/leucovorin, oxaliplatin, docetaxel) improved all efficacy endpoints in resectable gastroesophageal adenocarcinoma (GOA), compared to ECF/X. This analysis aims to assess the tolerability of patients of our institution, and to compare with the reported toxicity rates of the AIO-FLOT4 trial.

Methods: Clinical information was retrieved from patient notes and electronic files of patients undergoing neoadjuvant FLOT (November 2017-February 2018). All reported adverse events and hospital admissions were recorded and analysed. The analysis focused only on the neoadjuvant component of treatment.

Results: Thirty-nine patients with resectable GOA commenced FLOT. Only 33 patients that completed/discontinued their neoadjuvant course by the time of the analysis were included. Demographics: males ($n = 27$, 82%), mean age 62 (range: 38-84). Tumour location: gastric ($n = 3$, 9%), GOJ ($n = 16$, 49%), and lower oesophagus ($n = 14$, 42%). Sixteen patients had node-positive disease (48.5%). Performance status (PS) prior to treatment: 0 ($n = 26$, 78.8%) and 1 ($n = 7$, 21.2%). Twenty-two patients (67%) completed 4 cycles. Three patients (9%) discontinued treatment after 3 cycles, 4 (12%) after 2 cycles, and 4 (12%) after 1 cycle. Twenty-three patients (70%) had at least 1 hospital admission during treatment, with mean duration 5.8 days (range 1-22). Commonest reasons for admission were non-neutropenic fever/infection ($n = 9$, 27%) and diarrhoea ($n = 6$, 19%). Thirteen patients (39%) had at least one treatment deferral/delay. Eight patients (24%) required dose reduction. Twenty-four patients (73%) had a drop in PS compare to baseline. Weight loss >5% was observed in 11 patients (34%) during treatment. All patients (100%) experienced grade 1/2 toxicities. Twenty patients (61%) had at least one grade 3/4 toxicity. Commonest grade 3/4 toxicities: neutropenia ($n = 10$, 30.3%), neutropenic sepsis ($n = 3$, 9%) diarrhoea ($n = 4$, 12.1%), fatigue ($n = 4$, 12.1%) nausea/vomiting ($n = 2$, 6%) anorexia ($n = 2$, 6%), oral mucositis ($n = 1$, 3%) anaemia ($n = 1$, 3%). Life threatening adverse events included one case of

5FU-related MI, and one patient with bowel perforation. No treatment related deaths occurred. Patients older than 70 had a lower completion rate (28.5% vs. 77%, p = 0.016), higher admission rate (85% vs. 61%, p = 0.228) but similar grade 3/4 toxicity rate (57% vs. 61%, p = 0.832) compared to younger counterparts. Compared to AIO –FLOT4 trial, our patients had higher rates of: discontinuation (33.3% vs. 6%), dose reductions (24% vs. 6%) and serious adverse events (70% vs. 41%). The commonest grade3/4 toxicity was neutropenia in both cohorts, but was less frequent in our institution (30% vs. 52%) probably due to primary GCSF prophylaxis. Grade 3/4 nausea/vomiting was commonest in the AOI-FLOT 4 cohort (12% vs. 6%), while grade3/4 diarrhoea was more frequent in our institution (12% vs. 7%). Fatigue grade 3/4 was commonest in our cohort (12% vs. 9%). No grade 3/4 cases of neurotoxicity were reported in our cohort, compared with the AIO-FLOT4 (8%).

Conclusion: Neoadjuvant FLOT for resectable GOA was less tolerable and more toxic in our cohort, with higher rate of early treatment discontinuations, dose reductions, serious adverse events. The above results demonstrate that every day clinical practice often differs from trial results and underscore the importance of reporting real world experience data, especially regarding safety issues.

P – 008 Treatment decisions in adolescents and young adults with gastric cancer in North Estonia Medical Centre from 2007-2016

M Lõhmus[1], K Lepik[1], T Kütt[2], T Seufferlein[3], K Oselin[1]

[1]North Estonia Medical Centre, Tallinn, Estonia, [2]Tartu University Hospital, Tartu, Estonia, [3]Department of Internal Medicine I, University of Ulm, Ulm, Germany

Introduction: According to the Estonian National Cancer Registry, approximately 400 new GC cases are diagnosed in Estonia annually, among them 18 patients under the age of 45 years. The present study aimed to characterize the diagnosis and treatment of GC in young Estonian patients. The current work is a single institution experience of the last 10–year data from 2007 to 2016.

Methods: This is a retrospective cohort study from the North Estonia Medical Centre newly diagnosed with gastric adenocarcinoma. PFS and OS were calculated as time from initial histological diagnosis until progression evaluated by CT or last contact, date of death retrieved from Estonian Causes of Death Registry or date of cutoff for analysis (1 August 2017), respectively.

Results: 74 young patients diagnosed with GC were included in the current study, median age at diagnosis was 39 years (range: 19–45), the male to female ratio 1.13:1 (41 male, 33 female). 66% of patients (n = 49) had signet–cell carcinoma and 66% were grade 3 cancers. In total, 35 radical surgeries and 19 diagnostic laparoscopies were performed. 26 patients (74%) had total gastrectomy, 8 patients (23%) subtotal gastrectomy. 10 splenectomies were performed, of these two resections due to intraoperative trauma, and seven for greater curvature cancers. Cholecystectomy was performed in almost half of the surgeries (n = 17). Out of 35 resections, the histology results were not concordant in 31% of cases compared with the initial diagnostic biopsies. 50% of the patients were primarily diagnosed with stage IV disease, 15% had locoregionally advanced disease (stage III), 13% of the patients had stage II, 18% stage I. Extent of the primary tumors based on T-status at diagnosis was high, with 69% of patients diagnosed with T3 or T4 tumors. 50% of patients were considered node negative or with N1 disease at diagnosis. 28 patients were diagnosed with stage IB–IIIB GC, but only 54% (n = 15) of patients received neoadjuvant chemotherapy and 25% (n = 7) of patients received adjuvant treatment. 21% (n = 6) of patients with an indication for perioperative chemotherapy did not receive any treatment. Altogether 42 patients received first line and 20 patients second line palliative chemotherapy, the mean number of cycles administered was 4.95 (range: 1–16 cycles) and 2.85 respectively. 5-year OS for all stages combined is 34.5%. OS for 44 patients died was 493 days (16.3 months). OS for stage IV patients at diagnosis who had died during the study period (n = 33) was 306 days (10.0 months).

Conclusion: The current study demonstrated a decline in GC in Estonian population among AYAs from previously reported 6% to 4.5%. GC had been histologically proven for all 74 cases but the discrepancy of histology results between biopsies obtained during endoscopy and during surgery was 31%. 21% of patients with indication did not receive perioperative chemotherapy. The reported 5-year OS of 34.5% is consistent with the median survival data of European AYAs with GC and exceeds Estonian GC survival across all age groups.

P – 009 Epidemiology and overall survival of gastric carcinoma patients (about 210 cases) experience of medical oncology department of CHU Hassan II Fez

H Erraichi[1], Z Benbrahim[2], S Berrad[3], K Darif[4], L Nouikh[3], L Amaadour[2], K Oualla[2], F Lmrabet[5], S Arifi[6], N Mellas[6]

[1]Hassan II University Hospital, Fez, Morocco, [2]Medical Oncology Department, Hassan II University Hospital, Fez, Morocco, [3]Fez, Fez, Morocco, [4]Hassan II University Hospital Fez, Fez, Morocco, [5]Medical Oncology Unit, University Hospital of Hassan II, Fez, Morocco, [6]Department of Medical Oncology, Hassan II University Hospital, Fez, Morocco

Introduction: Gastric cancer is the second leading cause of cancer mortality in men and the fourth on women, due to its aggressiveness it represents a challenging oncology session. It is usually late-onset discovery, which leads to poor prognosis despite advances in surgery and therapeutic oncology.

Methods: Through retrospective study held in the medical oncology department of the Hassan II CHU in Fez, involving 210 patients with gastric cancer during a period of 5 years from January 2013 to January 2018. The aim of our study is to determine the epidemiological, paraclinical, and therapeutic aspects and especially the overall survival of these patients. The survival analysis was performed according to the Kaplan-Meier method and the comparison of the different survival rates according to the Log-Rank test.

Results: A clear male predominance was found with a rate of 62.5% and a sex ratio of 1.6. The median age was 59, 25 years (range, 20 to 86 yo) with a standard deviation of 13.46 yo. family history of cancer was found in 3.9%. Alcohol-toxic intoxication was noted in 31.3% of patients. The clinical symptomatology was dominated by epigastric pain (93.02%), impairment of general health (89.2%), vomiting (45.73%) and gastrointestinal bleeding (29.8%). Regarding endoscopic aspects, distal location was predominant in 62.7% and ulceroburging was the most common in 58% of cases. Histologically, adenocarcinoma was the most common sub type with 65.7% of cases followed by signet ring cell carcinoma ring. Moderately differentiated adenocarcinoma was found in 49% of cases. The extension investigation has assessed a metastatic disease in 38%. The peritoneal localisation was predominant with 47.6% of cases followed by liver and lung localization in 35.8% and 34.8% respectively. 52% of the patients who received a first line chemotherapy based on ECX or EOX with an average number of 4 cures, 36, 8% of the cases received a chemotherapy based on fluoropyrimidines in combination with oxaliplatin with an average number of 3 cures, and 11.2% who received exclusively 5FU due to their general condition. Surgery was indicated in only 30.8% of patients, including 54.5% of patients who received adjuvant chemotherapy with a median of 5 courses. Chemoradiation based FUFOL was administered in 27.3% of patients. The overall median survival is 6.1 months with a 95% confidence interval (CI 95%) ranging from 2.1 to 10 months. The median survival depending on the stage of the disease was 30 months in the localized stage, 4.26 month in the locally advanced stage and only 3 months in the metastatic disease with a statically significant difference ($p < 0.001$).

Conclusion: Gastric cancer remains a common cancer and has a poor prognosis. In our study, the stage of the disease has been identified as a factor influencing the overall survival of our patients, hence the interest of an early screening which be used to improve the prognosis.

P – 010 Berberine inhibits the migration and invasion depending on HNF4αvia Wnt/beta-catenin pathway in gastric cancer

Q Hu, P Yi

Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China

Introduction: Metastasis and invasion of cancer cells are important features of advanced gastric cancer. WNT/β-catenin signaling plays an important role in the metastasis and invasion of tumor cells. Previous studies found the relationship between the expression of HNF4α and gastric cancer invasion and metastasis, berberine can downregulate the expression of HNF4α in gastric cancer cells. Therefore, this study attempts to explain the anti-tumor effect of berberine by inhibiting the metastasis and invasion of gastric cancer cells.

Methods: In order to illustrate the expression of HNF4α, WNT5a and β-catenin in gastric cancer tissues, we used immunohistochemistry to detect 53 cases of pathological sections. In addition, AMPK, p-AMPK, HNF4α, WNT5a and β-catenin in SGC7091 and AGS cells which were treated with berberine were detected by western blotting. Transwell assays were used to detect the migration and invasion of gastric cancer cell AGS in the group of berberine, LV-HNF4A-RNAi and control.

Results: HNF4α, WNT5a and β-catenin expression were significantly higher in gastric cancer tissues than in adjacent tissues and in normal stomach tissues ($P < 0.01$), but HNF4α, WNT5a and β-catenin expression in gastric cancer were not related to tumor classification, tumor differentiation, lymph node metastasis and TNM staging. Furthermore, berberine can upregulate the expressions of p-AMPK and downregulate the expressions of HNF4α, WNT5a and β-catenin in gastric cancer cells. Further analysis revealed that berberine and LV-HNF4A-RNAi reduce gastric cancer cell metastasis and invasive ability ($P < 0.01$).

Conclusion: The AMPK/HNF4α/WNT5a/β-catenin pathway plays an important role in gastric cancer metastasis and invasion. It is through this pathway that berberine exerts its effect on the metastasis and invasion of gastric cancer cells.

P – 011 Estrone and prolactin can be markers of risk of metastasis and pre-metastatic niche in patients with stomach cancer

O Kit, E Frantsiyants, V Bandovkina, Y Pogorelova, Y Gevorkyan, N Soldatkina, N Samoylenko

Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Introduction: The tumor ability to metastasize can be determined by the characteristics of the tumor itself and of surrounding tissues. Together with the formation of the pre-metastatic niche, the tumor niche formation takes place in the primary tumor, and changes in hormonal profile are important. The peritoneum, including the greater

omentum, is the most common site of stomach cancer (SC) metastasis, while it is not a metastatic niche for colorectal cancer (CRC). Our purpose was to study changes in the hormonal profile of pre-metastatic niches – the peritoneum and omentum, and to determine parameters for predicting the stomach cancer progression and metastasis.

Methods: The study included 4 groups of patients: 1 - SC without metastases (mts) to the peritoneum and omentum (T2-4N0-3M0, n=20); 2 – SC with mts to the peritoneum and omentum (T2-4N0-3M1, n=25); 3 – CRC without distant mts (T2-4N0-3M0, n=18); 4 – controls without cancer operated on for cholecystitis and hernia (n=15). Estrone (E1) levels in tissues of the peritoneum and omentum, and estrone (E1) and prolactin (PRL) levels in tumor and peritumoral tissues were determined by ELISA. All patients gave their written informed consent. Statistical processing of the results was performed using Microsoft Office Excel 2010.

Results: Tumor tissues in patients of group 1 showed higher estrone levels and lower prolactin levels compared to group 2, while peritumoral tissues showed the opposite results (lower E1 and higher PRL levels in non-metastatic cancer). The ratio of E1 levels in tumor/peritumoral tissues in metastatic SC was 0.65, non-metastatic – 1.43. The ratio of PRL levels in tumor/peritumoral tissues in metastatic SC was 3.34, non-metastatic – 0.7. The E1 levels in the omentum of patients in groups 1 (T2-4N0-3M0), 3 (T2-4N0-3M0) and 4 were similar. The E1 levels in metastatic SC (T2-4N0-3M1) were 14.6 times higher than in non-metastatic SC (T2-4N0-3M0) and more than 9 times higher than in CRC and in controls. The exception was 35% of patients with SC without detected mts with a high content of E1 in omentum and peritoneal tissues and with increased ratio of PRL levels in tumor/peritumoral tissues. Distant metastases from SC were detected in one of the patients within 3 months.

Conclusion: The peritoneum and omentum affected by metastasis are characterized by high estrone levels. The ratios of E1 and PRL in tumor/peritumoral tissues change in metastasis development. Determination of E1 and PRL in tumor and peritumoral tissues and in the omentum can be an additional prognostic criterion for the cancer progression and the development of metastasis.

P – 012

WITHDRAWN

P – 013 Redox forms of glutathione mark the aggressiveness of stomach cancer

I Goroshinskaya, E Surikova, E Frantsiyants, I Neskubina, Y Pogorelova, D Medvedeva, A Maslov, O Kit

Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Introduction: The redox status is important for the gastric epithelium function. The purpose of the study was to compare levels of reduced and oxidized glutathione and thiol status in stomach tumors of various histological types and grades.

Methods: The levels of reduced (GSH) and oxidized (GSSG) glutathione and thiol status were determined by ELISA in tumor, peritumoral and visually intact tissues obtained during surgery from 52 patients with stomach cancer: 18 patients – G1-2 adenocarcinoma (AC, T2-4N0-2 M0); 8 – G3 AC (T2-4N0-3M0); 14 – combined gastric lesions (CGL), AC with signet ring cell fragments (T3-4N0-3M0-1); 6 – signet ring cell cancer (SRCC, T1-4N1-3M0-1); 6 – patients with a component of undifferentiated cancer, G4 (T2-4N1-3M0-1). The coefficient of GSH and GSSG was calculated (C=GSH/GSSG•10-3). The data were analyzed using Statistika 6.0 program and Student's t-test.

Results: With a decrease in the degree of AC differentiation, there was an increase in GSH levels in the tumor tissue and the peritumoral zone with the maximum in G4: 29.9% higher ($p = 0.0112$) in tumors and 40.7% higher ($p = 0.0026$) in peritumoral zone in comparison with G1-2 AC. GSH in all tissues of patients with CGL was 13-19% higher than in patients with G1-2 AC ($p < 0.05$). Tumor GSH levels in G3 AC and SRCC exceeded the values in visually intact tissues by 19.9% and 17% respectively ($p = 0.02$-0.05). The levels in visually intact tissues in SRCC were 17.3% lower than in G1-2 AC ($p = 0.0006$) and 27.7% lower than in CGL ($p = 0.0074$). A significant decrease in tumor GSSG levels was registered in SRCC only: 27.5% lower than in G1-2 AC and 30.3% lower than in G3 AC ($p = 0.0021$-0.0029). Patients with undifferentiated tumors (G4 AC) had increased GSH in all studied tissues: in tumor by 29.9% ($p = 0.0112$); in peritumoral zone by 40.7% ($p = 0.0026$); in visually intact tissues by 22.5% with increased GSSG – by 25.5% ($p = 0.0001$) compared to G1-2 AC, as well as compared to SRCC ($p = 0.02$-0.000002). G4 AC were characterized by a sharp increase in the thiol status in tumor tissues – by 80.2% and 89.9% higher than in visually intact and peritumoral tissues ($p = 0.0012$-0.0038), 72.6% higher than in G1-2 AC ($p = 0.00002$), 95.7% higher than in G3 AC ($p = 0.00018$), and 68-69% higher than in SRCC and CGL ($p = 0.0056$-0.0232). The coefficient of GSH and GSSG was the most informative. In comparison with the value in patients with G1-2 AC, the GSH/GSSG•10-3 index was 14.1% higher ($p = 0.0844$) in patients with G3 AC, by 34.5-35.6% ($p = 0.0021$-0.0345) with G4 AC and CGL, and by 75.1% ($p = 0.001$) in patients with SRCC.

Conclusion: Reduction of AC differentiation (in the row G1-2, G3, G4) and a change of histological tumor type (AC, SPL and SRCC), i.e. an increase in tumor aggressiveness, is accompanied by the enhancement of reduction processes in tumor tissue, as evidenced by the statistically significant increase in the GSH/GSSG coefficient and a sharp increase in the thiol status in the case of G4 AC. Changes in GSH and GSSG levels were found even in some visually intact tissues.

P – 014 Diagnostic and therapeutic efficacy of endoscopic enucleation for subepithelial tumors originating from muscularis propria layer

B Bang, E Ko, K Kwon, Y Shin, H Kim

Inha University College of Medicine, Incheon, Republic of Korea

Introduction: Gastric subepithelial tumors originated from the muscularis propria (MP) are partly benign tumors, but some MP tumors have malignant potential, especially gastrointestinal stromal tumors (GISTs). Therefore, accurate diagnosis of MP tumor is essential. The aim of this study was to evaluate the utility of endoscopic enucleation for the diagnosis and treatment of MP tumors.

Methods: From January 2010 to February 2018, eighty-seven patients with gastric MP tumor underwent endoscopic enucleation. Before endoscopic resection, all patients performed endoscopic ultrasound to determine the layer of origin and the accurate size. According to tumor size (12mm or 12mm), band ligation and resection (BLR) or endoscopic submucosal resection (ESD) was performed. Tumor characteristics, procedure time, complete resection rate and recurrence were analyzed.

Results: A total 87 patients were eligible for inclusion in this study. BLR method was used in 44 patients. Median procedure time was 10.5 minutes (range 3-85) and complete resection rate was 90.9% (40/44). Perforation was developed in four patients, which was closed by endoscopic clipping. ESD method was used in 43 patients. The median procedure time was 45 minutes (range 10 – 300) and complete resection rate was 86.0% (37/43). Nine cases were complicated by perforation. Five patients were treated using metal clips and four patient received surgery. Among 35 patients who were diagnosed as GIST, 30 patients showed low risk and very low risk. The mean follow-up time was 24.4 months (range 1-66) and recurrence was not developed in any patients during follow-up period.

Conclusion: Endoscopic enucleation appears to be effective and relatively safe method for the histologic diagnosis and removal of subepithelial tumor originating from MP layer. Especially, BLR is an effective, less time-consuming and relatively safe treatment for small MP tumor (12 mm).

P – 015 Patient derived xenografts from American minority gastric cancer patients

S Wang[1], M Zhu[1], S Hammer[1], J Shen[2], I Nassour[1], J Mansour[1], D Agarwal[1], H Zhu[1], M Porembka[1]

[1]UT Southwestern Medical Center, Dallas, Texas, USA, [2]Stanford University, Stanford, California, USA

Introduction: In the United States, race and ethnicity are associated with different gastric cancer epidemiology and outcomes with Black and Hispanic/Latino patients having worse outcomes than White and Asian patients. Notably, Black and Hispanic/Latino patients are significantly underrepresented in large gastric cancer clinical trials and thus it is unclear if currently defined treatment algorithms for gastric cancer are optimized for these patients. Patient derived xenografts (PDX) can be a useful surrogate to model human disease.

Methods: Consent was obtained from gastric cancer patients who were undergoing pre-treatment esophagogastroduodenoscopy (EGD) or gastric resection after neoadjuvant therapy. Tumor samples were coated with Matrigel and implanted into the subcutaneous tissue in the flanks of NSG mice. Approximately 10 mg of tumor obtained from EGD biopsies and approximately 100 mm3 obtained from resections were implanted into each flank. Two implants were performed for EGD samples and four implants were performed for resection samples. Tumors were serially measured and passaged when the greatest dimension reached 1.5 cm, or if there was overlying skin necrosis.

Results: We implanted EGD biopsies from 70 patients and resection samples from 26. There were 43 Hispanic/Latino and 16 Black patients in the pre-treatment EGD cohort and 15 Hispanic/Latino and 5 Black patients in the post-treatment resection group. The engraftment rates were 43% for EGD biopsies and 62% for resection samples. Median time to first passage was 10 weeks (range: 5.3 to 23) for EGD biopsies and 21 weeks (5.9 to 43) for post-treatment resection samples. Race/ethnicity, presenting clinical stage, Lauren status, tumor differentiation, lymphovascular invasion, perineural invasion, H. pylori status, and Her2 status were not associated with engraftment rates. Histology was generally maintained through passages but mucinous components were lost over time, leaving only solid, poorly differentiated tumor. Almost all samples were able to be serially passaged and reconstituted after deep freeze and thaw.

Conclusion: We have established multiple PDX lines from American minority patients. These lines will be a useful platform to investigate biologic factors that contribute to gastric cancer outcome disparities that are associated with race and ethnicity in the United States.

P – 016 Impact of HIF-1alpha and PKM1 expression on acquisition of paclitaxel resistance in gastric cancer

S Fushida[1], M Okazaki[2], J Kinoshita[1], T Yamaguchi[3], T Ohta[1]

[1]Kanazawa University Hospital, Kanazawa, Japan, [2]Gastroenterological Surgery, Kanazawa University, Kanazawa, Japan, [3]Department of Gastroenterologic Surgery, Division of Cancer Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

Introduction: In gastric cancer patients, one of the greatest obstacles to effective chemotherapy is the development of chemoresistance. It has been previously noted that HIF-1α was concerned with chemoresistance acquisition, and it was recently noted about the association of PKM1 and chemoresistance. The purpose of this study was to identify the effect of HIF-1α and PKM1 expression in leading to acquired chemoresistance using established paclitaxel-resistant gastric cancer cell line.

Methods: Cancer cell line resistant to paclitaxel was established from MKN45 by stepwise exposure. The expressions of HIF-1α, apoptosis, VEGF, multidrug transporters and glycolytic enzyme were examined by western blotting, ELISA and Immunohistochemistry. We also assessed the tumor proliferation by subcutaneous tumor and peritoneal dissemination of mouse xenograft model.

Results: The resistance index (RI) was 6.1 by determining as the ratio of the IC50 of rMKN45-PTX / IC50 of MKN45. Expression of NF-kB and HIF-1α was increased in rMKN45-PTX compared with those in the parent cells. Expressions of Bax and caspase-3 were significantly downregulated in rMKN45-PTX ($p<0.05$). In contrast, an increased expression of Bcl-xL, P-gp, MRP, and VEGF (2200 pg/ml) was observed in rMKN45-PTX. The expression level of PKM1 was 2 times up-regulated in rMKN45-PTX ($p<0.05$), on the other hand, PKM2 was almost similar to MKN45. We demonstrated that mouse subcutaneous tumors derived from rMKN45-PTX were significantly larger than those from MKN45 cells (1450 mm^3 vs 750 mm^3, $p<0.05$). Peritoneal dissemination model of rMKN45-PTX also showed larger than those of MKN45 (0.8 g/16 nodules vs 0.4 g/7 nodules, $p<0.05$). HIF-1α was key molecular of chemoresistance acquisition, which might be impacted the angiogenesis, cell proliferation, anti-apoptosis and multidrug transporter. Furthermore, PKM1 might be important molecular in chemoresistance acquisition.

Conclusion: Under the stress of chemotherapeutic agent exposure, high expression of HIF-1α affects downstream various genes. Although the underlying mechanism is unknown, our data suggest that PKM1 is also a molecular target for gastric cancer treatment.

P – 017 Overall survival of patients with HCC treated with sorafenib versus patients treated with supportive therapy in evidence in Oncology Cabinet of Municipal Hospital of Pascani in session 2013-2018

E Bosteanu, V Hincu

Emergency Municipal Hospital, Pascani, Romania

Introduction: Sorafenib is a standard systemic therapy in patients with advanced HCC and well preserved hepatic function (stage C BCLC)and the patients with HCC in intermediate stage who showing progression after TACE. In the case of the progression of the disease or the intolerance to sorafenib is preferred the administration of the BSC. In the patients with terminal disease and with sever diminished function and a poor performance status is recommended just BSC because the survival of these patients is 6 months maximum.

Methods: The study group was created from the patients with HCC who were treated with systemic therapy with sorafenib in Oncology Cabinet of Municipal Hospital Pascani in session 2013-2018 and from the patients with HCC which benefited only from supportive therapy. Because overall survival of the patients with advanced HCC not exceeding 2 years, we considered particularly desirable pursuit of the patients with HCC from the point of view of overall survival. Another aim of the paper was the incidence of side effects on the long term and progression free survival. They evaluated 44 patients with advanced HCC from witch 15 patients (34%) was treated with sorafenib, while 44 patients (100%) was treated with BSC (best supportive care). Of the 44 patients, 35 patients (79,6%) are males, 3 patients (7%) are age less than 50 years old. Of all patients with advanced HCC, 4 patients (9%) had a good performance status (ECOG 0-1), the other 91% from the patients had a poor performance status (ECOG 2-3). Of all patients treated with sorafenib, 12 patients (27%) had a history of viral B hepatitis, 11 patients (25%) had a history of viral C hepatitis, 14 patients (32%) had toxic hepatitis, 8 patients had a multicentric HCC (18%), 2 patients (5%) presented brain metastases, 5 patients (11%) had pulmonary metastases, 4 patients (9%) had bone metastases, 9 patients (20%) had hepatic metastases, 3 patients (7%) had lymph node metastases. Regarding the number of platelets, 17 patients (39%) had a thrombocytopenia grade II-III, with bleeding (melena and epistaxis). The patients with poor performance status who was been treated with BSC had an unfavorable evolution of the disease.

Results: Of all patients, 12 patients (27%) had an overall survival less than 3 months, 12 patients (27%) had three-month survival, 6 patients (14%) had overall survival less than 6 months, 12 patients (27%) had overall survival more than 6 months, 5 patients (11%) had overall survival more than 1 year and 1 patient (2%) had overall survival of 3,5 years. Of all 44 patients, 20 patients had a good evolution with a good survival. Regarding side effects of sorafenib a number of 9 patients (20%) presented palmar-plantar erythrodysesthesia, which was submitted with dose reduction (800 mg to 400 mg/day). Twelve patients (27%) presented with major asthenia with a favorable evolution. Three patients (7%) presented minor bleeding remitted under hemostatic therapy. Patients with HCC grafted on liver cirrhosis had an unfavorable evolution, reducing overall survival.

Conclusion: Patients treated with Sorafenib had a higher survival than those treated with BSC, with the condition that this treatment had been introduced at the early stages of the disease (Child Pugh A or B), without thrombocytopenia, with unique liver lesions and no history of liver cirrhosis.

P – 018 The role of endothelial filtration for locoregional targeting of hepatic tumours with endothelium-specific antibodies and nanoparticles

N Winkler, F Strübing, D Kyuno, B Qian, Z Wang, W Groß, W Mier, E Ryschich

University Hospital Heidelberg, Heidelberg, Germany

Introduction: Tumour targeting using the microvascular system represents a highly promising approach for therapy of hepatic tumours. The aim of this study was to assess the role of endothelial filtration for locoregional targeting of hepatic tumours using endothelium-specific antibodies (Abs) and nanoparticles (NP).

Methods: Fast-binding endothelium-specific Abs were selected based on histological analysis of their binding capacity. The capture efficacy and specific local enrichment of near-infrared and fluorescence-labelled Abs as well as Ab-coated NP (magnetic NP and doxorubicin-encapsulating liposomes) by hepatic endothelium under different hydrodynamic conditions was analysed using isolated liver perfusion models. The targeting potential of the fluorescence- or 125I-labelled carriers was studied in vivo in different hepatic tumour models using biodistribution analysis, scintigraphic imaging, and fluorescence microscopy.

Results: Several selected mouse and human Ab clones showed a very fast binding capacity to normal and/or tumour-associated endothelium. Upon injection into the tumour-feeding artery, the Ab was immediately captured in the microvasculature during the first passage. At doses not exceeding the saturation level of endothelial epitopes, the filtration efficacy was almost 90%. Our results showed that the efficacy of endothelial filtration is controlled by factors such as Ab affinity, number of binding sites on the endothelium, and microvascular flow rate. The method of endothelial Ab filtration demonstrated a very high intratumoural enrichment of targeting substance in vivo after locoregional intraarterial injection of 125I-labelled Abs in hepatic tumour models. In contrast to Abs, coated NP showed a strongly reduced potential for endothelial filtration under flow conditions. However, use of liposomes coated with one specific Ab clone achieved effective local liposome enrichment even under moderate flow reduction.

Conclusion: Here, we provide an initial demonstration of the phenomenon of endothelial filtration for specific tumour targeting and analyse hydrodynamic and molecular mechanisms that control this process in the microcirculation. This unique phenomenon can broadly prevent systemic circulation of the drug applied by intravascular injection and may have specific relevance for targeting of hepatic tumours using both Abs and NP.

P – 019 Clinic-pathological pattern of hepatocellular carcinoma (HCC) in Egypt

H Elghazaly[1], A Gaballah[2], N Bahie Eldin[3]

[1]Clinical Oncology Dept, Ain Shams University, Cairo, Egypt, [2]Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [3]Ain Shams University, Cairo, Egypt

Introduction: The incidence of liver cancer is one of the highest in the world. HCC represents up to 90% of all liver malignancies. In Egypt, HCC constitutes a significant

public health problem. Where it is responsible for 33.63% and 13.54% of all cancers in males and females respectively. Hepatocellular carcinoma occurs in a number of preexisting conditions that commonly includes hepatitis C and B, alcoholic and nonalcoholic cirrhosis. It has a poor prognosis after discovery, which is usually at a late stage of disease. This had been strongly linked to the hepatitis C virus epidemic that affected around 10-15% of the Egyptian population during the last 3 decades, and was reported as the highest prevalence of HCV in the world.

Methods: This retrospective study included 300 HCC patients. Clinical and demographic data were collected from medical records during the period between Jan 2011 till end of 2016.

Results: Results revealed that 53% of the studied HCC patients were younger than 60 years old, 81.5% male and 18.5% female, 40% of the patients had an a-fetoprotein level of at least 400 ng/ml and 95.7% were positive for hepatitis viral infection, 30% of the patients had Diabetes Mellitus (DM). Majority of the patients were Child Pugh Score A and 96.7% of the cases were diagnosed without tissue biopsy. About 36%of the cases presented with stage IV and 34.8% of the cases had lymph node involvement &vascular invasion radiological. Sorafenib was received by 30% patients as first line or after progression from local therapy.

Conclusion: HCC in Egypt occurred in men who developed a cirrhotic liver due to HCV infection. Epidemiological and histopathological data of HCC highlight the importance of an integrated strategy for the prevention and the treatment of viral hepatitis infections and chronic liver disease. Tissue biopsy is not required to make the diagnosis of HCC. There were well-defined tumor markers & imaging criteria for that. Many patients presented with advanced disease beyond curative surgery.

P – 020 Immunohistochemical study of KRAS, NRAS, BRAF and MSI phenotype in small bowel adenocarcinoma

V Michalaki[1], G Frangulidis[2], A Poydorou[2], T Theodosopoulos[3], A Vezakis[4], N Dafnios[4], M Frangou[5], E Karvouni[6], C Papadimitriou[7]

[1]Areteion Hospital University of Athens, Athens, Greece, [2]Areteion Hospital 2nd Department of Surgery, Athens, Greece, [3]Department of Surgery Areteion Hospital University of Athens, Athens, Greece, [4]Department of Surgery Areteion Hospital, Athens, Greece, [5]Areteion Hospital, Athens, Greece, [6]Histopathology Department, Athens, Greece, [7]Oncology Unit Areteion Hospital University of Athens, Athens, Greece

Introduction: Small-bowel adenocarcinomas (SBAs) are rare cancers with a significantly lower incidence, later stage at diagnosis, and worse overall survival than other intestinal-derived cancers. Activating KRAS and/or BRAF mutations have been identified as predictors of resistance to anti-epidermal growth factor receptor (EGFR) The aim of this study was to perform a comprehensive immunohistochemical analysis of KRAS, NRAS, V600E BRAF mutations and microsatellite instability using a cohort of surgically resected cases in our institution.

Methods: A total of 17 patients (10 males and 7 females; mean age, 56.2 years old; range, 45 75 years old) received chemotherapy due to non curative tumor resection, unresectable tumor or post operative recurrence. Twelve patents received fluoropyrimidine and oxaliplatin based first line chemotherapy. Molecular targeted agents were administered to 15 patients, for whom it was their first or second line therapy.

Results: KRAS mutations were found in 7 cases (41%), out of which 5 (29%) were in exons 12/13. BRAFV600E mutation was observed in 1/17 pt. Microsatellite instability was identified in 3/17pt (MSI; 18%), mainly related to a loss of expression of MLH1 protein. Univariate analysis revealed a PS of 0 ($P = 0.0226$) and treatment with platinum-based chemotherapy ($P = 0.0047$) were significant factors for an improved prognosis. Among the 12 patients who received oxaliplatin-based chemotherapy as a first-line chemotherapy, a PS of 0 ($P = 0.0255$) and treatment with anti-EGFR agents ($P = 0.0127$) were significant positive prognostic factors. Toxicities due to the molecular targeted agents were not experienced. The median overall survival time was 14.3 months (range, 3-52 months), the median DFS was 14.2 months and the median OS was 32 months.

Conclusion: To date, there is no standard chemotherapy regimen for advanced SBAs and little is known about their molecular characteristics. The results of the present study indicate that oxaliplatin based chemotherapy containing molecular targeted agents is a well-tolerated and effective treatment option for SBA. A better understanding of disease biology may help to identify therapeutic targets and advance precision medicine.

P – 021 Molecular profiling of gastrointestinal cancer

P Apostolou, M Papadimitriou, P Parsonidis, A Iliopoulos, I Papasotiriou

Research Genetic Cancer Centre S.A., Florina, Greece

Introduction: Gastro-intestinal cancer (GI) include a variety of cancers that affect esophagus, gallbladder, liver, pancreas, stomach, intestine and other organs involved in digestive system. The above types of cancers appear higher mortality rates in comparison with cancers in other systems. Therefore, it is essential the optimization of treatment management. Even though great achievements have been performed the last years in prediction of cancer therapy, treatment is based in specific markers, avoiding genes that affect or affected through signaling transduction pathways. The present study aimed to analyze the gene expression in cancer cells, representing different GI cancer types and compare them with circulating tumor cells (CTCs) from patients and cells from normal donors.

Methods: RNA was extracted from commercial cell lines representing gastric (MKN45, 23132/37), liver (Huh 7D-12), colon (CaCO2, HCT15, HCT116) and pancreatic (PANC-1) cancer. Blood was collected from two healthy donors as well as two colon cancer patients. PBMCs in healthy individuals and CTCs in cancer samples were isolated and RNA was extracted. qRT-PCR was performed including reference RNA as positive control. 80 primer pairs were designed for exon-exon amplification of genes involved in signaling pathways, invasion, receptors, cell cycle regulation, resistance etc. ACTB was used as housekeeping genes and DeltaCt analysis was followed. Experiments were performed in triplicates including appropriate controls. Hierarchical clustering was performed to identify gene expression patterns.

Results: The genes ERK1, ERK2, CDC6, JAK1, JAK2, FAS, NRAS, BCL2, NME1 and HSPB1 were not expressed in normal samples, while different expression patterns were observed in commercial cancer cells and cells derived from patients. Regarding the migration-invasion marker NME1, and genes ERK1, BAX, RRM1, ERCC1, ARAF, MET, E2F1, ERBB2, MTOR, TYMS, GART, PNP, RRBP1 and HSPB1, commercial cells had higher expression. On the contrary, patients-derived cells' gene expression was higher for ERK2, PTEN, RPSA, JAK1, JAK2, FAS, KRAS, TGFB1 and NANOG. For the rest genes that were studied, there was not observed clear molecular profile. The clustering among samples revealed that cancer cells' gene expression pattern is different than normal, while dissimilar pattern was also observed between commercial cancer cells and CTCs.

Conclusion: Taking everything into consideration it is well understood that personalized treatment is essential, since different expression profiles are observed among samples with the same type of cancer. The more genes that are studied, the more information are collected for the cancer; therefore a treatment with greater success can be achieved. In addition, the study of genes should not limited in receptors and/or pathways, but also to include genes involved in various cell processes. Further studies, in more samples, are imperative to confirm all the above and be able to use at clinical level.

P – 022 Clinico epidemiological and therapeutic profile of GIST: Oran center's experience

F Boudinar[1], Z Sara[2], B Larbaoui[1]

[1]Medical Oncology Department, EHSO Emir Abdelkader, Oran, Algeria, [2]CAC ORAN, Oran, Algeria

Introduction: A gastro-intestinal stromal tumor (GIST) is one of the most common mesenchymal tumors of the gastro-intestinal tract (1-3% of all gastro intestinal malignancies). Gastro intestinal stromal tumors are Kit – expressing and Kit (tyrosine kinase receptor – CD117) – signaling driven mesenchymal tumors. The most common location of GIST is stomach (50 – 60%) and small intestine (30 – 40%). Surgical resection of the local disease is the gold standard therapy, the mitotic count is a reliable parameter of prognosis. Imatinib mesylate has shown in main studies tumor control about 80% on metastatic GIST.

Methods: A retrospective analysis was performed on 16 patients treated for locally advanced and metastatic GIST in medical oncology department of Oran center from 2013 to 2017.

Results: Between January 2013 and December 2017, 16 patients (9 male/7 female) with GIST were diagnosed and treated in our center. Median age was 51 years with range (23-71). All patients had performance status 0 -1. Diagnoses were based on traditional methods of examination and immunohistochemistry for determination expression C-KIT protein (CD117- CD34) in 100% of cases. There were gastric localization in 56%, mesenteric tumors in 6, 25%, jejunal tumors in 6, 25%, retroperitoneal tumors 6,25%, rectal tumors 6,25%, duodenal tumors 6,25%. Surgery performed in 68, 7%, total gastrectomy in 27%, 2/3 gastrectomy in 9%, abdoperineal resection in 9%, anterior resection in 9%, ileal resection in 9%. High grade tumors in 25%, intermediate grade, low grade tumors in 18,7%. Medication with imatinib was initiated in high grade tumors in adjuvant for 83%. In the locally advanced and metastatic GIST, 1st line by imatinib 800 mg in 37,5%, 2nd line by sunitinib 50 mg in 25%, 3rd line by regorafenib 160 mg in 6,25%. The 3 years survival was 80%, progression in 37,5%, stability in 31,5%, complete response in 31,5%, 1 case of death.

Conclusion: A stromal intestinal stromal tumor (GIST) was rare. Diagnoses were based on traditional methods of examination and immunohistochemistry for determination C-KIT protein (CD117 – CD34). The surgical of GIST is the principle treatment. Imatinib indication in metastatic and unresectable forms.

P – 023 Gastrointestinal stromal tumours: Retrospective review of an institution

A Silva, H Magalhães, C Vieira, A Ferreira, J Dinis, M Soares

IPO-Porto, Porto, Portugal

Introduction: Gastrointestinal stromal tumours (GIST) are rare tumours, accounting 1-3% of all gastrointestinal (GI) cancers. Our purpose was to review the experience of a single institution in advanced GIST, aiming on demographics, treatment and outcomes.

Methods: Retrospective analysis of patients with unresectable e/or metastatic GIST between January 2003 and December 2016 in our institution. Descriptive analysis and

survival evaluation was determined by Kaplan-Meier method. Evaluation of differences between survival curves was calculated by log rank test.

Results: From the 62 patients included, 34 (54.8%) were male, and the median age was 62,5 years (range: 37-79). The majority of patients had an ECOG PS 0-1 at diagnosis of advanced disease (n = 47, 75.8%). The most common presenting symptoms were abdominal pain (n = 14; 22.6%) and GI bleeding (n = 9; 14.5%). Primary tumour site was predominantly in the stomach (50%) and small intestine (32.3%). At time of diagnosis, 42 patients (67.8%) presented with locally advanced or metastatic disease. The most common metastatic sites were liver (n = 34; 54.8%) and peritoneum (n = 35; 56.5%). Mutation in KIT exon 11 was present in 26 patients (41.9%). Surgery was performed in 51 patients (82.2%). First line treatment with imatinib had an overall response rate (ORR) of 53.2%; median time of treatment was 26.5 months (range 1-146). Adverse events happened in 45 patients (72.6%), the most common were oedema (41.9%), followed by diarrhea, nausea and abdominal pain. One patient discontinued treatment for persistent grade (G) 2 GI toxicity. Twenty patients (32.3%) received second line treatment with imatinib 800mg/d, with toxicity of any grade in 10 patients, mainly G1; one patient had oedema G3, warranting dose reduction. ORR was 15%. Seventeen patients (27.4%) were treated with sunitinib, with 17.6% of ORR. Almost all patients (82.3%) had adverse events; 4 patients (23.5%) had toxicity G $\geq$ 3. Four patients received regorafenib (6.5%), with ORR of 25%. Two patients had hand-foot syndrome demanding dose reduction. Median overall survival was 108.1 months (95% CI 47.7-168.4).

Conclusion: The results obtained in our sample are in agreement with the existing literature. All patients should be managed by a multidisciplinary team in a reference centre.

P – 024 Varying distribution of tissue plasminogen activators in gastrointestinal adenocarcinoma

O Kit, E Frantsiyants, L Kozlova, A Maslov, E Kolesnikov, E Dzhenkova, N Samoylenko
Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Introduction: The purpose of the study was to compare the activity of urokinase (uPA) and tissue (tPA) plasminogen activators and the content of their proenzyme forms (pro-uPA, pro-tPA) in adenocarcinoma of the esophagus (EA), stomach (SA), pancreatic head (PHA), sigmoid colon (SCA) and rectum (RA).

Methods: Tissues of tumors, perifocal area and resection line tissues were studied by ELISA in 143 patients (38-74 years) with EA (n=12, G2, T2-3N0-1M0), SA (n=28, G2, T2-3N0-1M0), PHA (n=46, G2, T2-4N0M0), SCA (n=31, G2, T2-3N0-1M0) and RA (n=26, G2, T2-3N0-1M0). Statistical analysis was performed using the Statistica 10 program.

Results: The tumor levels of pro-uPA and pro-tPA were the highest in SA: SA>RA>SCA>EA>PHA ($p<0.01$). The pro-uPA levels in tumors were higher than in the resection line in all cases ($p<0.01$). Levels of pro-tPA in EA, SCA and RA were lower than in the resection line ($p<0.01$). Tumor levels of pro-tPA in SA were similar to the values in perifocal tissues, and were 3.1-213 times higher than in other tumors. Perifocal levels of pro-uPA and pro-tPA were the highest in SA: SA>SCA>RA>EA>PHA ($p<0.01$). In EA and PHA, the perifocal levels of pro-uPA were lower than in resection line tissues ($p<0.01$), while in SA, SCA and RA they were higher ($p<0.01$). Perifocal levels of pro-tPA in EA and PHA were lower than in the resection line tissues ($p<0.01$), in SCA and RA – similar, in SA – exceeded the levels in all studied samples by 1-2 orders of magnitude ($p<0.0001$). The resection line tissues in EA showed the maximal pro-uPA content, while their uPA activity was similar to that in other tumors; the lowest levels of both components were observed in PHA. Pro-uPA and uPA in resection line tissues in other tumors varied but were comparable. Pro-uPA and uPA in all adenocarcinomas were higher in tumors than in surrounding tissues. The results confirmed the literature data that malignant tumors are capable of secreting pro-uPA and uPA into the surrounding tissue. Distribution of pro-tPA and tPA varied. The highest activity of tPA was observed in perifocal and tumor tissues in SA ($p<0.0001$, compared to other tumors), and then in perifocal and tumor tissues of SCA and RA, EA and PHA ($p<0.01$). Activity of tPA in PHA tumors was 1.3 times higher ($p<0.05$) than in resection line tissues. In SCA, activity of tPA was 1.3 times lower ($p<0.05$) than in resection line tissues. In RA, it decreased from the resection line to the tumor by 1.3 and 2.3 times, respectively. The levels were similar in resection line tissues in SCA and RA, being 2.5-128 times higher than in other tumors.

Conclusion: All adenocarcinomas secrete pro-uPA and uPA into surrounding tissues. The rate of pro-uPA secretion by the tumor and its activation into uPA in PHA differ from that in other tumors. In SA and PHA, tPA is a tumor-associated protein and has damaging functions. In EA, SCA and RA, tPA can play a protective role.

P – 025

WITHDRAWN

P – 026 Tumor-associated universal inhibitors and free plasmin in adenocarcinoma of stomach and pancreatic head

E Frantsiyants, O Kit, L Kozlova, A Maslov, E Kolesnikov, S Ilchenko
Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Introduction: Plasminogen, plasmin, α1 proteinase inhibitor (α1PI), and α2 macroglobulin (α2M) are mainly products of gastrobiliopancreatoduodenal organs (the liver, pancreas), so they are directly involved in the pathology of these organs. Plasmin provides the autolysis initiation both indirectly (through the activation of growth factor zymogens and matrix metalloproteinases) and directly, by participating in the hydrolysis of proteins and in the lysis of membrane and cellular structures. Physiological processes require a strict balance between the precursor, the enzyme and the inhibitors, as overactive proteolysis will lead to the destruction of the intercellular matrix and cells. The purpose of the study was to determine the levels of plasminogen, plasmin, α1PI and α2M in adenocarcinoma of the stomach (AS) and pancreatic head (APH) and in adjacent tissues.

Methods: Tumor, perifocal and resection line tissues were studied by spectrophotometry in 84 patients aged 43-72 years with AS (n = 38, G2, T2-3N0-1M0) and APH (n = 46, G2, T2-4N0M0) with calculation per 1 mg of protein. Statistical processing of the results was performed using the Statistica 10 program.

Results: Plasminogen levels were maximal in AS tumor tissues, an order of magnitude lower in its perifocal zone and two orders of magnitude lower in resection line tissues ($p < 0.001$). In APH, maximal levels of plasminogen were observed in perifocal tissues; plasminogen was 1.3 times lower in resection line tissues, and 1.7 times lower in tumor tissues than in the resection line ($p < 0.01$). Distribution of plasmin in AS was similar to that of plasminogen, and in APH the highest level of plasmin was registered in the resection line tissues, while in tumor and perifocal tissues the values were almost twice lower. The activity of α1PI and α2M was maximal in all tumor tissues, lower in perifocal tissues and even lower in resection line tissues ($p < 0.001$). The plasminogen/plasmin ratios decreased in AS from the tumor to the resection line tissues ($p < 0.001$); in APH - perifocal zone>tumor>resection line ($p < 0.001$). The α1PI/plasmin and α2M/plasmin ratios in APH decreased from the tumor to the resection line tissues ($p < 0.001$); in AS - resection line>tumor>perifocal zone ($p < 0.001$).

Conclusion: The possibility of the secretion of all studied proteins by AS is obvious and does not require proof. APH has such a potential (which was demonstrated by the distribution of the activity of both inhibitors), but the results on plasminogen and plasmin confirm a more complex relationship between the tumor and surrounding tissues. In the perifocal zone, the predominant level of plasminogen can also provide an increased content of plasmin, but instead plasmin "evades" even further into the area of intact tissues. The phenomenon of "evasion" of enzymes to surrounding tissues in APH and its rapid growth have long been known. Plasmin in intact tissues has a tumor origin, and this was confirmed by the ratios. An increase in the plasmin-antiplasmin complex in adenocarcinoma of the rectum was reported, in contrast to benign polyps. Perhaps, some amount of plasmin is bound with α2antiplasmin in tissues of gastrointestinal adenocarcinoma. The study demonstrated the production of tumor-associated α1PI, α2M and plasmin in AS and APH.

P – 027 Polymer hydrogels as innovative carriers for anticancer therapy

M Kędzierska[1], A Drabczyk[2], S Kudłacik–Kramarczyk[2], P Potemski[3], B Tyliszczak[2]

[1]Medical University of Lodz, Department of Chemotherapy, WWCOiT Copernicus Hospital, Lodz, Poland, [2]Cracow University of Technology, Krakow, Poland, [3]Medical University of Lodz, Department of Chemotherapy, WWCOiT Copernicus Hospital, Lodz, Poland

Introduction: Battle with cancer diseases is currently one of the greatest challenges of medicine. Recently, the number of cancer cases has doubled, that contributed to the fact that scientists are searching for new solutions that will help to deal with these illnesses. In the standard methods of administering cancer drugs, their therapeutic effect is not fully exploited. Traditional methods of treatment often cause undesirable side effects in the body of the patient. Additionally, introduced drug affects negatively not only diseased cells but also healthy ones. Therefore, numerous studies are currently conducted to develop materials used as carriers of such drugs. Such a carrier will enable the delivery of the drug directly to the place affected by the disease and after the completing its function it will biodegrade without affecting negatively the body of the patient.

Methods: In the presented research hydrogel polymers have been proposed as drug carriers due to their non-toxicity and biodegradability. Research included the synthesis of hydrogels by means of the photopolymerization process. Hydrogels have been obtained using chitosan - a polysaccharide widely used for biomedical purposes. Moreover, received materials have been modified with selected extracts of natural origin. Then, analyzes were conducted to determine the cytotoxicity of the hydrogels to tumor cells (Jurkat cells - lymphoblastic leukemia). Cytotoxicity was determined using MTT and XTT tests in accordance with the standard: PN-EN ISO 10993-5: 2009. Such a test allowed to determine the proliferation and viability of tumor cells cultured in the presence of the obtained materials. Cells that did not survive under the influence of the tested materials retained their enzymatic activity, which led to the transformation of the selected reagent into a colored form whose concentration could be determined spectrophotometrically.

Results: Studies were performed for 7 days, after certain periods of time viability of cells has been defined. In Table 1. results of analysis are presented.

Conclusion: Based on the presented research it can be concluded that obtained hydrogels in most cases had a negative impact on the growth of cancer cells. Such a negative impact has been noticed even after 3 days of contact with synthesized hydrogels. Therefore, it can be stated that such materials can be considered as materials interesting from a medical point of view with special emphasis on application in cancer treatment.
The authors would like to thank The National Centre for Research and Development (Grant no: LIDER/033/697/L-5/13/NCBR/2014).

P – 028 Lipoxin A4 inhibits the paracrine of Nodal in CAFs by suppressing FPRL1/ROS/NF-κB signaling to attenuate invasion and metastasis of gallbladder carcinoma

Y Shi[1], Y Fan[2], Y Hu[3], J Jing[3], E Li[3]

[1]Department of Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [2]Department of Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [3]Department of Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Introduction: Gallbladder carcinoma is a lethal disease in part because of its potential for aggressive invasion and metastasis, and cancer associated fibroblasts (CAFs) in gallbladder carcinoma exerts crucial role in this process. Lipoxin A4 (LXA4), an anti-inflammatory lipid mediator derived from the endogenous arachidonic acid metabolite, has recently been demonstrated to exhibit anti-cancer effects. However, the role of LXA4 in gallbladder carcinoma remains to be elucidated.

Methods: CAFs were isolated from tissues derived from patients diagnosed with gallbladder carcinoma, and treated with vehicle or LXA4. The levels of intracellular reactive oxygen species (ROS) was detected by 2'-7'-dichlorofluorescein diacetate, the expression of markers of CAFs, Nodal, IκBα and NF-κBp65 were determined by qRT-PCR, western blotting and immunofluorescence, and the paracrine of Nodal was detected by ELISA. Lentivirus carrier, si-RNA were used to overexpress p65 or silencing LXA4 receptor FPRL1. The conditioned medium (CM) of CAFs was collected after treated with or without LXA4 (400 nM) for 48 h, and indirect co-culture model was established to examine the effects of CAFs on the invasion of gallbladder carcinoma cells (GBC-SD cells). The subcutaneous xenograft model was applied to investigate the effect of LXA4 in vivo. The correlation between the Lipoxin effect score (LES) and the clinical-pathological features of gallbladder carcinoma was also analyzed.

Results: We found that in patients with gallbladder carcinoma, low LES was correlated with aggressive metastatic potential. LXA4 could significantly inhibit expression of markers of CAFs, IκBα and NF-κBp65, and suppress the level of ROS. The immunofluorescence staining exhibited that LXA4 can restrain nuclear translocation of p65. ELISA assay also showed LXA4 could refrain the secretion of Nodal in a concentration-dependent manner. Furthermore, the LXA4 activity was mediated by the LXA4 receptor FPRL1 and ROS/NF-κB signaling to suppress the expression and paracrine of Nodal in CAFs. Silencing FPRL1 by si-RNA, adding exogenous H2O2 or overexpressing of p65 in CAFs can respectively reverse the paracrine of Nodal in the presence of LXA4. The results of indirect co-culture model showed that compared with control group, CM of CAFs with vehicle can significantly enhance the invasion of GBC-SD cells, increase the expression of N-cadherin and Vimentin and decrease the expression of E-cadherin, while CM of CAFs with LXA4 administration could dampen the effects of CM of CAFs with vehicle on SD cells. Interestingly, when anti-Nodal neutralizing antibody was administered in CM of CAFs with vehicle or rhNodal (10 ng/mL) was administered in CM of CAFs with LXA4, the expression of EMT-associated markers and the invasion capacity of GBC-SD cells were reversed respectively. In the subcutaneous xenograft model exhibited LXA4 could inhibit the growth and metastasis of GBC-SD cells.

Conclusion: Our results demonstrated Lipoxin A4 could inhibit the paracrine of Nodal in CAFs by suppressing FPRL1/ROS/NF-κB signaling to attenuate metastasis of gallbladder carcinoma, which may provide a new strategy to prevent the metastasis of gallbladder carcinoma.

P – 029 The therapeutic effect of newly developed endoscopic irreversible electroporation ablative device in gastrointestinal tract: Application to live porcine esophagus, stomach and rectum

J Lee[1], S Choi[2], S Kim[1], J Lee[1], H Choi[3], E Kim[4], B Keum[1], Y Jeen[5], H Chun[4], H Lee[6], C Kim[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea, [2]Korea University Anam Hospital, Seoul, Republic of Korea, [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Institute of Gastrointestinal Medical Instrument Research, Korea University College of Medicine, Seoul, Republic of Korea, [4]Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea, [5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul, Republic of Korea, [6]Korea University College of Medicine, Seoul, Republic of Korea

Introduction: Irreversible electroporation (IRE) is known to remove undesired cells by affecting the cell membrane without thermally destructing connective tissues. Clinically IRE ablation is just performed recently on the target of pancreas and liver but not in gastrointestinal(GI) tract yet. We developed IRE ablative device that can be deployed through the channel of endoscopy and applied it to live porcine GI tract to study effectiveness and feasibility.

Methods: Endoscopic IRE ablation was performed on the live porcine mucosa of esophagus, stomach and rectum with a voltage of 1HZ but in different amplitude and pulse number each. On the esophagus, ablation was done in 3 points. Range of amplitude was 1.0KVcm to 1.5KVcm and pulse number was 20 to 50. The stomach was ablated in 10 different points with an amplitude from 500V/cm to 2KV/cm and pulse from 20 to 50. In rectum, 5 points were ablated with amplitude of 1.0KV/cm to 2.0KV/cm and pulse was 10 to 20. The pigs were sacrificed next day. Ablated tissues were collected with surgical technique. Following fixation, tissues were stained with H&E.

Results: Neither during the procedure nor in post-IRE ablation state, accompanied any complications in all porcine subjects. The novel endoscopic IRE device showed feasibility of effective ablation in live porcine GI tract. IRE ablative effect of electrical stimulus differs with variables such as amplitude and pulse number. Different range of mucosal and submucosal necrosis according to the degree of electrical stimuli without thermal damage to connective tissue such as submucosal vessel structure. Under certain circumstance of electrical stimulus, IRE ablative effect varies with each part of GI tract. When amplitude was 2000V/cm and pulse number was 50, necrosis was noted from mucosa, submucosa and even in muscle layer, prominent inflammation was noted. However, in case of esophagus, only squamous epithelial separation was noted with intact submucosa under the same electrical stimuli.

Conclusion: Our endoscopic IRE ablation device performed different degree of decellularization in accordance with different electrical stimuli in each part of GI tract. Endoscopic IRE ablation could be promising technique in the treatment of GI tract disease.

P – 030 Epidemiological profile and factors associated with mortality among patients with gastrointestinal cancers in a Haitian cancer program

J Bernard, V DeGennaro

Innovating Health International/St Luke Family Hospital, Tabarre, Haiti

Introduction: Gastrointestinal (GI) cancers are among the neoplasms with high burden in the low and middle-income countries. According to GLOBOCAN 2012, GI cancers are among the most common and the most lethal cancers in Haiti. A ten-year epidemiologic study on cancers in Haiti showed that GI cancers were the second most common cancer type (FD Jacques et al, 2017). Despite these data the epidemiology of GI cancers in Haiti remains poorly studied. The aim of this study was to describe the epidemiology and outcome of GI cancers in Haiti and to determine risk factors associated with mortality.

Methods: A two-year cross-sectional, retrospective study was conducted in the cancer program of Innovating Health International (IHI), in Port-au-Prince, Haiti. The charts of the patients with the clinical and/or pathological diagnosis of all GI cancers from January 1st, 2016 to December 31st, 2017 were reviewed to collect data on key variables

such as age, gender, cancer type, TNM clinical stage, alcohol and tobacco use, family history of cancer, baseline performance status and outcome. These variables were then evaluated to determine their association with mortality.

Results: Seventy-six (76) cases of gastrointestinal cancers were managed during the study period. GI cancers all types combined were the third most common cancer type in our cohort after breast cancer and gynecological cancers. The median age of the study population was 60 years [21-89] for 52.6% males and 47.4% females. 13.2% of the patients were regular alcohol users and 25% admitted tobacco use. 10.5% of the patients had a known family history of cancer. Colorectal cancer was the most common GI cancer type with 28.9% of the cases, followed by gastric cancer (23.7%), pancreatic cancer (10.5%), liver cancer (10.5%), biliary cancer (7.9%), esophageal cancer (5.3%) and anal cancer (2.6%). The remaining 10.5% were cases of carcinoma of unknown primary (CUP) identified as possible GI cancers. 96.4% of patients with TNM staging were diagnosed at stages III or IV. The overall mortality rate was 60.5%. The cancer types with the highest mortality rate were biliary cancer with 83.3%, gastric cancer with 77.8%, pancreatic cancer and esophageal cancer with 75%. Colorectal cancer had a mortality rate of 40.9%. Patients were more likely to die if they were female (Odds Ratio (OR)=2.1, $p = 0.16$), aged 70 years old or more (OR = 4.4, $p = 0.06$), had non-colorectal GI cancer (OR = 4.4, $p = 0.009$) or a baseline ECOG of 1 or more (OR = 7.5, $p = 0.0005$). 6.5% of the patients were lost to follow-up.

Conclusion: Gastrointestinal cancers are diagnosed at an advanced stage, which mainly explains the high mortality rate. Having non-colorectal GI cancer or a baseline ECOG ≥ 1 was significantly associated with mortality. Prevention and screening programs need to be implemented and cancer awareness reinforced in Haiti for earlier diagnosis. A prospective and multicenter study is needed to better evaluate the burden and risk factors of GI cancers in Haiti.

P – 031 Morbidity trends for selected gastrointestinal cancers in Poland and the costs of treatment

M Jarosz, E Rychlik

Institute of Food and Nutrition, Warsaw, Poland

Introduction: Gastrointestinal cancers are very prevalent in Poland, although in the last over 20 years there has been a favorable tendency of a decrease in the incidence of most of them. The costs of their treatment are very expensive. The decrease in morbidity allowed to reduce them. The aim of the study was to analyze the dynamics of selected gastrointestinal cancers in Poland and to estimate its influence on the costs of treatment.

Methods: The source of data on cancer incidence rates was the National Cancer Registry. The decrease in incidence of selected gastrointestinal cancers in the years 1990-2014 was assessed on the basis of the analysis of trends of potential growth curves and curves of actual, lower morbidity. Information on costs of treatment was derived from Central Statistical Office publications and additional information on these costs was taken from the estimates of Insurance Companies.

Results: Since the 1990s the incidence of most cancers of the gastrointestinal tract (gastric, pancreatic, oesophageal, liver and gallbladder) has decreased. Moreover, the growth rate of colorectal cancer is decreasing. It has been estimated that this has resulted in around 188,000 cases of illness less. The greatest reduction in the number of cases reported in gastric cancer - 33% of all cases. The direct costs of treatment of one patient are about 2,400 euro annually. These indirect costs included in the treatment are estimated at around 4,800 euro per year. In total, these costs amount to approx. 7,200 euro annually. The reduction in the number of cases of gastrointestinal cancer in the last 20 years has saved about 1.35 billion euro.

Conclusion: In 1990-2014 a significant reduction in the number of cancers of the gastrointestinal tract was noted in Poland. The number of cases of gastric cancer decreased the most. The decline in morbidity for most cancers related to favorable changes in diet and tobacco smoking in Poland contributed significantly to reduce the cost of treatment.

P – 032 FOLFIRINOX versus gemcitabine-cisplatin combination as first line therapy in treatment of pancreatic cancer

A Ozet[1], N Kayahan Satış[2], H Satış[3]

[1]Ankara Gazi University Hospital, Ankara, Turkey, [2]Gazi University Faculty of Medicine Hospital, Ankara, Turkey, [3]Gazi University Faculty of Medicine Hospital, Ankara, Turkey

Introduction: To purpose of this study was to compare efficacy and safety of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) and gemcitabine-cisplatin as first-line therapy in patients with pancreatic cancer.

Methods: We retrospectively evaluated pancreatic cancer patients with Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a scale of 0 to 5, with higher scores indicating a greater severity of illness) to receive FOLFIRINOX (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks) or gemcitabine plus cisplatin (gemcitabine at a dose of 1000 mg per square meter weekly for 1 and 2 week, cisplatin at a dose of 100 mg per square meter weekly for 1 week, every 3 weeks). Patients with at least three months chemotherapy given were included and primary end point was overall survival.

Results: There were 32 patients in FOLFIRINOX group and 36 patients in gemcitabine-cisplatin group. The median overall survival was 18.1 months (7,5-28,7) in the FOLFIRINOX group as compared with 9.7 months (6,5-13) in the gemcitabine-cisplatin group (P:0.009). Median progression-free survival was 16.2 months ((9-23.4) in the FOLFIRINOX group and 6.9 months (6,1-7,6) in the gemcitabine-cisplatin group (P:0.001). More adverse events were noted in FOLFIRINOX group in terms of grade 3-4 neutropenia and diarrhea while in Gemcitabine-Cisplatin group more adverse events were noted in grade 3-4 thrombocytopenia and sensorineural neuropathy.

Conclusion: As compared with gemcitabine-cisplatin combination, FOLFIRINOX was associated with a survival advantage and had increased toxicity. FOLFIRINOX is a safe and effective option for the first-line treatment of patients with pancreatic cancer and good performance status.

P – 033 Longitudinal assessment of neutrophil-to-lymphocyte ratio (NLR) from diagnosis until death reveals a biphasic trend in metastatic pancreatic adenocarcinoma patients

C Morelli[1], V Formica[2], S Pellicori[3], A Nardecchia[1], M Roselli[1]

[1]Medical Oncology Unit, Tor Vergata University Hospital, Rome, Italy, [2]Medical Oncology Unit, University of Rome Tor Vergata, Rome, Italy, [3]Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Milan, Italy

Introduction: Baseline NLR has been found to have a significant prognostic value in metastatic pancreatic adenocarcinoma (mPA) patients. However, NLR assessment during the entire course of mPA disease has never been reported.

Methods: We analyzed 1025 cell blood counts (CBCs) saved to PTV-BIO.CA.RE. (Biospecimen Cancer Repository) in 44 mPA patients (23.3 CBCs/patient) who had reached the overall survival endpoint (death ascertained) and NLR was calculated as per standard. Trend of NLR over the remaining weeks to death was analyzed, and where a clear correlation was observed a standard regression analysis was performed. Potential association between NLR trends and short survival was analyzed.

Results: NLR values over the time had a clear biphasic trend, remaining roughly constant (median NLR 2.5, 95% CI 2.2-2.7) up to 24 weeks prior to death (correlation coefficient R 0.03, p 0.603) and then displaying a marked rectilinear increase from week -24 to death (time 0) (R 0.48, $p < 0.001$). The equation that expressed the rectilinear increase of NLR during the last 24 weeks of life was NLR=9.663 – 0.325* (weeks-to-death), indicating an increase of about +0.3 in NLR for every week passing from -24 to 0 (death). A NLR above 3.0 with a confirmed increase of > +0.3 points/week in two subsequent CBCs was able to predict an imminent death (within 24 weeks) in 97.8% of cases (Relative Risk as compared with NLR < 3 and/or increase rate < 0.3points/week: 2.75, $p < 0.0001$).

Conclusion: Longitudinal assessment of NLR in mPA patients is able to predict with great precision death occurring within 24 weeks. Treatments able to lessen the unfavourable NLR increase rate of + 0.3 points/week are likely to change the natural history of this disease.

P – 034 Austrian real world data in elderly and younger metastatic pancreatic cancer patients: Interim results of a multicenter non-interventional study with nab-paclitaxel/gemcitabine

W Eisterer[1], A Gerger[2], L Öhler[3], B Mlineritsch[4], T Sliwa[5], K Wilthoner[6], A Petzer[7], P Pichler[8], E Hubmann[9], T Winder[10], S Burgstaller[11], M Korger[12], J Andel[13], E Wöll[14], H Neumann[15], M Pecherstorfer[16], K Philipp-Abbrederis[17], A Djanani[17], B Gruenberger[18], F Längle[19], G Prager[20]

[1]Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria, [2]Division of Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria, [3]St. Josef Krankenhaus, Vienna, Austria, [4]Universitätsklinik Salzburg, Salzburg, Austria, [5]Hanuschkrankenhaus Wien, Vienna, Austria, [6]Landeskrankenhaus Vöcklabruck, Vöcklabruck, Austria, [7]Ordensklinikum Linz BHS-EKH, Linz, Austria, [8]Universitätsklinikum St. Pölten, St. Pölten, Austria, [9]Krankenhaus der Barmherzigen Brüder Graz, Graz, Austria, [10]Landeskrankenhaus Feldkirch, Feldkirch, Austria, [11]Klinikum Wels-Grieskirchen, Wels, Austria, [12]Krankenhaus der Barmherzigen Brüder Eisenstadt, Eisenstadt, Austria, [13]Landeskrankenhaus Steyr, Steyr, Austria, [14]Krankenhaus St. Vinzenz, Innere Medizin, Zams, Austria, [15]Krankenhaus der Elisabethinen Klagenfurt, Klagenfurt, Austria, [16]Landesklinikum Krems, Krems, Austria, [17]Medizinische Universität Innsbruck, Innsbruck, Austria, [18]Bamherzige Brueder Wien, Dept Internal Med, Vienna, Austria, [19]Dept Surgery, Wr Neustadt, Austria, [20]Clinical Division of Medical Oncology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria

Introduction: Pancreatic cancer is the 4th leading cause of cancer-related death while accounting for only 3% of newly diagnosed cancer cases.[1] Nab-paclitaxel (Abraxane®, Celgene) plus gemcitabine (nab-P/G) has proven tolerability and superior

efficacy as first-line treatment for metastatic pancreatic cancer (mPCa) compared to gemcitabine alone in the MPACT randomized phase III trial.[2] Real-life clinical practice, however, is comprised of diverse treatment conditions and heterogenous patient populations. Here we report on prospective, non-interventional real-world data regarding the use of nab-paclitaxel in mPCa patients (pts) in the Austrian clinical routine.

Methods: Pts with confirmed mPCa who met the eligibility criteria were treated with nab-P/G at a dose regimen of nab-paclitaxel 125mg/m2 plus gemcitabine 1000mg/m2 on days 1, 8, 15 of every 28day cycle in its labeled indication until progression and prospectively observed until disease progression or unacceptable toxicity. Primary objectives were safety and tolerability of nab-paclitaxel, secondary objectives were the objective response rate (ORR) and assessment of real life dosing in daily clinical routine. Descriptive statistics were used to analyze the data.

Results: Between 5/2015 and 1/2018, 237 pts (median age: 70 years, range 44-89; 55% male, 108 (46%) >70 years) were included across 20 sites, 219 pts were eligible for analysis. At baseline, 46% (67/145) had grade 2 and 46% (66/145) grade 3 disease; CA19-9 was elevated in 85% of pts (161/190). A total of 1011 treatment cycles were applied, 46% (463 cycles) on days 1/8/15, while 34% (345 cycles) were initiated at a reduced dose intensity (days 1/0/15). Median treatment duration was 4 cycles (n = 219; range 1–17). Patients' performance status was ECOG 0-1 in 96% of administered cycles. The ORR of this interim analysis was conducted in 145 patients and consisted of 43% partial responses (PR), 41% had stable disease (SD) for a disease control rate (DCR) of 83%. In the elderly cohort (>70, n = 62), 45% had a PR and 42% had SD for a DCR of 87%. Median PFS was 5.1 months both in all pts (n = 151) and in evaluated subgroups (≤/>70 years, n = 82/n=69, HR = 0.941). Nab-P/G was well tolerated with comparable rates of adverse drug reactions (495 vs. 455) in the respective subgroups (≤/>70 years), 86% (both) being non-serious, 13 vs. 11% required hospitalization. Pts in both subgroups benefited from the scheduled dose regimen mostly on days 1/8/15 (n = 41/n=32) with a median PFS of 5.8 months. A less dose dense application mostly on days 1/0/15 resulted in a PFS of 6.1 vs. 5.1 months in pts ≤ 70 vs. > 70 years (n = 14/n=18; HR = 0.82). The most common reasons for treatment discontinuation (n = 171) were tumor progression (45%) or death in (19%); 5% of pts discontinued treatment due to toxicity. No new safety signals were identified.

Conclusion: These preliminary real-world data confirm the effectiveness and tolerability of nab-P/G in the clinical routine treatment of metastatic pancreatic cancer patients including a large cohort of elderly patients >70 years.

P – 035 Hepatic stellate cells (HSCs) activating HSF1-mediated COMP secretion promote liver metastasis of pancreatic cancer through CD36/AKT/FOXM1 signaling

L Sun[1], Y Wang[2], Q Li[2], L Wang[2], C Wang[2], B Yao[2], Z Liu[2], T Song[2], K Tu[2], Q Liu[2]

[1] Department of Hepatobiliary Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [2]Department of Hepatobiliary Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Introduction: Previous studies demonstrated that primary pancreatic cancer cells can release circulating factors or exosomes into the liver to form premetastatic niches. HSCs are important in forming premetastatic niches because they can transdifferentiate into the tumor-associated myofibroblasts, and then promote metastasis and growth of pancreatic cancer cells. The transcriptional regulator heat shock factor 1 (HSF1) is frequently activated in tumor stroma, and Cartilage oligomeric matrix protein (COMP) is a 524 kDa soluble glycoprotein particularly expressed in fibrotic conditions. However, the role of HSF1 and COMP in activated HSCs of premetastatic niches to facilitate metastasis and growth of pancreatic cancer remains to be elucidated.

Methods: Elisa assay was used to detect expression of COMP in serums of pancreatic cancer patients with or without liver metastasis. Human primary HSCs and LX2 cells were activated by the conditioned medium (CMpcs) of pancreatic cancer cells (Panc-1) in vitro. The expression of HSF1, HSP90, HSP47, COMP in HSCs; CD36, p-AKT, AKT and Forkhead box M1 (FOXM1) in Panc-1 cells was determined by qRT-PCR, western blotting and immunofluorescence. CHIP-qPCR assay and dual-luciferase reporter system were used to explore the correlation between HSF1and COMP. The conditioned medium (CMhscs/lx2) of activated HSCs or LX2 was collected after treated with or without anti-COMP neutralizing antibody, KRIBB11 (an inhibitor of HSF1) or si-HSF1for 48 h, and indirect co-culture model was established to examine the effects of activated HSCs on the invasion and growth of pancreatic cancer cells. Intrasplenic tumor injection was used to establish a standard liver metastasis model of pancreatic cancer.

Results: The secretion of COMP in serums is higher in pancreatic cancer patients than that in normal individuals, and it is highest in pancreatic cancer patients with liver metastasis. The expression of HSF1, HSP90, HSP47, COMP, α-SMA and collagen I were elevated in activated human primary HSCs and LX2 cells co-cultured with CMpcs. Double immunofluorescence staining showed that the expression of COMP and nuclear translocation of HSF1 was prominently enhanced in activated HSCs and LX2, and it was reversed in the presence of KRIBB11or si-HSF1. The secretion of COMP in CMhscs/lx2 of activated HSCs or LX2 was also increased. CHIP-qPCR assay and dual-luciferase reporter system showed that HSF1 can act on the promoter region of COMP. The results of indirect co-culture model displayed that CMhscs/lx2 can notably facilitate the invasion of Panc-1cells, increase the expression of EMT markers, p-AKT, FOXM1, and promote the nuclear translocation of FOXM1. These effects were reserved by silencing CD36 (a receptor of COMP), si-FOXM1, treated with LY294002 (an inhibitor of AKT), or added with Anti-COMP neutralizing antibody. In the liver metastasis model in nude mice, KRIBB11 or anti-COMP neutralizing antibody, could inhibit the metastasis of pancreatic cancer cells.

Conclusion: Our study demonstrated that HSCs in premetastatic niches activating HSF1-mediated COMP secretion promote liver metastasis of pancreatic cancer cells through CD36/AKT/FOXM1 signaling, which may provide a new strategy to prevent the metastasis of pancreatic cancer.

P – 036 High proliferation is independently associated with disease progression in metastatic pancreatic adenocarcinoma

S Temraz[1], M Salim Hammoud[1], I Makki[2], S Nassif[3], M Charafeddine[4], D Mukherji[1], A Shamseddine[1]

[1]American University of Beirut Medical Center, Beirut, Lebanon, [2]American University of Beirut, Beirut, Lebanon, [3]American University of Beirut Medical Center, Beirut, Lebanon, [4]American University of Beirut, Beirut, Lebanon

Introduction: Pancreatic cancer is an aggressive disease with a 5-year survival rate below 5%. It involves genomic alterations like mutated tumor suppressor gene p53 (TP53) and overexpressed Ki-67. We investigated the expression of Ki67 and p53 in metastatic pancreatic adenocarcinomas and analyzed their relationship with progression free survival (PFS).We also correlated their expression with PFS in two different groups of patients: gemcitabine-based treated patients (GT) versus FOLFIRINOX treated (FT) patients.

Methods: This is a retrospective study done at the American University of Beirut Medical Center (AUBMC) in which we included the medical records of sixty one patients diagnosed with metastatic pancreatic cancer over a period extending from May 2000–November 2013. Patients proved to have a stage IV pancreatic adenocarcinoma, with available tissue blocks, demographic, clinical and survival data were included in this study. Pancreatectomy and biopsy specimen slides were reviewed for immunohistochemistry (IHC) staining of both p53 and Ki67. Ki-67 proliferation index was determined using the following method: 1-the tumor area was screened and foci with the highest nuclear staining were selected; 2-these foci were further subdivided into quadrants and examined at 400x magnification; 3- tumor nuclei were counted in each quadrant, and the percentage of tumor nuclei with positive staining was determined. P53 staining results were noted as an overall estimate of positive tumor nuclei, throughout the entire tumor area in the stained section. All data were collected and analyzed using the SPSS v.23.0 statistical package.

Results: The mean of Ki-67 and P53 were significantly higher in the patients who had disease progression (31.0 vs 8.2, $p < 0.001$ and 46.9 vs 16.2; $p < 0.001$, respectively). The estimated cutoff value calculated by the ROC curve of Ki-67 was 12.5 and that of P53 was 15. In the overall study population, patients who had Ki67 and p53 levels greater than their corresponding cut off value had a significantly shorter PFS (Ki67 >12.5, p = 0.048; p53>15, p = 0.048). This effect was more prominent in the GT group compared to FT group. Multivariate analysis proved that Ki67 remained significantly associated with disease progression: for every one-unit increase in Ki-67 the progression risk will be increased by 1.017 times, controlling for other variables including grade, age, and P53. Ca19-9 levels were significantly higher in patients with a progressing disease (8885.3 vs 1714.4; p = 0.016). Moreover, 58% was identified by the ROC curve as the cutoff value after which there is an increased likelihood of the progression of the disease. Patients who had a decrease in CA19-9 levels 6-8 weeks after chemotherapy of > 58% had significantly longer PFS (p = 0.027). This effect was also more prominent in the GT group compared to FT group.

Conclusion: Our study highlights the negative impact of high P53 and Ki67 expression on PFS in patients with metastatic pancreatic cancer. Ki-67 is an independent prognostic factor for PFS especially in the GT group.

P – 037 Pancreatic cancer in Morocco: A retrospective review

A Haimer[1], F Habib[2], A Soulaymani[1], A Mokhtari[1], H Hami[1]

[1]Laboratory of Genetics and Biometry, Faculty of Science, Ibn Tofail University, Kenitra, Morocco, [2]Al Azhar Oncology Center, Rabat, Morocco

Introduction: Pancreatic cancer is an uncommon and aggressive cancer in Northern Africa. It is the 14th most commonly diagnosed cancer in men and women and the 11th leading cause of cancer-related death, with about 4 034 new cases of pancreatic cancer and 3 915 cancer deaths estimated to have occurred in 2012 (GLOBOCAN 2012). The aim of this study is to determine the epidemiological profile of pancreatic cancer in Morocco.

Methods: This is a descriptive retrospective study of pancreatic cancer cases, diagnosed and treated at Al Azhar Oncology Center in Rabat between 2005 and 2015.

Results: There were 120 new cases of pancreatic cancer diagnosed at Al Azhar Oncology Center (71 men and 49 women), accounting for 1.5% of all new cancer cases reported during the study period. The average age at diagnosis of pancreatic cancer was 59.6±15 years (range 0-94 years). The risk of developing pancreatic cancer increases with age. More than three-quarters of people diagnosed with pancreatic cancer (82.5%) were aged 50 years or older at the time of diagnosis, with 77.5% of new cancer cases occurring among those aged 50-79 years. Among all detected cases, 1.7% were

diagnosed with metastatic disease and 13.3% died from the disease during the study period, accounting for 2.4% of all cancer deaths.

Conclusion: Pancreatic cancer remains a significant public health issue. Early diagnosis is difficult because the disease is asymptomatic in its early stages "silent disease".

P – 038 Stereotactic body radiation therapy (SBRT) for locally advanced pancreatic cancer (LAPC)

M Vera Merino, C Niño de Guzmán, D Angel Schutte, D Venencia, L Suarez Villasmil, S Zunino

Instituto Privado de Radioterapia, Cordoba, Argentina

Introduction: SBRT would allow local control for LAPC with acceptable toxicity in a short time. The purpose of this work is to assess early and late toxicities and clinical response in patients treated with SBRT.

Methods: Between October 2013 and February 2018, 48 patients with LAPC, mean age 64 years (39-84y), treated with neoadjuvant, concomitant or adjuvant chemotherapy plus SBRT were retrospectively analyzed. The treatment dose was 25 Gy to 37.3 Gy given in 3 to 5 daily fractions, utilizing volumetric arc therapy, a 6-MV photon beam and Linac Novalis IGRT-ExaTrac accelerator. GTV and OARs were delineated in CT and PET-CT fused images. OARs were contoured according RTOG criteria. The treatment planning was done in Eclipse V15.1. Acute ($\leq$3m) and late (>3 m) toxicities grades were classified according to the CTCAE V.3.0.

Results: Of 48 LAPC patients (27 women/21 men), mean follow up 9.41 m (0.23-23.77), 35 (72.91%) received SBRT in pancreatic tumor as primary treatment, 11 (22.92%) were operated first, followed by SBRT; and 2 patients (4.17%) were rescued with SBRT because recurrence after conventional radiotherapy. 33 patients (68.75%) had adenocarcinoma diagnosis, and 15 (31.25%) had no biopsy. Early toxicity (48 pts) G1: asthenia in 7 (14.5%), nausea in 6 (12.5%) and abdominal pain in 9 (18.75%); G2: asthenia in 4 (8.34%), nausea in 1 (2.08%) and vomiting in 1 pt. (2.08%); G3: enteritis in 2 (4.17%), and one of them interrupted SBRT. Fourteen patients (29.17%) did not have any early toxicity. Late toxicities (21 pts) G1: enteritis in 1 (4.77%) and asthenia in 2 (9.52%); G3: abdominal pain in 1 (4.77%) and G4 in 1 pt. (4.77%) who suffered from intestinal perforation because disease progression. Relive of abdominal pain were observed in 23/48 patients after SBRT (47.92%). Kaplan-Meier survival at 12 and 18 months was 46% and 31% respectively. Thirteen live patients kept in good shape PS0-2.

Conclusion: Despite of the heterogeneity in dose and fractionation, we suggest that SBRT is a feasible and safe option for patients with pancreatic cancer.

P – 039 Vascular endothelial growth factor (VEGF) splice isoforms may hold the key to targeting tumour angiogenesis in oesophageal cancer

F Mehedi

Kettering General Hospital NHS Foundation Trust, Kettering, UK

Introduction: Angiogenesis is principally induced by Vascular Endothelial Growth Factor A (VEGF-A); however, the use of VEGF-A inhibitors in the treatment of oesophageal cancer (e.g. Bevacizumab) has not proven efficacious in clinical trials. It has subsequently been shown that splicing of the terminal exon of VEGF-A pre-mRNA generates two separate isoforms: pro-angiogenic VEGF165a and anti-angiogenic VEGF165b. These isoforms are balanced to regulate angiogenesis by the splicing factor SRSF1, phosphorylated by serine–arginine protein kinase 1 (SRPK1). The aim of this study was to investigate expression of VEGF-A, its isoforms, and SRPK1 in oesophageal cancer and their association with micro vessel density (MVD) and patient survival. Understanding the role of SRPK1 and VEGF-A splice isoforms in the regulation of oesophageal cancer angiogenesis may provide a new and potentially efficacious target for anti-angiogenic therapy. Angiogenesis is principally induced by Vascular Endothelial Growth Factor A (VEGF-A); however, the use of VEGF-A inhibitors in the treatment of oesophageal cancer (e.g. Bevacizumab) has not proven efficacious in clinical trials. It has subsequently been shown that splicing of the terminal exon of VEGF-A pre-mRNA generates two separate isoforms: pro-angiogenic VEGF165a and anti-angiogenic VEGF165b. These isoforms are balanced to regulate angiogenesis by the splicing factor SRSF1, phosphorylated by serine–arginine protein kinase 1 (SRPK1). The aim of this study was to investigate expression of VEGF-A, its isoforms, and SRPK1 in oesophageal cancer and their association with micro vessel density (MVD) and patient survival. Understanding the role of SRPK1 and VEGF-A splice isoforms in the regulation of oesophageal cancer angiogenesis may provide a new and potentially efficacious target for anti-angiogenic therapy.

Methods: Tumour samples from 36 patients with oesophageal adenocarcinoma undergoing curative resection following neo-adjuvant chemotherapy were examined using immunohistochemistry for VEGF-A, VEGF165a, VEGF165b, CD31 (for MVD) and SRPK1. Digital droplet PCR was used to quantify SRPK1 levels at the gene level.

Results: VEGF-A was not associated with MVD. There was a high (pro-angiogenic) VEGF165a/VEGF165b ratio in the majority of the oesophageal cancers examined. VEGF165a expression was positively correlated with SRPK1 expression ($p = 0.01$). There was a positive correlation between the pro-angiogenic (VEGF165a dominant) oesophageal cancers, MVD and poor overall survival; however, this did not reach statistical significance.

Conclusion: The dominance of the pro-angiogenic VEGF splice isoform and the splicing factor SRPK1 show greater correlation with oesophageal cancer angiogenesis and disease survival than the general target of VEGF-A. Further investigation of the control and potential inhibition of this angiogenic pathway in oesophageal cancer is required.

P – 040 Biochemical and radiological inflammatory markers in oesophageal squamous cell carcinoma treated with radical chemoradiation

N Khin[1], W Peh[2], W Tham[2], W Lam[2], M Wang[3], T Siow[1], F Lim[1], D Tan[1], F Chin[1], E Chua[1], F Wang[1], S Ho[1], C Yip[1]

[1]Radiation Oncology, National Cancer Centre Singapore, Singapore, [2]Nuclear Medicine & Molecular Imaging, Singapore General Hospital, Singapore, [3]Radiation Oncology, National Cancer Centr Singapore, Singapore

Introduction: Inflammatory markers have been shown to be associated with poor prognosis in various solid tumours. We aimed to evaluate the role of biochemical and radiological inflammatory markers in oesophageal SCC treated with radical chemoradiation (CRT).

Methods: We retrospectively evaluated 48 patients with primary oesophageal SCC who completed radical CRT in a single tertiary institution between 2006-2015. Baseline and post-CRT serum inflammatory markers (neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte ratios (PLR)) and baseline 18F-FDG PET parameters (SUV max, SUV mean, metabolic tumour volume (MTV) and total lesion glycolysis (TLG)) were derived and dichotomised using median values. Clinical parameters such as age and RT dose were obtained from medical notes. Univariate and multivariate overall survival (OS) analyses were performed using Cox regression model. Kaplan-Meier survival analysis was performed using dichotomised variables. A p-value

Results: All patients (median age 65; 44 males) received radical radiotherapy (RT) with platinum-based chemotherapy. Total RT doses ranged between 41.4-70Gy. Sixteen patients had baseline PET scans available for analysis. Median follow-up was 21.5 months (range 3.0-113.8 months). Median OS for all patients was 21.2 months. Baseline PLR (HR 1.007, 95% CI 1.003-1.010, $p < 0.001$), post-CRT PLR (HR 1.002, 95% CI 1.001-1.003, $p < 0.001$) and RT dose (HR 0.938, 95% CI 0.892-0.986, $p = 0.012$) were significant univariate parameters. Patients with lower baseline (median OS 31.3 vs. 13.3 months, $p = 0.007$) and post-CRT PLRs (median OS 32.7 vs. 14.4 months, $p = 0.001$), and who received RT doses >50.4Gy (median OS 32.0 vs. 10.0 months, $p < 0.001$) had improved OS. An elevated post-CRT PLR (HR 1.002, 95% CI 1.001-1.003, $p = 0.003$) was associated with inferior OS in multivariate analysis. Age (HR 1.010, 95% CI 0.978-1.042, $p = 0.556$), NLR (baseline: HR 1.083, 95% CI 0.861-1.362, $p = 0.495$; post-CRT: HR 1.016, 95% CI 0.977-1.055, $p = 0.432$) and PET parameters (SUVmax: HR 1.051, 95% CI 0.967-1.144, $p = 0.242$; SUVmean: HR 1.213, 95% CI 0.977-1.508, $p = 0.081$; MTV: HR 1.003, 95% CI 0.987-1.019, $p = 0.746$; TLG: HR 1.000, 95% CI 0.999-1.002, $p = 0.666$) were not associated with OS.

Conclusion: PLR, particularly in the post-CRT setting is a significant prognostic marker in oesophageal SCC but NLR and PET parameters are not associated with OS. Although the study is limited by the small sample size and retrospective bias, these results warrant larger confirmatory studies.

P – 041 Prognostic impact of C-reactive protein/albumin ratio in locally advanced esophageal cancer

J Simões, N Tavares, M Ribeiro, C Borges, D Almeida, A Costa, L Águas, S Meireles

Hospital S. João, Porto, Portugal

Introduction: Currently, esophageal cancer remains one of the cancers most associated with morbidity and mortality. In recent studies, the C-reactive protein/albumin ratio (CAR) has been described as an important marker of prognosis associated with the inflammatory status that influences the carcinogenic process.

Methods: Retrospective analysis of patients diagnosed with locally advanced esophageal cancer undergoing treatment with neoadjuvant chemoradiotherapy (NA CT – RT) followed by surgery, in the period between 2010 and 2017, at our institution. CAR analysis was performed prior to initiation of treatment, and clinical evidence of infection or inflammatory status at that time was excluded. It was considered a cut-off of 0,15. Survival analysis was performed using the Kaplan-Meier method and prognostic factors assessed by univariate analysis and by the Cox regression model.

Results: Of the 52 patients included in the sample, the median age at diagnosis was 60 years (36-79) and 89% were men. PS ECOG was 0 in 87% of patients. Regarding the histological type, 81% of the patients had epidermoid carcinoma and 19% adenocarcinoma. Regarding location, 31% of the tumors were of the middle third and 69% of the distal third or gastro-oesophageal junction. Forty percent had lymph node metastasis at diagnosis. About 42% of the patients (n = 22) presented low CAR and 58% (n = 30) high CAR. Patients were submitted to CT with cisplatin and 5-FU (54%) or carboplatin and paclitaxel (40%), concomitant with RT. The majority (67%) underwent Ivor-Lewis total esophagectomy and in 25% it was found irresectability during the surgical procedure. Downstaging was achieved in 38.5% of patients, and pathological complete response (pCR) was achieved in 21%. Overall survival (OS) at 2 years for patients with

CAR<0.15 was 65%, whereas for patients with CAR≥0.15 was 46% (p < 0.01). In the univariate analysis, the following were prognostic factors for OS: CAR (p = 0.02), tumor downstaging (p = 0.05) and pCR (p = 0.03). In the multivariate analysis, tumor downstaging (HR 0.23, 95% CI 0.06-0.91, p = 0.04) and low CAR (HR 0.09, 95% CI 0.01-8.8, p = 0.03) maintained a positive impact on OS.

Conclusion: According to these data, CAR was an independent prognostic factor for OS. It is a promising and innovative prognostic marker in several pathologies, among them esophageal cancer. However, CAR needs validation in prospective multicentric studies.

P – 042 Definitive chemoradiation in esophageal squamous-cell carcinoma: Carboplatin/paclitaxel versus cisplatin/5-FU

N Tavares[1], M Ribeiro[1], S Meireles[2], D Almeida[1], L Águas[1], A Costa[1], P Fontes[1], M Damasceno[2]

[1]Hospital S. João, Porto, Portugal, [2]Hospital de S. João, Porto, Portugal

Introduction: Patients with Esophageal squamous-cell carcinoma (ESCC) carry a bad prognosis. Definitive chemoradiation (dQRT) is a curative intent treatment for inoperable or unresectable tumors. Data suggests that treatment with carboplatin/paclitaxel (CP) is less toxic than cisplatin/5FU (CF) but it is currently unknown if there is any survival difference between these protocols. This study tried to compare overall survival (OS) and toxicity profiles in ESCC patients submitted to dQRT with CP or CF.

Methods: Retrospective cohort of patients with ESCC diagnosed between June 2011 and February 2016 in a tertiary university hospital and treated with CP (weekly carboplatin AUC 2 + paclitaxel 50 mg/m2) or CF (cisplatin 75 mg/m2 + 5-FU 1g/m2 in a 96h perfusion on days 1 and 29) and concomitant radiation therapy (45 Gy in fractions of 1.8 Gy). OS was estimated by Kaplan-Meier method and a significant level of 0.05 was chosen to assess the statistical significance.

Results: 30 patients were included, 90% (n = 27) of male gender with a median age at diagnosis of 63 years. Tumors were mainly located in the middle (53.3%, n = 16) or upper third (40%, n = 12) of the esophagus. Only two cases were located in the lower third (6.7%). Eighteen patients (60%) were treated with CP and 12 (40%) with CF. Overall survival was 7.6 months (CI 95% 2.8–12.4 months). There were no difference in OS between the two groups (CP 7.6 months vs. CF 6.8 months, p = 0.829). Twenty one patients had an ECOG=0 (CP = 11 vs. CF = 10) and 7 had an ECOG=1 (CP = 6 vs. CF = 1). All patients with cardiovascular comorbidities (n = 4) were treated with CP. Most common grade ≥3 toxicities were oral mucositis (CP = 7, CF = 1), fatigue (CP = 5, CF = 1), febrile neutropenia (CP = 3, CF = 1) and anemia (CP = 2, CF = 2). Fourteen patients (46.7%) didn't managed to perform all planned chemotherapy cycles: 6 due to grade ≥3 toxicity, 6 due to infections (2 of whom died) and 2 due to patient refusal to proceed. Patients treated with CP were more frequently unable to complete chemotherapy (CP = 12 vs. CF = 2; p = 0.007). Disease progression was confirmed in 86.7% of patients (n = 26) and only 23.1% of these (n = 6) were treated with a subsequent line of chemotherapy (3 patients treated with CP in first line and 3 patients treated with CF).

Conclusion: Inoperable or unresectable ESCC remains an entity with scarce treatment strategies and this study confirmed that these patients have a bad prognosis. There wasn't a statistically significant difference in OS between CP and CF protocols. Patients treated with CP seemed to have higher rates of toxicity and treatment withdrawal. This is probably due to preferential allocation of patients with more comorbidities and unfavorable performance status to a traditionally considered better tolerated scheme, still without any apparent impact on OS.

P – 043 Oncologic outcomes of elderly patients with localized esophageal cancer who underwent curative surgery compared with younger patients

H Choi[1], S Sung[2]

[1]The Catholic University of Korea, Uijeongbu-Si, Republic of Korea, [2]Department of Radiation Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, SuWon, Republic of Korea

Introduction: The management of older patients with esophageal cancer can be quite challenging because they have multiple comorbidities and physiological changes associated with aging that may hinder their ability to receive and tolerate combined modality therapy. We investigated this study to determine the toxicity and oncologic outcome of elderly patients (> 65 years) with localized esophageal cancer who underwent curative surgery compared to younger patients (≤ 65 years).

Methods: We performed a retrospective chart analysis from January 2010 to December 2016. A total of fifty-five esophageal cancer patients were included in this study. All patients received curative aimed surgery. Patients with locally advanced esophageal cancer received neoadjuvant chemoradiation at a dose of 50.4Gy in 28 fractions before surgery.

Results: Elderly patients were 24 (43.6%) and younger patients were 31(56.4%). The median age was 57 years for the younger patient group and 70 years for the elderly group. pT stage, pN stage, and neoadjuvant chemoradiation did not show any difference between two groups (p = 0.206, 0.567, 0.137). The 3-year recurrence free survival rate was not significantly different between elderly group and younger group (48.3% vs. 47.0%, p = 0.361). The 3-year local recurrence free survival and distant metastasis free survival did not show any difference between two groups (local recurrence free survival: 51.4% vs. 53.7%, p = 0.636; distant metastasis free survival: 60.0% vs. 63.9%, p = 0.678).

Conclusion: Elderly esophageal cancer patients with good performance status showed comparable recurrence-free survival compared with younger patients.

P – 044 Long term survival in advanced esophageal cancer, treated with a French modality of hypofractionated radiotherapy + chemotherapy with or without surgery, the experience at the Instituto Nacional de Cancerología, México

J Zamora Moreno[1], V Aiello-Crocifoglio[2], B García Pantoja[1], E Ruiz-Garcia[3], G Estrada[4], F Baillet[5]

[1]Instituto Nacional de Cancerología, Mexico City, Mexico, [2]Instituto Nacional de Cancerologia, Mexico City, Mexico, [3]Instituto Nacional de Cancerologia, Tlalpan, Mexico, [4]Instituto Mexicano del Seguro Social, Mexico City, Mexico, [5]Hopitaux de Paris, Paris, France

Introduction: Esophageal cancer, it is an aggressive malignancy with an increasing incidence. Its virulence, in terms of symptoms, mortality, and its geographic variation with a worst prognostic in developing countries, justifies a continued search for optimal therapy. In our country more of the 80% of the patients presents at first time with an advanced disease and a large proportion of them abandon the conventional treatment due to its toxicity. The aim of this retrospective study was to investigate the efficiency and toxicity of an hypofractionated radiotherapy regime, concurrent with a basic scheme of chemotherapy.

Methods: From February 2000 to January 2011, 85patients were treated. Radiotherapy was delivered with an hypofractionated Split course scheme of 5 Gy + 5Gy (days 1 and 3) and 6.5 Gy + 6.5 Gy (days 15 and 17) to a total radiation dose of 23 Gy in 3 weeks with a Split of 1 week+ concurrent chemotherapy with 5 Fu + CDDP for one or two cycles.

Results: The median age was 59.81 years (range: 30-85 years), female 25.9% (22) patients, <40y (3.5%) >70y (7.1%) male 74.1% (63) patients, <40y (5.9%) > 70y (20%), the tumor location was supracarinal in 37.6% (32) patients and infracarinal in 62.4% (53) patients, histology; squamous cell carcinoma 60% (51) patients, adenocarcinoma 36.5% (31) patients, unknown 3.5% (3) patients, obstruction ≥ 80% was observed in 57.64% (49) patients, and the length of the tumor was >70 mm in 37.6% (32) patients. The clinical stages (AJCC2002) stage II 1.2% (1) patient, stage III 44.7% (38) patients, stage IV 51.8% (44) patients, unknown III or IV 2.4% (2) patients. The median follow-up time was 17.44 months (range 3-184.31), and the overall survival (OS) at 5, 10, and 15 years was 23,%, 18% and 18%, respectively. The most common nonhematologic toxicity was esophagitis, toxicities grades 3 and 4, were not observed.

Conclusion: As retrospective study, it has several limitations, but the clinical benefit to be alive not, there are limitations inherent to the model of biological equivalent dose, no allowances can be made for any time gaps in Split course treatments. At our knowledge, this is the first report of advanced esophagus cancer with survival at 15 years, treated with an hypofractionated scheme of radiotherapy with concurrent chemotherapy ± surgery. This yielded satisfactory survival outcomes with minimum costs and toxicities. Randomized studies are warranted to further clarify this issue.

P – 045 Analysis of global factors associated with survival in esophageal squamous cell carcinoma: Our experience at Ramon y Cajal Hospital

A Barquín García[1], J Serrano Domingo[2], C Saavedra Serrano[1], V Albarrán Artahona[1], M Villamayor Delgado[3], O Martínez Saez[3], J Molina Cerrillo[4], R Martín Huertas[1], E Corral de la Fuente[1], R Ferreiro Monteagudo[4], M Rodriguez Garrote[4], V Pachón Olmos[4], M Vaz[5], P Reguera Puertas[4], C Guillén-Ponce[6], A Carrato[7], F Longo Muñoz[5]

[1]Ramón y Cajal Hospital, Madrid, Spain, [2], [3]Ramón y Cajal Univsersity Hospital, Madrid, Spain, [4]Ramón y Cajal University Hospital, Madrid, Spain, [5]Hospital Universitario Ramón y Cajal, Madrid, Spain, [6]H. Universitario Ramón y Cajal, IRYCIS, Madrid, Spain, [7]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain

Introduction: Rates for esophageal squamous carcinomas (ESCC) have been steadily decreasing because of long-term reductions in tobacco use and alcohol consumption. However, ESCC is still a highly lethal malignancy and distant metastases to the liver, bone, and lung are seen in nearly 30% of patients. Moreover, the prognosis is poor, with al 5-year overall survival (OS) of 10 - 20%. In patients treated with curative intent, the cure rate currently approaches 40%, with the majority of recurrences develop within one year. Nevertheless, it seems that there are no clear prognostic factors or biomarkers established to date.

Methods: We conducted an observational retrospective study. Patients with ESCC between 2000 and 2017 were identified, and data was collected for exploratory predefined variables including patient (age, weight, height, BMI, ECOG, tobacco and alcohol consumption, analytic parameters) and tumor characteristics (location, stage, grade), treatment procedures (chemotherapy, chemorradiotherapy (CRT) and surgery) and oncological outcomes. We analysed OS and relapse free survival (RFS) rates according

to the presence of these factors. Univariate Cox regression analysis was performed and those variables which obtained a $p<0.05$ were incorporated in a multivariate model. Stata 13.1 was used to analyze the data.

Results: 138 ESCC patients were identified: median age of 66 years; 87% were male; 62% located in the mid-esophagus; the majority were grade 2 (31%); 43% stage III and 35% stage IV; most patients were tobacco (91%) and alcohol consumers (62%). Treatments received: 51% chemoradiotherapy (CRT), 9% CRT + surgery, 10% chemotherapy (CT) and 12% radiotherapy (RT). Median follow up was 9.7 months and median OS was 11 months. In the univariate analysis for OS: ECOG, weight, height, platelets, leukocytes, neutrophils, grade, stage and treatment modality were prognostic. In the multivariate model: ECOG 0 (HR 0.44, p=0.039), stage IV (HR 4.28, p=0.05), treatment with RT (HR 0.21, p=0.001) and neutrophil count (HR 1.03, p=0.021) were seen as independent prognostic factors. Moreover, 89 patients (65%) presented as localized ESCC. Median RFS and OS were 16 and 21 months, respectively. In the univariate analysis for OS: ECOG, T, N and surgery were prognostic. In the multivariate model: ECOG 3 (HR 12.7, p=0.001), T4 (HR 9.22, p= 0.002) and N3 (HR 3.57, p=0.028) were identified as independent prognostic factors.

Conclusion: The multivariate analysis did show some independent risk factors for OS in ESCC according to patient and tumor characteristics, treatment procedures and oncological outcomes.

P – 046

WITHDRAWN

P – 047 **Feasibility of docetaxel, cisplatin and S-1 chemotherapy in elderly patients: Comparison with younger**

Y Nakamura[1], T Nishimaki[2], H Shimoji[1], H Karimata[1]

[1]Digestive and General Surgery, University of the Ryukyus, Nishihara, Japan, [2]Department of Surgery, University of the Ryukyus Faculty of Medicine, Nishihara-cho, Japan

Introduction: Choice of the therapy for esophageal cancer(EC) is often decided on a consideration of patient's age as well as performance status. Elderly patients sometimes tend to be undertreated for safety reasons, therefore the best practice for them is unknown. Standard therapy for unresectable EC in Japan is any of chemotherapy, radiotherapy or concurrent chemoradiotherapy. But the clinical outcome is still limited. Recently, some study showed the effectiveness of triplet induction chemotherapy with docetaxel, cisplatin and fluorouracil(DCF). By taking those results, we have treated EC patients with docetaxel, cisplatin and oral fluorouracil prodrug S-1(DCS) chemotherapy since 2010. In this study, we retrospectively assess the efficacy and safety of this triplet regimen for unresectable EC patients, especially for the elderly.

Methods: We enrolled the patients who received DCS for unresectable esophageal cancer. Patients received docetaxel (35mg/m2) plus cisplatin (35mg/m2) intravenously on day1 and 15, and S-1 (80mg/m2) on days 1-14, of a 28-day cycle. If the adverse event was tolerable, patients continued receiving cycles until the progression of the disease was observed or the tumor turned to be resectable. Response rate (RR), progression-free survival (PFS), overall survival (OS), and adverse events(AE) were compared between two age groups.

Results: Between May 2011 to November 2017, 55 patients were treated with the systemic regimen. Median age was 63 years (range 47-85). Eleven patients (20%) were more than 70 years old (elderly group) and forty-four were below 70 years (young group). Reasons for unresectable were locally advanced (74.5%), distant metastasis (16.4%) and recurrence (9.1%). The median number of therapy cycles applied was 3. The best clinical response to DCS in elderly group were complete response 0%, partial response 62.5% and stable disease 27.2% (RR 54.5%). Those in young group were 11.4%, 63.6% and 18.2%, respectively (RR 75.0%). Twelve patients of all were converted to surgery. The median PFS in all was 6.7 months (5.3 months in elderly group and 6.7 months in young group, $p = 0.85$). The median OS was 25.2 months (15.0 months vs 25.3 months, $p = 0.4$). Grade 3-4 toxicity were observed 90.9% of elderly group and 81.8% of young group, there was no statistical significance between two groups($p = 0.47$). There was no treatment related death.

Conclusion: In our study, DCS therapy in elderly patients was as effective and feasible as in young. High grade adverse events were observed regardless of age, but still manageable.

P – 048 **Neoadjuvant chemotherapy for locally advanced squamous cell carcinoma of esophagus: Clinical profile and outcomes from tertiary care cancer centre**

N Kumar[1], S Deo[1], N Shukla[2], S Bhoriwal[3], A Sharma[4], R Pramanik[1], R Sahoo[4], S Kumar[5]

[1]All India Institute Of Medical Sciences, New Delhi, India, [2]Dr B.R. Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India, [3]All India Institute of Medical Science, New Delhi, India, [4]All India Institute Of Medical Sciences, Delhi, India, [5]All India Institute of Medical Science, Delhi, India

Introduction: Esophageal cancer is the sixth most common malignancy in India. Squamous cell carcinoma (SCC) is the most common histology in the Indian subcontinent. Despite recent advances in the curative treatment of esophageal cancers, the benefit of neoadjuvant chemotherapy is quite limited and a definitive statement on the optimum perioperative treatment in terms of survival is still absent. Results from most of the trials from developed world would not be extrapolated in all patients. The multimodality approach for the carcinoma esophagus needs to be rethinking in the perspective of cost-effectiveness, regional biological and economic. In this study, we analyzed clinical profiles and both surgical and pathological outcomes of patients treated with curative surgery after neoadjuvant chemotherapy in our institute.

Methods: Retrospective analysis of prospective maintained esophageal cancer computerised database was performed from 2013 to 2017. Patients with biopsy-proven squamous cell carcinoma of esophagus who underwent curative surgery after preoperative radiotherapy were included in the study. All patients with potentially resectable disease on imaging received 3 cycles of neo-adjuvant chemotherapy either cisplatin+5FU or paclitaxel +carboplatin. Esophagectomy performed 3-4 weeks after the completion of chemotherapy.

Results: Total 52 patients with squamous cell carcinoma of esophagus underwent curative surgery during the study period. The most common presenting symptom was dysphagia in 48 (92%) patients. 22 (42%) patients had a history of weight loss (more than 10kgs). 28% of patients who present with absolute dysphagia required pre-treatment feeding interventions to improve the nutritional condition. 60% had a locally advanced disease and 40% patients had extraesophageal spread. Most common intervention performed was upper GI endoscopy guided nasogastric tube insertion. In the neo-adjuvant chemotherapy regimen; 30 (58%) patients received cisplatin+ 5FU and paclitaxel +carboplatin was given in 22 (42%) of the patients. Radiological response was seen in 70%. Majority of patients (62%) had the performance score of ECOG 2. 28 (55%) patients underwent McKeown esophagectomy with two field lymphadenectomy, 12(23%) patients underwent Ivor Lewis, Transhiatal in 2(3%) patients and 10 (19%) became inoperable. Post-operative early and late morbidity was documented in 10% and 03% of patients respectively. Pathological complete response (pCR) was achieved in 39% of patients. Maximum pCR achieved with cisplatin+FU 13(43%) and 32% with paclitaxel+carboplatin. 8% had pathological lymph nodes. 4 patients received adjuvant Radiotherapy. The loco-regional relapse rate was noted in 07% and systemic recurrence in 04%.

Conclusion: Management of esophageal cancer patients with poor nutritional and performance status is challenging. Neo-adjuvant chemotherapy for locally advanced squamous cell carcinoma of esophagus has good operability rate and pathological outcomes, which is comparable to the current standard Neo-adjuvant treatment. The

better long-term outcome is achieved by careful selection and tailoring the multimodality treatments according to patients' conditions.

P – 049 Liver metastases from esophageal carcinoma

D Kostov

Military Medical Academy, Varna, Bulgaria

Introduction: Hepatectomy for liver metastases from esophageal squamous cell carcinoma (LMESCC) remains controversial. We aimed at assessing the surgical results, clinicopathological features of LMEC and prognostic factors.

Methods: The outcome of 8 consecutive patients with synchronous (n = 3) or metachronous (n = 5) LMEC was retrospectively analyzed. Curatively, initial hepatectomies such as segmentectomy and hemihepatectomy or non-anatomical limited liver resection less extensive than segmentectomy followed complete primary esophageal cancer (EC) resections.

Results: Median survival time was 12 months (range, 8 - 22 months). The actuarial overall 12-, 36-, and 60-month survival rates after hepatectomy were 87.5% (n = 7), 37.5% (n = 3), and 12.5% (n = 1), respectively. In multivariate analysis, absent EC adventitia invasion-hazard ratio (HR) 1; 95% confidence interval (CI) 1.4 - 8.4; P = 0.040; solitary LM-HR 1; 95% CI 1.4 - 12.0; P = 0.004, and curative liver resection with negative resection margin (R0)-HR 1, 95% CI 1.2 - 15.0; P = 0.002 were independent prognostic factors.

Conclusion: Surgery of LMESCC is a good indication in well-selected patients with an absent EC adventitia invasion of primary tumor, single LMEC and attainment of R0 liver resection. For most LMESCC patients, however, there are no other therapeutic modalities. Thus, systemic radiochemotherapy remains the best hope for a longer patient's survival and an improved individual quality of life.

P – 050 Outcomes of minimal invasive three stage esophagectomy from a cancer centre in Pakistan

H Ali, IUI Nasir, AW Anwer

Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan

Introduction: Management of esophageal cancer has evolved over the last two decades with esophagectomy staying as the main treatment modality for early stage or post neoadjuvant resectable esophageal cancer. Minimal invasive three stage esophagectomy is becoming the routine procedure for resectable mid and lower esophageal cancer in our institution. The aim of this study is to evaluate the surgical and initial oncological outcomes after curative minimal invasive threes stage esophagectomy at our institution and to compare our results with current literature. Management of esophageal cancer has evolved over the last two decades with esophagectomy staying as the main treatment modality for early stage or post neoadjuvant resectable esophageal cancer. Minimal invasive three stage esophagectomy is becoming the routine procedure for resectable mid and lower esophageal cancer in our institution. The aim of this study is to evaluate the surgical and initial oncological outcomes after curative minimal invasive threes stage esophagectomy at our institution and to compare our results with current literature.

Methods: All adult patients with a diagnosis of oesophageal cancer who underwent minimal invasive three stage esophagectomy at our institute from 2005 to 2015 were included in this retrospective study. Patients' demographic and clinical characteristics were recorded through our hospital information system. Operative findings and histopathological reports were also recorded on a preformed data sheet. The short-term outcome measures were operative time in minutes, length of hospital and Intensive Care Unit (ICU) stay in days, post-operative complications and 30 days in-hospital mortality. Long-term outcomes were long-term procedure related complications over a minimum follow-up of 1 year and tumor recurrence.

Results: Total of 91 patients were included in our study with mean age of 52.7(10.2). Eighty-nine patients had neo-adjuvant chemo-radiation. Sixty patients presented with T3 disease and 48 of 91 patients were reported to have pathological complete response (pCR) at time of surgery. Mean number of lymph nodes dissected were 14. Nineteen patients had recurrence; with 7 loco-regional and 12 distant metastases. There were 2 mortalities. Forty-six patients had minor complications and 14 had major complications. Mean operative time was 345 minutes. Mean length of stay was 9 days with first post-op day in ICU.

Conclusion: We report our early experience with Minimal invasive three stage esophagectomy as a safe and oncologically feasible surgical option. We attained comparable surgical results with curative intent.

P – 051

WITHDRAWN

P – 052 A phase 3 study of chemotherapy + pembrolizumab versus chemotherapy + placebo as first-line therapy for patients with advanced esophageal or esophagogastric junction (E/EGJ) cancer: KEYNOTE-590 - Trial in progress

K Kato[1], M Shah[2], P Enzinger[3], J Bennouna[4], L Shen[5], A Adenis[6], J Sun[7], B Cho[8], M Ozguroglu[9], T Kojima[10], V Kostorov[11], C Hierro[12], Y Zhu[13], S Shah[13], P Bhagia[13], T Doi[10]

[1]National Cancer Center Hospital, Chuo-ku, Japan, [2]Weill Cornell Medical College and New York Presbyterian Hospital, New York, New York, USA, [3]Dana-Farber Cancer Institute, Boston, Massachusetts, USA, [4]University Hospital of Nantes, Nantes, France, [5]Beijing Cancer Hospital, Beijing, China, [6]Institut du Cancer de Montpellier, Montpellier, France, [7]Samsung Medical Center, Seoul, Republic of Korea, [8]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea, [9]Istanbul University, Cerrahpasa School of Medicine, Istanbul, Turkey, [10]National Cancer Center Hospital East, Kashiwa, Japan, [11]Leningrad Regional Oncology Dispensary, Saint Petersburg, Russian Federation, [12]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [13]Merck & Co., Inc., Kenilworth, New Jersey, USA

Introduction: Preferred first-line chemotherapy for advanced E/EGJ cancer is fluoropyrimidine in combination with cisplatin; however, no chemotherapy regimen has shown consistent benefit. In the phase 1b KEYNOTE-028 study, pembrolizumab monotherapy demonstrated manageable safety and durable antitumor activity in heavily pretreated patients with programmed death ligand 1 (PD-L1)–positive advanced esophageal carcinoma. Combining chemotherapy with pembrolizumab may be a potential therapeutic strategy for esophageal cancer. KEYNOTE-590 (ClinicalTrials.gov, NCT03189719) is a phase 3, randomized, double-blind, multicenter study to evaluate the efficacy and safety of cisplatin and 5-fluorouracil plus pembrolizumab versus cisplatin and 5-fluorouracil plus placebo in patients with previously untreated advanced E/EGJ carcinoma.

Methods: Key eligibility criteria are age ≥18 years; locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or metastatic Siewert type 1 adenocarcinoma of the EGJ; no prior therapy for advanced disease; measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); Eastern Cooperative Oncology Group performance status 0-1;

adequate organ function; no autoimmune disease; no active infection; can provide a newly obtained or archival tissue sample for later evaluation of PD-L1 expression and gene expression profiling. Patients will be randomly assigned in a 1:1 ratio to receive cisplatin 80 mg/m 2 IV every 3 weeks (Q3W) (capped at 6 doses) plus 5-fluorouracil 800 mg/m 2 continuous IV on days 1-5 Q3W plus pembrolizumab 200 mg IV Q3W or cisplatin 80 mg/m 2 IV Q3W (capped at 6 doses) plus 5-fluorouracil 800 mg/m 2 continuous IV on days 1-5 Q3W plus placebo Q3W IV. Treatment will be continued for up to 2 years or until confirmed disease progression, unacceptable toxicity, or physician or patient decision to discontinue. Crossover from the placebo arm to the pembrolizumab arm is not permitted. Co–primary end points are overall survival and progression-free survival per RECIST v1.1 by blinded independent central review in all patients and in patients with PD-L1–positive tumor expression (combined positive score $\geq$10%). Secondary end points include objective response rate per RECIST v1.1, duration of response, safety, and health-related quality of life. Response will be assessed using computed tomography (preferred) or magnetic resonance imaging every 9 weeks by central imaging review per RECIST v1.1. Adverse events will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 and will be monitored for at least 30 days (90 days for serious adverse events) after the last dose of trial treatment. Patients will be followed for survival until death, withdrawal of consent, or end of study, whichever occurs first. Enrollment is planned for approximately 700 patients.

P – 053 Pre-treatment peripheral neutrophil-lymphocyte ratio as a prognostic factor in gastric cancer

A Gaballah[1], T Hussein[2], A Ezzat[2], M Magdy[2]

[1]Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [2]Department of Clinical Oncology, Ain Shams University, Cairo, Egypt

Introduction: Gastric cancer is the fifth common cancer worldwide. Systemic inflammatory response increases metastasis through apoptosis inhibition and angiogenesis augmentation. The neutrophil-lymphocyte ratio (NLR) which is a balance between pro-cancer inflammatory response and anti-cancer immune response was proved as prognostic marker in malignancies. Peripheral NLR is a good reflection of tumor microenvironment.

Methods: We retrospectively collected data of gastric and gastro-esophageal cancer (GC) patients treated at our department from January 2013 till December 2016. Sixty-one patients were included. Pre-treatment absolute neutrophils-lymphocytes counts were collected and the NLR was calculated. We extracted the different clinic-epidemiological and pathological data of the patients and tumors. Event-free and overall survivals were plotted using Kaplan-Meier curves.

Results: Median age was 55. Male to female ratio was 1:1. Forty-seven patients (77%) were smokers. Most of the patients (93.4%) had good performance status (ECOG 0-2). Forty-six patients had gastric and 15 patients had gastro-esophageal cancer. According to Lauren's classification; 50.8% were diffuse type. Grade 3 represented 49.2% and grade 2 46%. Twelve patients (19.7%) had ascites at diagnosis. Staging at presentation was; 1.6% stage 1, 4.9% stage 2, 27.9% stage 3, 50.8% stage 4 and 14.8% unknown. The median NLR was 2.4. The patients divided into high NLR (>2.4) (30 patients) and low NLR ($\leq$ 2.4) (31 patients). The NLR showed no significant correlation with different clinic-epidemiologic and pathological variables except for presence of ascites; where ascites was associated with high NLR with $p = 0.046$. Median event-free survival (EFS) and overall survival (OS) were 6 and 8 months respectively. High NLR was significantly correlated with worse EFS; 5 months compared to 8 months in low NLR group (95% CI, $p = 0.001$). Also high NLR was associated with worse OS; 6 months compared to 9 months (95% CI, $p = 0.013$).

Conclusion: Gastric cancer is aggressive disease with short survival. Most of our patients presented with advanced stage. Pre-treatment NLR is an independent prognostic factor in GC; irrespective stage or any other prognostic factor.

P – 054 Predicting HER2 status in esophagogastric cancer: Development and validation of an easy-to-use nomogram

L Fornaro[1], A Parnofiello[2], C Ugolini[3], N Cardarelli[4], G De Maglio[5], I Pecora[6], F Crivelli[7], S Catanese[8], G Cardellino[9], G Musettini[8], N Pella[9], G Pasquini[10], S Pizzolitto[5], F Salani[11], M Clerico[7], G Fontanini[12], G Fasola[13], D Maurizio[4], C Vivaldi[8], F Montagnani[7]

[1]U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [2]Department of Oncology, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy, [3]Department of Laboratory Medicine, Section of Pathology, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [4]Department of Oncology, San Bortolo General Hospital, AULSS8 East District, Vicenza, Italy, [5]University Hospital Udine, Udine, Italy, [6]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, [7]Department of Oncology, Azienda Sanitaria Locale di Biella, Biella, Italy, [8]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [9]Department of Oncology, Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia, Udine, Italy, [10]Department of Oncology, University Hospital, Pisa, Italy, [11]Unit of Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [12]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy, [13]University Hospital Santa Maria della Misericordia, Udine, Italy

Introduction: HER2 currently represents the only available predictive biomarker in advanced esophagogastric cancer. Trastuzumab plus chemotherapy is the standard of care in tumors carrying HER2 protein overexpression by immunohistochemistry (IHC) or gene amplification by in situ hybridization (ISH). However, heterogeneity in protein expression, lack of adequate tumor samples for analyses and the need for rapid target assessment for patient management underline the need for a pre-test screening tool in order to anticipate the probability of carrying a HER2-positive disease.

Methods: The clinical and pathological data from 695 consecutive esophagogastric carcinomas analyzed at three different Institutions were collected. HER2 positivity was defined as IHC score of 3+ or 2+ with a positive ISH. 411 cases from one Institution were used to build a multivariate logistic regression model able to predict HER2 positivity. Both backwards and forward method were used to build multiple models. Collinearity was evaluated with Fisher's test, t-test and ANOVA, depending on the nature of the covariates, and Variance Inflation Factor (VIF). Final model was selected considering statistical significance of the covariates, clinical plausibility and global fit and it was used to develop a nomogram. Validation and calibration were performed on an external series of 284 patients treated at other two Institutions. C-index, visual inspection of the calibration plot, Brier score and Spiegelhalter z-test were used to assess the performance of the nomogram. 95% confidence intervals (CIs) of C-index were calculated with bootstrap method.

Results: 119 cases (17%) showed HER2 positivity in the development cohort. After univariate analyses and adjustment of collinearity, four variables were introduced in the final model: tumor grading (G1 vs. G2 vs. G3) ($p = 0.0018$), Lauren's histotype (intestinal vs. diffuse) ($p = 0.044$), type and adequacy of pathological material (surgical specimen vs. $\geq$5 biopsy samples vs. <5 biopsy samples) ($p = 0.19$) and site of sampling (primary cancer vs. metastasis) ($p = 0.034$). Tumor grading was associated to the greatest number of points, followed by site of sampling, Lauren's histotype and type of pathologic material. Visual inspection of the calibration plot revealed a very good overlap between predicted and observed probabilities, with a Brier score of 0.048 and a statistically significant Spiegelhalter z-test ($p < 0.0001$). C-index resulted in 0.84 (95%CI 0.75-0.93).

Conclusion: We developed a simple nomogram based on four immediately and always available pathological characteristics able to accurately predict the probability of HER2 positivity in esophagogastric cancer. This could be useful to minimize HER2 test heterogeneity and prompts re-biopsy in those cases of inadequate material but an anticipated high probability of HER2 positive status. A visual format of the nomogram will be presented.

P – 055 Prolonged overall survival of metastatic gastric cancer patients with BRCA germline mutations

N Halpern[1], A Grinshpun[2], B Boursi[1], T Golan[3], O Margalit[4], D Aderka[4], Y Laitman[5], E Friedman[5], A Hubert[6], T Peretz[6], T Hamburger[6], I Kedar-Barnes[7], Z Levi[8], I Ben-Aharon[9], Y Goldberg[10], E Shacham-Shmueli[3]

[1]Department of Oncology, Sheba Medical Center, Ramat Gan, Israel, [2]Sharett Institute of Oncology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [3]Sheba Medical Center, Ramat Gan, Israel, [4]Sheba Medical Center, Ramat Gan, Israel, [5]The Susanne Levy Gertner Oncogenetics Unit, The Danek Gertner Institute of Human Genetics, Ramat Gan, Israel, [6]Sharett Institute of Oncology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [7]Recanati Genetics Institute, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, [8]Division of Gastroenterology, Rabin Medical Center, Early Detection and High Risk Unit, Petch Tikva, Israel, [9]Institute of Oncology, Davidoff Center, Rabin Medical Center, Petach Tikva, Israel, [10] Recanati Genetics Institute, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel

Introduction: Gastric cancer is the fifth most frequently diagnosed malignancy worldwide and the third leading cause of cancer related death. The prognosis of gastric cancer remains poor with median overall survival rates of less than 12 months in the advanced setting. Significant efforts are made to identify prognostic and predictive markers to tailor treatment decisions. BRCA1 and BRCA 2 germline mutations are an established predictive marker to a favorable response to DNA-damaging agents (platinum agents

and Poly(ADP-ribose)polymerase inhibitors) in ovarian, breast prostate and pancreatic cancers. There is limited clinical data in regard to the efficacy of DNA-damaging agents on BRCA germline mutation carriers with gastric cancer.

Methods: A multi-center retrospective analysis of genetic databases and patient's files was performed in three medical centers to identify consecutive BRCA1/2 germline mutation carriers with gastric adenocarcinomas between the years 1994 to 2018. Patient's characteristics and disease course were collected and summarized.

Results: Nine BRCA1/2 carriers with gastric adenocarcinomas were identified. Five of them were females. Six patients were from an Ashkenazi origin. Seven patients had BRCA2 mutation. Three patients had a personal history of a second malignancy. Two patients had a first-degree family member with gastric cancer. Mean age at diagnosis was 64 (range of 52-74 years). One patient demonstrated positive HER2 staining (IHC +3) in her tumor. We did not identify unique patterns in term of tumor location or histology. Six patients had metastatic disease. Five patients with metastatic disease received DNA-damaging agents. The median overall survival of the six metastatic patients was 25 months (range 13-43), three of them have ongoing durable responses.

Conclusion: Germline BRCA1/2 mutations are associated with a relatively favorable prognosis in gastric cancer patients treated with DNA-damaging agents. Some patients in our cohort had a first degree relative with gastric cancer, possibly indicating a unique phenotype in some BRCA families. Further research is needed to determine the characteristics and long-term outcome of these patients.

P – 056 Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are independent prognostic factors for overall survival in Hispanic patients with gastric adenocarcinoma

A Ramos-Esquivel[1], D Brenes[2], E Cordero[3], W Alpizar-Alpizar[3]

[1]University of Costa Rica, San José, Costa Rica, [2]Universidad de Costa Rica, San Pedro, Costa Rica, [3]University of Costa Rica, San Pedro, Costa Rica

Introduction: High values of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are associated with poor prognosis in patients with gastric adenocarcinoma. However, the majority of these findings have been carried out in Asian countries. It is well known that outcomes of gastric cancer are different among regions, with better outcomes in patients from Asia in comparison to Western populations. Besides, recent trials have acknowledged that values of white cells can vary according to ethnicity. Therefore, in this retrospective study we aim to determine the prognostic value of NLR and PLR in Hispanic patients from Costa Rica where gastric cancer occupies the third cause of cancer-related death in both sexes.

Methods: We reviewed consecutive gastric cancer patients treated in four major hospitals in Costa Rica from 2009 to 2012. Pre-treatment (before surgery or systemic treatment) NLR and PLR, as well as clinical variables were collected from medical records. Univariate and multivariate Cox regression analyses were performed to assess the relationship between NLR, PLR, overall survival (OS) and disease-free survival (DFS). The best cutoff point was based on the maximization of the Log-rank test statistic.

Results: A total of 490 patients were included in this trial. Median follow-up was 26 months. Mean age was 61.8 ±16.6 years. A total of 282 patients were male (57.6%). Surgery was performed in 309 patients (63.1%) and the most frequent procedure was partial or total gastrectomy with D2 dissection (84.1%). Clinical stage distribution was as follows: stage I: 2.8%, stage II: 27.9%, stage III: 34.8%, and stage IV: 34.5%. The optimal cutoff point for NLR and PLR was set at 5 and 350, respectively. In univariate analysis, a NLR higher than 5 was associated with reduced DFS (Hazard Ratio (HR): 2.31; 95% Confidence Interval (CI): 1.78-3.00; $p < 0.001$) and poor OS (HR: 2.24; 95% CI: 1.72-2.92; $p < 0.001$). Similarly, a PLR higher that 350 was associated with worse DFS (HR: 2.28; 95% CI: 1.70-3.06; $p < 0.001$) and poorer OS (HR: 2.33; 95% CI: 1.73-3.13; $p < 0.001$). In the multivariate analysis, after adjustment for potential confounders and interactions such as clinical stage and performance status, only the NLR higher than 5 was independently associated with worse DFS (HR: 1.84; 95% CI: 1.33-2.56) and OS (HR: 1.61; 95%CI: 1-16-2.25).

Conclusion: A NLR greater than 5 was independently associated with worse OS and DFS in Hispanic patients with gastric cancer. This cheap and easy to obtain biomarker can predict long-term outcomes in our population.

P – 057 Predicting survival benefit of capecitabine plus cisplatin in patients with metastatic gastric cancer patients using quantitative proteomics

E An[1], M Ryu[2], D Yan[1], Y Park[2], H Na[2], J Ma[2], Y Tian[3], F Cecchi[4], T Hembrough[5], Y Kang[2]

[1]NantOmics, Rockville, Maryland, USA, [2]Asan Medical Center, Seoul, Republic of Korea, [3]NantOmics, LLC, Rockville, Maryland, USA, [4]Nantomics, Rockville, Maryland, USA, [5]NantOmics, Rockville, Maryland, USA

Introduction: Capecitabine plus cisplatin (XP) is a standard treatment for metastatic gastric cancer (mGC). Capecitabine activation requires the enzymes uridine-cytidine kinase 2 (UCK2) and orotate phosphoribosyl transferase (OPRT). We previously used mass spectrometry to quantitate UCK2 in tumor samples from 5-FUtreated patients with stage II/III colorectal cancer; UCK2 protein expression > 319 amol/ug of tumor protein was associated with improved survival. Here, we assessed whether these biomarkers would predict survival among mGC patients treated with XP.

Methods: Formalin-fixed, paraffin-embedded tumor samples from patients with mGC were microdissected and solubilized for mass spectrometric quantitation of 16 protein biomarkers. Kaplan-Meier survival curves were compared using a log-rank test. Multivariate Cox models of survival included clinical covariates and protein biomarkers.

Results: mGC tumor samples from 116 XP-treated patients were analyzed (males: 64%; median age: 55 years). All samples expressed OPRT protein (range: 202 – 1719 amol/ug), and 114 of 116 expressed UCK2 (range: 119 – 933 amol/ug). Patients with UCK2 expression above the pre-defined cutoff of 319 amol/µg ($n = 30$) had longer time to progression (TTP) (HR: 0.60; $p = 0.020$) than patients below the cutoff. Results for overall survival (OS) were similar (HR: 0.59; $p = 0.015$). OPRT protein expression > 790 amol/ug ($n = 24$) was associated with longer TTP (HR: 0.58; $p = 0.019$) and longer OS (HR: 0.60; $p = 0.029$). In multivariate analysis, UCK2 and OPRT remained independent predictors of survival after adjustment for age, gender, ECOG performance status, metastatic sites, and other clinical covariates.

Conclusion: XP-treated mGC patients with tumor expression of UCK2 and OPRT proteins above quantified thresholds survived longer than patients with lower expression. Mass spectrometric quantitation of these common tumor proteins at diagnosis may improve patient selection for XP. Studies to validate these and other chemopredictive biomarkers are ongoing.

P – 058 The prognostic value of systemic inflammatory factors in patients with HER2-positive metastatic gastric cancer

N Martínez-Lago[1], R Lesta-Mellid[1], C Reboredo Rendo[1], M Reboredo-Lopez[1], L Antón Aparicio[2]

[1]University Hospital of A Coruña, A Coruña, Spain, [2]Medical Oncology Department - University Hospital of A Coruña, A Coruña, Spain

Introduction: Multiple studies have reported prognostic association of neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLT) including patients with early and advanced gastric cancer. However, it is unknown the prognostic impact in patients with HER2-positive metastatic gastric cancer.

Methods: We conducted an observational, retrospective, unicentric study of patients with metastatic HER2 positive gastric cancer treated at University Hospital of A Coruña (Spain). Demographic, clinic and pathological data were retrospectively collected and correlated with overall survival (OS) and progression free survival (PFS).

Results: From 158 patients with metastatic gastric cancer treated between November 2010 to November 2017, we analyzed 18 HER2-positive cases. Clinicopathological characteristics: 100% intestinal histological tumor type, 44% low grade, 66.7% gastroesophageal junction location. With a median follow up of 39.6 months, median overall survival (OS) was 15.0 months and median first line progression free survival was 9.2 months. Neutrophil to lymphocyte ratio (HR 10.989; $p = 0.007$), and platelet to lymphocyte ratio (HR 6.329; $p = 0.013$) were independent prognostic factors for both OS and PFS. Patients with higher NLR (>3 vs. <3): had a significantly lower PFS 5.3 vs 16.8 (m) HR 4.444 (IC 95% 1.2-16.7) $p = 0.017$ and OS 8.4 vs 29.7 months (m) (HR 10.989; IC 95% 1.3-90.9, $p = 0.007$), while patients with lower PLR had a worse outcome (<200 vs. >200): with lower PFS 4.7 vs 16.8(m) HR 3.571 (IC 95% 1.1-13.0, $p = 0.041$) and OS 8.4 vs 27.3 (m) (HR 6.329; IC 95% 1.2-32.3, $p = 0.013$). Other prognostic factors were albumin ($p = 0.097$), histologic Grade ($p = 0.099$). Gender ($p = 0.123$), ECOG PS (p=.0637) or tumor location ($p = 0.818$), were not prognostic in this series.

Conclusion: NLR and PLR are highly significant prognostic factors in patients with HER2-positive metastatic gastric. This is the first series in which a specific association between HER2 status and prognostic effect of NLR and PLR is described, suggesting a possible interaction between systemic inflammatory factors and the response to HER2 targeted therapy.

P – 059 The overview of H. pylori prevalence in patients with dyspepsia and its association with gastric adenocarcinoma at different locations.

S Aghayeva

Azerbaijan Medical University, Baku, Azerbaijan

Introduction: H. pylori is proved to be strongly associated with development of gastric cancer. The aim of our study is to check H. pylori in newly diagnosed patients with gastric malignancy at different parts of the stomach and to define a correlation of it with H. pylori infection.

Methods: The study included 2500 patients (1133 males, 1367 females, age range 18-97) with dyspepsia who underwent upper GI endoscopy with rapid CLO-test biopsy, screened from January 2015 until June 2017. All patients were aged ≥18 years with no PPI and antibiotic use for the past month. Control group of 100 random people were evaluated for H. pylori with urea breath test. Out of 2500 patients, 126 with newly diagnosed and histologically submitted adenocarcinoma of different locations were also screened for Helicobacter pylori with rapid CLO-test obtained from antrum.

Associated factors were analyzed by the chi-square and multiple logistic regression with SPSS 20.0 and dispersion analysis (ANOVA).

Results: The overall prevalence of H. pylori infection in patients with dyspepsia was 87.6% (2189 patients) and 81% (81 patients) in control patient group with no symptoms. In a group of 126 patients (median age 64,5±9.8; 78 (61.9%) males and 49 (38.9%) females with newly diagnosed adenocarcinoma, in 58 (46%) the tumor was located in antrum, in 33 (26.2%) at the lesser curvature, in 13 (10.3%) at the greater curvature, in 17 (13.5%) at the cardial part and in 5 (4%) patients in the fundus. H. pylori test was positive in 52 (89.6%) of 58 patients with antral malignancy, in 29 (87.9%) of 33 patients with lesser curvature cancer, in 7 (53.8%) of 13 patients with greater curvature cancer, in 5 (29.4) of 17 patients with cardial malignancy and in 2 (40%) of 5 patients with fundus and body malignancy.

Conclusion: The prevalence of H.Pylori in patients with dyspeptic symptoms is 87.6% comparing to 81% of general population. Besides age and gender predisposion, H.Pylori infection is strongly associated with the development of antral and lesser curvature adenocarcinoma comparing to cardia, fundus and greater curvature malignancy locations. (P value <0.001 in females; P value <0.007 in males).

P – 060 Comparison of efficacy and safety between redo-endoscopic treatment and surgery for recurrent gastric neoplasms at the scar of prior endoscopic submucosal dissection

D Kim[1], H Na[1], J Ahn[1], J Lee[2], K Jung[1], K Choi[1], H Song[1], G Lee[1], H Jung[1]

[1]Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, [2]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Introduction: The clinical outcomes of treatment options for recurrent gastric neoplasms at the scar of prior endoscopic submucosal dissection (ESD) are not well known. Hence, clinicians decide treatment options case-by-case without much evidence. The aim of this study was to compare the efficacy and safety of treatments options for recurred gastric neoplasms at prior ESD scar.

Methods: From June 2010 to May 2017, we retrospectively investigated 51 patients who treated with redo-ESD, 23 patients with argon plasma coagulation (APC), and 18 patients with operation. We analyzed short-term and long-term outcomes of each treatment. Clinical outcomes between primary and redo-ESD were also compared.

Results: Median intervals between prior ESD and second treatment were 10.9, 13.2, and 9.6 months for redo-ESD, APC, and operation group, respectively ($p = 0.088$). Hospital duration was significantly different between groups [median (interquartile range), 3 (3-4) vs. 3 (2-3) vs. 8 (7-9), $p < 0.001$]. Adverse events, such as pneumonia ($p = 0.196$), gastrointestinal bleeding ($p = 0.390$), and perforation ($p = 1.000$), were comparable between the groups. Operation group exhibited significantly higher risk for outlet obstruction ($p = 0.037$) and mechanical ileus ($p = 0.037$) than other treatment groups. There was significant difference between groups about overall recurrence rate (19.6% vs. 39.1% vs. 0%) and local recurrence rate (13.7% vs. 30.4% vs. 0%). Kaplan-Meier plot showed local recurrence free survival differences between the groups and it was significantly different between the groups after adjusting overall follow-up duration (log rank test, $p = 0.026$). Redo-ESD exhibited longer median procedure time (31.0 vs 22.0 min, $p = 0.018$) and lower en bloc resection rate (68.6% vs. 94.1%, $p = 0.004$) than prior ESD. Complete resection rate (80.4% vs. 70.6%) and adverse event rate [bleeding (7.8% vs. 5.9%, $p = 1.000$) and perforation (3.9% vs. 2.0%, $p = 1.000$)] were comparable between redo-ESD and prior ESD. Recurred neoplasm larger than 15 mm was associated with lower complete resection rate [odds ratio (OR) 7.81, 95% confidence interval (CI) 1.6-57.5, $p = 0.018$]. And neoplasms located on upper two-thirds exhibited higher local recurrence rate (OR 10.5, 95% CI 1.6-207.8, $p = 0.037$) with redo-ESD.

Conclusion: Argon plasma coagulation exhibited much higher recurrence rate that should not be considered as a first line treatment for recurred gastric neoplasms at prior ESD scar. However, considering higher adverse event rate of outlet obstruction and mechanical ileus with operation, redo-ESD could be an alternative to operation for selected patients.

P – 061 Immunocytochemical method for diagnosis of metastases of signet ring cell carcinoma of the stomach

S Lukmonov[1], O Usmanov[1], M Ismailov[2], K Madatov[1], U Kurbankulov[1], U Allazarov[1]

[1]Tashkent Medical Academy, Tashkent, Uzbekistan, [2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Introduction: Evaluation of the informative value of the cytological method in the diagnosis of metastasis of cricoid-cell carcinoma of the stomach in ascites and pleural fluid.

Methods: The results of cytological diagnostics of patients with cricoid carcinoma of the stomach of 24 patients in ascitic fluid and of 10 patients in pleural fluid were evaluated. They were treated on the basis of the Department of Oncology and Radiology of the Tashkent Medical Academy. A method of light microscopy with staining of Pappenheim drugs and an immunocytochemical method using a liquid preparation method were used, using standard techniques carrying out immunocytochemical reactions. The results of the study were evaluated and compared with the final diagnosis.

Results: The patients' age was 48.5 ± 6.9 years, there were 16 men, 18 women. In 25 patients operated on for stomach cancer, ascites and pleurisy appeared 1-9 years. In the ascitic fluid of 9 patients, malignant tumor cells were detected during a primary examination. Without additional techniques, cricoid carcinoma in the fluid by the cytological method was established in 9 patients (26.5%). In the preparations, tumor cells with eccentrically located nuclei were noted, the individual cells took the form of a ring with a deformed nucleus and a vacuole with a mucus occupying almost the entire cellular body. Expression of EMA expression in the cytoplasm of tumor cells was noted in 61.5% (positive cases (in all cases, 8/13), Ber-EP4 in 100% (17/17), Claudin in 100% (4/4), CDX-2 in 35.3% (6/17), p53 in 100% (5/5), Ki-67 in 100% (3/3). Expression of cytokeratins was as follows: SC AE1/AE3 (13/13, 100%), SC MNF116 (13/13, 100%), CK5/6 (1/13, 7.7%), CK7 (15/17, 88, 2%), CK18 (17/17, 100%) and CK20 (8/17, 47.1%). In differential diagnosis of tumor cells and histiocytes, studies on CEAmono and CEApoly, which were 100% (15/15), were most significant, staining was pronounced. A positive reaction was noted in cells that were perceived as lightning microscopy as histiocytes. In histiocytes and leukocytes present in the liquid, a positive reaction to CD45 and CD68 was observed in the immunocytochemical study.

Conclusion: 1) the possibility of light microscopy for diagnosis of metastasis of cricoid carcinoma in ascites and pleural fluid was 26.5%, which dictates the need to use additional refinement techniques; 2) the immunocytochemical method allows to confirm the histogenesis of tumor cells, however, antibodies specific for cricoid-cell carcinoma were not detected; 3) the problem of differential diagnosis of histiocytes, cellular mesothelium cells and cellular tumor cells is easily solved using an immunocytochemical reaction to cancer embryonic and epithelial antigens, which allows affirmatively determining the affiliation of cells to the cricoid-cell carcinoma.

P – 062 Radiation therapy in locally distributed inoperable cancer of the stomach without the symptoms of obstruction

S Lukmonov[1], O Usmanov[1], K Madatov[1], M Ismailov[2], U Kurbankulov[1], U Allazarov[1]

[1]Tashkent Medical Academy, Tashkent, Uzbekistan, [2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Introduction: To assess the overall survival (OS) of patients with "asymptomatic" LAIGC in the groups of CRT and CT according to a randomized study.

Methods: Patients with LAIGC without signs and threats of dysphagia were selected from a randomized study aimed at comparing chemoradiation (CRT) and chemotherapy (CT), from 2015 to 2017 on the basis of the Department of Oncology and Radiology of the Tashkent Medical Academy. Twenty-nine patients with LAIGC with tumors localized in the body and antrum sections of the stomach were selected: 15 of them received CRT, 14 - HT. In the CRT group, treatment was started with a remote radiation therapy, which was carried out from two counter figured fields in the traditional fractionation mode to a total dose of 50-64 Gy. Chemotherapy included cisplatin 100 mg/m 2 per day + 5-fluorouracil 1000 mg/m 2 24-hour infusion from 1 to 5 days, every 28 days, 4-6 courses. Overall survival was assessed by the Kaplan-Mayer method using a log-rank test. The relationship between the risk of death in a single-factor and multivariate analysis was calculated using Cox's regression. All calculations were carried out using the statistical software package Stata 13.0 (College Station, Texas 77845 USA).

Results: Treatment groups were well balanced by baseline characteristics. In the distribution by sex, age, ECOG status, the severity of the concomitant pathology, trial laparotomy, gastroenteroanastomosis, the size of the primary tumor, lymph node involvement, stage of the process, tumor localization, histological variant, no statistically significant differences were found. At the time of analysis, the median time of follow-up was 52.0 (standard deviation, SD 6.9) months, 25 patients died. All four living patients - from the group of CRT (3 with localization of the tumor in the body of the stomach). Median OS, 1-and 3-year OS were 13 (95% confidence interval (CI) 4-20) vs. 20 (95% CI 7-43) months, 57% (95% CI 28-78%) vs. 80% (95% CI 50-93%) and 0% vs. 33% (95% CI 12-56%), log rank $\chi 2 = 4.7$, $p = 0.029$ in the CT and CRT groups, respectively. The ratio of the risk (RR) of death from any cause with the use of CRT was reduced to 0.39 (95% CI 0.17-0.94).

Conclusion: Adding RT to the standard used for LAIGC of chemotherapy leads to an improvement in the overall survival of patients in the absence of symptoms of dysphagia. A small number of observations, however, does not allow to consider the advantage of CRT as proven and requires more observations in phase III of the randomized trial. The reserves of improving the effectiveness of treatment are conformal irradiation techniques and simultaneous CRT.

P – 063 The clinical outcomes and the pathogenetic background of gastric MALT lymphoma in Korea

S Lee[1], D Cheung[2]

[1]Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea, [2]Yeouido St. Mary Hospital, Seoul, Republic of Korea

Introduction: Gastric MALT lymphoma is well known slowly progressing malignancy and has a pathogenic trigger, Helicobacter pylori infection, commonly with gastric

adenocarcinoma. Literatures report about 6 times higher incidence of adenocarcinoma in gastric MALT lymphoma patients compared to that of general population. However, the development of gastric MALT lymphoma and adenocarcinoma seems to have different pathways. In this study, authors investigated the clinical course of gastric MALT lymphoma and the pathogenic background in the view point of Correa's hypothesis.

Methods: Study was conducted by review of electronic medical record of patients who were diagnosed with gastric MALT lymphoma at an academic institute, the Yeouido St. Mary's Hospital, Seoul, Korea, from January 2001 to May 2017. Clinical course was evaluated with analysis of demographic features, treatment modality and clinical outcomes. pathogenetic background was investigated in by Helicobacter pylori infection status, histology and serology.

Results: A total of 46 subjects were enrolled and analyzed during the study period. The mean age was 57.19-year-old (range 36 ~ 85). The male to female ratio was 1.19 (25/21). Endoscopic appearances varied; thirteen subjects presented ulcerative mass (28.26%), 12 (26.09%) as flat atrophic patch of discoloration, 16 (34.78%) erosive patches, 2 (4.35%) multiple polypoid lesion and 3 (6.52%) subepithelial tumor like. Helicobacter pylori infection was proved in 82.6% (38/46). Atrophy and intestinal metaplasia were accompanied in background mucosa in 28.26% (13/46). Serum pepsinogen I and II, as serological marker for atrophy, was evaluated in 17 subjects. Only 9 of 17 (52.94%) showed compatible with gastric atrophy (pepsinogen I/II ratio of less than 3 or pepsinogen I of less than 70). The lymphoma stage by Lugano stage was I1E (80.43%), I2E (2.17%), II1E (15.22%) and IIIE (2.17%). genetic alternation, t(11:18), was proved in 4 of 15 patients (23.53%). The treatment of gastric MALT lymphoma varied. 32 patients were treated with Helicobacter eradication therapy. Four patients received chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) regimen, five patients received Radiotherapy and three patients underwent surgery. (Figure 1) Of the 46 patients with MALT lymphoma, except for two who was referred to another hospital, 44 patients (100%) had complete remission. The mean time to remission was 130.81 days, and there was no difference in remission frequency according to each treatment method. Patients were followed up for 3.5~114.9 months (mean 40.86 months) and there was no recurrence in patients.

Conclusion: Gastric MALT lymphoma is well associated with helicobacter pyloric infection and showed high prevalence of current infection (82.6%). However, the mucosal background of gastric MALT lymphoma showed low prevalence of atrophy and intestinal metaplasia, which in highly prevalent of and precedent to adenocarcinoma. It suggests that the pathogenic pathway of gastric MALY lymphoma and adenocarcinoma has different directions. The treatment for gastric MALT lymphoma varies according to kind of clinical conditions, and the result could achieve clinical remission regardless of treatment modalities.

P – 064 Early outcomes of a pilot study of neoadjuvant chemotherapy with S-1 plus oxaliplatin at dose of 130mg/m2 (nacG-SOX130) in stage III gastric cancer

S Konishi[1], D Manaka[1], H An[2], Y Nishikawa[2], T Ota[1], R Kudo[1], K Kawaguchi[1], S Hamasu[1], R Nishitai[1]

[1]Department of Surgery, Gastrointestinal Center, Kyoto Katsura Hospital, Nishikyo-ku, Japan, [2]Department of Surgery, Gastrointestinal Center, Kyoto Katsura Hospital, Nishikyo-ku, Japan

Introduction: Post-operative adjuvant chemotherapy with S-1 is a widely used standard-of-care in pStage II/III gastric cancer in Japan. However, S-1 monotherapy for 1 year is demonstrated to be not sufficient for the high risk group of recurrence, i.e. stage III. In addition, patients(pts) may not pursuit adjuvant doublet chemotherapy because of the poor postoperative compliance induced by surgical stress. In this pilot trial, we evaluated the safety and efficacy of nacG-SOX130 in Stage III gastric cancer.

Methods: A histologically proven resectable gastric cancer with stage IIIa-IIIc (JCGC 14th edition) were eligible. All pts were explored by laparoscopy before treatments to exclude tumor dissemination (CY0, P0). Pts were treated with two-cycles of nacG-SOX130 (S-1 80-120 mg/day according to BSA for 2 weeks, l-OHP 130 mg/m 2 on day 1, every 3 weeks), and radical gastrectomy with D2 lymphadenectomy were performed.

Results: From January 2016 to September 2017, 20 pts were enrolled. There were 15 males and 5 females with median age of 66 years (40 to 80). All pts were available for evaluating the clinical response. The completion rate of the protocol treatment was 100%. Relative dose intensity was 89.9% in S-1 (95% CI: 84.7-95.1) and 95.8% in oxaliplatin (95% CI: 91.8-99.4). Non-hematological toxicities were mostly the peripheral sensory neuropathy (Grade 1; 60%, Grade 2; 5%, Grade 3; 0%), and the most frequent hematological toxicity was neutropenia (Grade 1; 0%, Grade 2; 20%, Grade 3; 0%). Clinical response rate was 85% (95% CI: 52.7-82.6), complete response in 3 pts (15%) and partial response in 14 pts (70%). 3 pts had stable disease (15%) and no progressive disease was observed, which lead to the disease control rate of 100% (95% CI: 87-100). 3 pts were finally revealed as a pathological complete response (15%). Histological evaluation of therapeutic effect more than Grade 2 was 45%. Every patient was performed a curative resection (curative resection rate: 100%). No postoperative complications were observed more than G1 of Clavien-Dindo classification.

Conclusion: NacG-SOX130 in Stage III gastric cancer was well-tolerated and resulted in high rates of clinical and pathological responses without impairing the surgical treatment. nacG-SOX130 would be a promising choice of neoadjuvant chemotherapy in Stage III gastric cancer. Clinical trial information: UMIN000031388.

P – 065 Patterns of care and clinical outcomes for gastric and gastro-oesophageal cancers in South Australian population: Initial results of a state-wide audit

N Abbas[1], M Barnes[2], T Price[3], C Karapetis[4], T Bright[1], J Bull[5], R Gowda[6], N Rodgers[7], D Watson[1], C Connell[8], S Thompson[6], J Shenfine[5], N Singhal[6], A Roy[1]

[1]Flinders Medical Centre, Bedford Park, Australia, [2]Flinders University, Bedford Park, Australia, [3]Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia, [4]Southern Adelaide Local Health Network, Adelaide, Australia, [5]Finders Medical Centre, Bedford Park, Australia, [6]Royal Adelaide Hospital, Adelaide, Australia, [7]Clinpath Laboratories, Kent Town, Australia, [8]Adelaide Radiotherapy Centre, Bedford Park, Australia

Introduction: The South Australian state-wide Upper gastrointestinal (GI) cancer video linked multidisciplinary team (MDT) meeting encompassing four tertiary hospitals was established in 2009. The primary aim of the MDT is to discuss overall management and provide evidence based care to all newly diagnosed oesophageal, gastro-oesophageal junction (GOJ) and gastric cancer patients. We conducted a retrospective audit to review the patterns of care and patient outcomes for gastro-oesophageal junction (GOJ) and gastric cancers on the state-wide database.

Methods: Data is collected for patients with gastric and GOJ cancers (excluding lymphomas, neuroendocrine tumours, small cell and gastrointestinal stromal tumours) presented at the MDT from June 2012 to June 2016. Sources included upper GI MDT, public hospital electronic health records and pathology and pharmacy records from private health providers. Data on patient demographics, TNM stage, histological types, modalities used for diagnosis and treatment received was collected. Based on the treatment provided stage specific survival outcomes were analysed using descriptive statistics.

Results: 250 patients have been presented and of these, results of 61 are available for this analysis. Majority of patients were Caucasian (male 40, female 21) with mean age of 69 years (range 62 - 78 years). Fifty-one patients (84%) and 10 patients (16%) had gastric and gastro-oesophageal junction cancer respectively. Thirty (49%), 20 (33%) and 11(18%) patients had stage IV, III and I/II cancer respectively. Histological types included 53 (87%) adenocarcinomas, 7 (11%) signet ring carcinoma and 1 epithelial carcinoma. Diagnostic workup for early stage cancers (stage I-III) included twenty-three (74%) patients who underwent staging laparoscopy, 7 patients (23%) had PET scan and 4 patients (13%) had endoscopic ultrasound. Staging laparotomy, PET scan and endoscopic ultrasound was performed for 17 (57%), 5(16%) and 4 (13%) patients with stage IV disease. Surgery was performed in 25 patients (100%) for early stage disease (16 had total gastrectomy, 9 had subtotal gastrectomy) and 21 (84%) patients had complete resection (R0). Twenty-eight (46%) patients received palliative chemotherapy and radiotherapy and 6 (10%) patients were given symptom directed therapy alone. Median overall survival for stage IV, stage III and stage II disease was 6.6, 22.8 and 58.8 months respectively. Patients with stage IV cancer who received symptom directed therapy alone, palliative radiotherapy and palliative chemotherapy had median overall survival 1.4 months (95% CI, 0.8 to 3.0), 4.32 (95% CI, 3.4 to 6.9) months and 9.8 months (95% Confidence Interval, 8.6 to 13.4) respectively. Median overall survival for early stage cancer (stage I-III) patients who received perioperative chemotherapy and surgery was not reached (95% CI, 24.8 to Not Reached) and surgery alone had median overall survival 57.6 months (95% CI, 54 – Not Reached).

Conclusion: Patient outcomes analysed in the sample population reflect real world practice. Analysis of additional patients is ongoing and will be included in late breaking abstract.

P – 066 Feasibility study of intraperitoneal docetaxel combined with intravenous cisplatin and oral S-1 for gastric cancer patients with peritoneal carcinomatosis

K Lam[1], B Law[2], W Chan[2], Y Wong[3], K Chiu[4], T So[5], S Chan[6], V Lee[1], K Chu[3], D Kwong[7], S Law[7]

[1]Department of Clinical Oncology, LKS Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China, [2]Queen Mary Hospital, Hong Kong, China, [3]Dept. of Surgery, The University of Hong Kong, Hong Kong, China, [4]Dept. of Diagnostic Radiology, The University of Hong Kong, Hong Kong, China, [5]Department of Clinical Oncology, LKS Faculty of Medicine, University of Hong Kong, Hong Kong, China, [6]Queen Mary Hospital, Hong Kong, China, [7]The University of Hong Kong, Hong Kong, China

Introduction: Peritoneal carcinomatosis (PC) is common in advanced gastric cancer. Systemic therapy has been the mainstay of treatment but the outcomes remain poor. The V325 study demonstrated superior efficacy for the triplet regimen of IV docetaxel, cisplatin and 5FU at the cost of increased toxicity. Emerging evidence supports the role of intraperitoneal chemotherapy with potentially less systemic toxicity. The current phase I study evaluated the feasibility of a triplet regimen of intraperitoneal docetaxel, IV cisplatin and oral S-1 in gastric cancer patients with peritoneal carcinomatosis. (NCT02024841).

Methods: Patients with histologic confirmed gastric adenocarcinoma and peritoneal metastasis were enrolled. Those with prior systemic treatment in the palliative setting or other distant metastasis, except lymph node metastasis, were excluded. Intraperitoneal docetaxel was given over 1 hour on day 1 every 3 weeks. The dose of docetaxel was escalated from 40mg/m2(level I) to 50mg/m2(level II) and

60mg/m2(level III) according to phase I classical "3 + 3" protocol. DLT was determined in cycle I. IV cisplatin was administered at a fixed dose of 60mg/m2 on day 1 and oral S-1 was administered twice daily according to BSA on day 1-14 every 3 weeks. Patients were treated for three cycles unless unacceptable toxicities or patient withdrawal. Reassessment upper endoscopy and CT scan was performed 3 weeks after completion of chemotherapy. Staging laparoscopy was performed for all patients unless disease progression. In cases of no macroscopic residual PC, gastrectomy with D2 lymph node dissection was performed. Cases with residual PC continued chemotherapy and gastrectomy would not be performed. The primary objective was to determine the maximum-tolerated dose (MTD) and the recommended dose (RD) of intraperitoneal docetaxel in gastric cancer patients with PC.

Results: Twelve patients were enrolled from Dec 2013 to Mar 2017. Eight patients were female and the median age was 57.5 years. 3 patients were treated at level I and no DLT was observed. One patient treated at level II was hospitalised for syncopy. Although this was determined to be unlikely treatment-related, additional three more patients were treated at level II and confirmed no DLT. Three patients were treated at level III and no DLT was observed. All but one patients completed 3 cycles of treatment. In cycle II and III, four patients had delay of treatment cycle and one patient had dose reduction. The commonest > =G3 hematological toxicity was leucopenia and non-hematological toxicity was hyponatraemia. No treatment-related death was observed. Five out of 11 patients (45.5%) who have completed 3 cycles of treatment had no gross PC seen at re-staging diagnostic laparoscopy and they had gastrectomy with D2 LND done. The median PFS and OS for the overall population was 11 and 15 months, respectively. Patients who had gastrectomy done has significantly prolonged PFS (21 vs 6 months, $p = 0.025$) and a trend towards improved OS (26 vs 13 months, $p = 0.052$).

Conclusion: Intraperitoneal docetaxel, IV cisplatin and oral TS1 were well-tolerated with promising efficacy for gastric cancer with PC. The maximum tolerated dose is not reached in this phase I dose-escalation study and recommend dose of intraperitoneal docetaxel at 60mg/m2 every 3 weeks is suggested.

P – 067 Neutrophil-to-lymphocyte ratio as a predictive or prognostic factor for gastric cancer treated with nivolumab: A retrospective study

T Ogata[1], H Satake[2], M Ogata[1], Y Hatachi[3], H Yasui[4]

[1]Kobe City Medical Center General Hospital, Kobe, Japan, [2]Department of Medical Oncology, Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan, [3]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [4]Department of Oncology, Kobe City Medical Center General Hospital, Kobe, Japan

Introduction: The ATTRACTION-2 study showed that nivolumab is an effective treatment for advanced gastric cancer (AGC). Many studies have examined the effectiveness of predictive factors, such as programmed death ligand-1, mismatch repaired deficiency, and mutation burden. Several studies have demonstrated that the neutrophil-to-lymphocyte ratio (NLR) is effective as a predictive or prognostic factor for lung cancer treated with nivolumab. The objective of this study was to determine the effectiveness of NLR for AGC treated with nivolumab monotherapy.

Methods: This study was a retrospective study in a single center and we collected data on patients with AGC treated with nivolumab from June 2017 to December 2017. The NLRs were calculated before the first cycle (NLR pre) and two weeks after the first cycle (NLR post) of nivolumab. The parameters were tested for their association with progression-free survival (PFS) and overall survival (OS).

Results: Twenty-two patients (pts) were enrolled, and the median age was 64 years. Fifteen pts were male, and seven pts were female. Regarding the Eastern Cooperative Oncology Group performance status, twenty pts had a scores of 1 and two pts had scores of 2. The overall response rate was 13.6% (complete response, one pt; partial response, two pts), and the disease control rate was 40.9% (stable disease, six pts). With a median follow-up period of 140 days, the median PFS was 52 days (range, 11–265) and the median OS was not reached. The median NLR pre and NLR post were 2.42 (range, 1.00–17.4) and 2.84 (range, 1.27–12.3), respectively. Stratified with high NLR (≥ 5) and low NLR (<5), the median PFS was shorter in the high NLR pre arm (57 days vs. 45 days; $p = 0.161$) and significantly shorter in the high NLR post arm (67 days vs. 21 days; $p = 0.015$). The median OS was also shorter in the high NLR pre arm (not reached vs. 175 days; $p = 0.068$) and significantly shorter in the high NLR post arm (not reached vs. 111 days; $p = 0.012$).

Conclusion: NLR, especially NLR post, might be effective as a predictive or prognostic factor in gastric cancer treated with nivolumab monotherapy. Further study is warranted to develop this finding to detect progression cases as early as possible.

P – 068 Clinical outcomes of endoscopic submucosal dissection for lesions on the proximal location of the stomach

S Kim[1], C Choi[1], D Kang[1], H Kim[1], S Park[1], D Ryu[1], J Ko[1], H Kim[1], B Kwon[1], K Lee[2], J Lee[2], J Lee[2], H Nam[1]

[1]Pusan National University Yangsan Hospital, Yangsan, Republic of Korea, [2]Pusan National University Yangsan Hospital, Yangsan-si, Republic of Korea

Introduction: Tumors located on the proximal stomach are associated with the longer procedure time and lower en bloc resection of endoscopic submucosal dissection (ESD). Especially, ESD for lesions after distal gastrectomy is more difficult because of the narrow inner space. We aimed to evaluate the therapeutic outcomes of ESD for lesion on the remnant stomach compared with that on the upper third of whole stomach.

Methods: A total of 135 patients with neoplasm located on the proximal stomach who received ESD from Aug 2008 to Dec 2016. We retrospectively reviewed en bloc resection rate, complete resection rate, and complication rate according to the status of stomach whether distal gastrectomy was done or not.

Results: The rates of en bloc resection and complete resection showed no significant difference between the remnant stomach and entire stomach in the en bloc (92% [23/25] and 93.6% [103/110], $p = 0.674$) and complete resection (84% [21/25] and 90.0 [99/110], $p = 0.478$) rates. In a 1:3 matched data analysis, there was no significant difference in en bloc and complete resection rate. The tumor size and submucosa invasive cancer were associated with incomplete resection. In a multivariable analysis, the submucosa invasive cancer was an independent risk factor for incomplete resection.

Conclusion: ESD is feasible treatment for the lesion located on the proximal stomach regardless the operation history of distal gastrectomy. However, the complete resection rate decreases for lesion invade the submucosa.

P – 069 Associated factors with overlooked multiple synchronous gastric epithelial neoplasia

D Kang[1], C Choi[1], H Kim[1], S Park[1], S Kim[1], D Ryu[1], J Ko[1], J Lee[2], J Lee[2], K Lee[2], B Kwon[1], H Kim[1], H Nam[1]

[1]Pusan National University Yangsan Hospital, Yangsan, Republic of Korea, [2]Pusan National University Yangsan Hospital, Yangsan-si, Republic of Korea

Introduction: Since endoscopic submucosal dissection (ESD) has been accepted as the treatment of choice for early gastric cancer (EGC) without risk of lymph node metastasis, synchronous gastric epithelial neoplasia is no longer rare in the clinical practice. Knowledge about the characteristics associated with synchronous gastric epithelial neoplasia is of great importance to prevent delayed diagnosis.

Methods: Between November 2008 and December 2014, a retrospective study was conducted in a single tertiary referral hospital. Consecutive patients who underwent ESD due to EGC or high-grade dysplasia were analyzed to evaluate the incidence of synchronous gastric epithelial neoplasia and the factors associated with synchronous and overlooked synchronous lesions.

Results: A total of 488 patients were analyzed in this study. Synchronous lesions were found in 59 patients (12.1%) during the mean 37.7 months of follow-up. Among 77 synchronous lesions, 25 lesions (32.4%) were overlooked at the time of initial ESD. Age of $\geq$ 65 years, moderate to severe endoscopic atrophic gastritis, and elevated morphology of primary lesions were associated with synchronous gastric epithelial neoplasia. An important factor associated with overlooked lesions is the non-elevated morphology of lesions.

Conclusion: Careful endoscopic examination of the whole stomach is necessary in patients who are older and who have moderate to severe atrophic gastritis and elevated morphology of lesions to prevent delayed diagnosis of synchronous gastric epithelial neoplasia, especially non-elevated lesions.

P – 070 A multicenter phase II study of TAS-114 in combination with S-1 in patients with pre-treated advanced gastric cancer (EPOC1604): Interim analysis in the first stage

A Kawazoe[1], D Takahari[2], Y Nakamura[1], M Suzuki[1], H Tamura[1], M Fukutani[3], H Hasegawa[4], M Yano[1], M Wakabayashi[5], S Nomura[6], A Sato[7], K Shitara[8]

[1]National Cancer Center Hospital East, Kashiwa-shi, Japan, [2]Cancer Institute Hospital, Koto-ku, Japan, [3]National Cancer Center, Kashiwa, Japan, [4]National Cancer Center, Kashiwa, Japan, [5]Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [6]National Cancer Center, Kashiwa-city, Japan, [7]Clinical Research Support Office, National Cancer Center, Kashiwa-city, Japan, [8]National Cancer Center Hospital East, Kashiwa-city, Japan

Introduction: High deoxyuridine triphosphatase (dUTPase) in tumor tissue, as a gatekeeper enzyme for 5-fluorouracil (5-FU), is associated with its resistance. TAS-114 is an oral dUTPase inhibitor which enhances antitumor activity with 5-FU or fluoropyrimidines. Phase I study of TAS-114 in combination with S-1 showed its tolerability and preliminary antitumor signals for patients (pts) with non-small cell lung cancer and advanced gastric cancer (AGC). This phase II study has been conducted to evaluate efficacy and safety of TAS-114 and S-1 combination in pts with AGC. Here, we present the results of the first stage in the study.

Methods: The main eligibility criteria is pts with AGC after two or more previous chemotherapy regimens containing fluoropyrimidines, platinum agents, and taxanes or irinotecan. The primary endpoint is objective response rate (ORR) by investigators' judgement. Using Simon's optimal two-stage design with a one-sided alpha of 5% and power of 80%, 29 pts are required based on a null hypothesis of 5% and alternative hypothesis of 20%. In the first stage, 10 pts are evaluated and additional 19 pts are enrolled in the second stage if at least one objective response would be confirmed.

Results: From October 2017 to December 2017, 10 pts were enrolled in the first stage and assessed for anti-tumor response. All patients had been previously treated with

fluoropyrimidines, platinum agents, and taxanes. Among them, one patient achieved confirmed partial response, and five pts showed stable disease. The most common treatment-related adverse events (≥20% of pts) were rash (60%), anemia (30%), neutropenia (30%), thrombocytopenia (20%), and decreased appetite (20%). The second stage is ongoing.

Conclusion: TAS-114 with S-1 showed a preliminary efficacy signal with acceptable safety profiles for heavily pretreated pts with AGC, which would be further confirmed in the ongoing study.

P – 071 Comparative effectiveness of preoperative, postoperative and perioperative treatments for resectable gastric cancer: A network meta-analysis for the literature of past 20 years

Z Cai[1], Y Yin[2], C Shen[3], B Zhang[4]

[1]Gastrointestinal Surgery, West China Hospital, Chengdu City, China, [2]West China Hospital, Chengdu City, China, [3]West China Hospital, Chengdu, China, [4]West China Hospital, Sichuan University, Chengdu, China

Introduction: Different preoperative, postoperative or perioperative treatment strategies including chemotherapy or chemoradiotherapy are available for patients with gastric cancer, but conventional meta-analyses assessing two alternative treatments were not powered to compare differences in overall survival. Thus, we did a network meta-analysis to identify the best treatment strategy.

Methods: We systematically searched and assessed studies for eligibility, extracted data. We then pooled the data and conducted a bayesian network meta-analysis to combine direct comparisons with indirect evidence. Node-splitting method was used to assess the inconsistency. Rank probabilities were assessed by probability of treatments rankings.

Results: 33 eligible randomized controlled trials were included in the network meta-analysis. Four treatments which were shown to have a significantly improved prognosis compared with surgery only were postoperative chemotherapy [HR = 0.80 with 95% CrI: (0.73, 0.88)], postoperative chemoradiotherapy [HR = 0.73 with 95% CrI: (0.61, 0.87)], preoperative chemoradiotherapy [HR = 0.77 with 95% CrI: (0.62, 0.98)] and perioperative chemotherapy [HR = 0.69 with 95% CrI: (0.55, 0.84)]. Preoperative chemotherapy however, showed no survival benefits when compared with surgery alone [HR = 0.94 with 95% CrI: (0.71, 1.2)]. There was no statistically significant difference between postoperative chemotherapy, postoperative chemoradiotherapy, preoperative chemoradiotherapy and perioperative chemotherapy in term of overall survival. Chemoradiotherapy after D2 lymphadenectomy did not significantly improve OS as compared with postoperative chemotherapy. [HR = 0.95 with 95% CrI: (0.73, 1.3)].

Conclusion: Among patients with operable gastric cancer the perioperative chemotherapy had the highest probability of being the best treatment. Further clinical resources may be required to assess the efficacy and safety of the perioperative chemotherapy for patients with gastric cancer.

P – 072 Is there a prognostic effect of etiologies in patients with gastric cardia cancer during a recent decade of Korea?

W Chung[1], Y Kim[2], S Oh[3]

[1]St. Vincent Hospital, the Catholic University of Korea, Suwon Si, Republic of Korea, [2]St. Vincent Hospital, the Catholic University of Korea, Suwon Si, Republic of Korea, [3]St. Vincent's Hospital, Suwon, Republic of Korea

Introduction: There are two different etiologies of gastric cardia cancer - Barrett's esophagus and Helicobacter pylori (H. pylori) associated atrophy/intestinal metaplasia. We aimed to evaluate the clinical characteristics and outcome between gastric cardia and non-cardia cancer. Also, we evaluated the clinical outcome according to obesity, H. pylori infection, and gastric atrophy.

Methods: We performed a retrospective cohort study of 90 patients with gastric cardia cancer from Jan. 2003 to 2013. The control group was randomly selected in a 2:1 ratio compared with the case group, and 180 patients with gastric non-cardia cancer were selected as age and sex matched control during the same period.

Results: The rate of curative resection (R0), disease free survival and overall survival duration were significantly lower in gastric cardia cancer. The rate of recurrence was significantly higher in gastric cardia cancer (28.4% vs 8.0%, P < 0.01). The rate of H. pylori (-) and gastric atrophy (-) of gastric cardia cancer was statistically higher than non-cardia cancer (P < 0.01), but there was no difference in the rate of obesity. Irrespective of obesity or the presence of H. pylori/gastric atrophy, there were no differences of overall survival, recurrence rate and disease-free survival.

Conclusion: Gastric cardia cancer had a negative prognostic impact, compared with gastric non-cardia cancer. Although a possible heterogeneity in the pathogenesis and biological behavior of gastric cardia cancer would be present, there was no difference in prognosis.

P – 073 Prognostic factors for gastric cancer after curative gastrectomy

S Karrit[1], I Belaid[2], F Ezzairi[3], A El Ghali[4], A Bedioui[5], N Bouzid[6], M Ben Mabrouk[7], F Bouzaiene[8], Y Ben Cheikh[9], I Chabchoub[3], M Hochlaf[10], L Ben Fatma[3], S Ben Ahmed[3]

[1]Farhat Hached Sousse, Department of Medical Oncology, Sousse, Tunisia, [2]Medical Oncology Unit, Ibn El Jazzar Hospital, Kairouan, Tunisia, [3]Department of Medical Oncology, Farhat Hached Hospital, Sousse, Tunisia, [4]Department of General Surgery, Farhat Hached University Hospital, Sousse, Tunisia, [5]Department of Pathology, Farhat Hached University Hospital, Sousse, Tunisia, [6]Farhat Hached Sousse Hospital, Department of Radiotherapy, Sousse, Tunisia, [7]Department of General Surgery, Sahloul University Hospital, Sousse, Tunisia, [8]Department of Radiology, Farhat Hached University Hospital, Sousse, Tunisia, [9]Sahloul University Hospital, Sousse, Tunisia, [10]Department of Medical Oncology, Fathat Hached Hospital, Sousse, Tunisia

Introduction: Lymph node metastasis is the most important prognostic factor for patients with resected gastric cancer. The aim of this study was to determine other prognostic factors for gastric cancer after curative gastrectomy.

Methods: A single-center series of 115 patients with gastric cancer treated between 2010 and 2017 in a department of Medical Oncology in Tunisia was retrospectively investigated. Fifty patients (43.5%) underwent curative surgery.

Results: Median age was 56 years old [26-89] with a female to male ratio of 1. 75.5% of the patients had a good performance status (0-1). 32% of tumors were complicated by digestive stenosis (52.2%). Increased tumor markers were found in 12.9% of the patients. 45.9% (n = 17) of patients had peri-operative chemotherapy, 45.9% had surgery followed by adjuvant chemotherapy (from whom 24% had concomitant radiotherapy) and 8.1% had only neoadjuvant chemotherapy. Total gastrectomy was performed in 54% of the patients, with a D1 lymphadenectomy in 38.1% of the cases. Gastrectomy was considered R1 (positive surgical margin) in 12% of the cases. The mean number of removed lymph nodes was 16 [5-49]. The median lymph node ratio was of 0.33. This ratio was higher than 0.5 in 40% of cases. Most common stage was stage III (38.2%). Vascular emboli, perineural invasion and lymphatic emboli were present in respectively 19.4%, 16.7% and 8.6% of the cases. Perioperative chemotherapy regimens were FOLFOX (33.3%), LV5 FU2 Cisplatin (22.2%) and DCF (27.8%). The most common chemotherapy-induced toxicities ones were digestive intolerance (78.3%), neutropenia (56.5% with 45.5% of grade IV) and peripheric neuropathy (40.9%). Relapse rate was 30%. Distant relapses occurred in 64.3% of the cases. Median time to relapse was 13.5 months [1-39]. Patients who received FUFOL and TPF chemotherapy had a higher relapse rate than those who received other chemotherapy protocols (p = 0.06). 60% of relapsed patients received palliative chemotherapy, 13.3% underwent palliative surgery, 6.7% had both and the others only had best supportive care. Median OS and PFS were 23 and 18 months. In univariate analysis, factors significantly associated with a poor OS were poor performance status (p = 0.01), weight loss (p = 0.05), cardia carcinomas (p = 0.03), III and IV stages (p = 0.01), a 0.5 lymph node ratio (p = 0.006), R1 resection (p = 0.01), high level of tumor markers (p = 0.005), perineural invasion (p = 0.008) and lymphatic emboli (p = 0.004). Patients who had adjuvant radiotherapy had significantly better OS (p = 0.02). In multivariate analysis, identified independent prognostic factors increased tumor markers (p = 0.007) and perineural invasion (p = 0.012).

Conclusion: Almost half of our patients with gastric cancer are treated in a curative intent. Relapse rate is still high, and survival remains poor. Increased tumor markers at diagnosis and perineural invasion were both independent risk factors for OS in gastric patients after radical surgery.

P – 074 Outcome and prognostic factors of gastric cancer in Tunisia

S Karrit[1], I Belaid[2], F Ezzairi[3], A El Ghali[4], A Bedioui[5], N Bouzid[6], M Ben Mabrouk[7], F Bouzaiene[8], Y Ben Cheikh[9], I Chabchoub[3], M Hochlaf[10], L Ben Fatma[3], S Ben Ahmed[3]

[1]Farhat Hached Sousse, Department of Medical Oncology, Sousse, Tunisia, [2]Medical Oncology Unit, Ibn El Jazzar Hospital, Kairouan, Tunisia, [3]Department of Medical Oncology, Farhat Hached Hospital, Sousse, Tunisia, [4]Department of General Surgery, Farhat Hached University Hospital, Sousse, Tunisia, [5]Department of Pathology, Farhat Hached University Hospital, Sousse, Tunisia, [6]Farhat Hached Sousse Hospital, Department of Radiotherapy, Sousse, Tunisia, [7]Department of General Surgery, Sahloul University Hospital, Sousse, Tunisia, [8]Department of Radiology, Farhat Hached University Hospital, Sousse, Tunisia, [9]Sahloul University Hospital, Sousse, Tunisia, [10]Department of Medical Oncology, Fathat Hached Hospital, Sousse, Tunisia

Introduction: The aim of this retrospective study was to evaluate the influence of clinicopathological factors and treatment modalities on overall survival (OS) and progression free survival (PFS) of patients treated for gastric cancer.

Methods: A single-center series of 115 patients treated between 2010 and 2017 in a department of Medical Oncology in Tunisia was retrospectively investigated.

Results: A male predominance was noted (56.5%). Median age was 55 years old [26-89]. CA19-9 and ACE rates were increased in 34.8% of cases. Majority of patients were metastatic (43.9%) and 27% developed metachronous metastases. 62% of the metastases occurred in the peritoneum. 62.6% of the patients had surgery with a curative intent in 70.4%. 73.9% of patients received chemotherapy. Only 13.2% received radiotherapy. The median OS was 8 months. In univariate analysis, poor initial performance status,

weight loss, elevated tumor markers, stages III and IV and a lymph node ratio of 0.5 were significantly ($p < 0.0001$) associated with a poor prognosis (OS and PFS). OS and PFS were significantly better in patients undergoing curative surgery, receiving chemotherapy and radiotherapy ($p<0.001$). In multivariate analysis, only pN3 stage was an independent prognostic factor for OS ($p = 0.02$).

Conclusion: Gastric carcinoma is still diagnosed in an advanced stage in relatively young patients. Many factors are correlated with survival. Lymph node metastasis (pN3 stage) is the most important indicator to determine the prognosis of patients with resected gastric cancer. More aggressive treatments should be considered in patients with poor prognostic factors.

P – 075 Dendritic cell vaccine-based immunotherapy in combination with salvage chemotherapy for patients with advanced or relapsed gastric cancer

M Ogasawara
Sapporo Hokuyu Hospital, Sapporo, Japan

Introduction: Gastric cancer is one of the most lethal cancers despite many advances in therapy. Recently, immune checkpoint blockade agents have been demonstrated to be effective for patients with gastric cancer in advanced stage. However, the efficacy is in the range of 10-30%. New therapeutic modalities are needed for patients with refractory disease. We conducted a phase I/II clinical trial of dendritic cell (DC) vaccination for patients with advanced or relapsed gastric cancer in combination with salvage chemotherapies.

Methods: Twenty patients (14 males, 6 females; aged 24-88 years) were enrolled in the present study. Autologous DCs were generated using a standard protocol. Wilms' tumor 1 (WT1) and/or mucin 1 (MUC1) peptide-loaded mature DCs and OK432, a toll-like receptor 4 agonist, were administered intradermally every 2 weeks, 7 times in combination with salvage chemotherapies. Induction of vaccine-induced T cell responses was evaluated by an enzyme-linked immunospot (ELISPOT) or CD107a mobilization assay. Primary endpoints were safety and disease control rate. Secondary endpoints were overall survival (OS) and peptide-specific T cell responses. This study was registered in University Hospital Medical Information Network (UMIN) in Japan (UMIN 000027279).

Results: The treatment was well tolerated and none of the patients experienced more than grade 2 adverse events except for hematological toxicities. Two had partial response (PR), 7 had stable disease (SD) and 11 had disease progression (PD) following DC vaccination. Median OS from the date of the first vaccination was 10.5 months with the median observation period of 10.3 months. OS of patients achieving PR or SD after DC vaccination (responder) was significantly longer than those who did not respond to the treatment (non-responder) (median OS; 26.3 vs 6.4 months, $p < 0.001$). ELISPOT assays showed a marked increase in mean number of WT1 or MUC1-specific spots in responders in comparison with non-responders following DC vaccination; 41.4 and 7.0 fold in responders and non-responders, respectively. Similarly, CD107a mobilization assays demonstrated significant increase in responders following vaccination, suggesting that tumor specific immunity augmented by DC vaccination might result in the stabilization of disease and the prolongation of survival. There was a trend toward moderate increase in the percentage of NK cells, NKT cells and γδT cells following vaccination in responders. The percentage of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) decreased by 22% and 41%, respectively in responders. On the other hand, both the percentage of Treg and MDSC increased by 25% and 32%, respectively in non-responders, indicating that DC vaccination may contribute to the reversal of immunosuppression by these cells.

Conclusion: DC vaccine-based immunotherapy combined with a salvage chemotherapy was demonstrated to be safe and elicit both innate and acquired cellular immune responses which might be correlated to clinical outcome.

P – 076 The correlation between RhoA, CDH1 expression and clinicopathological characteristics in Chinese gastric cancer patients

Q Wei, Q He, Q Xu, J Li, L Chen, C Luo, J Ying
Zhejiang Cancer Hospital, Hangzhou, China

Introduction: The expression of RhoA and CDH1, are reported to be involved in cell adhesiveness. However, their clinicopathological characteristics in Chinese gastric cancer patients are controversial.

Methods: Between December 2007 and January 2014, a total of 108 gastric cancer patients receiving surgery were enrolled in this study. Immunohistochemical (IHC) staining of the RhoA and CDH1 protein was performed. The results of IHC staining were classified as low expression group and high expression group. Clinicopathological characteristics and survival data were compared between groups with different expression levels.

Results: There is no significant difference between the clinicopathological characteristics and RhoA expression. However, with regard to CDH1 expression, signet-ring cell component was significantly associated with low CDH1 expression($P < 0.001$). TTF (medial time to treatment failure)($P = 0.042$) and OS(medial overall survival)($P = 0.024$) were longer in patients with low RhoA expression compared to those with high RhoA expression, which was not observed in CDH1 group. On multivariate analysis of patients, RhoA expression was an independent negative prognostic factor for overall survival whereas high CDH1 expression was not associated with a favorable prognosis.

Conclusion: Taken together, our findings show that high CDH1 expression are associated with specific clinicopathologic characteristics. RhoA expression is an independent negative prognostic factor for gastric cancer.

P – 077 Benefit of neoadjuvant chemotherapy for resectable gastric cancer

N Chorna[1], A Lukashenko[2], Y Ostapenko[1], O Kolesnik[2], A Boiko[2]
[1]National Cancer Institute of Ukraine, Kiev, Ukraine, [2]National Cancer Institute, Kiev, Ukraine

Introduction: The gastric cancer (GC) is remains as one of the most common malignancies in Ukraine and other countries around the world, despite of a steady decline in the incidence. Over the last decades the major treatment strategy has been postoperative systemic therapy. The results of published trials were reviewed. In addition, neoadjuvant chemotherapy (NAC) was evaluated. The aim of this study was to assess the efficacy and safety of neoadjuvant chemotherapy in patients with resectable gastric cancer.

Methods: Patients with GC ($n = 98$) randomly underwent NAC (ECF) followed by planned surgical resection, group A ($n = 47$) or surgery alone, group B ($n = 51$) at clinic of National Cancer Institute of Ukraine, between 2009 and 2016. Overall survival (OS), local control (LC) and biological markers were estimated.

Results: Correlations between expression levels of molecular marker VEGFR-1 and gastric cancer tumor cells sensitivity to chemotherapy were found. Significant difference were found in 5-year overall survival rates (37,2% vs 23.4% for groups A and respectively). Primary tumors volumetry showed difference between the average value before and after NAC, 182 ± 11.4 mm3 vs 112 ± 8.7 mm3, $p < 0.001$.

Conclusion: Performed analysis has been established as an evidence of practical importance of the modern molecular technologies application for the improvement of the treatment strategies for stomach cancer patients. The significance of sensitivity of VEGFR-1 to chemotherapy in patients with GC has been estimated. Determination of sensitivity to NAC is quite prospective in order to provide a reasonable treatment of patients with GC and reduce the overall cost of the treatment.

P – 078 Management, outcome and prognostic factors of metastatic gastric cancer

S Karrit[1], I Belaid[2], F Ezzairi[3], A El Ghali[4], A Bedioui[5], N Bouzid[6], M Ben Mabrouk[7], F Bouzaiene[8], Y Ben Cheikh[9], I Chabchoub[3], M Hochlaf[10], L Ben Fatma[3], S Ben Ahmed[3]
[1]Farhat Hached Sousse, Department of Medical Oncology, Sousse, Tunisia, [2]Medical Oncology Unit, Ibn El Jazzar Hospital, Kairouan, Tunisia, [3]Department of Medical Oncology, Farhat Hached Hospital, Sousse, Tunisia, [4]Department of General Surgery, Farhat Hached University Hospital, Sousse, Tunisia, [5]Department of Pathology, Farhat Hached University Hospital, Sousse, Tunisia, [6]Farhat Hached Sousse Hospital, Department of Radiotherapy, Sousse, Tunisia, [7]Department of General Surgery, Sahloul University Hospital, Sousse, Tunisia, [8]Department of Radiology, Farhat Hached University Hospital, Sousse, Tunisia, [9]Sahloul University Hospital, Sousse, Tunisia, [10]Department of Medical Oncology, Fathat Hached Hospital, Sousse, Tunisia

Introduction: Patients with gastric cancer are usually diagnosed at an advanced stage. Metachronous metastases are also frequent. Survival rates of metastatic gastric cancer remain poor. Identifying prognostic factors is necessary to improve current treatment approaches.

Methods: This is a retrospective study carried out in a department of medical oncology in Tunisia between 2010 and 2017. 115 patients were treated for gastric cancer. Patients with synchronous or metachronous metastases of gastric cancer were included. We aim to analyse management of these patients, their outcome and prognostic factors.

Results: A total of 74 patients (64.3%) were studied. Median age was 55 years old [26-85] with a male predominance (60.8%). Median time to diagnosis was 3 months and main complaint was epigastric pain (53.5%). 63% of patients had good performance status [0-1]. Most tumors were proximal (56.2%). Adenocarcinoma (94.6%) was the most common histological type with a poor differentiation in 58.5%. 68.5% of the patients were metastatic at diagnosis, 24% developed experienced metastases during or after neo adjuvant treatment and the other were metachronous. The most common sites of metastases were the peritoneum (65.8%), followed by the liver (36.6%) and the lungs (26.4%). 52.7% of patients had surgery from whom 47.7% had a palliative surgery. Digestive derivation was done in 12.8% of cases. Hepatic metastasectomy was performed in one patient. 92.2% of our patients received a first line chemotherapy. LV5 FU2-CISPLATIN, FOLFOX and DCF were the most frequently used regimens (respectively 58.7%, 13% and 8.7%). 54.8% of patients progressed, 13% had a stable disease, 29% experienced a partial radiological response and 13% experienced a complete response. All complete responses were reported after treatment by LV5 FU2 CISPLATIN ($p = 0.2$). However, FOLFOX allowed better disease control rate (partial remission and stability) than LV5 FU2 CISPLATIN and DCF (respectively 50%, 47.1%

and 33.3%; p = 0.9). 23.4% of patients received second line treatment. The two most commonly used regimens were FOLFIRI (36.4%) and Capecitabine (27.3%). FOLFIRI seemed to be more effective than Capecitabine (respectively 66.7% of progression vs 100%, p = 0.5). Only 4.3% of patients received a third line chemotherapy based on capecitabine or FOLFIRI. All patients progressed. The median number of received chemotherapy cycles was 4. 41.9% of our patients developed grade 3-4 toxicity during chemotherapy. There was no treatment-related death. Median overall survival (OS) and progression free survival (PFS) were respectively 6 and 5 months. On univariate analysis, factors associated with poor OS were elevated tumor markers (p = 0.001), hepatic metastases (p = 0.003) and radiologic progression after first line treatment (p = 0.03). Those related with a better survival were receiving first (p<0.001) and second line chemotherapy (p = 0.01) and having a surgery (p = 0.01) even with a palliative intent (p = 0.04). Multivariate analysis demonstrated that the only independent factor positively impacting on survival was receiving chemotherapy (p = 0.01).

Conclusion: Metastatic spread of gastric cancer is fatal. This study confirms the survival benefit and manageable toxicity of palliative chemotherapy but survival increase remains poor compared to improvements in other gastrointestinal cancers.

P – 079 Efficacy and safety of nivolumab monotherapy for metastatic gastric cancer

K Akiyoshi[1], Y Tsuboguchi[1], S Ueda[1], S Okazaki[1], A Tsuya[1], S Tokunaga[1], H Daga[2]
[1]Osaka City General Hospital, Osaka, Japan, [2]Osaka City General Hospital, Dept of Medical Oncology, Osaka, Japan

Introduction: In Japan, nivolumab was approved in September 2017 ahead of the rest of world, so that patients with metastatic gastric cancer were able to receive nivolumab monotherapy refractory to, or intolerant of, at least two previous chemotherapy.

Methods: We retrospectively reviewed metastatic gastric cancer patients in our hospital who received nivolumab monotherapy since September 2017. All patients received 3 mg/kg nivolumab intravenously every 2 weeks.

Results: Between September 26, 2017, and January 31, 2018, 13 patients were received nivolumab. Baseline patient characteristics were as follows: median age (range), 70 (52-84) years; male/female, 8/5; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0/1/2, 0/10/3; previous gastrectomy yes/no, 7/6; histology intestinal/diffuse, 9/4; previous treatment regimens 2/3/≥4, 6/4/3; organs with metastases 1/2/≥3, 6/6/1. The median cycles of nivolumab was three (range 2-7). With respect to disease responses by CT scan, no patient had partial response, one patient had stable disease, 8 patients had progressive disease and 4 were not yet evaluated. After progression, 2 patients received post-treatment (one in capecitabine plus oxaliplatin, one in S-1 plus oxaliplatin plus trastuzumab) and 4 patients received best supportive care. All grade toxicities included fatigue (69%), decreased appetite (38%), nausea (31%), diarrhea (8%), rash (8%), ALT increased (8%), hypothyroidism (8%) and intestinal lung disease (8%). No patients had Grade3/4 toxicities.

Conclusion: Although these data included some patients with an old age or PS 2 due to real world, we show that nivolumab monotherapy for metastatic gastric cancer has been well tolerated. At this point, we have not yet confirmed responder, but we will accumulate cases to report further efficacy and feasibility.

P – 080 Gastric cancer in young patients under the age of 45 years old: A comparative study with older patients

S Karrit[1], I Belaid[2], F Ezzairi[3], A Bedioui[4], A El Ghali[5], N Bouzid[6], M Ben Mabrouk[7], F Bouzaiene[8], Y Ben Cheikh[9], I Chabchoub[3], M Hochlaf[10], L Ben Fatma[3], S Ben Ahmed[3]
[1]Farhat Hached Sousse, Department of Medical Oncology, Sousse, Tunisia, [2]Medical Oncology Unit, Ibn El Jazzar Hospital, Kairouan, Tunisia, [3]Department of Medical Oncology, Farhat Hached Hospital, Sousse, Tunisia, [4]Department of Pathology, Farhat Hached University Hospital, Sousse, Tunisia, [5]Department of General Surgery, Farhat Hached University Hospital, Sousse, Tunisia, [6]Farhat Hached Sousse Hospital, Department of Radiotherapy, Sousse, Tunisia, [7]Department of General Surgery, Sahloul University Hospital, Sousse, Tunisia, [8]Department of Radiology, Farhat Hached University Hospital, Sousse, Tunisia, [9]Sahloul University Hospital, Sousse, Tunisia, [10]Department of Medical Oncology, Fathat Hached Hospital, Sousse, Tunisia

Introduction: Over the last decade the incidence rate of gastric cancer in young patients has a trend towards a gradual increase. This retrospective comparative study aims to identify clinico-pathological characteristics of young patients with gastric cancer and to analyse prognostic factors influencing their survival.

Methods: Patients diagnosed with gastric cancer at our department between 2000 and 2017 were identified and divided into two groups: the group of the young patients who are under the age of 45 years old (A group) and the group of old patients who are over this age limit (B group).

Results: A total of 115 patients were studied. 22 patients (19%) were younger than 45 years. Weight loss was frequent in both groups (54.5% in A group and 61% in B group). Preserved general status was more common in A group (85.8% had a 0-1 PS vs 69%, p = 0.1). Proximal tumors were respectively seen in 63.6% and 51.7% of cases. Linitis was more frequent in A group (20%, p = 0.3). Signet ring cell adenocarcinoma was more common in A group (81.3% versus 74.1%). Adenosquamous carcinomas and well differentiated tumors were only found in older patients (respectively 6.8% and 10.1%; p = 0.2, p = 0.8). Synchronous metastases were more frequent in young patients (50% vs 39.1%, p = 0.5). Young patients had more surgery than old ones (respectively 68.2% vs 61.4%, p = 0.5). Advanced stages after surgery were more common in A group: pT 3-4 stages (90.9% vs 63.2%; p = 0.6) andpN3 stage (41.7% vs 23.1%; p = 0.3). They also had a higher positive lymph node ratio (respectively 0.4 vs 0.33, p = 0.5). 73.9% of the patients received chemotherapy: DCF was the preferred neo adjuvant chemotherapy regimen in A group (50%) whereas it was FOLFOX in B group (37.5%). Complete radiological responses were only seen in older patients (11.1%; p = 0.3). Similar proportion of young and old patients received first and second lines palliative chemotherapy (respectively: 92.3% vs 92.1% and 25% vs 25.7%) but a higher proportion of young ones received a third line treatment (8.3% vs 2.9%; p = 0.4). LV5 FU2 Cisplatin was the most commonly used protocol in first line in the two groups (respectively 58.3% vs 57.1%). Higher proportion of radiologic progression was noted in older patients after first line palliative chemotherapy (55.5% vs 45.5%; p = 0.6) and after second line (85.7% vs 50%; p = 0.2). Younger age was not associated with significantly better PFS or OS: respectively in young patients 10 and 10.5 months versus in old ones 6.5 and 8 months (p = 0.6; p = 0.4). Some factors influenced OS and PFS specifically in younger patients: long time (>3months) to diagnosis (p = 0.04), low BMI (p = 0.005), proximal tumors (p = 0.04) with especially cardial ones (p = 0.03), stage pT4 (p = 0.008) and presence of bone metastases (p = 0.03).

Conclusion: Young patient with gastric cancer seemed to have more aggressive tumors: more linitis, signet cell adenocarcinoma subtype, metastases at diagnosis, and advanced pTN stages. More aggressive treatments should be recommended for this group of patients.

P – 081 Early experience on the histopathological response to perioperative docetaxel, oxaliplatin and 5-FU/Sodium levofolinate (FLOT) for patients with resectable gastric adenocarcinoma when compared to cisplatin/5-fluorouracil (CF)

A Rolo[1], S Campelos[2], P Carvalho[3], L Oliveira[1], B Lima[1], A Teixeira[1], C Carvalho[1], I Faustino[1], C Coutinho[1]
[1]Department of Oncology, Hospital Senhora da Oliveira, Guimarães, Portugal, [2]Department of Pathologic Anatomy, Hospital Senhora da Oliveira, Guimarães, Portugal, [3]Department of Gastroenterology, Hospital Senhora da Oliveira, Guimarães, Portugal

Introduction: Gastric cancer is the fifth most common cancer in the Portuguese population, with 3018 new cases/year and an incidence of 13.1 cases/100000. Portugal has one of the highest gastric cancer incidence rate in Europe, particularly Northern Portugal. Perioperative chemotherapy with epirubicin, cisplatin and 5-fluorouracil (ECF) is currently the standard treatment, but CF is an effective alternative with a more favorable toxicity profile. Recently presented at ASCO and ESMO in 2017, perioperative chemotherapy with FLOT significantly improved rates of curative resection, progression-free-survival and overall survival in patients with resectable gastroesophageal adenocarcinoma compared to ECF/X (capecitabine). We aimed to assess whether FLOT would also result in improved outcomes in gastric cancer, when compared to CF.

Methods: We retrospectively compared histopathological tumor regression using the Becker and College American of Pathologists (CAP) regression criteria in consecutive patients with resectable gastric cancer (≥ cT2 and/or nodal positive disease) treated at our center in Northern Portugal between January and December of 2017 with FLOT (docetaxel 50 mg/m2, oxaliplatin 85 mg/m2, 5-FU 2600 mg/m2 infusion 24h, sodium levofolinate 100 mg/m2, all in d1, 14/14 days, 4 cycles) or CF (cisplatin 100 mg/m2, d1, 5-FU 1000 mg/m2, d1-d5 28/28 days, 3 cycles) prior to surgical resection. The pathologist was blinded to the chemotherapy regimen. Intention-to-treat statistical analysis was performed, using SPSS.

Results: Twenty-six patients were included, 13 in the CF group and 13 in the FLOT group, with a mean age at diagnosis of 55 years (45-81), 81% were male. All patients in the CF group and 12 (92%) in the FLOT group completed all planned preoperative treatment cycles. Two patients (15.4%) in the FLOT group had pathological complete regression (pCR) according to the Becker criteria Tumor Regression Grade (TRG) 1a versus 0% in the CF group (p = 0.182). More patients in the FLOT group obtained complete and subtotal regression (TRG1a/1b) (38.5% vs 7.7% in the CF group, p = 0.16). Finally, the vast majority (76.9%) of the patients in CF group had minor or no regression (TRG3) after neoadjuvant chemotherapy, twice as much as patients in the FLOT group (38.5%). When the CAP system was assessed, FLOT was significantly associated with a higher incidence of pCR (Tumor Regression Score 0 [TRS0]: 15.4% vs 0% in the CF group, p = 0.008), as well as with a significant reduction of partial or poor response/no response in the resected specimen (TRS2/3: 53.8% versus 100% in the CF group, p = 0.015). We found no statistically significant differences in the toxicity profile for both groups prior to surgery.

Conclusion: We report on our early experience with the FLOT regimen on a region with a very high incidence of gastric cancer. In our study, perioperative chemotherapy with FLOT was well tolerated, safe, and, crucially, resulted in significantly higher rates of complete histological regression when compared to CF (CAP TRS0: 15.4% versus 0%, p = 0.008). These encouraging results with the FLOT regimen will likely translate into improved clinical outcomes, and could hallmark a change in paradigms in the treatment of patients with gastric adenocarcinoma.

P – 082 Neoadjuvant chemotherapy in gastric cancer

A Bounedjar[1], R Yaici[1], MA Melzi[1], N Kechad[2], M Abada[3]

[1]Medical Oncology Department CHU Blida, Blida 1 University, Blida, Algeria, [2]Medical Oncology Department EPH, Medea, Algeria, [3]Medical Oncology Department EPH, Aindela, Algeria

Introduction: Gastric cancer currently ranks second in global cancer mortality. Most patients are diagnosed at an advanced stage when systemic chemotherapy is the only available treatment option, which may improve its prognosis. This study was conducted to evaluate the response to neoadjuvant chemotherapy in patients with advanced gastric cancer, based on the surgical resectability rate.

Methods: We carried a retrospective study from January 2015 to December 2017 on patients treated at the medical oncology department of BLIDA University Hospital and other department in Algeria, and received neoadjuvant chemotherapy for their locally advanced gastric cancer (T3-4 / N1-3M0). The objectives of the study are the evaluation of the resectability rate and the R0 resection rate.

Results: During this study period, 66 patients were included for neoadjuvant chemotherapy of a locally advanced gastric tumor. The average age of these patients is 64 years [44 years-90 years]. There is a clear male predominance, 21 women (32%) and 45 men (68%). The result of fibroscopy showed: the least frequent localization of gastric tumor was cardia with 13% followed by practically the same rate 45% of antrum and pylore, the macroscopical aspect was dominated by the ulcerative-vegetative form in 57%. In 73% the adenocarcinoma was the most frequent histological type of the gastric tumor. 28 patients (42.4%) underwent surgery, with 23 of them had R0 resection (82.1%).

Conclusion(s): Neoadjuvant chemotherapy has improved the surgical resectability rate in patients with locally advanced gastric cancer as well as the quality of surgery.

P – 083 Impact of the length of the resection margin on local recurrence after curative endoscopic submucosal dissection for early gastric cancer

H Chung[1], J Park[2], S Shin[2], S Lee[2], Y Lee[2]

[1]Seoul National University, Seoul, Republic of Korea, [2]Yonsei University College of Medicine, Seoul, Republic of Korea

Introduction: Little is known about safe resection margin in endoscopic submucosal dissection (ESD) for early gastric cancer (EGC). The aim of this study was to assess the clinical significance of the resection margin.

Methods: A total of 1548 patients underwent ESD for EGC between 2007 and 2014, at a tertiary hospital, Seoul, Korea. The curative resection rate was 90.3% (1399/1548). Among them 30 patients (2.14%), 17 adenomas (1.21%) and 13 adenocarcinomas (0.92%), had local recurrence. Data from 90 patients without recurrence, and who were matched by age and gender, were extracted on a 1:3 basis and their clinical and histological parameters were compared.

Results: The median time for detection of local recurrence at previous ESD sites was 9.1 months (range, 3–34 months) after ESD, and patients without recurrence had a median follow-up of 43.6 months (range, 26–104 months). The mean tumor-free lateral margin length was 1.38 $\pm$ 0.44 mm in patients with recurrence compared to 5.40 $\pm$ 2.51 mm in those without recurrence ($P < 0.001$). No factor other than lateral margin length was statistically different between the two groups. In multivariate analysis, a lateral free margin of less than 1 mm (hazard ratio [HR], 3.075; 95% confidence interval [CI], 1.094–8.646) and EGC arising from an adenoma (HR, 2.761; 95% CI, 1.109–6.875) were related to local recurrence.

Conclusion: A tumor-free lateral resection margin less than 1 mm and cancer arising from an adenoma were significantly associated with local recurrence even after curative ESD for EGC. These patients should undergo stricter surveillance endoscopy for early detection of possible local recurrence in the first year after ESD. Further research is required to elucidate the optimal length of resection margin in ESD for EGC.

P – 084 First-line mFOLFOX6 for peritoneally disseminated gastric cancer with massive ascites or inadequate oral intake

H Osumi[1], D Takahari[2], K Chin[1], M Ogura[3], T Ichimura[2], T Wakatsuki[4], I Nakayama[5], Y Ota[6], M Suenaga[1], E Shinozaki[1], K Yamaguchi[7]

[1]Department of Gastroenterology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Japan, [2]Cancer Institute Hospital, Koto-ku, Japan, [3]Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Japan, [4]Cancer Institute Hospital Department of Gastroenterology, Koto-ku, Japan, [5]NTT Medical Center Tokyo, Shinagawa-ku, Japan, [6]Cancer Institute Hospital, Japanese Foundation of Cancer Research, Tokyo, Japan, [7]Department of Gastroenterology Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-ku, Japan

Introduction: Oral fluoropyrimidine plus platinum is a standard 1st line treatment of the advanced gastric cancer (AGC). However, it is difficult to use it for AGC patients with massive ascites or inadequate oral intake. There were a few evidences about the efficacy and safety of FOLFOX for them. This study aimed to evaluate the efficacy and safety of modified FOLFOX-6 (mFOLFOX6) regimen for patients with massive ascites or inadequate oral intake.

Methods: This retrospective study was conducted at a single Japanese institute from November 2015 to December 2017. The mFOLFOX6 regimen consisted of oxaliplatin 85 mg/m2, bolus of 5-FU 400 mg/m2 and leucovorin (LV) 400 mg/m2 on the first day, followed by 2400 mg/m2 of 5- FU as a continuous infusion in 46 hours for first-line treatment. The definition of inadequate oral intake was the need for total parenteral nutrition (TPN). The massive ascites was defined as continuous ascites from the pelvic cavity to the upper abdomen. Improvement in oral intake was defined as no TPN for more than 7 days and improvement in ascites was defined as a decrease in ascites of more than one grade defined by the JCOG0106 trial.

Results: Among the 364 patients with gastric cancer who received first-line therapy, a total 17 patients (4.7%, 11 males, 6 females) with a median age of 67 (29-74) were included. The median follow up time of the study was 8.8 months. Among all the patients, four patients (23.5%) had ECOG PS of 2, Two patients (11.7%) had human epidermal growth receptor 2 (HER2)-positive tumors. 16 patients had metastasis at the beginning of the treatment and only one patient had locally advanced tumors. Median number of metastatic organs was 2 (1-5). 13 (76.4%) were inadequate oral intake and 4 (23.5%) had massive ascites. The median PFS and OS were 4.8 months [95% confidence interval (CI), 1.5–7.5] and 8.8 months (95% CI, 2.3–NA), respectively. 10 of 17 patients (58.8%) had target regions and objective response rate was 50%. Objective improvement in oral intake was seen in 11 of 13 patients (84.6%). Improvement of ascites was observed in 6 of 12 patients (50%). Major grade 3 or 4 adverse events were neutropenia (35.2%), febrile neutropenia (5.8%), fatigue (5.8%), anorexia (5.8%) and infection (5.8%); no treatment-related deaths were observed.

Conclusion: Our study suggests that mFOLFOX6 is feasible and has a clinical activity and regarded as a newly treatment option in AGC patients with massive ascites or inadequate oral intake.

P – 085 The impact of the difference in total diameter of metastatic tumor as a prognostic factor for advanced gastric cancer treated with systemic chemotherapy

Y Sasaki[1], J Hirota[2], J Konno[3]

[1]Medical Oncology Division, Hakodate Central General Hospital, Hokkaido, Japan, [2]Hakodate Central General Hospital, Hokkaido, Japan, [3]Department of Internal Medicine, Hakodate Central General Hospital, Hakodate, Japan

Introduction: In a previous study, patients with resectable gastric cancer and enlarged lymph nodes that had a diameter $\geq$ 15 mm preoperatively were found to have worse outcomes. However, data on the significance of metastatic tumor diameter for stage IV gastric cancer treated with systemic chemotherapy are not available.

Methods: This is a retrospective review of patients who received chemotherapy with fluoropyrimidine and platinum for stage IV gastric cancer at our institution between June 2009 and February 2017. Tumor lesions with long-axis diameters $\geq$ 10 mm and lymph nodes with short-axis diameters $\geq$ 15 mm as measured on CT scan before chemotherapy were regarded as measurable lesions. Patients were divided into groups based on the total diameters of all measurable lesions. Patient characteristics, toxicities, and survival were compared between the groups.

Results: Among the 104 patients who received fluoropyrimidine and platinum based chemotherapy for stage IV gastric cancer, 62 had measurable lesions. The median total diameter was 54 mm, and 55 mm was set as the cut-off value for grouping patients into large ($\geq$55 mm) and small

Conclusion: A total metastatic tumor diameter $\geq$ 55 mm was a negative prognostic factor for advanced gastric cancer treated with systemic chemotherapy.

P – 086 Treatment and testing patterns among patients with HER2+ advanced/metastatic gastric, esophageal or gastroesophageal junction (GEJ) adenocarcinoma in the United States

Y Janjigian[1], L Hess[2], Y Zhu[3], Y Fang[4], A Liepa[3], C Kuder[2], S Chin[3]

[1]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA, [2]Eli Lilly & Co, Indianapolis, Indiana, USA, [3]Eli Lilly and Company, Indianapolis, Indiana, USA, [4]InVentiv Health, Indianapolis, Indiana, USA

Introduction: It is estimated that 9-23% of patients diagnosed with advanced or metastatic gastric, esophageal or GEJ adenocarcinoma have tumors that overexpress HER2 in the United States. Current treatment guidelines recommend HER2 testing as part of the initial workup of patients diagnosed with unresectable disease. For patients with tumors that overexpress HER2, trastuzumab-based therapy is recommended in the first-line (1L) setting. Despite evidence for HER2 testing and 1L treatment guidelines for patients whose tumors overexpress HER2, data are lacking with regard to the implementation of testing practices and recommended treatment patterns in real-world practice settings. The aim of this study was to fill this gap in knowledge.

Methods: This retrospective observational study analyzed data from the Flatiron Gastric/Esophageal electronic medical records database of US community and

academic clinics, which at the time of analysis included longitudinal data from >5600 patients diagnosed with advanced or metastatic gastric, esophageal or GEJ cancers from 2011 to 2017. Eligible patients for this study were 18+ years of age at diagnosis who initiated anti-cancer systemic therapy on or after 01 Jan 2013. Patients with squamous tumors were excluded. Descriptive statistics were used to define the patient characteristics, HER2 testing patterns (only reported by community practices in the dataset), and treatment regimens and sequences across lines of therapy.

Results: community practice settings. Of community practices, 24.7% of patients in this study were not tested for HER2 at any time during the study period; 21.1% of patients with gastric, 28.9% with esophageal, and 24.1% with GEJ adenocarcinoma were not tested for HER2. Of the 2035 patients who had a HER2 test during the study period, 1587 (78.0%) had testing completed from baseline through start of 1L therapy. Of those tested, 504 patients (24.8%) had a HER2+ result during the study period and 732 (36.0%) had multiple HER2 tests. Among the 504 patients with HER2+ tumors, 293 (58.1%) received trastuzumab; 207 (41.1%) received it in the 1L setting and 88 (17.5%) received it across multiple lines of therapy (1L plus 2L and/or 3L).

Conclusion: Despite clinical guidelines and recommendations for HER2 testing and treatment among patients with gastric, esophageal or GEJ adenocarcinomas, only about 3/4 of patients are tested before 1L and less than half of patients with HER2+ tumors received trastuzumab in the 1L setting as recommended. Despite the lack of evidence for continuation of HER2 targeted therapy across lines of therapy, this practice was observed in this study. There is a need for educational efforts to improve testing rates and for the appropriate care of the patient whose tumor overexpresses HER2.

P – 087 Hyperthermic intraperitoneal chemotherapy (HIPEC) in combined treatment of locally advanced and disseminated gastric cancer: Results of a single-centre study

R Yarema[1], M Ohorchak[2], Y Oliynyk[1], M Matusak[3], M Zubarev[1], P Gyrya[2], Y Kovalchuk[2], V Safiyan[2], I Karelin[4], T Semotuk[2], T Novicka[2], L Laba[2], M Yarysh[2], T Fetsych[5]

[1]Danylo Halytsky Lviv National Medical University, Department of Oncology and Medical Radiology, Lviv, Ukraine, [2]Lviv Regional Cancer Center, Lviv, Ukraine, [3]Lviv Regional Oncology Center, Lviv, Ukraine, [4]Lviv Oncological Regional Center, Lviv, Ukraine, [5]Lviv Medical University, Lviv, Ukraine

Introduction: Patients with locally advanced gastric cancer (GC) and/or peritoneal metastases have a poor prognosis despite systemic chemotherapy or palliative surgery. The aim of this retrospective comparative non-randomized study was to evaluate aggressive cytoreduction in combination with hyperthermic intraperitoneal chemoperfusion (HIPEC) as a novel treatment strategy for patients with intraperitoneal disseminated and locally advanced GC.

Methods: 59 GC patients with serosal invasion (n = 24), limited peritoneal metastases (n = 25), or disseminated peritoneal metastases and tense ascites (n = 10) underwent combination therapy with HIPEC. Three matched control groups undergoing standard therapies were retrospectively identified.

Results: Combination therapy for serosa-invasive GC reduced the level of metachronous peritoneal carcinomatosis from 75% in the surgical control subgroup to 33.3% (p = 0.004) and increased median survival from 13,3 months to 32.5 months (p=0.0006). The median and 1-year survival rates for intraperitoneal disseminated GC patients undergoing therapy with the use of HIPEC were 12 months and 54.2% compared with 8,4 months and 20%, respectively (p = 0.004) for control subgroup patients (palliative chemotherapy). For patients with complete cytoreduction median survival was 14 months, one patient (4%) alive more than 5 years. The symptomatic use of HIPEC in GC patients with diffuse peritoneal carcinomatosis complicated by symptomatic ascites does not significantly increase survival, it allows effective elimination of recurrent ascites. The independent prognostic factors in GC patients with peritoneal metastases undergoing combined treatment with HIPEC are the stage of peritoneal dissemination in compliance with the classification of the Japanese Gastric Cancer Association and the score of cytoreduction completeness.

Conclusion: HIPEC is an effective method of adjuvant therapy for gastric cancer with high risk of intraperitoneal progression. Cytoreduction followed by HIPEC improves survival in patients with limited peritoneal carcinomatosis of gastric origin.

P – 088 Genetic polymorphisms and PG1/PG2 and G17 levels can predict gastric carcinoids in autoimmune atrophic chronic gastritis patients

R Cannizzaro[1], R Magris[2], S Maiero[1], M Fornasarig[1], M De Zorzi[2], G Zanette[3], C Mazzon[4], E Canton[2], A Steffan[2], V Canzonieri[1], V De Re[5]

[1]Centro di Riferimento Oncologico, Aviano, Italy, [2]Centro di Riferimento Oncologico, IRCCS, Aviano, Italy, [3]Azienda per l'Assistenza Sanitaria n.5, Pordenone, Italy, [4]Azienda per l'Assistenza Sanitaria n.5, Pordenone, Italy, [5]Centro di Riferimento Oncologico, Aviano, Italy

Introduction: Autoimmune Chronic Atrophic Gastritis (ACAG) is epidemiologically and biologically linked to the development of gastric carcinoids type I (GCs) and gastric adenocarcinoma. ACAG is often associated to multiple autoimmune disorders. The aim of the study was to evaluate the incidence of GCs development and to discover potential diagnostic markers related to GCs in patients (pts) with ACAG.

Methods: 141 pts with ACAG were enrolled between years 2006-2017 and endoscopy was performed. Pepsinogen I (PG1), Pepsinogen II (PG2) and Gastrin 17 (G17) serum levels were quantified using an enzyme-linked immune-sorbent assay kit. Serum levels of PGs and G17 were used to discriminate among pts with ACAG and pts affected by GCs in univariate and in multivariate analysis. A panel of genetic polymorphisms of PG2 gene and miRNA, that are known to modulate PG2 expression (rs9471643 C/G; rs6458238 A/G; rs8111742 A/G; rs121224 C/G; rs1002765 A/G; TATA-BOX length), was tested by real time PCR.

Results: Out of the 141 ACAG pts (26 M, 115 F; mean age 54,5), 21 (15%) (4M, 17F) presented GCs. A secondary autoimmune disorder was displayed by 98 pts (69,5%) and autoimmune thyroiditis was the most frequent (61,9%). A statistically significant difference in PG1/PG2 and G17 levels was found between ACAG pts with or without GCs (r=-0,3768 95% CI-0,5499 to -0,1726 p = 0,0005). Although it is known that PG2 levels correlate with Helicobacter Pylori (HP) infection in our series of ACAG and GCs and ACAG pts there wasn't a statistical significant difference nor in number of HP positive (+) pts nor in IgG anti HP load (HP+ GCs pts 17,6%, HP+ ACAG pts 30,2%; GCs pts IgG anti HP mean 19,42 SD: ±27,71, ACAG pts IgG anti HP mean 33,43 SD: ±41,43 p=ns). Among the 6 genetic polymorphisms, we found that rs8111742 A/G, rs121224 C/G were associated to a difference in serum PG2 levels and GCs (p = 0,0016 and p = 0,0051). No significant differences were found between pts with thyroiditis and GCs and pts without thyroiditis and with GCs (6,3% and 8,5% p = 0,07).

Conclusion: GCs are often diagnosed incidentally during endoscopy. We found a higher association between GCs type I and ACAG than data present in literature and of interest we found a statistically significant difference in PG1/PG2 and G17 levels between ACAG pts with or without GCs. The identification of a different level of PGs ratio and G17 in GCs-positive ACAG could be proposed as a potential indicative marker for a further endoscopic targeted evaluation for GCs in ACAG pts.

P – 089 Gastric cancer in Lynch Syndrome: Are precancerous conditions co-risk factors?

M Fornasarig[1], R Magris[2], S Maiero[1], A Viel[2], E Canton[2], V Canzonieri[1], R Cannizzaro[1]

[1]Centro di Riferimento Oncologico, Aviano, Italy, [2]Centro di Riferimento Oncologico, IRCCS, Aviano, Italy

Introduction: Gastric cancer (GC) risk in Lynch Syndrome (LS) is up to 13% instead of less than 1% in general population. LS is an autosomal dominant disorder caused by germ-line mutations in one of the mismatch repair (MMR) genes (MSH2, MLH1, MSH6, PMS2) or EpCAM gene determining mainly risk of colorectal and endometrial cancer and a lower risk of small bowel, urothelial and gastric cancer. GCs in this setting are usually intestinal type and show microsatellite instability (MSI-H) and loss of MMR protein expression. There are not clear guidelines for surveillance because the histopathologic transformation pathway is unknown. Since Helicobacter Pylori (HP) infection represents a clinical condition predisposing to gastric cancer its eradication is suggested. In our study we investigate clinical features of GC that develop in patients with this syndrome.

Methods: 139 patients with LS were registered in hereditary tumor register settled in 1994 at our Institution. Thirty-three had mutation in MLH1, 10 in MSH6 and 96 in MSH2 (83 F,56 M; mean age 53).The average follow up time was 10,5 years (2-26 years). Patients were inserted in surveillance program consisting in: colonoscopy starting at 20 years every 2 years until 40 and then annually. Gynecological surveillance for women starting at 30 years, upper GI endoscopy staring at 35 years with an interval of 3 years and abdominal ultrasound and urinal cytology starting at 35 with an interval of 2 years.

Results: Out of 139 Lynch patients 4 (2,8%) (2M; 2F) developed GCs. Three were symptomatic and one was diagnosed for surveillance. MSH2 was mutated in three of them and MLH1 in one. No family history of GC was reported. All GCs displayed MSI-H and loss of related miss match repair (MMR) protein at immunohistochemical analysis. MSH2 mutation patients were a man (62 years) and two women (73 and 50 years). Their GCs were intestinal type linked to HP infection at early stages (T2N0; T2N1; T1N0). MLH1 carrier was a man (53 years). His GC was a diffuse-type adenocarcinoma (T2N0) at fundus without HP infection. Four years before autoimmune gastritis was diagnosed with already atrophic gastritis and deficit of acid secretion and two pyloric gland adenomas were removed at corpus.

Conclusion: Our data suggest that our GCs developed in association to MMR mutation and atrophic gastritis caused by HP infection or autoimmune gastritis. Actually pyloric gland adenomas have been reported as precancerous lesions in autoimmune gastritis. Guidelines suggest gastric surveillance only in selected cases with family history of gastric cancer and suggest testing and treatment of HP infection. Our cases did not display gastric cancer family history. Thus, HP and anti parietal cells antibodies tests should be taken in consideration to select LS patients for gastric surveillance instead of family history.

P – 090 Ethnic and racial disparities among young patients with noncardia gastric cancer

C Hester, A Yopp, P Polanco, J Mansour, S Wang, M Porembka
UT Southwestern Medical Center, Dallas, Texas, USA

Introduction: Although up to 15% of patients with gastric cancer present at young age, the characteristics of these patients are not well described. We sought to determine the clinical and pathologic characteristics of young noncardia gastric cancer patients in the United States to identify differences between ethnicities.

Methods: Patients with noncardia gastric cancer younger than 50 years were selected from the National Cancer Database between 2004 and 2013. We analyzed patient, tumor-, and treatment-related factors as well as overall survival using standard statistical methods.

Results: 7,036 patients younger than 50 were identified with 38% Non-Hispanic Whites (NHW), 28% Hispanics (HS), 22% Non-Hispanic Black (NHB) and 12% Asians (AS). HS patients presented at a younger age compared to other ethnicities (37.6% were 18-39 years vs 27% NHW, 28% NHB, and 31% AS $p < 0.01$). HS was more likely to be uninsured (24% vs 7% NHW, 13% NHB, and 10% AS, $p < 0.001$) and presented with metastatic disease (47% vs 38% NHW, 41% NHB, and 37% AS, $p < 0.001$). After adjusting for early stage, NHB and HS were less likely to undergo resection compared to NHW and AS (68% and 70% vs 82% and 77%, $p < 0.001$). AS had longer median overall survival of 34.4 months compared to 19.7 months for NHW, 19.1 months for HS and 18.3 months for NHB ($p < 0.01$). Independent variables associated with favorable survival included HS or AS ethnicity (HR 0.76 95%CI 0.7-0.9 and 0.78 95%CI 0.7-0.9), low Charlson Comorbidity Index, private insurance, early clinical stage, and receipt of treatment.

Conclusion: There is ethnic and racial variability in disease presentation, treatment delivery, and outcomes in young noncardia gastric cancer patients. HS patients present earlier with more advanced disease. Resection was underutilized in minority patients (NHB and HS). Despite presentation and receipt of therapy, HS race is independently associated with improved survival. Additional studies are warranted to determine underlying biologic and socioeconomic/geographic factors influencing these disparities.

P – 091 Influence of the visceral vessels structure variations on peculiarity of radical surgical treatment of stomach cancer

S Khoshimov, S Lukmonov
Tashkent Medical Academy, Tashkent, Uzbekistan

Introduction: Optimization of the choice of diagnostic volume, adequate lymphodissection in patients with stomach cancer.

Methods: On the basis of the Department of Oncology and Radiology of the Tashkent Medical Academy, multislice computed tomography is performed in angio-graphic mode for all patients suffering from stomach cancer, followed by a three-dimensional reconstruction of the main vessels. After the research, the preoperative planning of the operation is carried out. With the application of this method, 224 patients were examined. For radical surgical treatment, 125 patients were selected, while in 36 of them a variant anatomy of the visceral vessels of the upper abdominal wall was revealed. Given a thorough preoperative examination, all patients were radically operated in the volume of gastrectomy or distal subtotal resection of the stomach, lymphodissection in the volume of D2 and D2 + was performed.

Results: In multislice computed tomography of the abdominal cavity in angiographic mode with subsequent three-dimensional modeling, one patient was identified with significant variations: all arteries of the celiac trunk separated from the aorta; the left hepatic artery (LHA) and the splenic artery moved away from the aorta, the right hepatic artery (RHA) retreated from the celiac trunk, the left gastric artery (LGA) receded from the LHA; The celiac trunk (CT) is represented by the RHA bifurcation and the splenic artery, the LHA moved away from the aorta, the LGA departed from the LHA; CT is represented by RHA bifurcation and splenic artery, LHA receded from the splenic artery, LGA departed from the LHA; The CT is represented by bifurcation of the LGA and splenic artery, the common hepatic artery (CHA) is receding from the superior mesenteric artery (SMA). In 1 case, a single celiac-mesenteric trunk was identified. In 2 patients, the CHA or splenic artery (1 patient) moved away from the aorta. In 4 patients, CT was represented by bifurcation of CHA and splenic artery, LGA departed from the aorta. In 4 cases, a cranial LHA was detected, which departs from the CT, followed by the withdrawal of the LGA. In 3 cases, the RHA was withdrawn from the SMA and there was an aberrant LHA that departed from the CT, followed by the withdrawal of the LGA. After all the operations, the lymph nodes were labeled according to the classification of the Japanese Association for the Treatment of Stomach Cancer (JGCA, 2010). In all operated patients, there were no specific complications associated with the volume of lymph node dissection.

Conclusion: Performing multislice CT in angiographic mode at the preoperative stage is an effective way of visualization of the main vessels, which allows planning the volume and technique of surgical intervention depending on the revealed vascular variation, reducing the risks of intraoperative complications, more accurately performing lymphodissection and thus achieving greater radical surgical intervention.

P – 092 Multivisceral resections for locally advanced gastric cancer

Y Ostapenko[1], A Lukashenko[2], O Kolesnik[2], N Chorna[1], A Boiko[2]
[1]National Cancer Institute of Ukraine, Kiev, Ukraine, [2]National Cancer Institute, Kiev, Ukraine

Introduction: Multiple organ resection for locally advanced (T4) gastric cancer (AGC) is associated with high morbidity and mortality and poor outcomes. Our aim was to evaluate the efficacy of these surgeries in relation to surgical morbidity, mortality and survival.

Methods: Medical records of 1065 patients with AGC who undergone total or subtotal gastrectomy with multivisceral resection and D2 or D3 lymphatic dissection were evaluated between 1998 – 2017 years at the Clinic of National Cancer Institute (Ukraine).

Results: The figure of AGC spreading: colon – 41,9%; pancreatic body/tail and spleen – 38.9%; pancreatic head – 11.1%; liver left lobe – 8,1%. Gastrectomy with resection of three and more adjacent organs – 21%; two organs - 22%, one organ – 57%. Surgical mortality and morbidity rate were 6,8% and 23,9%, respectively. Main causes of postoperative mortality were pancreatic necrosis (5,2%) and abdominal abscesses (2,7%). The overall 5-year survival rate was 25%. Survival of patients with R0 and R1 resections was 37% and 13%, respectively ($p < 0,05$). Histopathologic examination has confirmed involvement of adjacent organs (pT4) in 91,2% of multivisceral resection cases, other 9,8% invasions were false-spreading due to desmoplastic tumor reaction (pT3) without differences in long term outcomes in both groups.

Conclusion: Complete tumor R0 resection including adjacent organs is the key to successful treatment for AGC. Aggressive multivisceral resection for AGC is technically feasible and can be achieved with low mortality and acceptable morbidity, providing good disease free and overall survival.

P – 093

P – 094 A phase 3, double-blind, randomized study of pamiparib versus placebo as maintenance therapy in patients with inoperable, locally advanced, or metastatic gastric cancer that responded to platinum-based first-line chemotherapy - Trial in progress

F Ciardiello[1], Y Bang[2], J Bendell[3], A Cervantes[4], R Brachmann[5], Y Zhang[5], M Raponi[5], H Farin[6], L Shen[7]
[1]University of Campania, Naples, Italy, [2]Seoul National University Hospital, Seoul, Republic of Korea, [3]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee, USA, [4]University Hospital of Valencia, Valencia, Spain, [5]BeiGene USA, Inc, Emeryville, California, USA, [6]BeiGene USA, Inc, Cambridge, Massachusetts, USA, [7]Beijing Cancer Hospital, Beijing, China

Introduction: Gastric cancer is the fifth most common cancer and is the third leading cause of cancer deaths worldwide. A subset of gastric cancers exhibit platinum sensitivity and genomic instability that is characteristic of homologous recombination deficiency (HRD). Poly(ADP-ribose) polymerase proteins 1 and 2 (PARP1/2) are involved in DNA damage repair, and their inhibition is cytotoxic for cells with HRD. Pamiparib

(previously known as BGB-290) is a selective PARP1/2 inhibitor that crosses the blood-brain barrier, has shown potent DNA–PARP trapping, and has demonstrated robust antitumor activity in preclinical models. In early phase clinical studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed promising antitumor activity. These studies also established 60 mg orally twice daily as the recommended pivotal dose.

Methods: The purpose of this double-blind, placebo-controlled, randomized, multicenter Phase 3 study (NCT03427814) conducted in Asia, Australia, Europe, and North America is to compare the efficacy, safety, and tolerability of pamiparib with placebo as maintenance therapy in ~540 patients with advanced gastric cancer who have responded to first-line, platinum-based chemotherapy. Patients who are ≤8 weeks after their last platinum dose of first-line chemotherapy will be randomized 1:1 to receive either pamiparib 60 mg twice daily or placebo in 28-day cycles. Patient randomization will be stratified by genomic loss of heterozygosity status (ie, high versus low), region, and ECOG status. Radiologic assessments will be centrally evaluated per RECIST every 8 weeks after first dose. Safety will be assessed on Day 1 of each cycle, and Day 15 of Cycles 1 and 2, and as needed. Blood samples will be collected at various time points to determine the pharmacokinetics of pamiparib in inoperable, locally advanced gastric cancer patients. The primary endpoint is progression-free survival; key secondary endpoints include safety/tolerability, overall survival, objective response rates, time and duration of response, and time to second subsequent treatment. Correlative biomarker analyses in tumor tissues and blood will be performed.

P – 095 A randomized clinical trial of apatinib on an intermittent versus continuous dosing schedule in combination with docetaxel for advanced gastric cancer in second-line setting - Trial in progress

Y He[1], Y Yan[2], L Ke[2], X Hu[3], S Wu[2], J Niu[2], H Li[1], H Xu[1], H Luo[1], L Cao[1], W Chen[1], C Ji[4], Y Sun[4], G Wang[4], T Xu[4], B Hu[4]

[1]Department of Oncology, Anhui Provincial Cancer Hospital, The First Affiliated Hospital of University of Science and Technology of China, Hefei, China, [2]Department of Oncology, Anhui Provincial Cancer Hospital, The First Affiliated Hospital of University of Science and Technology of China, Hefei, China, [3]Department of Oncology, Anhui Provincial Cancer Hospital, The First Affiliated Hospital of University of Science and Technology of China, Hefei, China, [4]The First Affiliated Hospital of USTC, Anhui Provincial Hospital, Hefei, China

Introduction: Apatinib, a small molecule oral tyrosine kinase inhibitor (TKI) that mainly targets vascular endothelial growth factor receptor-2, has been approved in the treatment of advanced gastric cancer in China. Whereas, many patients treated with apatinib experienced toxicity necessitating dose reduction. Maintaining adequate dosing and drug levels are essential for optimizing clinical efficacy. Thus, it is urgently needed to explore optimal dosing strategy of apatinib treatment in advanced gastric cancer. Other small molecule TKIs such as sunitinib [J Clin Oncol, 27 (22): 3584-3590], sorafenib [Future Oncol, 13(8): 679-693] and anlotinib [J Hematol Oncol, 9(1): 105] have demonstrated efficacy and acceptable tolerability in advanced cancers via an intermittent dosing schedule. The current study was conducted to compare the efficacy and safety of intermittent (5days on/2 days off schedule) vs continuous apatinib therapy in combination with docetaxel as second-line treatment for advanced gastric cancer.

Methods: This study is designed as an open-label, randomized clinical trial. To enroll, patients are required to have pathologically or histologically confirmed advanced gastric cancer and have experienced treatment failure with first-line chemotherapy. Other inclusion criteria include ≥18 years; Eastern Cooperative Oncology Group performance status of 0-2; life expectancy more than 3 months. Eligible patients are randomized to the treatment arms in a ratio of 1:1. In intermittent dose schedule, patients receive oral apatinib 500 mg/d for 5 days followed by 2 days off treatment. In continuous dose arm, patients received oral apatinib 500 mg/d as a continuous daily dosing. Docetaxel 60 mg/m2 is administered intravenously to patients on day 1 in a 21-day cycle in both groups. Treatment is continued until disease progression, intolerable toxicity or withdraw of consent. The primary outcome is progression free survival. The secondary outcomes include objective response rate, disease control rate, overall survival, quality of life and safety. Tumor response is assessed according to Response Evaluation Criteria in Solid Tumors guideline version 1.1. The incidence and severity of adverse events are defined by the Common Terminology Criteria for Adverse events version 4.0. Approximately 60 patients will be enrolled, with 30 subjects in each arm. Enrollment opened on September, 2017. As the cutoff date of February 27 2018, 19 patients were enrolled: 11 patients in the intermittent dose arm and 8 patients in the continuous dose arm. Clinical trial information: NCT03334591.

P – 096 A phase 3 study of chemotherapy + pembrolizumab vs chemotherapy + placebo as neoadjuvant/adjuvant treatment for patients with gastric or gastroesophageal junction (G/GEJ) cancer: KEYNOTE-585 - Trial in progress

Y Bang[1], E Van Cutsem[2], C Fuchs[3], A Ohtsu[4], J Tabernero[5], D Ilson[6], W Hyung[7], V Strong[6], T Goetze[8], T Yoshikawa[9], L Tang[6], P Hwang[10], K Shitara[11]

[1]Seoul National University Hospital, Seoul, Republic of Korea, [2]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium, [3]Yale Cancer Center, New Haven, Connecticut, USA, [4]National Cancer Center Hospital East, Kashiwa, Japan, [5]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain, [6]Memorial Sloan Kettering Cancer Center, New York, New York, USA, [7]Yonsei Cancer Hospital, Yonsei University Health System, Seoul, Republic of Korea, [8]Institute of Clinical Cancer Research, UCT University Cancer Center, Frankfort, Germany, [9]Kanagawa Cancer Center, Yokohama, Japan, [10]Merck & Co., Inc., Kenilworth, New Jersey, USA, [11]National Cancer Center Hospital East, Kashiwa-city, Japan

Introduction: Pembrolizumab monotherapy demonstrated promising efficacy and manageable safety patients with advanced metastatic G/GEJ adenocarcinoma who have received ≥2 prior lines of therapy, resulting in FDA approval for patients with PD-L1–positive tumors (combined positive score [CPS] ≥1) whose disease progressed on or after ≥2 prior lines of therapy. When combined with cisplatin and 5-fluorouracil (5-FU), pembrolizumab demonstrated promising efficacy and manageable safety in patients with previously untreated metastatic G/GEJ cancer in the phase 2 KEYNOTE-059 study. Combining chemotherapy with pembrolizumab in the neoadjuvant/adjuvant setting may be beneficial for patients with locally advanced, resectable G/GEJ cancer. KEYNOTE-585 (ClinicalTrials.gov, NCT03221426) is a phase 3, randomized, double-blind study to evaluate the efficacy and safety of chemotherapy + pembrolizumab versus chemotherapy + placebo as neoadjuvant/adjuvant treatment for locally advanced resectable G/GEJ cancer.

Methods: Key eligibility criteria are age ≥18 years; previously untreated localized G/GEJ adenocarcinoma (Siewert type 2 or 3 tumor; eligibility of Siewert type 1 tumors is limited to those for whom planned treatment is perioperative chemotherapy and resection), defined by T3 or greater primary lesion or the presence of any positive clinical nodes without evidence of metastatic disease; planned surgery after preoperative chemotherapy; Eastern Cooperative Oncology Group performance status 0/1; adequate organ function; no active autoimmune disease. Eligible patients will be randomly assigned in a 1:1 ratio to receive chemotherapy + pembrolizumab (arm 1) or chemotherapy + placebo (arm 2). Patients will receive neoadjuvant (preoperative) chemotherapy + pembrolizumab every 3 weeks (Q3W) for 3 cycles (arm 1) or chemotherapy + placebo Q3W for 3 cycles (arm 2) followed by surgery, then adjuvant chemotherapy + pembrolizumab Q3W for 3 cycles (arm 1) or chemotherapy + placebo Q3W for 3 cycles (arm 2), then monotherapy with pembrolizumab (arm 1) or placebo (arm 2) Q3W for 11 cycles; treatment will occur for up to 17 cycles. Chemotherapy is cisplatin 80 mg/m 2 IV + either capecitabine 1000 mg/m 2 orally twice daily or 5-FU 800 mg/m 2 IV (investigator's choice). Pembrolizumab 200 mg was administered IV. In a separate safety cohort, 5-FU 2600 mg/m 2 IV + docetaxel 50 mg/m 2 IV + oxaliplatin 85 mg/m 2 IV + leucovorin 200 mg/m 2 IV every 2 weeks (FLOT) is being evaluated as a potential chemotherapy option. If adequate safety is demonstrated, FLOT may be incorporated as a chemotherapy backbone option in the main study. Primary end points are overall survival, event-free survival per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), by central review, and pathologic complete response (no invasive disease and histologically negative nodes) rate by central review. Secondary end points include safety and tolerability and disease-free survival per RECIST v1.1 by central review. Adverse events will be graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and will be monitored for 30 or 90 days after treatment. Patients will be followed for survival status until death, withdrawal of consent, or study end, whichever occurs first. Planned enrollment is 800 patients in the main study and 60 patients in the safety cohort.

P – 097 SIRT therapy with Yttrium-90 resin microspheres in patients with liver cirrhosis Child Pugh B7-9 and unresectable nonmetastatic hepatocellular cancer

J Eick[1], M Burbelko[2], M Plotkin[3], J Steinberg[4], W Ring[4], C Schwertner[4]

[1]Innere Medizin-Gastroenterologie, GI Onkologie und Infektiologie, Vivantes-Klinikum Am Urban, Berlin, Germany, [2]Institut für Radiologie und Interventionelle Therapie, Vivantes-Klinikum Am Urban, Berlin, Germany, [3]Institut für Nuklearmedizin, Vivantes-Klinikum Am Urban, Berlin, Germany, [4]Innere Medizin-Gastroenterologie, GI Onkologie und Infektiologie, Vivantes-Klinikum Am Urban, Berlin, Germany

Introduction: Treatment options of unresectable hepatocellular cancer (HCC) are limited. Drug therapy with sorafenib, regorafenib or lenvatinib was approved only for HCC-patients with good liver function, i.e. liver cirrhosis Child Pugh A. Sorafenib therapy in HCC-patients with Child Pugh B-cirrhosis results in a median overall survival of 5.2 months (GIDEON trial: Marrero J et al., J Hepatology 2016, 65: 1140–47). Yttrium-90 (Y-90) resin microspheres are effective in nonmetastatic HCC but have not been studied in advanced cirrhosis. We evaluated the safety and efficacy of Y-90 microspheres in HCC-patients with liver cirrhosis B7-9.

Methods: 12 patients (8 men, 4 women) with a median age of 64.5 years [range 44-83] suffering from both liver cirrhosis B7-B9 and unresectable nonmetastatic HCC were treated once or twice with Y-90 resin microspheres in our hospital in the years 2013-2017. In most patients alcohol abuse was the cause of liver cirrhosis. TACE was considered not to be effective in these patients. Our exclusion criteria for selective internal radiotherapy (SIRT) were either serum bilirubin >2.4 mg%, infiltration of the portal vein by tumor, portal vein thrombosis, extrahepatic metastasis, significant ascites, renal insufficiency, concurrent infection, uncontrolled bleeding or significant encephalopathy. Patients with bilobar HCC were scheduled for 2 separate unilobar SIRT sessions (1 right-sided, 1 left-sided, 4-6 weeks apart).

Results: All patients adhered well to therapy and follow-up. Y-90 resin microspheres were well tolerated by the patients. In 2 patients transient flares of AST and/or ALT and/or bilirubin were noted. Epigastric discomfort for 1-2 days was reported by 5 patients. 10 patients died due to progressive disease, 2 patients are still alive. At 3 months after 1st SIRT the disease control rate was 50%. A median overall survival of 10.0 [range 4-16] months as calculated from 1st unilobar application of Y-90 microspheres was observed at this interim analysis; mean overall survival (after SIRT) amounts now to 9.3 + 3.7 months (11.8 months for B7 and 7.5 months for B9 patients). Due to angiographic evaluation and ordering of Y-90 microspheres from overseas 4-6 weeks (without specific treatment) passed by between decision making and the first SIRT.

Conclusion: SIRT therapy is safe in patients with unresectable nonmetastatic HCC and liver cirrhosis Child Pugh B7-9, as the chosen exclusion criteria are respected. Overall survival of our patients is better than the one reported for sorafenib treatment in HCC-patients with liver cirrhosis B7-9 of the GIDEON trial. Thus, SIRT with Y-90 resin microspheres should be considered for patients with unresectable nonmetastatic HCC and liver cirrhosis B7-9, if our exclusion criteria are observed.

P – 098 Treatment patterns and costs of care for patients diagnosed with hepatocellular carcinoma (HCC) in the United States (U.S.)

L Hess[1], Z Cui[2], X Li[2], Y Wu[3], A Girvan[2], P Abada[4]

[1]Eli Lilly & Co, Indianapolis, Indiana, USA, [2]Eli Lilly and Company, Indianapolis, Indiana, USA, [3]Syneos Health, Indianapolis, Indiana, USA, [4]Eli Lilly and Company, Indianapolis, USA

Introduction: Cost considerations are increasingly becoming important in the care of patients with HCC, and may influence treatment decision making. The objective of this study was to describe treatment patterns and evaluate the direct medical costs of HCC to patients and third-party payers.

Methods: This retrospective cohort study analyzed de-identified data from the Truven MarketScan database, which contains longitudinal claims data from more than 175 million patients in the USA. Patients aged 18 or older, initially diagnosed with HCC (identified by ICD-9 and ICD-10 codes) between 2008-2015, with continuous enrolment from 6 months prior through ≥1 month following HCC diagnosis, received anticancer systematic therapy, and had no evidence of liver sarcomas or other cancer diagnoses were eligible for this study. Adjusted for inflation and reported in 2015 US dollars using medical care component of the Consumer Price Index. Descriptive and logistic regression analyses were conducted using SAS v9.2.

Results: A total of 2285 patients were eligible for inclusion: 75.8% male, median age 61 years, 23.7% with evidence of metastatic disease at diagnosis. 1190 (52.1%) patients received first-line sorafenib; as expected, patients who received sorafenib were more likely to be older, insured with Medicare, have metastatic disease, and without liver disease, hepatitis C or cirrhosis than those who did not (all $p \leq 0.001$). Only 18.8% of patients treated with first-line sorafenib received second-line treatment. Concomitant health care use after HCC diagnosis in the study cohort included supportive care (92.5%), pain medications (84.8%), transarterial chemoembolization (52.3%), hepatitis treatments (51.5%), antidepressants (46.9%), and hospice care (27.8%). Hospitalizations occurred in 74.7% of patients (average stay 14 days), and 53.2% had at least one emergency room visit. Patient out-of-pocket costs for first-line treatment were right-skewed (median US$478.50, range $0-$184,818.37), as were third-party payer costs (median US$35,411.96, range $0-983,355.19). Total median costs of care for patients after initial diagnosis through end of follow up was $4431.62 (patient out-of-pocket costs) and $158,057.33 (third-party payer costs). Average monthly patient out-of-pocket ($507.71 vs $618.95) and third-party payer costs ($18,822.45 vs $26,376.53) have both significantly increased over time (patients diagnosed in 2008 vs 2015 respectively, both $p < 0.0001$). Factors associated with higher total all-cause patient out-of-pocket costs included older age, longer time from diagnosis to first-line therapy, and higher number of concomitant medications (all $p < 0.0001$). Factors associated with higher total all-cause payer costs included pre-systematic therapy radiation ($p = 0.005$) or surgery ($p < 0.001$) and higher number of concomitant drugs ($p < 0.0001$), presence of cirrhosis ($p = 0.0003$), longer time to first-line therapy ($p = 0.0004$), presence of hepatitis C ($p = 0.008$), male gender ($p = 0.005$), and having commercial insurance ($p = 0.01$). Total costs of care for patients diagnosed with HCC and for payers are increasing at an average annual rate of 2 and 3.4%, respectively.

Conclusion: Costs of care for patients diagnosed with HCC are increasing, despite the small proportion of patients receiving additional therapy post-progression on sorafenib. The majority of HCC patients receive supportive care and experience hospitalizations and emergency room care; there is a need for more effective treatments that are better able to manage the impact of the disease on patients.

P – 099 Predictive factor for early recurrence of resected hepatocellular carcinoma

T Kato[1], H Noda[2], A Yoshizawa[1], N Kasahara[1], F Watanabe[3], Y Endo[1], Y Kaneda[1], T Rikiyama[4]

[1]Saitama Medical Center, Jichi Medical University, Saitama, Japan, [2]Saitama Medical Center, Jichi Medical University, Saitama, Japan, [3]Saitama Medical Center, Jichi Medical University, Saitama, Japan, [4]Department of Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan

Introduction: Recurrence rate of hepatocellular carcinoma (HCC) after surgical resection is over 10% per year, and it reaches 70-80% after 5 years. Early recurrence after hepatectomy occurs in some patients, but its risk factors have not been clarified yet. We carried out to clarify the risk factors of early recurrence after hepatectomy for HCC.

Methods: We reviewed 107 patients with surgically resected HCC in Saitama Medical Center, Jichi Medical University between January 2008 and February 2018. Two patients who did not underwent enhanced computed tomography (CT) before surgery, 12 patients who developed multiple synchronous HCC, 4 patients who took warfarin, 4 patients who died of other diseases, and 5 patients whose postoperative follow-up was less than 12 months were excluded from this study. We reviewed these 80 patients and compared between 17 patients who developed tumor recurrence within a year after hepatectomy named early recurrence (ER) group, and other 63 patients named non-ER group. Retrospectively, we calculated the tumor volume (TV) by 3DCT and greatest tumor dimension (GTD) on enhanced abdominal CT. Then, we calculated the ratio between preoperative serum AFP and TV (AFP/TV), and GTD (AFP/GTD), and the ratio between preoperative PIVKA-II and TV (PIVKA-II/TV), and GTD (PIVKA-II/GTD). We compared these two groups about the clinicopathological characteristics, including AFP/TV, PIVKA-II/TV, AFP/GTD and PIVKA-II/GTD to investigate the risk factors of ER of HCC after hepatectomy.

Results: Among these 80 cases, 36 patients developed tumor recurrence. Of all, 17 patients developed tumor recurrence within a year. In multivariate analysis, large GTD (Odds ratio OR1.59 (1.09-2.32) $P = 0.0162$) and high values of PIVKA-II/TV (OR 1.01 (1.0-1.01) $p = 0.0037$) are associated with high risk of developing tumor recurrence within a year after hepatectomy.

Conclusion: Large GTD and High PIVKA-II/TV might be a significant new predictive factor for early recurrence after hepatectomy for HCC. We have to do closer follow-up for patients who had large GTD or high PIVKA-II/TV after hepatectomy.

P – 100 Efficacy, safety, and pharmacokinetics of the anti-programmed cell death receptor-1 (PD-1) monoclonal antibody, tislelizumab (BGB-A317) in a phase 2, open-label, multicenter study to investigate in patients with unresectable hepatocellular carcinoma - Trial in progress

A Cheng[1], G Abou-Alfa[2], Z Ren[3], E Assenat[4], A Cubillo[5], S Pluntke[6], L Rimassa[7], P Ross[8], L Wyrwicz[9], J Hou[10], C Li[11], J Wu[12], M Ducreux[13]

[1]Department of Oncology and Internal Medicine, National Taiwan University Hospital, Taipei, Republic of Taiwan, [2]Memorial Sloan Kettering Cancer Center, New York, New York, USA, [3]Zhongshan Hospital, Fudan University, Shanghai, China, [4]CHRU Saint Eloi, Montpellier, France, [5]HM Universitario Sanchinarro, Centro Integral Oncológico Clara Campal (CIOCC), Madrid, Spain, [6]Kliniken Essen-Mitte, Essen, Germany, [7]Humanitas Research Hospital – IRCCS, Rozzano, Italy, [8]Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, UK, [9]Centrum Onkologii-Instytut im. M. Sklodowskiej Curie, Warsaw, Poland, [10]Beigene USA, Inc, Emeryville, California, USA, [11]BeiGene (Beijing) Co., Ltd., Beijing, China, [12]BeiGene USA Inc., Fort Lee, New Jersey, USA, [13]Gustave Roussy Cancer Campus Grand Paris, Villejuif, France

Introduction: Tislelizumab (BGB-A317) is a humanized IgG4 monoclonal antibody with high affinity and specificity for PD-1 that was specifically engineered to minimize FcgR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and had preliminary antitumor effects in patients with solid tumors, including HCC. A recommended dose of tislelizumab administered at 200 mg intravenously (IV) every 3 weeks (Q3W) has been established.

Methods: This phase 2, multicenter study (NCT03419897) was designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics of tislelizumab in patients with previously treated, unresectable HCC. This study will enroll patients who are ≥18 years of age with histologically confirmed locally advanced or unresectable HCC. This includes patients who are not amenable to, or who have relapsed after, locoregional therapy and are not amenable to a curative treatment approach. To be enrolled, patients must also have a Child-Pugh classification Grade A, ECOG performance status ≤1 and must have experienced sorafenib, regorafenib, or chemotherapy in 1 – 2 lines of prior systemic therapy. Radiological assessment of tumor-response status will be performed every 6 weeks in the first 18 weeks then every 9 weeks thereafter. Patients with prior PD-1 or PD-L1 treatment or who received sorafenib or regorafenib within 14 days of the first study drug administration will be excluded. A total of 228 patients worldwide will be treated with tislelizumab 200 mg IV Q3W. The primary endpoint of this study is objective response rate assessed by Independent Review Committee per RECISIT v1.1; secondary endpoints include duration of response, progression-free survival, disease control rate, clinical benefit rate, overall survival, quality-of-life

outcomes, and assessment of the tislelizumab pharmacokinetic and safety/tolerability profiles. Exploratory endpoints include assessment of potential biomarkers, assessment of host immunogenicity to tislelizumab. Safety/tolerability assessments will include monitoring of adverse events (AEs), including immune-related AEs, as well as physical examinations, vital signs, and electrocardiograms.

P – 101 HEPANOVA: A phase 2 trial of tumor treating fields concomitant with sorafenib for advanced hepatocellular carcinoma - Trial in progress

A Grosu[1], J Strouthos[2], T Brunner[1], U Weinberg[3]

[1]Department of Radiation Oncology, University Hospital Freiburg, Freiburg, Germany, [2]Medical Center – University of Freiburg, Freiburg, Germany, [3]Novocure, Root D4, Switzerland

Introduction: Tumor Treating Fields (TTFields) are a non-invasive, regional antimitotic treatment modality, which has been approved for the treatment of glioblastoma by the FDA. TTFields predominantly act by disrupting the formation of the mitotic spindle during metaphase. TTFields are delivered at specific frequencies (150 to 200 KHz) to the tumor region through transducer arrays placed on the skin surface. TTFields (200 KHz) are approved for the treatment of patients with recurrent and newly diagnosed glioblastoma. TTFields were effective in multiple preclinical models of hepatocellular carcinoma (HCC), leading to a significant increase in cell death. The optimal TTFields frequency leading to the highest reduction in cell counts was 150 kHz for both HepG2 and Huh-7D12 cells. TTFields at 150 kHz led to 53-64% reduction in cell counts and over 70% reduction in the clonogenic potential. The combined treatment of TTFields and Sorafenib led to a significant reduction in the number of HepG2 and Huh-7D12 cells as compared to each treatment alone. The Phase 2 HEPANOVA study is the first trial of TTFields in HCC patients, and is designed to test the safety and efficacy of adding TTFields to sorafenib in advanced HCC.

Methods: Patients (N = 25) with unresectable HCC who are not amenable to any local treatment will be enrolled in this prospective, single-arm study. The study enrolls patients with ECOG score of 0-2 and Barcelona clinic liver cancer (BCLC) stage 0-C. Patients must have a measurable disease per RECIST Criteria. Having implanted electronic devices in the torso is exclusionary. Sorafenib will be administered at standard dose (400 mg daily). TTFields (150 kHz) will be delivered for 18 hours/day until local disease progression per RECIST Criteria. Transducer arrays are placed on the back and front of the patient to deliver the highest field intensities to the hepatic region. Clinical follow-up will be performed q4w, and a CT/MRI scan q12w. Following disease progression in the liver, patients will discontinue TTFields and be followed monthly for survival. Overall response rate will be the primary endpoint and in-field control rate, progression-free survival rate at 12 month (PFS12), OS rate at 1 year and toxicity will all be secondary endpoints. Sample size was calculated using an Exact test for proportions considering the weighted average of ORR of patients who had either complete or partial response per RECIST criteria in historical studies with sorafenib is 4.5%. A sample size of 25 patients was required to achieve a power of approximately 80% at a one-sided alpha level of 0.05 using a single sample Exact test for proportions.

P – 102 A retrospective review of neutrophil-lymphocyte ratio as a predictive prognostic marker in upper gastrointestinal cancers in three UK hospitals over a nine year period

N Wreglesworth[1], C Roberts[2], P Innominato[1]

[1]North Wales Cancer Centre, Bangor, UK, [2]Betsi Cadwaladr University Health Board, University of Wales, Bangor, UK

Introduction: Several studies suggest the predictive role of a high neutrophil-to-lymphocyte ratio (NLR) leading to poor pan-cancer prognosis. We explored the predictive value of NLR in a cohort of upper GI cancer patients but also the potential additive predictive effects to NLR of platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR) and total protein (TPROT). We retrospectively reviewed data from a cohort of consecutive upper GI cancer patients collected over a 9 year period (2007 to 2016).

Methods: We reviewed our digital prescribing system across three UK based hospitals. All the patients included were referred to oncology services after their initial diagnosis. The data BMI, eGFR, PS, chemotherapy details, presence of metastases, sex and blood parameters were retrieved before chemotherapy started. Overall survival (OS) was the primary outcome. Multivariate Cox proportional hazard models were built using NLR as either quantitative or median-split variable.

Results: Our cohort included 302 cancer patients with: 113(37.3%) of the oesophagus, 84(27.6%) of the stomach, and 105(34.5%) of the pancreas. The median age of the patients was 66 years old (range 30-85). There was a 1:2 female:male ratio. Of these patients; 92(30%) were categorised as metastatic (M1) and 262(86.2%) had died at the time of analysis (March 2017). Over a nine-year period across three cancer locations chemotherapy regimens changed so we included number of cycles of chemotherapy the patients had received, the mean being 4.7 (0-35). Median NLR was 2.57 (a similar figure to previous studies), and respective 25th and 75th percentiles were 1.34 and 5.29. A higher than 2.57 NLR was significantly and robustly associated to a poor prognosis independently of age, location of primary, eGFR, number of chemotherapy cycles, presence of metastases, sex, BMI and PS (where available) (HR: 1.445; p = 0.018). Thus, median OS was 15.14 months [95% confidence limits (CL): 11.45-18.84] in the group of patients with low NLR in comparison to 7.524 [6.02-9.02] in patients with high NLR. The difference in outcomes according to NLR was comparable in each cancer separately: oesophagus, median OS dropping from 12.6 to 9 months; stomach, 18.0 to 8.7; pancreas, 13.0 to 5.3 ($p < 0.001$). We could not identify any individual or additive effects of PLR, MLR or TPROT either as continuous or quartile-categorized data.

Conclusion: NLR appears a reliable prognostic predictor in this cohort of upper GI cancers. There was no apparent effect of PLR, MLR nor TPROT in our study. A high NLR suggests significantly poorer prognosis. In this study, results are similar amongst all three upper GI cancers investigated over a long-time period during which chemotherapy regimens were variable. The results appear independent of other commonly associated poor prognostic indicators such as presences of metastases, BMI, eGFR and age. Baseline NLR is confirmed here as a simple measure to predict prognosis in upper GI oncology patients about to embark on chemotherapy. Additional research is warranted to assess such an easy marker with regards to prediction of optimal therapeutic option and as a time-dependent variable, to substantiate its relevance in potentially influencing clinical practice.

P – 103 The prospective multicenter study of relation between 5-HIAA/substance P plasma concentration transition and nausea/vomiting in patients with gastrointestinal cancer receiving moderately emetogenic chemotherapy

T Muranaka[1], Y Komatsu[2], S Ohnishi[3], M Yagisawa[1], K Sawada[1], Y Kawamoto[1], H Nakatsumi[1], S Yuki[3], M Dazai[4], T Saiki[5], A Ishiguro[5], M Tateyama[6], K Ono[7], N Sakamoto[8]

[1]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [2]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [3]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [4]Department of Gastroenterology, Sapporo Medical Center NTT EC, Sapporo, Japan, [5]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan, [6]Department of Internal Medicine, Tomakomai Nisshou Hospital, Tomakomai, Japan, [7]Department of Biostatistics, Hokkaido University Hospital Clinical Research and Medical Innovation Center, Sapporo, Japan, [8]Department of Gastroenterology and Hepatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Introduction: Chemotherapy-induced nausea and vomiting (CINV) is one of the serious adverse events after anti-cancer chemotherapy. We usually administrate 5-HT3 receptor antagonist to prevent from acute CINV, and an aprepitant, which is a NK1 receptor antagonist to block substance P, to prevent from delayed CINV. There are some reports that plasma substance P concentration raised up after administration of high dose cisplatin which is categorized as high emetogenic chemotherapy (HEC), but there are few reports to check their transition in patients after receiving oxaliplatin or irinotecan which is categorized as moderately emetogenic chemotherapy (MEC).

Methods: This is a multicenter exploratory observational research in Japanese patients receiving chemotherapy for gastrointestinal cancer registered as UMIN000021072. The key eligibility criteria are as follows: 1) Diagnosed gastrointestinal cancer; 2) Planned to receive high dose cisplatin (for up to five patients in cohort 1, for validation of measurement), oxaliplatin or irinotecan; 3) 20 years of age or older; 4) ECOG PS of 0, 1 or 2; 5) Keeping adequate major organ function. By sampling the patients' blood before and 4, 24, 48, 72 and 96 hours after HEC/MEC administration, we measured the changes in plasma concentration of substance P/5-HIAA after chemotherapy, and survey the relevance of plasma concentrations of substance P/5-HIAA and CINV measured by visual analogue scale (VAS). We defined over 25 millimeter in 100 millimeter by patients-oriented VAS as positive nausea, and recorded the number of vomiting. Plasma 5-HIAA concentration was measured by SRL Inc. and plasma substance P concentration was measured by Kyowa Medex Co., Ltd.

Results: We could measure plasma concentration of both plasma 5-HIAA and Substance P concentration in all 3 consecutive HEC cases, and 36 patients were enrolled who received MEC for gastric cancer or colorectal cancer. 5 patients were excluded (one was violated exclusion criteria, 4 did not write VAS), and 31 patients were fully analyzed. Delayed CINV was occurred in 15 of 31 patients. The change ratio (%) of plasma concentration of 5-HIAA in 4, 24, 48, 72 and 96 hours after MEC administration compared with the baseline in patients "without" vs "with" delayed CINV were 131.04 vs 63.33 (p = 0.0086), -2.17 vs 7.14 (p = 0.46), -10.17 vs 9.30 (p = 0.12), 5.17 vs 0.00 (p = 1.00), 5.26 vs 2.29 (p = 0.56), respectively. Those of substance P were 9.46 vs 21.83 (p = 0.61), -0.01 vs -0.30 (p = 0.97), -2.74 vs -2.83 (p = 0.99), 2.83 vs 2.78 (p = 1.00), 4.59 vs -1.30 (p = 0.59), respectively.

Conclusion: Small ratio between 5-HIAA 4 hours after MEC administration and before might be an early predictive marker of delayed CINV. Plasma concentration of SP may not reflect CINV due to substance P.

P – 104 Amrubicin in patients with platinum-refractory metastatic neuroendocrine carcinoma of the gastrointestinal tract

H Osumi[1], E Shinozaki[1], K Chin[1], D Takahari[2], M Ogura[3], T Ichimura[2], T Wakatsuki[4], Y Ota[5], I Nakayama[2], M Suenaga[1], K Yamaguchi[6]

[1]Department of Gastroenterology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Japan, [2]Cancer Institute Hospital, Koto-ku, Japan, [3]Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Japan, [4]Cancer Institute Hospital Department of Gastroenterology, Koto-ku, Japan, [5]Cancer Institute Hospital, Japanese Foundation of Cancer Research, Tokyo, Japan, [6]Department of Gastroenterology Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-ku, Japan

Introduction: Patients with gastrointestinal neuroendocrine carcinoma (GI-NEC) have a poor prognosis. Platinum-based combination chemotherapy is commonly used as first-line treatment; however, there are a few reports about the role of amrubicin (AMR) and salvage chemotherapy for GI-NEC. This study aimed to analyze the efficacy and safety of AMR monotherapy in patients with platinum-refractory GI-NEC.

Methods: We retrospectively analyzed platinum-refractory GI-NEC patients who received AMR monotherapy between April 2012 and September 2017 at the Cancer Institute Hospital. The dose of AMR administered was 30–45 mg/m2 on days 1–3 every 3–4 weeks. We evaluated the overall response rate (ORR) according to the RESICT ver1.1, progression-free survival (PFS), overall survival (OS), and adverse events by CTCAE ver 4.0. OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. All reported P values were the result of two-sided tests; $P < 0.05$ was considered significant.

Results: 14 males and 3 females (median age, 65 years (range, 60–75)) were received platinum-based chemotherapy before AMR monotherapy. (cisplatin plus irinotecan (n = 14, 82.3%), cisplatin plus etoposide (n = 1, 5.9%), and fluoropyrimidine plus platinum (n = 2, 11.8%) Primary sites of NEC included stomach (n = 10, 58.8%), colorectal (n = 3, 17.6%), esophagus (n = 3, 17.6%), and duodenum (n = 1, 5.9%). The median cycles of AMR administration were 3 (range, 1-15). The ORR rate was 5.8%, the median PFS was 2.1 months (1.4–6.9), and the median OS was 13.7 months (6.9–17.2). Grade 3/4 neutropenia occurred in 41.1% of patients and febrile neutropenia occurred in 5.8%. Other non-hematological toxicities were not severe and treatment related deaths were not observed. 11 patients received the subsequent chemotherapy after AMR and they had significantly longer OS than those who couldn't be received the subsequent chemotherapy. (17.2 months (5.9–NA) vs. 8.9 months (1.1–NA), p = 0.0427).

Conclusion: AMR showed minimum activity and safety when used for the treatment of platinum-refractory GI-NEC. Neutropenia was encountered as the most serious adverse event. It should be considered to perform the subsequent chemotherapy after AMR if possible.

P – 105 Clinical outcomes and toxicity of chemoradiation with IMRT for anal cancer

J Fonseca, N Ferreira, C Viveiros, G Fernandez, C Travancinha, L Mirones, S Esteves, I Rosa, M Limbert, J Freire, F Santos

Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal

Introduction: Anal carcinoma is an uncommon diagnosis whose treatment carries risks of significant morbidity due to the complex target volume and multiple adjacent organs at risk. Intensity modulated radiation therapy (IMRT) offers the potential to reduce toxicity while maintaining or improving the dose distribution to the target volume. Our purpose was to evaluate the outcomes of our center since the implementation of IMRT in the treatment of squamous cell carcinoma (SCC) of the anal canal.

Methods: Retrospective single-center study of patients with SCC of the anal canal treated with IMRT between 2011 and 2015. Overall survival (OS), disease free survival (DFS), colostomy free survival (CFS) and local control (LC) were calculated by the Kaplan-Meier method. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events v4.0.

Results: Thirty-five patients were included (males 78%, females 22%, median age 64 years). T stage distribution was Tx 8%, T1 6%, T2 40%, T3 40% and T4 6%. 63% had nodal involvement. 11% were HIV positive. Median follow-up time for surviving patients was 3 years (range 1-7 years). IMRT was used in all patients with median doses to the pelvis of 45 Gy and 59 Gy to the primary tumor, using a sequential boost. Most patients (95%) were treated with chemoradiation (CRT) and only 2 patients received RT alone. The most frequent chemotherapy regimen was 5-fluoracil and mytomycin C (94%). Median overall treatment time was 44 days. Three patients (9%) had a treatment break and one patient did not complete treatment due to severe acute toxicity. Thirty-two patients (91%) had complete response. Three patients had persistent disease and three patients developed local recurrence. These patients had abdominoperineal resection (APR), except one who refused surgery. Three-year LC was 82%. Three patients (9%) developed distant metastases as the site of first failure. Three-year OS, DFS and CFS were 84, 77% and 84%, respectively. On univariate analysis, age, sex, T stage, HIV status or nodal disease had no impact on the outcomes. Grade 3 acute skin toxicity was observed in 13 patients (37%) and one patient had grade 4 toxicity. Grades 1-2 gastrointestinal (GI) toxicity occurred in 14 patients (40%) and grade 3 toxicity in one patient. Genitourinary (GU) grade 1 acute toxicity was observed in 6 patients (17%). Major late GI toxicity (grade 3-4) was reported in 2 patients (6%) and grade 2 in 7 patients (20%). There was no relevant late skin or GU toxicity.

Conclusion: Chemoradiation with IMRT achieves good clinical outcomes and low treatment-related morbidity with minor treatment interruptions and acceptable late sequelae. The small sample size may explain the lack of impact of the tested variables on univariate analysis and requires longer follow-up of our patients.

P – 106 Prognostic factors in patients with advanced biliary tract cancer treated with first-line gemcitabine plus cisplatin chemotherapy: retrospective analysis of 142 patients

H Engin

Bulent Ecevit University School of Medicine Department of Medical Oncology, Zonguldak, Turkey

Introduction: Biliary tract cancer (BTC) is a heterogeneous group comprising intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer. Although gemcitabine plus cisplatin (GEMCIS) has been established as the standard first-line chemotherapy for advanced biliary tract cancer based on the ABC-02 trial, more data are needed to define the clinical course of BTC and its prognostic factors with the standard GEMCIS treatment.

Methods: Between May 2010 and June 2017, 142 patients with histologically documented cholangiocarcinoma and gallbladder cancer were treated with first-line GEMCIS in Bülent Ecevit University Oncology Center, Zonguldak, Turkey.

Results: In 97 patients with measurable disease (68.3%), the objective response rate was 19.6% (n = 19) and there was no significant difference between primary tumor sites (p = 0.52). With a median follow-up duration of 28.2 months (95% CI 23.8-31.5), the median progression-free survival (PFS) and overall survival (OS) were 6.3 months (95% CI 5.2-7.1) and 12.1 months (95% CI 10.6-12.9), respectively. In multivariate analysis, male gender (female versus male, hazard ratio HR 0.73), baseline CA 19-9 level (elevated versus normal, HR 1.31), baseline CEA level (elevated versus normal, HR 1.27), metastatic disease (versus locally advanced disease, HR 1.82), poor performance status (2 versus 0-1, HR 1.35), and measurable disease by RECIST criteria (versus non-measurable, HR 1.40) were significantly associated with a poorer OS (all $p < 0.05$).

Conclusion: Our retrospective analysis found comparable efficacy outcomes to the ABC-02 trial. The prognostic factors identified here may help to predict clinical outcomes and design future clinical trials for advanced BTC.

P – 107 Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: A single center experience

H Engin

Bulent Ecevit University School of Medicine Department of Medical Oncology, Zonguldak, Turkey

Introduction: Few data are available on second-line chemotherapy (CT2) for advanced biliary tract cancer (ABTC). The aim of this retrospective study was to describe the CT2 regimens used, the response rates, and the outcomes of patients treated with various CT2 regimens.

Methods: Patients who received CT2 for ABTC at Bülent Ecevit University Oncology Institute after the failure of the gemcitabine-platinum combination were retrospectively studied. Progression-free survival (PFS) and overall survival (OS) were estimated with the Kaplan-Meier method. Cox models were used for multivariate analyses.

Results: Among 142 patients who received first-line chemotherapy (CT1) for ABTC, 96 received CT2: 5-fluorouracil (5-FU) and irinotecan (n = 30), 5-FU and oxaliplatin (n = 25), 5-FU and cisplatin (n = 16), 5-FU or capecitabine (n = 25). Among the 60 assessable patients, there were 7 partial responses and 17 stabilizations. After a median follow-up of 23.4 months, the median PFS and OS were 3.3 and 7.0 months, respectively. There was no significant difference in PFS or OS between CT2 regimens. Fluoropyrimidine-based doublet chemotherapy was not superior to fluoropyrimidine alone in terms of OS and PFS. In a multivariate analysis, a performance status of 0 to 1, disease control with CT1, a carbohydrate antigen 19-9 (CA 19-9) level $\leq$ 300 IU/mL, and age <50 years were significantly associated with longer PFS and OS.

Conclusion: CT2 might provide disease control for selected patients with ABTC after the failure of gemcitabine-platinum, but the prognosis remains poor. No particular regimen seems superior to others.

P – 108 Effectiveness of radical radiochemotherapy (RCT) in patients with anal cancer managed at the Bank of Cyprus Oncology Centre: 15 years' experience

V Vassiliou[1], M Pittaka[2], A Gudenian[3], K Michailidou[4], L Michael[5], I Constantinou[6], P Kountourakis[6], D Andreopoulos[6], M Talias[7], M Kantaris[6], M Charalambous[7]

[1]Bank of Cyprus Oncology Centre, Strovolos, Cyprus, [2]Limassol General Hospital, Limassol, Cyprus, [3]Larnaca General Hospital, Larnaca, Cyprus, [4]Department of Electron Microscopy/Molecular Pathology, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, [5]University of Patras Medical School, Patras, Greece, [6]Bank of Cyprus Oncology Centre, Nicosia, Cyprus, [7]Open University Cyprus, Nicosia, Cyprus

Introduction: Anal cancers are rare, accounting for 2% of gastrointestinal malignancies. Their incidence is increasing, particularly in women. The current standard of care is concurrent RCT. Overall 5-year survival rates reach 75%, colostomy free survival rate is 65-70% and complete pathological response rates reach 90%. While treatment outcomes are excellent, associated toxicities are high. Clinician-reported acute grade 3/4 toxicities can be as high as 80% (1).

Methods: The files of patients diagnosed with non-metastatic anal cancer managed with radical RCT were retrospectively reviewed in respect to effectiveness and toxicity. All patients underwent staging MRI prior and post RCT. CT scans were performed prior to RCT onset, 6 monthly up to 2 years and yearly up to 5 years. Patients were clinically evaluated 3 monthly for the first 2 years and 6 monthly thereafter. Toxicity was recorded by using CTCAEv4 criteria. Statistical analysis of time-to-event data was done using Kaplan-Meier plots.

Results: From 2003 to 2017 sixty-nine patients (38 females, 31 males) received RCT with 2 cycles of MMC-5FU. Radiotherapy dose ranged between 5220-5940cGy. Median age was 63 years. Two patients had stage I disease, 22 stage II, 9 stage IIIA and 36 stage IIIB. IMRT technique was used in 56% of patients and conformal RT (CRT) in 44% of patients. Median follow up (FU) was 31 months. Complete clinical response rate at 3 months was 84%. Three-year overall survival (OS), Disease free survival (DFS), Locoregional disease free survival (LDFS), metastasis free survival (MFS) and colostomy free survival (CFS) rates were 85%, 82%, 87%, 89% and 82% respectively. 3 year OS was 100% for stage I, 89.5% for stage II, 83.3% for stage IIIA and 75.2% for stage IIIB patients. Rates remained unchanged after 3y FU. No significant differences in survivals were noted between patients managed with IMRT vs CRT, apart from OS that favoured those managed with IMRT ($p < 0.023$). Acute grade 3/4 toxicity rates were: skin dermatitis 43.5%, diarrhoea 10.1%, proctitis 39.1%, cystitis-urinary frequency 2.8%, neutropenic fever 7.2%, thrombocytopenia 2.9%, and Leukopenia 13%. Late grade 3/4 toxicity rates were minimal with 2 patients developing a fistula (2.8%) and 3 anal stenosis (3.3%). One patient developed a secondary malignancy (sarcoma) at 4 years of FU. Acute grade 3 dermatitis was more frequent in patients managed with CRT (53.3% vs 35.9%) whereas no differences were noted in acute grade 3 diarrhoea (10% each). Grade III leukopenia was more frequent in CRT patients.

Conclusion: We herein report the results of a single institutional study involving patients with anal carcinoma. Survival rates are comparable to those of published literature data. An interesting characteristic of this study is the possibility to compare the results between patients managed with CRT vs IMRT. Interestingly OS was statistically significantly higher in patients treated with IMRT. Moreover, grade 3/4 acute toxicity rates were higher in CRT patients.

P – 109 Detection and management of hyperglycaemia in oncology patients receiving systemic anti-cancer therapy

L Morrison[1], R Gillmore[2], R Pierce[3]

[1]The Royal Free Hospital, London, UK, [2]Royal Free London NHS Foundation Trust, London, UK, [3]Royal Free Hospital, London, UK

Introduction: Hyperglycaemia is a significant cause of morbidity in cancer patients accounting for up to 5% of emergency oncology admissions (1). The incidence of hyperglycaemia in non-diabetic patients receiving anti-cancer therapy has been shown to be as high as 11.6% (2). One significant factor is the high doses of steroids administered either as part of the systemic anti-cancer treatment to control nausea and vomiting, or to palliate other cancer-related symptoms such as pain or anorexia. Patients with gastro-intestinal (GI) malignancies, in particular, often receive high doses of steroids as part of their chemotherapy regimens eg for bowel cancer FOLFOX, FOLFIRI and FOLFOXIRI treatments, platinum-containing regimes for patients with upper GI cancers and for the pancreas population FOLFIRINOX treatment. There is currently no consensus regarding blood glucose level (BGL) monitoring in patients receiving anti-cancer treatments. We therefore carried out a prospective audit aiming to identify the prevalence of abnormal blood sugars using random capillary blood glucose measurements.

Methods: During a three-week period, all patients attending the oncology outpatient clinic for systemic anti-cancer treatments had their blood sugar checked using a capillary blood glucose machine. The rationale for using BGL is that it can be more reliable than HBA1C in patients with anaemia or in those who have recently been commenced on steroids (3). Blood glucose diagnostic cut off figures were used as per diabetes UK guidelines for normal, borderline diabetic, diabetic values. Information on primary tumour type, anti-cancer treatment, cycle number, steroid dose and pre-existing diabetic diagnosis were collected.

Results: A total of 166 patients had their BGL checked during the time period. 18 (11%) had a blood sugar diagnostic of diabetes mellitus (DM), 25 (15%) had a borderline blood sugar and 123 (74%) patients had normal blood sugars. Of the 43 patients with an abnormal result 24 (56%) were NOT known to have diabetes. Furthermore, in the group with blood sugars diagnostic of diabetes 4 (22%) were NOT known to be diabetic and in the borderline group 20 (80%) were NOT known to have diabetes. One patient was admitted to hospital as a direct result of the BGL measurement during this audit. The highest proportion of abnormal results was in the GI cancer group (24% of the total cohort). Within this cohort 20% had malignancies of pancreatic origin and 80% were colorectal in origin. Treatment regimens included FOLFOX (80%) and FOLFIRI (20%).

Conclusion: 10 (27%) GI patients and 43 (25.8%) of all oncology patients tested had abnormal blood sugars showing either high risk of developing or consistent with a diagnosis of DM. All of these patients were receiving steroids as part of their anti-cancer treatments. NICE advocate frequent monitoring of all patients on high dose steroids. We suggest that routine BGL monitoring of all patients on systemic anti-cancer therapy and early liaison with the local diabetes team could prevent unnecessary hospital admission and reduce associated morbidity. As well as one direct admission during this audit, 9 oncology patients were admitted to our unit over a twelve-month period with complications related to hyperglycaemia.

P – 110 Squamous cell carcinoma of the anal canal and the results of radical treatment with intensity-modulated radiotherapy

I Oblak[1], V Velenik[1], F Anderluh[1], E Brecelj[1], J But-Hadzic[1], A Secerov-Ermenc[2], A Jeromen[1]

[1]Institute of Oncology, Ljubljana, Slovenia, [2]institute of oncology, Ljubljana, Slovenia

Introduction: Anal canal cancer is predominantly a locoregional disease and distant metastases are found in only 5–10% of the patients. The treatment of choice is radical radiochemotherapy with the sphincter preservation rates of around 80%, even in cases with locally advanced disease. Surgery is a salvage treatment used only in cases of residual or recurrent disease after radiochemotherapy and for complications of radiotherapy. Before 2013, in our institution 3D conformal radiotherapy using a four-field box technique on a 15 MV linear accelerator, was used. Several authors have reported that intensity-modulated radiation therapy (IMRT) for anal cancer can dramatically reduce rates of acute and late adverse effects, while maintaining excellent rates of cure and sphincter preservation. The aim of the study was to retrospectively asses the results of treatment with IMRT and concomitant chemotherapy with fluoropyrimidine derivatives and mitomycin C in patients with squamous cell carcinoma of the anal canal, who were treated at our institution.

Methods: Between January 2013 and January 2018, 48 (38 female, 10 male) patients with anal canal cancer were treated with radical intent. Patients were irradiated with IMRT with simultaneous integrated boost technique in 30 fractions to the dose of 45 Gy to the elective volume and 54 Gy or 57 Gy (in cases of bulky disease with tumor diameter of more than 3 cm) to the tumor bed. Actuarial rates of locoregional control (LRC), disease-free survival (DFS), disease-specific survival (DSS), overall survival (OS), colostomy-free survival (CFS) and the rates of acute and chronic side-effects were estimated.

Results: Forty-four (93.7%) patients completed treatment according to the protocol. The median follow-up time in 44 (91.7%) survivors was 23 months (range 6-55 months). At 2-years LRC, DFS, DSS, OS and CFS rates were 80.3%, 80.3%, 94.8%, 94.8% and 87.1%, respectively. The most frequent acute side effect of the treatment was radiodermatitis (grade 3 in 79.2% of patients). Dysuria, diarrhoea, infection and hematologic side effects grade 3 were noticed in 4.2%, 6.3%, 10.4% and 8.3% of patients, respectively. Grade 3 late radiation side effects according to the LENT-SOMA scoring system were observed in 5 (10.4%) patients. The most frequent late side effects grade 3 were skin changes and anal sphincter dysfunction with incontinence in 4 (8.3%) and 2 (4.2%) of colostomy-free survivors, respectively.

Conclusion: Radiotherapy with IMRT and concurrent chemotherapy with fluoropyrimidines and mitomycin C is feasible and with acceptable toxicity. By comparing our present results of acute toxicity with the results of 3D conformal radiotherapy toxicity published in 2012, we can conclude that treatment with IMRT is less toxic. However, further analysis with longer follow up is needed for the comparison of late side effects.

P – 111

WITHDRAWN

P – 112 **Prevalence and genotyping of HPV in anal squamous cell carcinoma**

S Iseas[1], M Coraglio[2], J Gonzalez[3], E Slutsky[4], D Carvajal[4], A Cabanne[5], M Carballido[1], G Mendez[1], M Picconi[3], E Roca[1]

[1]*Hospital de Gastroenterología Bonorino Udaondo-Oncology Unit, Buenos Aires, Argentina,* [2]*Hospital de Gastroenterología Bonorino Udaondo-Coloproctology Unit, Buenos Aires, Argentina,* [3]*Oncogenic Virus Department, National Institute of Infectious Diseases, ANLIS "Dr. Malbrán", Caba, Argentina,* [4]*Hospital de Gastroenterología Bonorino Udaondo-Oncology Unit, Caba, Argentina,* [5]*Hospital de Gastroenterología Bonorino Udaondo-Pathology Unit, Buenos Aires, Argentina*

Introduction: Anal squamous cell carcinomas (ASCC) account for approximately 2% of all gastrointestinal malignancies. The annual incidence of ASCC has increased by 2.9% per year in recent decades. In 2012, according to GLOBOCAN, 40,000 cases of anal cancer were reported worldwide, 35,000 (87%) attributable to HPV, being HPV-16 the most frequent serotype. A highly active HPV infection is associated with a more immunogenic tumor microenvironment with strong expression of immune markers, such as CD8+ and PD- 1+ tumor infiltrating lymphocytes (TILs), PD-L1+, FOXP3+ Tregs, caspase 8.

Methods: 52 FFPE samples of patients with histologically confirmed ASCC were analyzed for HPV genotyping. The DNA, from the histological sections (previous step of deparaffinization) and the swab cells were purified using the QIAamp DNA Mini Kit that included 36 HPV genotypes. A retrospective review of the medical records was performed to correlate clinical data and treatment response with HPV results. The FFPE samples analyzed were exclusively obtained from the primary tumor. The selection was identified as a random sample of patients with FFPE available for HPV analysis, but were not selected by behavioral risk groups as men who have sex with men (MSM), a history of cancer of the cervix or vulva, immunosuppressed as HIV + or history of organ transplantation.

Results: Median age 59 (31-80y); gender: F 35/52(65%). HIV+: 17% (9/52). HPV was detected in 84%(44/52) of which 80% had HPV16+. Multiple-serotype HPV infection was detected in 13% of the samples that included other high-risk serotypes 18, 33, 42, 44, 45, 52, 54, 72. Serotypes of low oncogenic risk as HPV6-11 were detected in 5% of the cases. We obtained follow up data from 42/52 cases treated in our institution. The initial treatment approach was Local Resection: 3 patients, Definitive CRT: MMC+5FU:17pts (5-FU 1000 mg/m2/d IV d1–4 and 29–32 mitomycin 10 mg/m2/d IV bolus d1) MMC+Cape: 3pts. (capecitabine 825 mg/m2 PO BID days 1–5 weekly-mitomycin 12 mg/m2 IV bolus day 1), CDDP+5FU: 15pts. (5-FU 1000 mg/m2/d IV d1–4 and 29–32 CDDP 75 mg/m2/d IV bolus d1) and Palliative Care treatment 4 pts. Response assessment after CRT was Complete Response: 80% (28/35), Partial Response: 14% (6/35) and Disease Progression: 6% (2/35). In the subgroup of HPV+ patients, CR was observed in 82% (23/28). Median OS in complete responder was 54 m (14-190m) and OS in non-complete responders was 18m (16-52m) p = 0.003. Median Colostomy free survival in CR was 46m (14-190m).

Conclusion: The HPV prevalence in our cohort is similar to that described in other regions. The serotype spectrum is limited with a remarkable predominance of HPV16 and a minority of multiple infections. The presence of HPV 6 and 11 reconfirms the transformative potential of these low risk viruses in the anus. There is still a certain lack of homogeneity in the response rate of HPV+, probably related to the immune response in the host. Collaborative efforts for these rare types of cancer are needed towards a broad comprehensive classification for both patient staging and improved treatment strategies.

P – 113

WITHDRAWN

P – 114 **The prognostic values of tumor characteristics and clinical factors of neuroendocrine tumors: Two centers experience**

E Sezer[1], K Eser[2], V Ercolak[3], Y Acıkgoz[4], B Ozturk[5]

[1]*Mersin University Medical Faculty, Department of Medical Oncology, Mersin, Turkey,* [2]*Mersin university Medical Faculty, Department of Medical Oncology, Mersin, Turkey,* [3]*Mersin University Medical Faculty Dept. of Medical Oncology, Mersin, Turkey,* [4]*Health Sciences University Ankara Numune Education and Research Hospital Dept. of Medical Oncology, Ankara, Turkey,* [5]*Health Sciences University, Antalya Education and Research Hospital, Division of Medical Oncology, Antalya, Turkey*

Introduction: Neuroendocrine tumors are large, heterogeneous tumors. Prognostic factors were not clearly established yet. We aimed to investigate clinical and pathological findings of our pts with NETs and detect most reliable factor on prognosis of NETs.

Methods: A retrospective study with neuroendocrine tumors (NETs) performed in two different centers. The effects of clinic and pathologic factors on survival were investigated using the log rank test. The Kaplan- Meier survival estimates were calculated. Cox regression analyses were performed to investigate predictive factors on survival.

Results: A total of 100 (F/M=36/64) pts were included to study. Median age was 59±14.6 (range: 31-90) years. Most of pts were gastro-entero-pancreatic (GEPNET) (57%), long and other localizations were 20 and 15%, respectively. According to WHO grading system, 27 pts were NET G1, 24 pts, NET G2, 37 pts were neuroendocrine carcinoma (NEC). At the time of diagnosis, 33% pts were metastatic. Median PFS was 9.2±2.3 and OS was 20.1±8.4 months. According to tumor grades, median PSF times

were 18.5, 9.2 and 7.3 months (log rank p = 0.066) and OS were 103.3, 53.1 and 10.1 months (log rank p < 0.0001), respectively. Median PFS and OS were longer in GEPNETs than lung and other NETs (log rank p < 0.05). Only tumor grade was found as an independent prognostic factor for OS; age, sex, primary tumor localization and tumor stage had no significant effect on survival.

Conclusion: Despite of rarity of disease, we collected a total of 100 pts with NETs data. Most of pts were GEPNET. Tumor grade was independent prognostic factor on survival. GEPNETs and grade 1 tumors had best survival rates.

P – 115 Starting a tumor board meeting at a public sector hospital – problems faced and its impact on patient care: A lower middle income country experience

A Malik[1], M Afzal[2]

[1]Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan, [2]Lahore General Hosptial, Lahore, Pakistan

Introduction: The importance of tumor board meeting in care or cancer patients cannot be ignored. No dedicated tumor boards are held in any public sector hospital in Lahore. We decided to start a regular tumor board in a public sector hospital in Pakistan. We will discuss the problems faced in conducting these meetings and how they affected patient management.

Methods: Department of Surgery at Lahore General Hospital has started conducting Tumor board meetings on monthly basis since Jan 2017. We share our one year experience of the meetings done and problems faced in conducting those meetings.

Results: A total of 9 MDT Meetings were conducted in which 26 patients suffering from different malignancies were discussed for a better treatment plan. Patients discussed included 10 pre operative and 16 post operative patients respectively. Specialty wise 12 patients were from colorectal, 09 patients were from Hepatobiliary, 02 patients were suffering from Endocrine tumors, 01 patient with malignancy of neuromuscular origin and 02 with CA Esophagus. The biggest issue faced by us was getting all the departments on board for conducting the meetings. We lack a dedicated oncology department at LGH and had to request involvement of personnel from INMOL for decision making. Unfortunately only 5 out of 9 meetings were attended by an oncologist. Similarly pathologist was present in 8 out of 9 meetings. Radiology and surgery had a 100 attendance at the tumor board meetings. Pathological slides were not available for any patients and discussion was done on the basis of the available report of histopathology only in all of the discussed patients. Radiological images were not available on CDs and had to be discussed on films. 2 out of 20 patients didn't even have films available. Management decisions were unaffected in 17 patients and were changed in 09 patients.

Conclusion: Although we are faced with multiple problems in conducting tumor board meetings at a public sector hospital regularly but it is mandatory for all cancer patients and we believe that with persistence we can achieve a management goal where all patients presenting with cancer will be discussed and managed through a tumor board meeting.

P – 116 A long-term analysis of imatinib palliative treatment in gastrointestinal stromal tumors

I Domingues[1], J Carvalho[1], E Pratas[1], S Pinheiro[1], S Amaral[1], N Bonito[2], E Jesus[3], J Ribeiro[3], A Chaves[4], A Pais[3], G Sousa[3]

[1]Instituto Português de Oncologia de Coimbra, Coimbra, Portugal, [2]Portuguese Oncology Institute of Coimbra, Coimbra, Portugal, [3]Portuguese Institute of Oncology of Coimbra, Coimbra, Portugal, [4]IPO Coimbra, Coimbra, Portugal

Introduction: Gastrointestinal stromal tumor (GIST) is the most common sarcoma accounting for 18% of all sarcomas. It can occur anywhere along the gastrointestinal tract, but mostly in the stomach and small bowel. Historically, GISTs are aggressive tumors with poor prognosis. Imatinib is the first line therapy for GIST patients with unresectable, recurrent, or metastatic disease.

Methods: We collected to our analysis patients with GIST treated with imatinib between November/2002 and February/2018. Clinical, pathological and molecular characteristics were retrospectively analyzed. The long-term impact of imatinib in palliative setting was evaluated along the past 16 years, in our medical oncology department.

Results: Imatinib therapy was made in 42 patients. A total of 37 were included in our analysis, after the exclusion of 5 patients due to loss of follow-up. Palliative treatment with imatinib was performed in 62.2% (n = 23) of these patients. Their median age was 47 years (± 16.9; 25 to 76), 56.5% male patients (n = 13). Gastric GIST represented 47.8%, followed by small bowel (34.8%) and rectum (8.7%). KIT exon 11 mutation was detected in 54.5% of these patients, 9.1% were wild type, the remaining patients had unknown or unevaluated mutation. No survival differences were detected between these groups. They were all treated with imatinib 400mg as frontline therapy. Median time since primary diagnosis until imatinib was 11.7 months. Best treatment response to the frontline imatinib was stable disease in 56.5% (n = 13), partial response in 26.1% (n = 6), complete response in 13.0% (n = 3) of patients. Frontline imatinib median duration was 25.5 months (0.9 to 84.6). Disease progression led to imatinib discontinuation in 83.3% (n = 15) patients. A 2nd line therapy was performed in 73.9% (n = 17) patients, with imatinib 800mg in 52.9% (n = 9), sunitinib 50mg in 23.5% (n = 4), imatinib 600mg in 17.6% (n = 3), surgery in 5.9% (n = 1) patients. A 3rd line was performed in 52.2% (n = 12), with sunitinib 50mg in 41.7% (n = 5), imatinib 400mg 25% (n = 3), sunitinib 37.5mg in 25% (n = 3), and imatinib 800mg in 8.3% (n = 1) of these patients. A 4th line treatment was made in 21.7% (n = 5) patients. Grade 3 or 4 toxicities have become more frequent in the course of successive therapeutic lines: anemia, neutropenia, nausea, dyspeptic symptoms, hypertension. Median overall survival was 6.9 years (3.2 to 10.6; 95% CI). Considering a survival greater than 5 years as a long-survival in advanced GIST, we observed 47.8% (n = 11) long-survivors. However, no statistically significant differences were found between long and non-long survivors.

Conclusion: Comparing to literature, these patients presented a superior overall survival, but KIT exon 11 mutation and long-survivors were mostly similar. The long-term impact of this treatment should be evaluated in order to better understand clinical, pathological and molecular features of this disease.

P – 117 30-day mortality associated with systemic anti-cancer therapy (SACT) in gastrointestinal malignancies: The Christie experience

F Marti Marti[1], A McGurk[1], N Alam[1], L Bhatt[2], M Braun[1], R Hubner[1], W Mansoor[1], C McBain[1], M McNamara[3], S Mullamitha[4], M Saunders[5], H Sheikh[2], F Thistlethwaite[1], J Valle[6], G Wilson[1], J Hasan[1]

[1]The Christie NHS Foundation Trust, Manchester, UK, [2]The Christie Hospital, Manchester, UK, [3]The Christie NHS Foundation Trust/University of Manchester (Institute of Cancer Sciences), Manchester, UK, [4]The Christie Hospital NHS Foundation Trust, Manchester, UK, [5]Christie Hospital NHS Foundation Trust, Manchester, UK, [6]University of Manchester, Dept. Medical Oncology, The Christie Hospital, NHS Foundation Trust, Manchester, UK

Introduction: Although SACT has very well-known associated toxicities, the safe delivery of it is of paramount importance in current oncology practice. The systematic and prospective analysis of deaths occurring within 30 days of SACT administration provides an optimal opportunity to identify trends, appraise current practice and improve patient care. Here, we present the data from our cancer centre.

Methods: GI cancer patients constitute 20% of the caseload at The Christie NHSFT which sees on average 8000 new patients and delivers 60000 chemotherapy episodes yearly. A prospective database to record and analyse deaths occurring within 30 days of SACT was established in September 2009. This database recorded the deaths registered within the GI oncology group, which included Upper GI (Gastro-oesophageal and Hepatobiliary) and Lower GI malignancies. The database included basic demographics for each individual patient and recorded details of the chemotherapy regimen, dosing, etc. The treatment intent was recorded for each case. As part of the exercise, deaths were discussed within the group where causality of the death in relation to SACT treatment was allocated. The four causality categories were: definitely treatment related, probably treatment related, possibly treatment related and non-treatment related. Any suggested improvements and recommendations for future practice were also annotated. The data reported here are for the period between September 2009 and February 2017.

Results: 469 deaths within 30 days of SACT were recorded during this period. Of those, 258 (55%) patients had been treated for a lower GI and 211 (45%) for an upper GI cancer. Average age at death was 65 years (18- 88). 307 of the reported deaths (65%) were in male patients. The number of chemotherapy cycles delivered prior to death ranged from 1 to 33. About one third of deaths (n = 149; 31.8%) occurred after the first cycle of chemotherapy. Overall, 245 (52%) deaths occurred within the first two cycles of chemotherapy. In terms of causality, 21 (4.4%) deaths were felt to be definitely related to SACT; 28 (6%) probably related; 88 (18.7%) possibly related and 332 (70.7%) non-related to SACT administration. Of those deaths definitely related to SACT, 8 (38%) were caused by neutropenic sepsis. Disease progression accounted for 248 (75%) of the deaths felt not to be related to SACT. When split by treatment intent, 12 deaths (2.5%) were reported in patients having adjuvant chemotherapy and 8 (1.7%) in the neo-adjuvant group. 7 deaths occurred in patients having radical treatment (1.5%). The rest of the deaths occurred in patients with metastatic disease (n = 442; 94%).

Conclusion: The systematic report and analysis of deaths within 30 days of SACT delivery in our institution provided a well-structured platform to identify specific patterns of occurrence. The early stages of chemotherapy delivery emerged as a crucial period. Increased monitoring of toxicity during the early phases of SACT delivery might lead to reduced mortality. Further understanding of the patients that die as a consequence of SACT might help identify those at risk and lead to a change in follow-up protocols and/or upfront dosage. Mature data will be presented at the meeting.

P – 118 Chemoradiation for anal canal carcinoma in a comprehensive cancer center: Retrospective cohort study

J Dias, F Pereira, N Sousa, P Ferreira, D Gomes, O Sousa

Portuguese Institute of Oncology, Porto, Portugal

Introduction: Squamous cell carcinoma of the anal region is a rare tumor largely caused by HPV. Radiotherapy concurrent with chemotherapy is the standard of care

for localized disease, aiming to avoid abdominopelvic amputation and preserve quality of life.

Methods: We conducted a retrospective chart review of patients with squamous cell carcinoma of the anal canal treated at our institution with definitive chemoradiotherapy, between January 1st 2012 and December 31st 2017. Baseline clinical and demographic variables were obtained, as well as treatment details and early and late toxicities.

Results: 34 patients met inclusion criteria, of which 29(85,7%) were female, with a median age at diagnosis of 62 y (min-max: 39-79 y). The median time from the first symptom to diagnosis was 14,5 weeks (min-max: 3-48 weeks). The most common presenting symptom was local pain (n = 13; 41,9%), followed by hemorrhage (n = 11; 35,5%). Only 1(7,7%) patient was HIV-positive. Median SCC levels at diagnosis was 1.9 ng/mL, with 16(64%) cases with SCC levels above the institutional reference level. Tumor stage according to the 7th edition of the AJCC manual was distributed as follows: Stage I: 2 cases (5,7%); Stage II: 10 cases (29,4%); Stage IIIA: 8 cases (23,5%), stage IIIB: 14 cases (41,2%). Median tumor dimension was 43mm, and 4(12,5%) cases were cT4 tumors. Most patients were treated with a dose of 45Gy to nodal basins and a total dose between 50 and 60Gy to the tumor volume, using VMAT in all but 4(11,8%) cases, in which IMRT was used. Median treatment duration was 44 days (min-max: 32-90). Radiotherapy delays due to toxicity – that was mostly hematologic – occurred in 22 (62,9%) cases. The chemotherapy regimen used was mitomycin combined with 5-fluorouracil, that was substituted for capecitabine in one patient. Grade 3 or greater acute treatment toxicities occurred in 27(79,4%) cases and there was one death during treatment due to neutropenia and mesenteric ischemia. In 8(23,5%) cases, only one cycle of chemotherapy was administered due to toxicity, and 7(20,6%) of patients underwent dose reductions. Febrile neutropenia occurred in 6(17,6%) cases. Persistent disease after therapy was seen in 3(8,8%) patients, that underwent abdominopelvic amputation with clear margins. Median follow up was 24 months. Relapse occurred in 9(26,5%) cases, of which most were local relapses (n = 7; 77,8%). Distant relapse occurred in 4(11,8%) cases. Most relapses were treated with surgery (n = 6; 66,7%) and palliative chemotherapy was done in 2 cases. The three year overall survival rate was 57,9%. All but one deaths were due to relapse or persistent disease. Late complications occurred in 5 cases (14,7%) – mostly radiation proctitis, followed by chronic lymphedema. One case of radiation proctitis lead to diverting colostomy.

Conclusion: In our experience, combined modality treatment with chemotherapy and radiation showed to have a similar efficacy to other published studies, despite a high rate of acute toxicities. Due to the rarity of the disease and its complex management, treatment should be done at experienced centers. Strict adherence to treatment guidelines and careful follow-up is mandatory to optimize outcomes.

P – 119 The feasibility study of short hydration with oral rehydration therapy in chemotherapy with cisplatin plus gemcitabine for biliary tract cancer (KHBO-1302)

T Ioka[1], D Sakai[2], H Wada[3], H Eguchi[4], K Yanagihara[5], H Satake[6], J Shimizu[7], M Kanai[8], K Hashimoto[9], T Ajiki[10], M Nakamura[11], Y Takeda[12], K Yoshimura[13], E Hatano[14], H Nagano[15]

[1]Osaka International Cancer Institue, Osaka, Japan, [2]Osaka University Graduate School of Medicine, Dept of Gastroenterological Surgery, Suita, Japan, [3]Osaka International Cancer Institute, Osaka, Japan, [4]Department of Surgery, Graduate School of Medicine, Osaka University, Suita, Japan, [5]Department of Medical Oncology, Kansai Electric Power Hospital, Osaka, Japan, [6]Department of Medical Oncology, Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan, [7]Department of Surgery, Osaka Rosai Hospital, Sakai, Japan, [8]Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [9]Department of Surgery, NTT West Osaka Hospital, Osaka, Japan, [10]Kobe University Hospital Hepato-Biliary-Pancreatic Surgery, Kobe, Japan, [11]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan, [12]Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [13]Department of Biostatistics, Innovative Clinical Research Center, Kanazawa University, Kanazawa, Japan, [14]Department of Surgery, Hyogo College of Medicine, Nishinomiya, Japan, [15]Yamaguchi University Graduate School of Medicine, Department of Gastroenterological, Breast and Endocrine Surgery, Ube, Japan

Introduction: Gemcitabine plus cisplatin (GemCis) is a standard chemotherapy for advanced biliary tract cancer. It needs to take long time for hydration to prevent renal toxicity due to cisplatin. This prospective study evaluated the feasibility of short hydration regimen of GemCis with oral rehydration solution in patients with advanced biliary tract cancer.

Methods: The major eligibility criteria included patients with biliary tract cancer for whom a cisplatin-gemcitabine combined chemotherapy was indicated and adequate organ function. For the patients in oral rehydration treatment (ORT) group, cisplatin and gemcitabine were administered via infusion as follows; 500 ml of 0.9% saline including cisplatin (25 mg/m2) over 1 hour followed by 250 ml of 0.9% saline including gemcitabine over 30 minutes. Before and after the infusion, each 500ml bottle of oral rehydration solution (OS-1 ®) will be taken respectively. Primary endpoint was completion rate during the 12 weeks.

Results: From July 2013 to January 2016, 71 patients were enrolled from 11institusions in Japan, and 50 were allocated to oral rehydration group. The complete rate in ORT group was 65.4% (95% CI: 50.9 - 78.0) (n = 34/53). Progression free survival and overall survival in ORT group were 6.0 (95% C.I.: 4.4-8.3) and 15.1 (95% C.I.: 10.8-18.2) months, respectively. The proportion of Creatinine increased were 14% in ORT arm (grade 1 14%), and 26% in CHT arm (grade 1 21%, grade 2 5%), respectively.

Conclusion: The short hydration regimen with oral rehydration solution for cisplatin regimen for the patient with BTC is as safe as the conventional hydration regimen.

P – 120 Comparison of different risk classification systems in patients with high risk gastrointestinal stromal tumors

Y Yin[1], Z Cai[2], B Zhang[3], C Shen[4]

[1]West China Hospital, Chengdu City, China, [2]Gastrointestinal Surgery, West China Hospital, Chengdu City, China, [3]West China Hospital, Sichuan University, Chengdu, China, [4]West China Hospital, Chengdu, China

Introduction: To assess and compare the accuracy of different risk classification systems for predicting recurrence risk in patients with high risk GIST (Modified NIH classification) after R0 resection.

Methods: The clinicopathological and follow-up data of patients with high-risk GIST without adjuvant IM therapy in our hospital from January 2009 to April 2015 were retrospectively analyzed. Receiver Operating Characteristic (ROC) curves were used to analyze the accuracy of different risk classification systems for predicting recurrence risk in patients with high risk GIST after R0 resection.

Results: The research identified 82 patients with a median follow-up of 37 months. During the follow-up period, 36 patients had recurrent or metastatic disease. Univariate analysis showed that tumor site ($P = 0.026$), size ($P = 0.002$) and mitotic count ($P < 0.001$) were associated with recurrence or metastasis disease after surgical resection. Logistic regression analysis showed Logit (P1) = -0.081 * a + 0.031 * b + 0.155 * c-2.113 for predicting the recurrent or metastatic disease in patients with high-risk GIST without adjuvant IM therapy. In this study, the prognostic contour maps, AFIP criteria and Logit models have high accuracy in predicting the risk of postoperative recurrent disease (AUC = 0.882,0.813,0.928, respectively), the prognostic contour maps and Logit models were superior to the AFIP criteria.

Conclusion: The prognostic contour maps, AFIP criteria and Logit model provide high accuracy predictions of the risk of postoperative recurrence in patients with high risk GIST, which help guide clinical management of GIST.

P – 121 Impaired quality of life of caregivers of patients with gastrointestinal cancer undergoing palliative chemotherapy

N Takeuchi[1], K Koike[1], S Yoshida[1], N Sekiguchi[2], T Noguchi[2]

[1]Ina Central Hospital, Ina, Japan, [2]Shinsyuu University, Matsumoto, Japan

Introduction: Support of caregivers to patients with gastrointestinal (GI) cancer undergoing palliative chemotherapy is an essential factor in maintaining the safety and continuity of the treatment. Given the insufficient knowledge regarding the quality of life (QOL) of caregivers, no durable strategy exists for their support through the treatment. We aimed to assess the QOL of caregivers of patients with GI cancer undergoing palliative chemotherapy.

Methods: This single institutional prospective observational study was approved by the institutional review board of Ina Central Hospital held on 20 July 2016. Fifty-nine patients with GI cancer and their caregivers have been included in this study. EORTC QL-C-30 was used for measuring QOL. This study included 36 male and 23 female patients aged 68.7 years in average, and 18 male and 41 female caregivers aged 64.4 years in average. The locations of the primary lesions were identified as follows: pancreas (19), colorectal (13), stomach, (13), biliary tract (7) and oesophagus (7). QOL measurement was conducted at the commencement of the first-line chemotherapy in 45 patients and on the second-line chemotherapy after the failure of the first line in 14 patients. Of the 59 patients, 15 were evaluated both at the commencement of the first- and second-line chemotherapies. The average period between the two assessments was 5.5 months. The change in their QOL scores and scales along the treatment has been included in the discussion. Statistical analysis was performed using JMP® 13 software (SAS Institute Inc., Cary, NC, USA).

Results: Global health score (GHS) and Summary Score (SS) of caregivers were 62.8 and 85.0, respectively. Both scores are significantly higher than those of the patients (46.2 and 73.5, respectively). Among each score and scale of QOL identified from QL-C-30, "emotional function" (73.1 for caregivers, 70.3 for patients), "cognitive function" (77.2 for patients, 79.7 for caregivers) and "insomnia scales" (24.3 for patients, 19.8 for caregivers) did not show a significant difference between patients and their caregivers. All scores and scales other than the three were significantly higher in caregivers. In the comparison of the QOL of patients during first-line and second-line chemotherapies, no significant concordance of improvement or worsening of GHS and SS during treatment ($\chi 2 = 0.00$, $P = 1.00$ in both scores) was found between patients and caregivers.

Conclusion: Even at the commencement of the treatment, caregivers of patients with GI cancer suffered from the impairment of their daily QOL, especially in emotional and cognitive functions comparable with those of the patients. This impairment did not seem to improve with the improvement of the QOL of the patients; therefore, this necessitates the continuous and independent support from the commencement of the treatment for caregivers of patients with cancer.

P – 122 Primary gastric diffuse large B cell lymphoma: A single center experience from developing country

A Gogia, V Raina, M Sharma

All India Institute Of Medical Sciences, New Delhi, India

Introduction: Primary gastric diffuse large B cell lymphoma (PGDLBCL) accounts for 1% of gastric malignancies and 20% of all gastrointestinal lymphoma. There is paucity of data regarding PGDLBCL from developing countries.

Methods: In this retrospective study, 70 patients with PGDLBCL from 2006 to 2015 were included at All India Institute of Medical Sciences (AIIMS), New Delhi, India. Their clinical features, pathological characteristics, base line IPI score, stage at presentation, type of treatment and outcome were analyzed.

Results: Median age was 41.5 years (range 20-77yrs). B-symptoms were present in 42 (60%) patients and 35 (50%) patients were presented with poor performance status (ECOG 3/4). According to Ann Arbor staging, 49 patients (70%) were in stage I, 14 (20%) stage II, 02 (2.8%) stage III and 05 (7%) in stage IV. IPI risk categorizations, low risk 30%, low intermediate risk 20%, high intermediate risk 20% and high risk 30%. Sixty three cases (90%) were non germinal center/Activated B cell type (ABC). Twenty eight patients were treated with CHOP, 27 patients with R (Rituximab) +CHOP and rest were treated with CVP +/- R. Radiation therapy (RT) was received as consolidative treatment in 50% of cases. Complete remission (CR) was observed in 75% of cases. Median event free (EFS) and overall survival (OS) was 72% and 58% with median follow up period of 42 months. Helicobacter pylori (HP) antibody testing was positive in 14 cases (20%) and all patients received anti-HP treatment. HP associated PGDLBCL were associated with less B symptoms, low IPI, better CR rate (P

Conclusion: PGDLBCL consists 60% of all gastric lymphoma at our centre. Around half of them are presented with B symptoms and poor performance status. H. Pylori positivity is seen in 20% of cases and associated with low risk IPI with good survival. Addition of rituximab to CHOP has a statistical significant survival impact in patients with PGDLBCL. RT may be omitted in selective cases of PGDLBCL, where RCHOP/RCVP (rituximab based chemotherapy) is being considered, to avoid radiation induced side effect with same survival. Chemotherapy may be omitted in some selected cases of HP associated PGDLBCL.

P – 123 Quality of life by Karnofsky index in patients with gastrointestinal cancer subject to parenteral nutritional therapy

T Pessoa[1], A Pessoa[2], P Aguiar[2], F Moreira[2], R Pessoa[3], C Silva[2]

[1]Laboratory of Molecular Biology and Development, University of Fortaleza, Fortaleza, Brazil, [2]University of Fortaleza, UNIFOR, Fortaleza, Brazil, [3]Federal University of Ceará, Fortaleza, Brazil

Introduction: The inaccessibility to early parenteral nutrition therapy (NPT) or delayed administration, by a large part of the Brazilian population with gastrointestinal cancer, has a disastrous consequence for the tertiary level of health and fundamentally for the patient due to worsening of its clinical state and tolerance to oncological treatment generating a functional and emotional dependence, reflected in a decrease in their Quality of Life. Currently, 20% of the deaths of cancer patients are secondary to malnutrition, since it influences energy expenditure in a heterogeneous manner. This study aimed to recognize the nutritional repercussions of NPT in patients with gastrointestinal cancer.

Methods: This was a longitudinal and quantitative study performed in hospital institutions in Fortaleza, Brazil, comprising 212 patients with cancer of the gastrointestinal tract undergoing NPT. The research was carried out in three phases (I, II and III). In the phase I was performed Global Subjective Nutritional Assessment (ANSG), determination of the Karnofsky Performance Status Scale (KPS) to assess the quality of life, data referring to the fasting time from the prescription of the therapy to its initiation, type of NPT administered and intercurrent in its infusion, in addition to serum lymphocyte and albumin dosage for the evaluation of immunological competence. In Phase II a PPH (Health Promotion Program) was applied in the conscious and familiar patients, from educational actions on NPT. The phase III occurred after 10 uninterrupted TNP pockets where new KPS were determined and new data were collected. It was SPSS software, paired t-test and significance level ($p < 0.05$).

Results: The results showed that 77.67% of the oncology patients had started the NPT severely malnourished and almost half of them still remained approximately 6 to 10 days without any nutritional support until the beginning of NPT. The NPT reduced the risk of complications in patients when it increased the immunological competence of 78.21% and improved the Quality of Life, in functional aspect, raising the KPS = 40 of 76.78% of the patients to KPS = 70, making them able to self-care. The lack of knowledge of NPT was reported by 79.41% of the conscious patients, who presented fear and sadness, replaced after educational actions, by feelings of hope and confidence associated with the improvement of thirst, hunger and weakness. The NPT indices with interruptions were 53.65%, followed by lack of data regarding nutritional status in patients' charts.

Conclusion: It was concluded that NPT had a positive impact on patients with improvement in their clinical status and quality of life, but its use in Brazil has not yet been satisfactory and immediate even when the alarming numbers of malnutrition in patients with gastrointestinal cancer are confirmed and your need is essential.

P – 124 De novo malignancies in patients after liver transplantation: A single centre experience

K Chmelova[1], J Spicak[2]

[1]Institute for Clinical and Experimental Medicine, Prague 4, Czech Republic, [2]Institute for Clinical and Experimental Medicine, Prague, Czech Republic

Introduction: De novo malignancy is a major cause of long term morbidity and mortality in patients after liver transplantation (LTx). The overall risk is estimated to be 2-4 times higher as compared to general population. Neither cancer screening protocols, nor universal recommendations have yet been established. The aim of this study was to evaluate incidence of de novo malignancies, identify potential risk factors and characterise the overall outcome of patients after LTx.

Methods: We retrospectively reviewed adult 1295 patients (765 male and 530 female) who underwent LTx in IKEM between 1995 and 2016. Clinical characteristics and demographic data were collected in patients who survived at least one month post-transplant. Patients with non-melanoma skin cancer were excluded (as it does not affect mortality), as well as patients with recurrence of hepatocellular carcinoma.

Results: In our cohort we identified 144 malignancies in 136 liver graft recipients (10.5%), 85 male and 51 female. The median time between LTx and diagnosis of the tumour was 64 months (range 4-234) at the age of 60 years (range 18-74). The most common malignancy was post-transplant lymphoproliferative disease – PTLD (2.2%), followed by lung cancer (1.77%) and head/neck cancer (1.62%). Mean age of cancer occurrence in these groups was lower as compared to general Czech population: 58, 63 and 58.5 years of age vs. 60, 74 and 62 years of age, respectively. Furthermore, only 9 cases of colon cancer were identified (2 of them in patients with ulcerative colitis). Smoking was identified as an independent risk factor for cancer development in the study cohort. Tumour was found in 81 non-smokers and 55 smokers compared to 269 smokers and 890 non-smokers in patients without any malignancy ($p < 0.001$). The most common cause of liver injury was alcoholic liver disease (47/136 patients), followed by viral hepatitis (35/136 patients) and primary sclerosing cholangitis (12/136 patients). Patients with de novo malignancy achieved 3-, 5- and 10-year survival of 91.1%, 78.1%, and 61.4%, which was comparable with patients without cancer (85.9%, 81.2%, and 62.9% respectively).

Conclusion: Liver transplantation is related to increased occurrence of malignancy development. PTLD, lung cancer and head/neck cancer were most common malignancies in our study group. Future establishment of proper screening programs in patients after LTx is highly warranted.

P – 125 Laparoscopic liver resection for tumors in proximity to major vasculature and the impact of neo-adjuvant systemic therapy

M D'Hondt[1], E Willems[1], I Parmentier[2], H Pottel[3], C Verslype[4], C De Meyere[1], F Vansteenkiste[1], M Besselink[5]

[1]Department of Digestive and Hepatobiliary/Pancreatic Surgery, Groeninge Hospital, Kortrijk, Belgium, [2]AZ Groeninge Kortrijk, Oncology and Statistics, Kortrijk, Belgium, [3]Interdisciplinary Research Center, Leuven University, Campus, Kortrijk, Belgium, [4]Department of Gastroenterology and Hepatology, KU Leuven, Leuven, Belgium, [5]Academic Medical Center Amsterdam, Amsterdagm, Netherlands

Introduction: Only small case series have been published regarding laparoscopic liver resection (LLR) for tumors in proximity to major vessels (MVs). The aim of this study is to compare peri-operative outcomes of LLR for tumors < 20 and ≥ 20mm from MVs.

Methods: Retrospective analysis of a prospectively collected database of consecutive LLR (October 2011 – August 2017) performed by a single surgeon. Proximity to MVs was defined as a distance of 20 mm or less to the caval vein, hepatic veins and portal vein (main trunk and first branches).

Results: A total of 235 LLR were performed, of which 60 patients (24%) had lesions in proximity to major vasculature, median distance to MV 10 mm (range 0-17 mm). Significantly more patients in the close-to-major-vessels group (CTMV) received neo-adjuvant chemotherapy (36.7% vs 24.2%, $p = 0.0094$). In the CTMV group, the median Difficulty Score for LLR was significantly higher (8.5 (IQR: 6.0-9.0) vs 5.0 (IQR: 3.0-6.0), $p < 0.001$) as was the use of CUSA ($p < 0.001$) and Pringle manoeuver (8.3% vs 1.7%; $p = 0.028$). Operative time was significantly longer (180min (IQR: 140-210) vs 120min (IQR: 75-150), $p < 0.001$) and blood loss was significantly higher (190ml (IQR: 100-325) vs 75ml (IQR: 50-220), $p < 0.001$) in the CTMV group. This did not result in a difference in perioperative blood transfusion (3.3% vs 1.7%, $p = 0.60$) or in postoperative morbidity (15.0% vs 14.3%, $p = 0.89$). There was no mortality in both groups. There was no significant correlation between the distance to MVs and blood loss ($p = 0.80$) or operative time ($p = 0.95$). Correlation between central venous pressure drop and blood loss was borderline significant ($p = 0.06$). There was a significantly higher R1 resection rate in the CMTV group (10% vs 1.7%, $p = 0.0098$). On long-term follow-up, there were no significant differences in 5-year overall survival (41% VS 69%, $p = 0.12$) and 5-year disease-free survival (31% VS 20%, $p = 0.98$) between the CTMV group and the other group.

Conclusion: In selected patients, LLRs of lesions in proximity to MVs is safe and feasible with acceptable long-term and oncological results. These patients received more neo-adjuvant systemic therapy.

P – 126 Impact of revision surgery timing on overall survival in incidentally detected gall bladder cancer: An experience from tertiary care centre of Northern India

A Mishra[1], M Gowda[2], S Bhoriwal[3], S Deo[4], N Shukla[1], A Sharma[5], S Pathy[2], S Kumar[6]
[1]All India Institute of Medical Sciences, New Delhi, India, [2]All India Institute of Medical Sciences, Delhi, India, [3]All India Institute of Medical Science, New Delhi, India, [4]All India Institute Of Medical Sciences, New Delhi, India, [5]All India Institute Of Medical Sciences, Delhi, India, [6]All India Institute of Medical Science, Delhi, India

Introduction: Gall bladder cancer is very common in South East Asia. It is an aggressive malignancy. Currently half of the patients of GBC are being detected as incidental. Most of these incidentally detected gall bladder cancer found to be early staged. As per current literature, there is no consensus on ideal time of revision or completion surgery if required. The timing of surgery may play crucial role in outcome of these early staged gall bladder cancer.

Methods: Retrospective analysis of prospectively maintained computerized data-base of GBC patients was carried out at Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India. We analyzed the patient's details pertaining to clinical presentation, preoperative therapy, operative procedure, histopathological examination, postoperative complications, adjuvant treatment, and outcomes.

Results: Total of 135 GBC patients underwent gall bladder surgery in between January 2010 to December 2016. Out of these 134 patients, 74 (54.81%) were incidentally detected gall bladder cancer. 48.7% incidentally detected GBC patients found to be Stage I (AJCC 8th) while 43.24%, 8% restaged as Stage II and III respectively. During intra-operative assessment, 52 (70.27%) patients were found operable and underwent Completion Radical cholecystectomy. In rest 22 (29.73%) patients the procedure was abandoned in view of metastatic or inoperable disease. For analysis, these 52 patients were divided into two groups. Group A patients (n = 37) underwent Completion radical cholecystectomy within 4 months of primary surgery while Group B patients (n = 15) underwent Completion radical cholecystectomy after 4 months. In Group A, 46.1% & 40.8% patients were in TNM stage I and stage II respectively compare to 37.5 & 44.6%, each in stage I & II respectively in Group B. DFS in Group A & Group B patient were 28.7 months and 19.4 months respectively ($p < .05$).

Conclusion: The outcome of completion radical cholecystectomy is inversely proportional to the interval between primary and definitive surgery even in similarly staged patients.

P – 127

WITHDRAWN

P – 128 Surgical resection of primary tumor site is associated with prolonged survival in metastatic pancreatic neuroendocrine carcinoma

T Feng[1], S Ling[2]
[1]Zhejiang Cancer Hospital, Hangzhou, China, [2]The First Affiliated Hospital of Zhejiang University, Hangzhou, China

Introduction: Most of pancreatic neuroendocrine carcinoma (PanNEC) present with distant metastases. According to more aggressive biological behaviors, surgery is not recommended for metastatic PanNEC patients considering the limited survival benefits compared to well differentiated grade patients. However, limited evidences could support these recommendations. The aim of this study was to evaluate the impact of surgical resection of the primary tumor in the patients with PanNEC and distant metastases, as well as identify variables associated with prolonged survival in this patient population.

Methods: We used the Surveillance, Epidemiology and End Results (SEER) database to identify patients with PanNEC and distant metastases. The specific criteria are as follows: 1.The histologic subtypes and their International Classification of Disease codes (ICD-O-3) included in the cohort were: large cell neuroendocrine carcinoma(8013), small cell carcinoma(8041) and neuroendocrine carcinoma (8246); 2.Patients with distant metastases according to the "SEER historic stage" variable or AJCC stage IV; 3.histologic differentiation grade included were: poorly differentiated and undifferentiated; 4. the age of patients meet more than 18 years and less than 85 years. Group comparisons of categorical variables were performed using Chi square testing. The Kaplan–Meier method was used to perform a set of actuarial analyses on survival data beginning at the diagnosis date. The difference in survival among groups was determined using a log-rank test. The primary outcome measure in this study was overall survival. Survival times were censored according to the "cancer-specific death" variable. Univariate and multivariable analyses were performed using the Cox proportional hazards regression method. Univariate and Multivariable logistic regression analysis was used to determine the simultaneous impact of factors, which were associated with performing surgery or not.

Results: We identified 506 patients with metastatic poorly differentiated and undifferentiated PanNEC and survival data. 15.4%(78/506) of patients had surgical removal of their primary tumor, 24.4% (19/78) of whom had surgical removal of their primary tumor and metastasis. Median survival of patients undergoing surgery was 28 (95% CI: 12.309-43.691) versus 6 (4.671-7.329) months for those without surgery ($p < 0.0001$). COX multivariable analysis showed tumor site in the body/tail ($p = 0.019$) and surgical resection of the primary tumor site ($p < 0.001$) and diagnosis during or after 2010 ($p = 0.04$), were significantly associated with prolonged survival of patients with PanNEC and distant metastases. Patients diagnosed after 2010 (n = 193, 38.1%) were more likely to undergo an operation than those diagnosed earlier ($p<0.001$) .To gain insight on patient selection, we analyzed the factors associated with removal of the primary tumor from patients with PanNEC and distant metastases, using a logistic regression model stratified by year of diagnosis since that was not a controllable factor. We found that tumor location in the body/tail of the pancreas were significantly associated with removal of primary tumor, independently of the time period in which patients were diagnosed. In the time period after 2010, female was also associated with removal of primary tumor while age<65y in the time period before 2010.

Conclusion: This study suggests that surgical removal of primary PanNEC is associated with longer survival in patients with distant metastases and could therefore be considered as an additional treatment option in this patient population.

P – 129 Comparing efficacy of 1-L Peg-Asc with prucalopride versus 2-L Peg-Asc for bowel preparation

S Jang[1], Y Jeen[2], S Choi[3], J Lee[4], S Kim[4], J Lee[4], H Choi[1], E Kim[5], B Keum[4], H Lee[6], H Chun[5], C Kim[4]
[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Institute of Gastrointestinal Medical Instrument Research, Korea University College of Medicine, Seoul, Republic of Korea, [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul, Republic of Korea, [3]Korea University Anam Hospital, Seoul, Republic of Korea, [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea, [5]Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea, [6]Korea University College of Medicine, Seoul, Republic of Korea

Introduction: Though numerous researches enabled decrease of the bowel preparation solution volume, it is still a major complaint of patients preparing colonoscopy. There have been studied that additional administration of laxatives could lessen the amount of aqueous formula with prokinetic effect. Prucalopride is a serotonin (5-HT4) receptor agonist which stimulate colonic mass movements and provide main propulsive force for defecation. The aim of this study is to compare 2-L PEG-Asc and 1-L PEG-Asc plus prucalopride for quality of bowel cleansing while preparing for colonoscopy and patient compliance.

Methods: Two hundred patients were prospectively enrolled. Patients referred for colonoscopy were divided into group A (the split-dose 2-L PEG-Asc) and group B (1-L PEG-Asc + prucalopride) randomly. During colonoscopy, each patient's bowel preparation quality was evaluated with The Boston Bowel Preparation Scale (BBPS) and Aronchick Preparation Scale (APS). The tolerability and satisfaction of patients was determined based on a questionnaire-based survey.

Results: One hundred patients received either 2-L PEG-Asc or 1-L PEG-Asc with prucalopride. Regarding colon cleansing outcome (BPPS and APS), the 1-L PEG-Asc with

prucalopride group showed similar, but non-inferior results compared to the 2-L PEG-Asc group on both BBPS (7.65±1.27 vs 7.52±1.40, p = 0.586) and APS scales (93.3% vs 95%, p = 0.717). Tolerability was similar for both 1-L PEG-Asc with prucalopride and 2-L PEG-Asc.

Conclusion: 1-L PEG-Asc plus prucalopride preparation showed comparable result to traditional 2-L PEG-Asc preparation. 1-L PEG-Asc plus prucalopride preparation method could be an alternative method for bowel preparation which can relieve patient's discomfort.

P – 130 A phase I/II Trial of CRISPR-Cas9-mediated PD-1 knockout Epstein-Barr virus cytotoxic lymphocytes (EBV-CTLs) for advanced stage EBV associated malignancies - Trial in progress

J Wei[1], J Yan[2], S Su[2], J Shao[2], Y Zhao[2], Q Xu[2], Y Yang[1], Z Zou[1], X Huang[3], B Liu[4]

[1]The Comprehensive Cancer Center of Drum-Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China, [2]The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China, [3]School of Life Science and Technology, Shanghai Tech University, Shanghai, China, [4]The Comprehensive Cancer Center of Drum-Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China

Introduction: EBV associated malignancies exhibits high amplification of PD-L1 as distinguished from EBV non-associated malignancies (Kim et al. Gastroenterology 2015; Chen et al. Clinical Cancer Research 2013). The up-regulation of PD-L1 restricts antitumor effect of EBV-CTLs by immune tolerance and results in poor prognosis of patients. Our previous work has generated PD-1-disrupted CTLs by CRISPR-Cas9 system which could up-regulate IFN-γ production and enhance cytotoxicity in tumor cell lines and mouse model (Su et al. Oncoimmunology 2016).

Methods: This phase I/II prospective single center clinical study (clinicaltrials.gov NCT03044743) was designed to evaluate the safety of PD-1 knockout EBV-CTLs in treating EBV positive advanced stage malignancies. Patients included should be pathologically verified EBV positive stage IV gastric carcinoma, nasopharyngeal carcinoma or lymphoma progressed after standard treatment with measurable lesions. Patients will be divided into three groups and receive 2 to 4 cycles of cell therapy according to their tolerance. PD-1 knockout EBV-CTLs from autologous origin will be generated and 2 x 107/kg of specific T cells will be infused in one cycle. Each cycle is divided into three administrations, with 20%, 30% and 50% respectively. To modify immune microenvironment, Fludarabine at 30mg/m2 and cyclophosphamide at 300mg/m2 will be administered 3 days (intravenous injection, i.v.) before cell infusion. Interleukin-2 will be given daily (i.v.) from the first day of the cell infusion for 5 consecutive days at the dose of 4000,000 international unit (IU)/day to sustain the survival of infused T cells. The adverse events will be evaluated after each cycle by Common Terminology Criteria for Adverse Events (CTCAE v4.0) as primary endpoint. Progression-free survival (PFS), the duration of the normalization of tumor marker and immunological markers will be evaluated as the secondary endpoints. Immunological markers will continuously be examined every two cycles.

P – 131 Endoscopic detachable auxiliary manipulator in endoscopic submucosal dissection: Animal model studY

H Jeon[1], H Chun[2], B Keum[3], J Lee[3], S Choi[4], S Kim[3], J Lee[5], H Choi[6], E Kim[2], Y Jeen[7], H Lee[8], C Kim[3]

[1]Division of Gastroenterologyh and Hepatology, Department of Intermal Medicine, Gastrointestinal Medical Instrument Research, Korea University College of Medicine, Seoul, Republic of Korea, [2]Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea, [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea, [4]Korea University Anam Hospital, Seoul, Republic of Korea, [5]Korea University College of Medicine, Seoul, Korea, [6]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Institute of Gastrointestinal Medical Instrument Research, Korea University College of Medicine, Seoul, Republic of Korea, [7]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul, Republic of Korea, [8]Korea University College of Medicine, Seoul, Republic of Korea

Introduction: Endoscopic submucosal dissection (ESD) is a difficult procedure due to lack of counter traction for unskilled endoscopists. Recently, auxiliary devices have been developed to alleviate the difficulties of ESD. We also developed new endoscopic technique using robotic manipulator. The purpose of this study is to evaluate the efficacy and safety of endoscopic detachable auxiliary manipulator (EDAM) in vitro animal study.

Methods: A novel robotic manipulator is composed of a control panel and a working arm, which grasp and move objects at the end of scope. A total of 40 porcine stomachs were used for the test. Endoscopists were classified as expert or novice. As a preliminary work, operation time and perforation rate of the experts and novices were recorded when ESD was performed by the conventional method. (C-Expert group, C-Novice group). The same experiment was performed using EDAM (M-Expert group, M-Novice group). During this procedure, robotic manipulator lifts up dissected tissue of stomach to make better visibility. The results were compared.

Results: The safety of the operation was greatly improved when using the EDAM. Perforation rate of the EDAM method was significantly lower than that of the conventional method in the novice group. (10% vs 60%, P = 0.002) There was no significant difference between the conventional method and the EDAM in the operation time in the novice group.

Conclusion: As a result of this In-vitro test, the EDAM significantly improved the safety of ESD in the case of the novice, with no increase in operation time.

P – 132 Poly-Ligand Profiling differentiates pancreatic cancer patients according to treatment benefit from gemcitabine+placebo versus gemcitabine+evofosfamide and identifies candidate targets

V Domenyuk[1], X Liu[1], D Magee[1], Z Gatalica[1], A Stark[1], P Kennedy[1], M Rosenow[1], A Barker[2], D Berry[3], G Poste[4], D Halbert[1], C Hart[5], M Famulok[6], G Mayer[6], M Korn[1], M Miglarese[1], D Spetzler[1]

[1]Caris Life Sciences, Phoenix, Arizona, USA, [2]Arizona State University, Tempe, Arizona, USA, [3]Berry Consultants, Austin, Texas, USA, [4]Arizona State University, Scottsdale, Arizona, USA, [5]Threshold Pharmaceuticals, San Francisco, California, USA, [6]University of Bonn, Bonn, Germany

Introduction: The accumulation of a multitude of subtle molecular aberrations during tumor progression limit the efficacy of anti-cancer drugs. A vast array of these variations can be assessed with Poly-Ligand Profiling (PLP), which is utilizing libraries of trillion unique ssDNA with aptamer binding properties. The aims of this study were to develop a PLP library that differentiate pancreatic cancer patients who can benefit from gemcitabine+evofosfamide (GE) or gemcitabine+placebo (G) and identify its molecular targets.

Methods: Patients: locally advanced or metastatic pancreatic cancer patients randomized to G vs GE in the unsuccessful phase III MAESTRO trial (Threshold Pharmaceuticals, Merck KgaA). FFPE tissues of patients with good (OS > 13 mos) or poor (OS < 7 mos) outcome from GE were used for PLP library development. Affinity maturation and testing of library for binding FFPE tissue is done with IHC-like protocol. Assay conditions and algorithm were locked based on the training set (n = 12) and used for testing assay performance in the blinded set (n = 172, primary and metastatic sites). PLP-assay performance metrics from blinded test set served to estimate the impact on the MAESTRO study (n = 693) by performing 1000 simulations. For target ID, FFPE tissue of patients with poor outcome, stained with enriched library, was recovered, lysed, underwent affinity-based pull-downs, purified with PAGE gel and subjected to high resolution mass-spectrometry (MS).

Results: 1,000 simulations of projected PLP-positive patients from MAESTRO study revealed a median OS increase of 37.6% (mean) in G+E cohort, compared to G (17.4% OS increase in MAESTRO) with mean Hazard Ratio (HR) 0.72 (0.84 in MAESTRO). 96.9% of simulated trials achieved statistical significance. For primary tumor samples the median OS increase for G+E patients was 53.4% with mean HRs of 0.64 with 100% of trials exhibiting log-rank p < 0.05. MS reliably detected 20 proteins, 11 of which have reported associations with pancreatic cancer and 6 have been associated with resistance to gemcitabine: vimentin (VIM), pyruvate kinase (PKM), endoplasmic reticulum chaperone BiP (HSPA5), heat shock protein HSP 90-alpha (HSP90AA1), Histone H3-1 (HIST1H3A), heat shock protein beta-1 (HSPB1). Vimentin is a mesenchymal marker whose expression increases during epithelial–to-mesenchymal transition (EMT) and tumor progression. EMT results in the suppression of human equilibrative/concentrative nucleoside transporter and protects tumor cells from gemcitabine. GRP78 overexpression confers resistance to gemcitabine and its knockdown sensitizes tumor cells to drug treatment. Alternative splicing of PKM promotes gemcitabine resistance in pancreatic cancer cells most likely by boosting glycolysis-fueled proliferation. Heat shock proteins regulate multiple tumor survival and progression pathways and their inhibition attenuates resistance of cancer cells to gemcitabine. Pancreatic tumors demonstrate increased histones acetylation, which was correlating with increased protection against gemcitabine. Further characterization of these candidate targets is ongoing.

Conclusion: PLP is a novel platform for classifying pancreatic cancer patients according to their benefiting from GE treatment. MS of the PLP library pull-downs reveals targets associated with gemcitabine resistance. In principle, the novel PLP platform could be applied to different therapeutic regimen for the development of urgently needed companion diagnostic tests in cancer and other diseases.

P – 133 The use of NLR, PLR and CA19.9 as prognostic markers for locally advanced pancreatic cancer

A Dean[1], D Higgs[1], A Das[2], S Fennessy[2], M Rogers-Seeley[2], C McGarvey[2], M McNulty[2]

[1]St John of God Hospital Subiaco, Subiaco, Australia, [2]St John of God Hospital Subiaco, Perth, Australia

Introduction: The routine use of gemcitabine with nab-paclitaxel and FOLFIRINOX is changing the approach to locally advanced pancreatic cancer. This study aims to assess

the accuracy of pre-treatment CA19.9, neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) as markers of prognosis patients with locally advanced pancreatic cancer.

Methods: A retrospective cohort study was conducted for 66 patients with locally advanced pancreatic cancer who received chemotherapy only (C), chemotherapy plus radiotherapy (CRT) or chemotherapy plus radiotherapy then surgery (CRTS) between January 2014 and February 2017. After excluding 31 patients' due to insufficient data, 35 of them were analysed for full blood count, NLR and PLR, prior to starting treatment and CA19.9 level before and during treatment. Patients were divided according to the type of treatment they received (C [n = 15], CRT [n = 12] or CRTS [n = 15]).

Results: Using the C only patients as a control group, there was a significant difference in the mean PLR between C and CRT (196.7 vs 121.0, p = 0.008), and C and CRTS groups (196.7 vs 129.1, p = 0.025). No significant difference in means seen between CRT and CRTS for PLR, nor for NLR amongst the three groups. The pre-treatment level of CA19.9 did not appear to correlate if a patient who underwent chemotherapy, progresses to radiotherapy or surgery. Median survival for the C group was 17 months, CRT was 26 months and CRTS group has not yet been reached.

Conclusion: This retrospective study showed that the platelet lymphocyte ratio was the only predictor of prognosis in our locally advanced pancreatic cancer cohort. Once median survival has been reached in the group receiving trimodality therapy (CRTS) we may be able to provide further data on PLR, NLR and rate of change in CA19.9 in predicting resection and survival. We aim to further expand our locally advanced cohort and hope to develop a novel formula may be predictive of prognosis and likelihood of resection.

P – 134 Antibodies matter: A meta-analysis of the prognostic value of human equilibrative nucleoside transporter 1 (hENT1) antibodies in pancreatobiliary cancer

D Yusuf[1], L Vos[1], A Lui[1], Z Abdelaziz[1], S Ghosh[2], J Spratlin[1], J Mackey[1]

[1]Cross Cancer Institute, Edmonton, Alberta, Canada, [2]Cross Cancer Institute, Edmonton, AB, Canada

Introduction: Gemcitabine, the primary drug for the treatment of pancreatobiliary cancer (PC), requires human equilibrative nucleoside transporter 1 (hENT1) to enter cells. High tumoral hENT1 expression has been linked to improved survival among PC patients treated with gemcitabine, however this finding has been inconsistent and studies used different anti-hENT1 immunohistochemistry (IHC) antibody assays.

Methods: We reviewed the literature for studies that examined hENT1 and clinical outcome in PC. Of the 138 publications, we identified 45 studies, 36 of which used immunohistochemistry (IHC) with one of eight anti-hENT1 protein antibody assays, while 9 used polymerase chain reaction for hENT1 RNA expression. In order to assess the contribution of antibody choice on outcomes and the prognostic value for gemcitabine benefit in PC we only examined the studies that utilized IHC. Three of the studies were excluded because they were ampullary or gallbladder cancer treated with surgery only and an additional 4 studies were removed from the analysis for population redundancy. Twenty-nine studies underwent detailed review.

Results: Among the 29 studies that underwent detailed review, 22 were in the adjuvant or neoadjuvant setting and 7 were of patients with locally advanced, metastatic, or recurrent disease. Of the 29 studies, 27 reported median overall survival (OS) values with p-values in 26, 22 reported progression-free survival (PFS). disease-free survival (DFS), or time to treatment failure (TTF) (21 of which reported p-values), and 19 reported p-values for both. High hENT1 expression was found in an average of 52% (range 24-92%) of tumor samples examined. Among studies that examined hENT1 expression and OS, 58% (15/26) showed an association between high tumoral hENT1 and improved OS for gemcitabine-treated patients. Among 10D7G2 antibody studies, 88% (7/8) demonstrated an association. Studies with other antibodies – in particular SP120 (2/9) – were less consistent. The ability to detect an association between high hENT1, with the 3 most commonly used antibodies (10D7G2, SP120, and PAB2255), and improved survival was antibody-dependent (Chi-square p = 0.0237). The progression-free survival (DFS) and recurrence-free survival (RFS) results were similar with 71% (15/21) of studies demonstrating an association between high tumoral hENT1 expression and improved survival. Among 10D7G2 antibody studies, 100% (6/6) demonstrated an association while only 43% (3/7) of studies that used SP120 demonstrated an association between high hENT1 and improved PFS/DFS. Pooled hazard ratio (HR) analyses of all antibody studies still demonstrate a link between high hENT1 tumor expression and improved OS (HR for death 0.754, 95% CI 0.665-0.854) and DFS (HR for relapse 0.832, 95% CI 0.709-0.976).

Conclusion: High tumoral hENT1 expression on IHC with 10D7G2 is a strong and reproducible prognostic marker for improved OS among gemcitabine-treated patients with PC. The use of other antibodies should be discouraged.

P – 135 The impact of inflammatory biomarkers on overall survival of patients with pancreatic cancer treated with chemoradiation

K Holub, C Conill

Hospital Clínic de Barcelona, Barcelona, Spain

Introduction: Systemic inflammation is a recognised feature of cancer progression and some inflammatory biomarkers such as Neutrophil-to-Lymphocytes Ratio (NLR) emerge as important prognostic factors of survival outcomes and several studies were carried out to explore NLR in pancreatic cancer. Despite the great interest in the role played by neutrophils in antitumour immunity, other subpopulations of leukocytes, such as eosinophils, seem to be overlooked in cancer setting. We evaluated the prognostic value of NLR in patients diagnosed with pancreatic carcinoma and treated with chemoradiation in our institution, and subsequently we proposed new eosinophil-based ratio expressed as Eosinophil-to-Lymphocyte Ratio (ELR), and we analysed its impact on overall survival of the same cohort of patients.

Methods: A total of 60 consecutive patients diagnosed with pathologically-confirmed locally advanced pancreatic cancer in stage I-III and treated with chemo-radiotherapy in our institution from September 2010 to November 2017 were retrospectively evaluated. Three patients who did not complete radiotherapy were eliminated, hence the analysis was based on the data of 57 patients. We analysed the relation between overall survival (OS) and systemic inflammatory biomarkers in blood tests at cancer diagnosis. The ELR was calculated as follows: eosinophil count/lymphocyte count. All patients were divided into two groups using the most discriminative cut-off value of 1.9 for NLR and 0.11 for ELR according to the ROC curves. Statistics: Chi2, Kaplan-Meier test (SPSSv.23), p-value 0.1.

Results: Median age at diagnosis was 66.0 years (range 43-83), 33 patients were males (57.9%). Cancer stage at diagnosis was IA in 5 patients (8.8%), IB-5 (8.8%), IIA-9 (15.8%), IIB-30 (52.6%), III-8 (13.5%). Main histology was adenocarcinoma 44 patients (77.2%), localised in the head of the pancreas (41 patients, 71.9%). All patients were treated with chemoradiation based on weekly gemcitabine and External Beam Radiotherapy (EBRT) at a dose of 45Gy (range 32 – 45Gy). Twenty six patients underwent surgery. After a median follow-up of 15.6 months (range 3.4 – 122.0, mean 18.9, SD 16.8), 47 patients (82.5%) were dead at the time of data collection. Kaplan-Meier analyses showed that a high NLR ($\geq$ 1.90) correlated significantly with a shorter OS of cancer patients showing a median OS of 14.6 months in group with NLR $\geq$ 1.90 (IC 95% 10.8 – 18.4) vs. 26.2 months (IC 95% 13.4 – 38.9) in group with NLR $<$ 1.9 (p = 0.033 Log Rank test, Chi2=4.3, p = 0.019 Breslow, Chi2=5.1). However, a high ELR ($\geq$ 0.12) were associated with better OS, showing a median OS of 21.4 months (IC 95% 11.0 – 31.7) vs. 15.6 months (IC 95% 11.5 – 19.7) in a low ELR group (p = 0.067 Log Rank test, Chi2=3.4, p = 0.057 Breslow, Chi2=3.6).

Conclusion: Increased value of NLR was related with worse OS but high ELR correlated with better survival outcome in pancreatic cancer treated with chemoradiation. These results could help identifying patients with higher risk of progression, with the additional benefit that both NLR and ELR are inexpensive and easy to get from the pre-treatment analysis. To our best knowledge, this is the first report evaluating the prognostic value of ELR in pancreatic cancer.

P – 136 Timed-flat infusion (TFI) 5-fluorouracil with irinotecan and oxaliplatin in pancreatic adenocarcinomas: A single institution experience with FIr/FOx regimen

A Cortellini[1], A Parisi[2], K Cannita[3], O Venditti[3], F Pavese[1], C D'Orazio[4], P Lanfiuti Baldi[3], V Vicentini[5], R Vicentini[5], G Porzio[4], L Verna[6], C Ficorella[1]

[1]Medical Oncology Unit, St. Salvatore Hospital, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [2]Medical Oncology Unit, St. Salvatore Hospital, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy, [3]Medical Oncology Unit, St. Salvatore Hospital, L'Aquila, Italy, [4]Medical Oncology Unit, St. Salvatore Hospital, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [5]Department of Hepatobiliar-Pancreatic Surgery, St. Salvatore Hospital, L'Aquila, Italy, [6]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

Introduction: Triplet chemotherapies, with fluoropyrimidines, platin derivatives and irinotecan, represent an option for first line treatment of metastatic/advanced pancreatic ductal adenocarcinoma (PDAC). FOLFIRINOX was often considered difficult to handle in common clinical practice, due to toxicity profile and features of PDAC patients, often frail with symptomatic disease. To increase tolerability and dose intensity (DI), we previously developed an alternative way of administration of 5Fluorouracil (5FU), with nocturnal "timed-flat infusion" (TFI) (from 10:00 PM to 10:00 AM), in several combination-schedules (breast, colorectal and gastric cancers). TFI mimics the chronomodulation of 5FU, without the dose-spike at 04.00 AM, 5FU bolus and folinic acid.

Methods: We report a retrospective analysis of 19 metastatic PDAC patients treated with FIr/FOx regimen, a schedule of weekly TFI/5FU for two nights at 900 mg/m2/night, associated to alternating irinotecan at 160 mg/m2 on days 1 and 15, and oxaliplatin at 80 mg/m2 on days 8 and 22, cycles repeated every 4 weeks.

Results: From February 2011 to February 2018, 19 patients were treated: 9 (47.4%) with standard FIr/FOx and 10 (52.6%) with modified regimens (defined as any projected dose reduction compared to standard) due to age, PS and comorbidities. Median age was 65 years (range 54-75), male/female ratio was 11/8. Ten patients (52.6%) had

ECOG-PS 0/1, 9 patients (47.4%) ECOG-PS 2. Fourteen patients (73.7%) had a primary/intermediate Cumulative Illness Rating Scale stage, 5 patients (26.3%) a Secondary one. Sixteen patients (84.2%) had un-resected primary tumor, 9 (47.4%) were located to the head and 10 (52.6%) to the body/tail. Two patients (10.5%) had obstructive jaundice at onset (carriers of biliary prosthesis). Thirteen patients (68.4%) had $\geq$ 2 involved organs. One patient had a metachronous disease previously treated with adjuvant gemcitabine and chemo-radiation therapy. Among 17 evaluable patients ORR was 35.2% (95%CI: 14.2-61.6) ad DCR was 58.8% (95% CI: 32.9-81.5). All patients were evaluable for efficacy: after a median follow-up of 42.6 months, median PFS and median OS were 4.4 months (95%CI: 2.3-11.8) and 11.8 months (95%CI: 2.3-19.9). Median Number of administered cycles was 3 (range: 1-11). The only G4 toxicity was mucositis in one patient (5.2%); G3 were: leuco/neutropenia (10.5%), asthenia (10.5%), diarrhea (5.2%), hypokaliemia (5.2%) and hypertransaminasemia (5.2%). No febrile neutropenia was observed; one patient died as result of adverse events. The median received DI were ~ 80% of standard full dose for each drug: Irinotecan 60 mg/m2/week, oxaliplatin 34 mg/m2/week and 5FU 1380 mg/m2/week. Four patients (21.1%) were switched to a doublet regimen after the induction (6 months) due to toxicities. Two patients (10.5%) underwent ablative locoregional treatments of primary tumors after FIr/FOx. Nine out of 18 patients who progressed to FIr/FOx underwent a second line therapy (2 rechallenges with FIr/FOx, 6 gemcitabine-Abraxane, 1 gemcitabine).

Conclusion: Even if requires a careful management, FIr/FOx seems to be a feasible option for first line treatment of metastatic PDAC patients, particularly in needing of tumor shrinkage, with significant activity, high rDIs, and acceptable safety profile when compared to literature.

P – 137 Intraperitoneal chemotherapy for pancreatic cancer with peritoneal metastases: A single center retrospective analysis of 25 patients

Y Tsuji[1], T Takayama[1], N Okamura[1], J Sugiyama[1], S Oiwa[2], M Yoshida[2], Y Okagawa[2], M Hirayama[2], D Sato[3], Y Suzuki[3]

[1]Department of Medical Oncology, Tonan Hospital, Sapporo, Japan, [2]Department of Gastroenterology, Tonan Hospital, Sapporo, Japan, [3]Department of Surgery, Tonan Hospital, Sapporo, Japan

Introduction: Unresectable pancreatic cancer is one of the unfavorable prognosis cancers with merely one year of median overall survival (OS). Furthermore, the prognosis becomes even worse with peritoneal metastases due to reduced delivery capacity of anti-cancer drugs and lots of associated complications. Recently, the efficacy and safety data of intraperitoneal paclitaxel (ip PTX) in combination with systemic chemotherapy for gastric cancer with peritoneal metastases has been published by Ishigami at the ASCO 2016. We have participated in this intraperitoneal chemotherapy study projects and here we applied this strategy to pancreatic cancer with peritoneal metastases.

Methods: Data from 25 patients with pancreatic cancer with peritoneal metastases who underwent intraperitoneal chemotherapy from August 2013 to January 2018 at our hospital were retrospectively analyzed.

Results: Of the 25 patients, 8 were chemotherapy-naïve, and the remaining 17 had been adopted after prior non-intraperitoneal chemotherapy. 9 patients had undergone primary tumor resection before peritoneal recurrence. The intraperitoneal regimens were assigned mainly according to the prior treatment: ip PTX plus S-1/PTX was the most frequent (8 cases), followed by ip PTX plus FOLFIRINOX (7 cases), ip PTX plus gemcitabine (6 cases), and the rest. The median progression free survival (PFS) for all 25 patients was 6.1 months, and the median OS was 17.3 months. The median PFS and OS for the chemotherapy-naïve group were 8.6 and 17.3 months and for the prior-chemotherapy group were 3.1 and 11.9 months, respectively. The median PFS and OS for 11 patients without non-excision factors other than peritoneal metastases were 11.5 and 18.4 months. A point of extreme interest is that 5 of 11 patients achieved conversion surgery after confirmed complete disappearance of peritoneal metastases. Adverse events of grade 3 or 4 were observed: leukopenia at 40%, neutropenia 64% and anemia 24%, which we attributed to the systemic treatments. 2 cases of localized infection of peritoneal port were observed specific to intraperitoneal therapy. All treatments were well tolerable and there were no treatment-related deaths.

Conclusion: This suggests, the combination of ip PTX with systemic chemotherapy for pancreatic cancer with peritoneal metastases provides survival benefit superior to conventional chemotherapy. We now only need to confirm these very promising results by a multicenter trial, and as soon as possible.

P – 138 Predictive factors for early relapse and survival in resected pancreatic cancer: A single institution experience

C Saavedra Serrano[1], P Reguera Puertas[2], O Martínez Saez[3], F Longo Muñoz[4], A Barquín García[1], V Albarrán Artahona[1], M Villamayor Delgado[3], J Molina Cerrillo[2], E Corral de la Fuente[1], R Martín Huertas[1], J Serrano Domingo[5], V Pachón Olmos[2], R Ferreiro Monteagudo[2], M Rodriguez Garrote[2], M Vaz[4], R Fuentes[1], C Guillén-Ponce[6], A Carrato[7]

[1]Ramón y Cajal Hospital, Madrid, Spain, [2]Ramón y Cajal University Hospital, Madrid, Spain, [3]Ramón y Cajal Univsersity Hospital, Madrid, Spain, [4]Hospital Universitario Ramón y Cajal, Madrid, Spain, [5,6]H. Universitario Ramón y Cajal, IRYCIS, Madrid, Spain, [7]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain

Introduction: Pancreatic cancer is an aggressive tumor with a high mortality rate. Upon diagnosis only 15-20% of cases are amenable to surgery. Despite achieving a complete resection, relapse free survival (RFS) and prognosis remain poor (RFS 60% at 12 months and 20% 5-year overall survival (OS)). Several studies suggest that early recurrence predicts poor prognosis. However, cut-offs to define early relapse (ER) are variable between reports. The aim of our study is to propose an optimal cut-off for ER and finding clinicopathological factors that predict ER in resected pancreatic cancer.

Methods: We conducted an observational retrospective study in the Ramón y Cajal University Hospital. Patients with resected pancreatic cancer between 2010 and 2016 were identified, and data was collected for predefined variables about patients and tumor clinicopathological characteristics, treatment procedures, oncological outcomes and follow up. Hazard ratio for overall survival was estimated for 3, 6, 9 and 12 months as potential cut-off points for ER. Univariate analysis with logistic regression were performed for factors potentially associated with ER risk. Significant factors identified were included into a predictive multivariate model using logistic regression. An estimative model for potential confusion factors was made for significant variables in the previous step. We obtained Kaplan-Meier curves and performed Cox regression for RFS and OS to confirm prognostic value of variables identified, and screened for confusion factors.

Results: 67 patients who met inclusion criteria were identified. 54% were women. Median age at surgical intervention was 70 years old (range 44-85 years). 83.6% of tumors were located in the pancreatic head and R0 resection was achieved in 38.8%. 70.2% of patients received adjuvant chemotherapy (AC). At a median follow up of 39.2 months, relapse was confirmed in 56.7% of cases, of which 86.8% received further chemotherapy. The optimal cut-off point to define ER was 6 months in our cohort, as it showed the greatest difference in overall survival (HR 3.98; 95%CI 1.98-8.00). With this cut-off point, 2 year OS was 41% in the late relapse group and 10% in the ER group. AC and postoperative morbidity were identified as predictive factors for ER in the univariate analysis. The multivariate predictive model including these factors only showed a statistically significant difference for AC (OR 0.10; 95%CI 0.03-0.33; p 0,000). Additional test for confusion factors on AC effect was negative. Cox regression model showed a significant effect of AC both in RFS (HR 0.30; 95%CI 0.169-0.562) and OS (HR 0.303; 95%CI: 0.15-0.60). In a multivariate model, the effect of AC was maintained for RFS, but not for OS when adjusted for performance status. No other confusion factors were found.

Conclusion: In our cohort, the best cut-off point to define early relapse in resected pancreatic cancer is 6 months. This cut-off point differentiates two groups with different prognosis. Patients receiving adjuvant chemotherapy were less likely to have an early relapse, regardless of other factors. Also, adjuvant chemotherapy impacts RFS and OS. Extrapolation of our results to general population is limited by its retrospective nature.

P – 139 HGCSG 1403: Phase I trial of oxaliplatin/irinotecan/S-1 (OX-IRIS) as first line chemotherapy for unresectable pancreatic cancer

A Ishiguro[1], Y Kawamoto[2], S Yuki[3], S Nakano[3], M Yagisawa[2], K Sawada[2], T Muranaka[2], H Hayashi[4], H Nakatsumi[2], T Saiki[1], K Harada[5], Y Kobayashi[5], I Iwanaga[6], K Hatanaka[7], Y Sakata[8], Y Komatsu[9]

[1]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan, [2]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [3]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [4]Division of Clinical Cancer Genomics, Hokkaido University Hospital, Sapporo, Japan, [5]Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan, [6]Department of Medical Oncology, Japanese Red Cross Kitami Hospital, Kitami, Japan, [7]Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan, [8]Misawa City Hospital, Misawa, Japan, [9]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan

Introduction: In recent years, FOLFIRINOX has become one of the primary standard treatment for unresectable pancreatic cancer (PC) with distant metastasis. OX-IRIS is the combination therapy of oxaliplatin (L-OHP), irinotecan (IRI) and S-1. It is the useful treatment to dispense with a continuous infusion of 5FU by administering S-1 orally. For establishing OX-IRIS therapy as a new standard treatment, we planned this study for evaluating dose limiting toxicity (DLT) and maximum tolerated dose (MTD). Furthermore, we exploratorily considered the efficacy (UMIN ID: 000017002).

Methods: This study was carried out as a multicenter phase I study in 6 institutions. Chemotherapy-naïve patients with unresectable PC were included. L-OHP and IRI were administered on day1 and 15, and S-1 was taken twice a day in day1-14, and 14

days were rest for 1 cycle. This study used a standard 3 plus 3 design, and we evaluated safety and tolerability in 3 to 6 cases of each levels. It was assumed until 1 cycle completion for the evaluation period of DLT. MTD was defined as the highest dose beyond a more of one-third within DLT evaluation period. The primary endpoint was the frequency of DLT and MTD. Secondary endpoints were the frequency of adverse events, response rate, progression-free survival (PFS) and overall survival (OS).

Results: Between January 2016 and August 2017, 13 cases were enrolled. The patients' backgrounds were median age 62 years old, man/woman; 9/4, the primary tumor sites head/body and tail; 8/5, ECOG PS 0/1; 7/6, UR-LA/UR-M; 4/9. The metastatic sites were lymph nodes/liver/lung/peritoneum; 2/7/1/1. Two of five patients enrolled in level 0 (L-OHP: 85 mg/m2, IRI: 100 mg/m2, S-1: 80 mg/m2) had DLT. In two of eight patients enrolled in level -1 (L-OHP: 65 mg/m2, IRI: 100 mg/m2, S-1: 80 mg/m2), DLT was impossible to evaluate because the treatment of 1 cycle was not accomplished. And one of remaining six cases had DLT. At level 0, 100% of cases had anemia and fatigue, 80% had anorexia, diarrhea, peripheral sensory neuropathy, 60% had platelet count decrease. At level -1, 100% of cases had anemia, 75% had nausea and fatigue, 63% had anorexia. Response rate was 10% and disease control rate was 70% in ten cases with the evaluable lesion. Median PFS was 4.1 months (95%C.I.; 0.0-8.6 months).

Conclusion: In this study, MTD was estimated to be level 0, and determined that recommended dose (RD) was level -1 in the planned future study. We are going to evaluate efficacy and the safety in a phase II study.

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WITHDRAWN

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PanCO: An open-label, single-arm pilot study of Oncosil™ in patients with unresectable locally advanced pancreatic adenocarcinoma in combination with FOLFIRINOX or gemcitabine+nab-paclitaxel chemotherapies

M Harris[1], D Croagh[2], M Aghmesheh[3], A Nagrial[4], N Nguyen[5], H Wasan[6], T Ajithkumar[7], A Kraszewski[8], T Maher[8], P Ross[9]

[1]Monash Cancer Centre, Melbourne, Australia, [2]Monash Medical Centre, Melbourne, Australia, [3]Wollongong Hospital, Wollongong, Australia, [4]Westmead Hospital, Sydney, Australia, [5]Royal Adelaide Hospital, Adelaide, Australia, [6]Hammersmith Hospital, London, UK, [7]Addenbrooke's Hospital, Cambridge, UK, [8]OncoSil Medical, Sydney, Australia, [9]Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, UK

Introduction: Locally advanced pancreatic cancer (LAPC) is associated with a poor prognosis. Current standard treatment is limited to chemotherapy or chemo-radiotherapy. Novel treatment approaches are crucial in attempting to combat this unmet medical need. Phosphorus-32 (P-32) Microparticles is a brachytherapy device that implants a predetermined dose of the beta radiation emitting isotope (P-32) directly into pancreatic tumours via endoscopic ultrasound (EUS) guidance. The presented data are early results from an ongoing international, multi-institutional, single-arm pilot study. The study objective is to determine the safety and efficacy of P-32 Microparticles in a patient population undergoing standard chemotherapy for unresectable LAPC.

Methods: Eligible patients were allocated to receive either gemcitabine+nab-paclitaxel or FOLFIRINOX by physician choice. P-32 implantation took place during the 4th or 5th week following the initiation of chemotherapy. P-32 was implanted directly into the pancreatic tumour via EUS guidance, using a fine needle aspiration (FNA) needle. Each patient's dose was calculated from the tumour volume where the absorbed dose of P-32 to the tumour was calculated to equal 100 Gy. Diffusion pattern of the P-32 suspension following implantation was assessed by EUS and by bremsstrahlung SPECT/CT imaging. Chemotherapy was continued after the implantation. Safety data was collected weekly and toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE). Centrally-read CT scans were conducted every 8 weeks to assess response defined as complete response [CR], partial response [PR], and stable disease [SD]) rate, according to RECIST 1.1 criteria. FDG-PET scans were performed at baseline and at week 12.

Results: Data is reported on the first 15 implanted patients (10 males and 5 females, median age 65 years [range 54-73]) up to week 16 of follow up. At 16 weeks, the objective response rate was 20% - PR in 3/15 patients. The local disease control rate (CR, PR and SD) was 87% - either PR or SD in 13/15 patients. Median change in tumour volume from baseline to week 16 was -33% (range +36% to -72%). Total lesion glycolysis (TLG) as measured via FDG-PET scan showed a median reduction of 52% (range +45% to -100%) from baseline to week 12. The EUS-guided implantation was carried out successfully in all patients and without any complications. By week 16, 223 adverse events (AEs) were reported. Twenty-four Grade 3 AEs (11%) and 5 (2%) Grade 4 toxicities were reported. The most common AEs of Grade 3 and 4 severity were neutropenia (6), anaemia (2), constipation (2), vomiting (2) and fatigue (2). None of the G3 and G4 AEs were attributable to the device or the implantation procedure.

Conclusion: Early data indicates that the use of EUS-guided implantation of P-32 is highly feasible, well tolerated and has an acceptable safety profile in combination with standard first-line chemotherapy for LAPC. Preliminary data shows evidence of tumour regression and local disease control. These results, however, warrant further evaluation. The clinical trial is ongoing and additional safety and efficacy data will be presented. ClinicalTrials.gov Identifier: NCT03003078. Acknowledgement: Nab-paclitaxel was supported by Specialised Therapeutics Australia Pty Ltd.

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Updated results of biweekly gemcitabine/nab-paclitaxel as first-line treatment for advanced pancreatic cancer

S Kokkali[1], M Drizou[1], E Tripodaki[1], D Stefanou[1], E Magou[1], D Zylis[2], M Kapiris[1], D Nasi[1], C Georganta[1], A Ardavanis[2]

[1]St Savvas Anticancer Hospital, Athens, Greece, [2]First Department of Medical Oncology, Aghios Savvas Anticancer Hospital, Athens, Greece

Introduction: The combination of gemcitabine and nab-paclitaxel for first-line treatment for advanced pancreatic cancer has shown better results in response and survival over gemcitabine monotherapy. The standard administration on days 1, 8 and 15 of a 4-week cycle has some practical disadvantages. We present the updated results of an observational study for which we adopted a biweekly regimen with the same dose density.

Methods: Between 30 May 2014 and 02 March 2018, 56 patients with ECOG/PS 0-2 diagnosed with locally advanced or metastatic, histologically or cytologically confirmed pancreatic cancer and no prior treatment, were enrolled in the study. The regimen included 1.5 g/m2 gemcitabine and 175 mg/m2 nab-paclitaxel given every two weeks until disease progression or unacceptable toxicity. All patients were informed and signed a consent form. Study endpoints were PFS, OS and toxicity profile. The survival analysis was performed using Kaplan-Meier method.

Results: 56 patients received this treatment. After a median follow-up period of 7.1 months, the median PFS and OS were 5.3 and 10 months respectively. There was no toxic death during the study and the adverse events noted were similar to those of the original regime.

Conclusion: Biweekly combination of gemcitabine and nab-paclitaxel seems to be as safe and efficient as the original regimen. It reduced the patients' discomfort as well as the cost of the treatment.

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Safety of gemcitabine plus nab-paclitaxel in advanced pancreatic cancer patients presenting with hyperbilirubinemia secondary to bile duct obstruction

M Sasaki[1], H Imaoka[2], M Kan[2], Y Suzuki[2], G Kimura[2], K Umemoto[2], K Watanabe[2], H Takahashi[2], Y Hashimoto[2], I Ohno[2], S Mitsunaga[2], M Ikeda[2]

[1]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Chuo-ku, Japan, [2]National Cancer Center Hospital East, Kashiwa, Japan

Introduction: The MPACT study demonstrated a significant survival benefit of gemcitabine plus nab-paclitaxel (GN) as compared to gemcitabine alone, however, patients with abnormal elevation of the serum total bilirubin (Tbil) levels were excluded from

the study. Patients with advanced pancreatic cancer (APC) often present with extrahepatic bile duct obstruction, which can result in elevated Tbil levels. Normalization of Tbil by biliary drainage can take weeks, so safety data to support treatment initiation in patients with elevated Tbil levels are desirable. Therefore, we attempted to evaluate the safety of GN, in terms of the risk of hematological toxicity in APC patients presenting with hyperbilirubinemia secondary to bile duct obstruction.

Methods: Data of a total of 351 patients with APC who were treated with GN as first-line treatment at our department between Dec. 2014 and Dec. 2017 were reviewed retrospectively. Patients who underwent biliary drainage before the initiation of GN and received no initial dose reduction were included, while patients with irreversible hyperbilirubinemia due to liver metastasis were excluded. The patients were divided into two groups according to the Tbil levels at the initiation of GN: the normal bilirubin group (NB-G group; Tbil ≦1.5 mg/dL) and hyperbilirubinemia group (HB-G group; Tbil >1.5 mg/dL). The incidence of severe hematotoxicity during the first cycle of treatment was compared between the two groups. The p-values < 0.05 were considered statistically significant and all p-values were two sided.

Results: A total of 78 patients, including 59 from the NB-G group and 19 from the HB-G group were included in this analysis. The patient characteristics (NB-G vs. HB-G groups) were as follows: median age, 66 vs. 69; ECOG-PS 0-1/2, 56/3 vs. 19/0; male/female, 28/31 vs. 9/10; UICC-TNM stage III/IV, 22/37 vs. 8/11; primary site head/body-tail, 56/3 vs. 19/0; biliary intervention with plastic stent/metallic stent/surgical bypass, 12/45/2 vs. 3/16/0; median pretreatment Tbil, 0.72 mg/dL (0.22-1.49) vs. 1.8 mg/dL (1.51-2.76). During the first cycle of treatment, severe hematologic adverse events (grade 3/4 neutropenia and/or grade 3/4 thrombocytopenia) occurred in a total of 31 patients and febrile neutropenia in a total of 7 patients. There were no significant differences in the incidence of severe hematological adverse events between the two groups (22 in the NB-G group and 9 in the HB-G group; $p = 0.59$).

Conclusion: The safety of GN, in terms of the risk of hematological toxicity was similar between the NB-G and HB-G groups in this study. For APC patients presenting with hyperbilirubinemia secondary to bile duct obstruction, it might be safe to initiate GN without dose reduction if a suitable procedure for biliary drainage is undertaken prior to the initiation of the treatment.

P – 144 Pancreatic ductal adenocarcinoma (PDAC) and type 2 diabetes mellitus: Cause or consequence? Analysis of the prevalence of alterations in glucose metabolism (AGM) in a patients' cohort with PDAC

L Medina Rodriguez[1], C Sanchez Cendra[2], M Pantin Gonzalez[2], D Gutierrez Abad[3], I Juez Martel[3], M De Torres Olombrada[3]

[1]Hospital de Fuenlabrada, Fuenlabrada, Spain, [2]Hospital Universitario de Fuenlabrada, Fuenlabrada, Spain, [3]Hospital Universitario Fuenlabrada, Fuenlabrada, Spain

Introduction: Type 2 diabetes mellitus is likely the third modifiable risk factor for pancreatic cancer (PDAC) after cigarette smoking and obesity. Epidemiological investigations have found that long-term type 2 diabetes mellitus is associated with a 1.5- to 2.0-fold increase in the risk of PDAC. On the other hand, new-onset diabetes may indicate subclinical PDAC, and patients with new-onset diabetes may constitute a population in whom PDAC can be detected early. Use of the antidiabetic drugs, such as metformin, has been associated with reduced risk of PDAC in diabetics and recognized as an antitumor agent with the potential to prevent and treat this cancer. Several ongoing clinical trials are exploring this potential benefit in different settings of PDAC.

Methods: We aimed to study the prevalence of AGM in patients diagnosed by PDAC at our service and explore their potential interactions between other known risk factors for PDAC. This is an observational and retrospective study based on clinical data from 60 patients diagnosed by PDAC between January 2013 to December 2017. Clinical and epidemiological variables were collected as well as variables associated to risk factors for PDAC. Overall survival (OS) and progression-free survival (PFS) were estimated with the use of the Kaplan–Meier method.

Results: Data from 60 patients were analysed. The median age at the diagnosis was 61 years. Male represented 55% of the total, and female the 45%. 86% of the patients presented metastatic (M1) disease at the analysis moment and 70% of the patients had died. The median OS was 26 months for early stage tumours and 16 months for metastatic setting. The PFS for M1 patients was 6,1 months. From all patients, 55% showed AGM, and between these patients, the 55% were diagnosed "de novo", and the 28% suffered from long-term hyperglycaemia or diabetes. This trend was maintained in M1 patients. Only in M1 patients, we observed that about 60% of the patients experienced a worsening of AGM during the disease showing a tendency to statistical significance between this worsening and progression disease ($p = 0,06$). Between patients with AGM only 41% had received corticoid treatment during the disease. Use of corticoids does not seem to be associated with AGM evolution. Only the 20% of patients with were referred to the Endocrinology Department for control.

Conclusion: The relationship between PDAC and diabetes is very complex. Frequently, de novo alterations in glucose metabolism are underdiagnosed and trivialized. Based on our results we are starting a prospective observational study in collaboration with Endocrinology Department to evaluate PDAC patients with AGM in order to optimize the diabetes treatment and explore its influence in tumour natural history.

P – 145 FOLFIRINOX in pancreatic cancer: A careful review

E Una Cidon[1], P Alonso[2]

[1]Oncology Department, Royal Bournemouth Hospital, NHS Foundation Trust, Bournemouth, UK, [2]Clinical University Hospital, Valladolid, Spain

Introduction: Pancreatic cancer approach should be multimodal. FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) has shown effectiveness in the treatment of this disease by increasing response rate with an impact on median survival. Toxicity could be concerning but supportive measures can help significantly. We carried out a retrospective review of pancreatic cancer patients receiving this treatment. We assessed them for response after 3 months of treatment.

Methods: All patients diagnosed with metastatic pancreatic cancer were discussed at a multidisciplinary team. Those consider fit enough, were treated with FOLFIRINOX. We assessed primarily the response after three months of treatment and also side-effects.

Results: We evaluated 73 patients, 47 female. Median age was 61 (50-69). The most common toxicities grade 3 or higher were gastrointestinal, mainly diarrhoea and nausea/vomiting. 17 patients required admission due to diarrhoea and dehydration. Haematological toxicities such as neutropenia grade 3-4 occurred in 39 patients, 12 of them needed admission due to neutropenic sepsis. Fatigue was also a relevant side-effect present in all the patients, grade 1 in most of them but grade 3 or higher in 43 patients. Dose of chemotherapy was reduced in 48 patients. In 11 of them the reason for a reduction was peripheral neuropathy. 45 patients had a response, 18 stable disease, and the rest progression.

Conclusion: FOLFIRINOX as a therapy for metastatic pancreatic adenocarcinoma is a good option providing good supportive measures are in place to reduce the side-effects.

P – 146 Circulating tumor DNA (ctDNA) as a predictor of treatment for locally advanced pancreatic cancer

G Botiralieva

National Cancer Research Centre, Tashkent, Uzbekistan

Introduction: By today R0 – curative resection is possible following neoadjuvant treatment for LAPC, however still there is no method to determine patients beforehand who will have a favorable surgical outcome. The aim of this study was to evaluate the prediction possibilities of ctDNA during chemo-radiotherapy after surgical treatment of locally advanced pancreatic cancer.

Methods: 42 patients were enrolled in this study who were treated in National Cancer Research Centre. Pts received neoadjuvant FOLFIRINOX followed by CRT: either short-course ($n = 12$, 25 Gy/5 fractions), or longcourse ($n = 30$, 50.4 Gy/28 fractions). Serum ctDNA was measured at baseline, every week during CRT, and preoperatively. After extracting DNA from plasma, a tumor mutation specific droplet digital PCR assay was used to detect the fraction of ctDNA molecules. Outcomes of treatment were based on: CA19-9, CEA, RECIST score, tumor grade, T stage, tumor regression grade (TRG), R-resection status, pathologically involved lymph nodes, LVI, and PNI.

Results: The median age of patients was 64 years (range 39-82 years). Following CRT, 33 (78,5%) were operable. The overall R0-node negative (R0-NN) resection rate was 59% for the entire cohort. The rate of R0-NN resection higher among patients with an undetectable preoperative ctDNA ($n = 16$) compared to those with a detectable ($n = 26$) preoperative ctDNA (88% R0-NN vs 50% R0-NN, respectively). Only ctDNA status was significantly associated with R0-NN resection ($p = 0.025$), whereas preoperative RECIST score, CA19-9, and CEA were not associated. For patients who received surgery, the ctDNA was significantly correlated with TRG (Pearson $R = 0.399$, $p = 0.024$).

Conclusion: Detection of ctDNA is associated with poorer surgical outcome in patients treated with neoadjuvant CRT for locally advance pancreatic cancer. At the same time absence of ctDNA in blood serum leads to a better surgical outcomes, this fact is one more evidence for implementing this technique into a daily routine for more appropriate selection of patients who will benefit from surgical treatment.

P – 147 Use of gemcitabine and nab-paclitaxel as a third-line treatment following failure of first line gemcitabine for advanced pancreatic adenocarcinoma

M McNulty[1], A Dean[2], A Das[1], M Gordon[1]

[1]St John of God Hospital Subiaco, Perth, Australia, [2]St John of God Hospital Subiaco, Subiaco, Australia

Introduction: First line treatment for advanced pancreatic adenocarcinoma is well documented and typically involves therapy with FOLFIRINOX or gemcitabine plus nab-paclitaxel. The CONKO-003 trial demonstrated efficacy of 2nd line treatment with the OFF regimen (oxaliplatin, 5-fluorouracil and folinic acid) and more recently the phase III trial, NAPOLI-1, established a tolerable and effective 2nd line treatment option, combining nal-irinotecan with 5-fluorouracil and leucovorin. Despite these advances, there remains minimal amount of data regarding the options for or the

efficacy of 3rd line treatment in these patients. This retrospective analysis assessed the use of gemcitabine plus nab-paclitaxel as a 3rd line treatment option in a single hospital settling.

Methods: Using an electronic database, we conducted a retrospective analysis of 20 patients with locally advanced or metastatic adenocarcinoma of the pancreas who received third line treatment with gemcitabine and nab-paclitaxel between 2013 and 2017. We selected patients who had received first line gemcitabine-based therapy, to assess the subsequent outcome of retreatment with gemcitabine and nab-paclitaxel (800 mg/m2 and 125 mg/m2 respectively, on days 1, 8 and 15 every four weeks). Overall survival (OS) was estimated by the Kaplan-Meier method.

Results: Twenty patients were reviewed. Median age was 70 years (range, 44 – 81). 55% of the patients were females. Majority of the studied patients had locally advanced cancer at diagnosis (85%). The median OS was 6.0 months (95% CI, 4.0 – 26.0) from re-initiation of gemcitabine plus nab-paclitaxel.

Conclusion: This retrospective study showed that retreatment of advanced pancreatic adenocarcinoma patients with gemcitabine plus nab-paclitaxel could be a suitable third-line treatment option. In order to evaluate the actual efficacy of this third-line chemotherapy regimen, phase III trials would need to be conducted to compare gemcitabine plus nab-paclitaxel with other chemotherapeutic agents.

P – 148 Nimotuzumab bi-weekly/low dose combined to chemotherapy in advanced pancreatic cancer: A clinical study

M Lima[1], V Jennifer[2], C Dominguez[3], G Robin[2], M Dunia[2], O Alexander[4], G Giselle[4], M Amparo[5], R Ivan[2], B Noyde[2], J Soriano[2]

[1]Clinical Oncology Department, Ameijeiras Hospital, Havana, Cuba, [2]Ameijeiras Hospital, Havana, Cuba, [3]Clinical Pathology Department, Ameijeiras Hospital, Havana, Cuba, [4]Molecular Biology Department, Ameijeiras Hospital, Havana, Cuba, [5]Center of Molecular Immunology, Havana, Cuba

Introduction: Pancreatic cancer is the fourth most common cause of death by an oncological disease worldwide and treatment for advanced stages has not shown satisfactory results in terms of survival. The primary end points were overall survival and the frequency and severity of adverse events.

Methods: Outcomes of advanced and/or metastatic pancreatic cancer, treated with nimotuzumab (between January 2012 and December 2015) were retrospectively analyzed (n = 63). Patients were treated with nimotuzumab (dose:200 mg q2w) in combination with standard chemotherapy, according with Cuban Clinical Practice Guidelines. Once chemotherapy was discontinued, nimotuzumab was continued, at the same dose, until symptomatic disease progression or death of patients. Univariate survival analysis was performed by Kaplan-Meier curves, as compared by the Log-rank and/or Breslow test, considering p<.05 statistically significant.

Results: Median age was 59 years old. Patients were mostly man (63.5%) with comorbidities (60.3%), ECOG= 1 (54%) and ECOG= 2 (33%). Tumors were mostly differentiated (69.8%) with metastasis (60.3%). Treatment combinations were mainly with gemcitabine (73.0%). Achieved median OS was 9.6 months (CI 95%: 5.7; 13.1). Survival rate at 6 and 12 months were 73.2% and 42.5%, respectively. Patients with ECOG=0 and ECOG=1 achieved median OS of 14.1 months (6.9; 21.3) p=.03 and 11.1 months (5.9; 16.3) p=.01, respectively. Patients who achieved stable disease, showed an OS of 39.5 months (29.3; 49.6) p=.00. KRAS status was determined in 33% of the patients. Despite that median OS of KRAS wild-type patients (45%) was 2.2 months higher compared with patients with muted KRAS, this was not significant [11.6 vs 9,4 months (p=.66)]. Toxicity was detected in twenty six patients. Six patients developed increase of transaminases (grade 1-2). Five patients presented diarrhea (grade 1-2) and 1 patient presented diarrhea grade 3. Only one patient developed neuropathy grade 3 and other three developed neuropathy grade 1-2. 36.5% of the patients required adjustment of the gemcitabine or the oxaliplatin, according to the chemotherapy regimen. These adjustments generated delays in the following dose administration. No allergy or skin rashes were observed.

Conclusion: Survivals obtained with the use of lose doses of nimotuzumab, in combination with chemotherapy, was similar to the one observed in other groups with a higher dose and a lower toxicity. The addition of nimotuzumab to standard chemotherapy does not increase toxicity and it is well tolerated. Other trials must be developed in order to confirm obtained results.

P – 149 Risk factors and epidemiological features of pancreatic cancer in Iran

A Pourshams

Digestive Diseases Research Institute, Tehran University of Medical Sciences., Tehran, Iran

Introduction: Pancreatic cancer (PC) has the lowest survival rate of all cancers worldwide. PC is more common in affluent nations, but it is on the rise in developing countries. Although increasing in PC incidence is largely because aging, it is necessary to know its risks, to be able to control PC in developing countries.

Methods: In a prospective study, cases (new incident pathology confirmed pancreatic adenocarcinoma) and controls (patients with GI motility disorders, but not any pancreatic disease or any cancer) were selected from who were referred to Shariati Hospital in Tehran, Iran from January 2011 to January 2018. A validated structured questionnaire was used to interview 462 PC cases and 476 matched controls (age and sex) before to made final diagnosis for the cases and controls. All cases and controls were under active follow up.

Results: The median (±SD) age at time of PC diagnosis was 65±11 years and 60.8% were male with a male-to-female ratio of 3:1. After adjustment for potential confounders, opium use (OR = 1.97, 95% CI 1.09–3.28) and alcohol consumption (OR = 3.88, 95% CI 1.89–8.63) were significantly associated with an increased risk of PC. No association was found between ever tobacco smoking and PC risk (OR = 0.91, 95% CI 0.60 –1.43). Increasing consumption of barbecuing red meat and deep fried vegetables was associated with 67% and 70% increased risk of PC (p-value 0.025 and 0.006, respectively). In contrary to increasing frequency of fish consumption was associated with a lower risk of PC (OR = 0.93, 95% CI 0.59–1.47; p for trend 0.009). Strong association was found between PC and obesity (OR = 3.52, 95% CI 2.20 - 6.48) as well as long term diabetes mellitus (OR = 2.01, 95% CI 1.26 - 3.31). High-wealth status were inversely associated with risk of PC. Age at menarche and menopause, number of parity, gravidity, and abortion were not associated with PC risk in women. Median overall survival was 6.3 months. Only 5.3% of cases underwent a curative surgery. Cases who were married (6.4 vs 5.8 months; log-rank P =.01), had university education (10.4 vs 5.9 months; log-rank P =.004) and were urban residents (6.5 vs 5.3 months; log-rank P =.03) had longer survival. Patients with a tumor >4 Cm, stage ≥III and those who consumed opium had the worst prognosis. Chemotherapy alone did not increase the patient's longevity.

Conclusion: Obesity, diabetes mellitus, low socio-economic status, opium use and alcohol consumption, but no cigarette smoking, were associated with an increased risk of PC in our population.

P – 150 Prognostic effect of primary tumor location in the NAPOLI-1 phase 3 study in metastatic pancreatic ductal adenocarcinoma (mPDAC)

T Macarulla Mercadé[1], A Wang-Gillam[2], L Chen[3], J Blanc[4], K Lee[5], G Bodoky[6], A Dean[7], J Siveke[8], B Mirakhur[9], J Chen[10], F de Jong[11]

[1]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [2]Division of Oncology, Washington University, St. Louis, Missouri, USA, [3]National Institute of Cancer Research, National Health Research Institutes, Miaoli, Republic of Taiwan, [4]Hôpital Haut-Lévêque, Bordeaux, France, [5]Seoul National University Hospital, Seoul, Republic of Korea, [6]Department of Oncology, Szent László Hospital, Budapest, Hungary, [7]St John of God Hospital Subiaco, Subiaco, Australia, [8]West German Cancer Center, University Hospital Essen, Essen, and German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Essen, Germany, [9]Ipsen Biopharmaceuticals, Inc., Basking Ridge, New Jersey, USA, [10]Shire plc, Cambridge, Massachusetts, USA, [11]Shire International GmbH, Glattpark-Opfikon, Switzerland

Introduction: In NAPOLI-1 (NCT01494506), treatment with liposomal irinotecan + 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) significantly increased median overall survival (mOS) vs. 5-FU/LV (6.1 vs. 4.2 months; unstratified hazard ratio [HR]=0.67, 95% confidence interval [CI]:0.49–0.92; P = 0.012) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who had progressed following gemcitabine-based therapy. A potential prognostic impact of primary tumor location on metastatic pancreatic cancer outcomes has been reported. We investigated the effect of primary tumor location on survival following inclusion in the NAPOLI-1 study.

Methods: This post-hoc analysis explored outcomes in patients with primary tumor locations of the pancreatic head only (H only), body only (B only), tail only (T only), and multiple locations including (H_incl) and excluding (H_excl) the head.

Results: Of 417 patients, 239 (57%) had a primary tumor location of H only, 54 (13%) B only, 62 (15%) T only, 17 (4%) H_incl and 30 (7%) H_excl. Karnofsky performance status was lower in patients with a primary tumor location of T only versus the intent-to-treat population. The mOS (HRs: 0.87–1.06) and median progression-free survival (mPFS) (HRs: 0.82–0.98) were similar across primary tumor location subgroups and no clear prognostic signal for OS was detected. The mOS and mPFS in patients with a primary tumor location of H only were 5.0 and 2.7 months, respectively, versus 5.4 and 2.8 months, respectively, for those with B only (mOS: HR = 1.06, 95%CI:0.75–1.50, P = 0.737; mPFS: HR = 0.98, 95%CI:0.70–1.37, P = 0.925). For patients with T only, mOS and mPFS were 4.3 and 1.7 months respectively (mOS H only vs. T only: HR = 0.89, 95%CI:0.64–1.23, P = 0.469; mPFS H only vs. T only HR = 0.89, 95%CI:0.66–1.22, P = 0.471). For patients with H_incl, mOS and mPFS were 5.7 and 2.3 months respectively, while for H_excl patients they were 4.6 and 1.4 months, respectively. For the comparison of mOS between the H only and B only+T only+H_excl subgroup (mOS=4.4, mPFS=1.7 months), HR = 0.88 (95%CI:0.69–1.11, P = 0.285) while for mPFS HR = 0.83 (95%CI:0.66–1.05, P = 0.116). For the comparison of mOS between the H only and B only+T only+H_excl+H_incl subgroup (mOS=4.6, mPFS=1.7 months), HR = 0.91 (95%CI:0.72–1.15, P = 0.421), while for mPFS HR = 0.87 (95%CI:0.70–1.09, P = 0.233). For the comparison of mOS between the H only+H_incl and B only+T only+H_excl subgroup HR = 0.87 (95%CI:0.69–1.10, P = 0.240), while for mPFS HR = 0.82 (95%CI:0.65–1.03, P = 0.084). Both mOS and mPFS were higher in patients treated with nal IRI+5 FU/LV vs. 5 FU/LV across primary tumor location subgroups (mOS: HRs: 0.39–0.88; two groups with n < 10 per arm were discounted). Safety, drug related AEs and dose modifications/discontinuations in the PTL subgroups were broadly similar to the overall NAPOLI 1 study arms.

Conclusion: In NAPOLI-1, 61% of patients had a primary tumor location including the pancreatic head. This analysis did not detect a clear prognostic effect of primary

tumor location on survival for mPDAC patients progressing after gemcitabine-based treatment. Patients with primary tumors in the head only or including head had similar mOS and mPFS to other patients. A consistent treatment benefit was shown with nal-IRI+5-FU/LV vs. 5-FU/LV regardless of primary tumor location.

P – 151 Prognostic value of baseline biliary stents on outcomes in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in the NAPOLI-1 trial

G Lakatos[1], K Lee[2], J Siveke[3], J Blanc[4], T Macarulla Mercadé[5], A Dean[6], G Bodoky[7], B Mirakhur[8], J Chen[9], A Wang-Gillam[10], L Chen[11], F de Jong[12]

[1]Department of Oncology, St. István and St. László Hospital, Budapest, Hungary, [2]Seoul National University Hospital, Seoul, Republic of Korea, [3]West German Cancer Center, University Hospital Essen, Essen, and German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Essen, Germany, [4]Hôpital Haut-Lévêque, Bordeaux, France, [5]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [6]St John of God Hospital Subiaco, Subiaco, Australia, [7]Department of Oncology, Szent László Hospital, Budapest, Hungary, [8]Ipsen Biopharmaceuticals, Inc., Basking Ridge, New Jersey, USA, [9]Shire plc, Cambridge, Massachusetts, USA, [10]Division of Oncology, Washington University, St. Louis, Missouri, USA, [11]National Institute of Cancer Research, National Health Research Institutes, Miaoli, Republic of Taiwan, [12]Shire International GmbH, Glattpark-Opfikon, Switzerland

Introduction: In the NAPOLI-1 phase 3 study of patients with mPDAC who progressed following gemcitabine-based therapy (NCT01494506), nal-IRI+5-FU/LV significantly increased median overall survival (mOS) vs 5-FU/LV control (6.1 vs 4.2 months; unstratified hazard ratio [HR]=0.67 [0.49–0.92]; P = 0.012). Biliary stenting is used to treat malignant obstructive jaundice and associated complications, allowing bile efflux resulting in normalised bilirubin levels. Patients with a biliary stent were allowed to enter the NAPOLI-1 study if plasma bilirubin was normal.

Methods: This post-hoc analysis explored outcomes in patients in the NAPOLI-1 study population with or without biliary stent at baseline (BL).

Results: Prior to study entry, 37/417 (9%) patients had a biliary stent. A higher proportion of patients with a BL stent had a primary tumour located in the head of the pancreas at diagnosis vs patients without a BL stent (89% vs 58%). In the overall intent-to-treat (ITT) population, mOS and median progression-free survival (mPFS) were similar for patients with or without a BL stent (mOS: 5.3 vs 4.8 months, HR = 0.97, P = 0.90; mPFS: 3.5 vs 2.4 months, HR = 0.82, P = 0.32). Patients with a BL stent demonstrated a higher objective response rate (ORR) (16% vs 6%; P = 0.03) and a greater proportion of cancer antigen 19-9 (CA19-9) responses (37% vs 20%; P < 0.05) than those without. mOS was similar among patients in the nal IRI+5 FU/LV arm with (n = 15) vs without (n = 102) a BL stent (6.2 vs 6.1 months, HR = 0.91, P = 0.78); mPFS (4.5 vs 3.0 months, HR = 0.79, P = 0.47), ORR (27% vs 15%, P = 0.26) and CA19 9 responses (42% vs 27%, P = 0.31) were numerically lower. Patients with a BL stent receiving nal-IRI+5-FU/LV (n = 15) exhibited trends towards increased mOS (6.2 vs 5.2 months, HR = 0.44, P = 0.16) and ORR (27% vs 0, P = 0.26), improved mPFS (4.5 vs 1.5 months, HR = 0.21, P < 0.01), and similar CA19-9 responses (42% vs 40%, P = 1.00) vs patients receiving 5-FU/LV (n = 8). Patients without a BL stent receiving nal IRI+5 FU/LV (n = 102) had improved mOS (6.1 vs 4.2 months, HR = 0.68, P = 0.02), mPFS (3.0 vs 1.5 months, HR = 0.59, P < 0.01), ORR (15% vs 1%, P < 0.01) and CA19 9 responses (27% vs 8%, P < 0.01) vs patients receiving 5 FU/LV (n = 111). Treatment-related grade 3–4 adverse events were similar for patients with or without a BL stent, including infectious complications such as febrile neutropenia (overall safety population n = 1/34 vs n = 7/364; nal IRI+5 FU/LV arm n = 1/14 vs n = 1/103), diarrhoea (overall safety population n = 4/34 vs n = 48/364; nal-IRI+5-FU/LV arm n = 2/14 vs n = 13/103) and decreased neutrophil count (overall safety population n = 7/34 vs n = 43/364; nal IRI+5 FU/LV n = 2/14 vs n = 21/103). Incidence of dose modifications with nal IRI+5 FU/LV was broadly similar to the overall NAPOLI 1 population for patients with or without a BL stent.

Conclusion: No clear prognostic effect of biliary stent at BL on efficacy outcomes was observed in patients with mPDAC who progressed on gemcitabine-based therapy, both in the NAPOLI-1 ITT population and the nal-IRI+5-FU/LV treatment arm. Both patients with and without a BL stent benefitted from treatment with nal-IRI+5-FU/LV compared with 5-FU/LV alone. These findings indicate that irrespective of the presence of a biliary stent before treatment initiation, nal-IRI+5-FU/LV is well-tolerated and can benefit patients with mPDAC who progressed on gemcitabine-based treatment.

P – 152 The effect of best response to prior anticancer therapy on efficacy outcomes in the NAPOLI-1 trial of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) previously treated with gemcitabine-based therapy

T Macarulla Mercadé[1], A Wang-Gillam[2], L Chen[3], J Blanc[4], K Lee[5], G Bodoky[6], A Dean[7], J Chen[8], B Mirakhur[9], J Siveke[10], F de Jong[11]

[1]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [2]Division of Oncology, Washington University, St. Louis, Missouri, USA, [3]National Institute of Cancer Research, National Health Research Institutes, Miaoli, Republic of Taiwan, [4]Hôpital Haut-Lévêque, Bordeaux, France, [5]Seoul National University Hospital, Seoul, Republic of Korea, [6]Department of Oncology, Szent László Hospital, Budapest, Hungary, [7]St John of God Hospital Subiaco, Subiaco, Australia, [8]Shire plc, Cambridge, Massachusetts, USA, [9]Ipsen Biopharmaceuticals, Inc., Basking Ridge, New Jersey, USA, [10]West German Cancer Center, University Hospital Essen, Essen, and German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Essen, Germany, [11]Shire International GmbH, Glattpark-Opfikon, Switzerland

Introduction: In the NAPOLI-1 phase 3 study of patients with mPDAC who progressed following gemcitabine-based therapy (NCT01494506), nal-IRI+5-FU/LV significantly increased median overall survival (mOS) vs 5-FU/LV control (6.1 vs 4.2 months; unstratified hazard ratio [HR] 0.67 [0.49–0.92]; P = 0.012). Best response to prior therapy may influence treatment outcomes, prognosis and subsequent therapy choices.

Methods: This post-hoc analysis explored outcomes in NAPOLI-1 patients based on best response to prior anticancer therapy. Treatment response groups were: complete response/partial response as prior best response (CR/PR) vs not CR/PR, and complete response/partial response/stable disease as prior best response (CR/PR/SD) vs not CR/PR/SD.

Results: Prior to study entry, 55/417 patients (13%) had CR/PR on prior anticancer therapy, and 211 (51%) had CR/PR/SD. In the overall intent-to-treat (ITT) population, trends towards improved outcomes were observed in CR/PR vs not CR/PR patients (mOS 5.6 vs 4.8 months, HR = 0.73, P = 0.08; median progression-free survival [mPFS] 3.8 vs 2.4 months, HR = 0.73, P = 0.06; objective response rate [ORR] 13% vs 6%, P = 0.085). mOS, mPFS and ORR were similar in CR/PR/SD vs not CR/PR/SD patients (mOS 4.9 vs 4.9 months, HR = 0.95, P = 0.68; mPFS 2.5 vs 2.6 months, HR = 1.00, P = 0.95; ORR 7% vs 7%, P = 1.00). In the nal-IRI+5-FU/LV arm, a trend towards improved mOS, mPFS and ORR was observed in patients with CR/PR (n = 11) vs not CR/PR (n = 106) (mOS 9.3 vs 6.1 months, HR = 0.64, P = 0.34; mPFS 4.2 vs 3.0 months, HR = 0.53, P = 0.13; ORR 27% vs 15%). mOS, mPFS and ORR were similar in patients with CR/PR/SD (n = 58) vs not CR/PR/SD (n = 59) (mOS 6.2 vs 6.1 months, HR = 1.04, P = 0.88; mPFS 4.0 vs 3.3 months, HR = 1.18, P = 0.45; ORR 14% vs 19%, P = 0.62). Patients with CR/PR numerically benefited from treatment with nal IRI+5 FU/LV (n = 11) vs 5 FU/LV (n = 21) (mOS 9.3 vs 5.1 months, HR = 0.46, P = 0.14; mPFS 4.2 vs 1.4 months, HR = 0.33, P = 0.03; ORR 27% vs 0, P = 0.03). Patients with not CR/PR also benefited from treatment with nal IRI+5-FU/LV (n = 106) vs 5-FU/LV (n = 98) (mOS 6.1 vs 4.0 months, HR = 0.69, P = 0.03; mPFS 3.0 vs 1.5 months, HR = 0.58, P < 0.01; ORR 15% vs 1%, P < 0.01). Similar trends towards improved outcomes were also observed in patients with CR/PR/SD when treated with nal-IRI+5-FU/LV (n = 58) vs 5-FU/LV (n = 61) (mOS 6.2 vs 4.8 months, HR = 0.68, P = 0.09; mPFS 4.0 vs 1.4 months, HR = 0.53, P < 0.01; ORR 14% vs 2%, P < 0.05). A treatment benefit was observed for patients with not CR/PR/SD when treated with nal IRI+5-FU/LV (n = 59) vs 5-FU/LV (n = 58) (mOS 6.1 vs 3.6 months, HR = 0.63, P = 0.04; mPFS 3.3 vs 1.6 months, HR = 0.56, P < 0.01; ORR 19% vs 0%, P < 0.01).

Conclusion: In both the overall ITT NAPOLI-1 population and the nal-IRI+5-FU/LV arms, there was a trend towards improved efficacy outcomes in patients with CR/PR vs not CR/PR, however this trend was not observed in CR/PR/SD vs not CR/PR/SD patients. Patients in all treatment response subgroups benefited from treatment with nal-IRI+5-FU/LV vs 5-FU/LV, regardless of best response to prior therapy.

P – 153 Decreased appetite (DA) at baseline impacts prognosis in the NAPOLI-1 phase 3 study in metastatic pancreatic ductal adenocarcinoma (mPDAC)

K Lee[1], G Bodoky[2], J Blanc[3], J Siveke[4], T Macarulla Mercadé[5], A Wang-Gillam[6], L Chen[7], B Mirakhur[8], J Chen[9], F de Jong[10]

[1]Seoul National University Hospital, Seoul, Republic of Korea, [2]Department of Oncology, Szent László Hospital, Budapest, Hungary, [3]Hôpital Haut-Lévêque, Bordeaux, France, [4]West German Cancer Center, University Hospital Essen, Essen, and German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Essen, Germany, [5]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [6]Division of Oncology, Washington University, St. Louis, Missouri, USA, [7]National Institute of Cancer Research, National Health Research Institutes, Miaoli, Republic of Taiwan, [8]Ipsen Biopharmaceuticals, Inc., Basking Ridge, New Jersey, USA, [9]Shire plc, Cambridge, Massachusetts, USA, [10]Shire International GmbH, Glattpark-Opfikon, Switzerland

Introduction: In NAPOLI-1 (NCT01494506), treatment with liposomal irinotecan + 5-fluorouracil/leucovorin (nal-IRI+5-FU/LV) significantly increased median overall survival (mOS) vs. 5-FU/LV (6.1 vs. 4.2 months; unstratified hazard ratio [HR]=0.67,

95% confidence interval [CI] 0.49–0.92; P = 0.012) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) who had progressed following gemcitabine-based therapy. We investigated the effect of metabolism and nutrition disorders (MNDs) on survival in NAPOLI-1 patients.

Methods: This post-hoc analysis explored outcomes in patients with vs. without MNDs (based on MedDRA v14.1), including diabetes mellitus (DM), decreased appetite (DA; which included anorexia, poor appetite, lack of appetite, loss of appetite), hypercholesterolemia (HC), and dyslipidemia.

Results: At baseline, 267/417 intent-to-treat (ITT) patients had any MND. Differences in baseline characteristics were observed in some MND subgroups vs. the ITT population: e.g. Karnofsky performance status (DA), gender and race (HC), albumin (DA, HC). Both mOS (3.6 vs. 5.3 months; HR = 1.65, 95% CI 1.25–2.18; P < 0.001) and median progression-free survival (mPFS) (1.6 vs. 2.6 months; HR = 1.42, 95% CI 1.09–1.85; P = 0.010) were significantly lower in patients with (n = 77) vs. those without DA (n = 340). A trend for lower OS was also noted in patients with HC but this did not reach statistical significance. mOS was 4.4 vs. 5.1 months in patients with (n = 47) vs. without HC (n = 370) (HR = 1.37, 95% CI 0.98–1.91; P = 0.063) while mPFS in these populations was 2.3 vs. 2.6 months, respectively (HR = 1.15, 95% CI 0.83–1.60; P = 0.390). No significant difference was observed in survival between patients with (n = 159) vs. without DM (n = 258) or those with (n = 87) vs. without dyslipidemia (n = 330). mOS was 5.6 vs. 4.8 months for patients with vs. without DM (HR = 0.88, 95% CI 0.70–1.11; P = 0.279) while mPFS was 2.8 vs. 2.3 months (HR = 0.86, 95% CI 0.69–1.08; P = 0.191). mOS was 4.7 vs. 5.1 months for patients with vs. without dyslipidemia (HR = 1.13, 95% CI 0.86–1.48; P = 0.375) while mPFS was 2.2 vs. 2.6 months (HR = 1.19, 95% CI 0.91–1.54; P = 0.196). For patients with vs. without any MND, mOS was 4.8 vs. 5.3 months (HR = 1.10, 95% CI 0.87–1.39; P = 0.412) while mPFS was 2.5 vs. 2.6 months (HR = 1.11, 95% CI 0.88–1.39; P = 0.358). In patients treated with nal-IRI+5-FU/LV, mOS (4.6–6.7 vs. 2.7–6.1 months; HR = 0.46–1.05) and mPFS (2.8–4.1 vs. 1.4–1.6 months; HR = 0.24–0.60) were generally improved vs. 5-FU/LV in all subgroups. Safety data, drug-related AEs and dose modifications/discontinuations were broadly similar to the overall NAPOLI-1 study arms.

Conclusion: DA at baseline appears to have a prognostic impact on OS (P < 0.001) in mPDAC patients who progressed after gemcitabine-based therapy. The presence of HC may also impact OS. It is important to consider and appropriately manage patients with DA. Treatment with nal-IRI+5-FU/LV provides a benefit regardless of the presence/absence of MNDs. The effect of DM treatment should be explored further.

P – 154 Real life triplet FIr/FOx chemotherapy in first line metastatic pancreatic ductal adenocarcinoma: Recommended schedule for expected activity and safety and phase II study

G Bruera[1], S Massacese[2], R Manetta[3], A Giordano[3], S Carducci[3], E Ciacco[2], E Ricevuto[1]
[1]Oncology Territorial Care, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [2]Pharmacy Unit, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, L'Aquila, Italy, [3]Radiology, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, L'Aquila, Italy

Introduction: Gemcitabine/nab-paclitaxel and FOLFIRINOX demonstrated significantly increased survival vs gemcitabine in metastatic pancreatic ductal adenocarcinoma (PDAC): objective response rate (ORR) 23 and 31.6%, progression-free survival (PFS) 5.5 and 6.4 months, overall survival (OS) 8.7 and 11.1 months. Phase II study investigated first line triplet FIr/FOx.

Methods: Simon two-step design: p0 10%, p1 30%, power 80%, α 5%, β 20%. Projected ORR: I step, 1/10; II 5/29. Schedule: 12h-timed-flat-infusion/5-fluorouracil 750-800-900 mg/m2 d1-2,8-9,15-16,22-23; irinotecan 120-140-160 mg/m2 d1,15; oxaliplatin 70-80 mg/m2 d8,22; every 4 weeks, according to clinical parameters (age, comorbidities, performance status (PS), liver function). Activity, efficacy were evaluated, compared using log-rank; limiting toxicity syndromes (LTS) using chi-square.

Results: Twenty-nine consecutive patients ≤65, >65≤75, ≥75 years enrolled, discriminated according to primary/intermediate/secondary Cumulative Illness Rating Scale (CIRS). Median age 62; elderly 13 (44.7%); PS2 3 (10.4%), secondary CIRS 5 (17.2%). Primary endpoint was met: OR 7/13 as-treated (53%), 50% intent-to-treat. Cumulative G3-4 toxicities: diarrhea 17%, asthenia 14%, vomiting 3%, hypertransaminasemy 7%, mucositis 7%, anemia 3%, thrombocytopenia 3%. LTS: 27.5% overall, 38.4% in elderly, multiple vs single site not significantly different. At 3 months follow-up, PFS 4 months, OS 11 months, not significantly different in elderly vs non-elderly. PFS and OS not significantly different according to dosage, tumor location, metastatic sites. PS2 patients showed significantly worse OS (P 0.022).

Conclusion: Intensive first-line triplet FIr/FOx is tolerable at adapted doses, confirms high activity/efficacy in metastatic PDAC. Careful selection of patients, PS2 exclusion, to maintain safety profile and efficient dose intensity can increase OS, compared to gemcitabine, in real life.

P – 155 Open-label, multicenter, single-arm study of FABLOx (metronomic 5-fluorouracil plus nab-paclitaxel, bevacizumab, leucovorin, and oxaliplatin) in patients with metastatic pancreatic cancer: Phase I results

V Sahai[1], W Saif[2], A Kalyan[3], P Philip[4], C Rocha-Lima[5], A Ocean[6], M Ondovik[7], D Simeone[8], M Karnoub[7], C Louis[7], V Picozzi[9]
[1]University of Michigan, Ann Arbor, Michigan, USA, [2]Tufts Medical Center, Boston, Massachusetts, USA, [3]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA, [4]Karmanos Cancer Center, Detroit, Michigan, USA, [5]Gibbs Cancer Center and Research Institute, Spartanburg, South Carolina, USA, [6]Weill Cornell Medical College, New York, New York, USA, [7]Celgene Corporation, Summit, New Jersey, USA, [8]New York University Langone Perlmutter Cancer Center, New York, New York, USA, [9]Virginia Mason, Seattle, Washington, DC, USA

Introduction: Pancreatic cancer (PC) is a leading cause of cancer-related deaths globally, with a dismal all-stage 5-year survival rate of 8%. Systemic chemotherapy can prolong survival and palliate symptoms in patients with metastatic PC (MPC). The phase III MPACT trial demonstrated superiority of first-line nab -paclitaxel plus gemcitabine vs gemcitabine monotherapy across all endpoints, including the primary endpoint of overall survival (OS) in patients with MPC. Promising results have been observed with regimens containing nab -paclitaxel and 5-fluorouracil (5-FU); however, toxicity is a major concern with high-dose intermittent therapy. The goal of this study is to determine whether metronomic therapy (continuous, low-dose treatment) with FABLOx can reduce the associated toxicities without affecting efficacy.

Methods: Patients (aged 18 - 65 years) with previously untreated, histologically or cytologically confirmed MPC and an ECOG performance status of 0 or 1 were eligible. Patients with preexisting peripheral neuropathy grade > 1 were excluded. Phase I of the study assessed potential dose-limiting toxicities (DLTs) to determine the recommended phase II dose (RP2D); phase II was designed to evaluate efficacy and further assess safety of the RP2D. During the dose-determining phase, a minimum of 6 patients were to be enrolled in each consecutive dosing cohort, and 5-FU, nab -paclitaxel, and oxaliplatin doses were to be de-escalated to the next lower dose if ≥ 2 of 6 patients experienced a DLT in cycle 1 (to a maximum of dose level −2). Patients received 5-FU 180 mg/m 2/day on days 1 to 14; nab -paclitaxel 75 mg/m 2 on days 1, 8, and 15; bevacizumab 5 mg/kg on days 1 and 15; leucovorin 20 mg/m 2 on days 1, 8, and 15; and oxaliplatin 40 mg/m 2 on days 1, 8, and 15 of each 28-day cycle in cohort I (the starting dose level). The primary endpoint of phase I was incidence of DLTs, and the secondary endpoint was safety. Patients were treated until disease progression, unacceptable toxicity, withdrawal of consent, physician decision, or death.

Results: Two DLTs were observed in 1 patient (grade 3 anemia requiring a transfusion and grade 3 mucositis unresponsive to medical treatment within 4 days of onset); cohort I was expanded from 6 to 12 patients. The median age was 57.5 (range, 41 - 64) years; 3 women and 9 men were enrolled, and 3 patients continue to be followed up for survival analysis. Patients received a median of 7.0 treatment cycles of nab -paclitaxel, bevacizumab, leucovorin, and 5-FU and 5.5 cycles of oxaliplatin. The evaluation of grade ≥ 3 treatment-emergent adverse events is pending. The objective response rate was 42% (5 partial responses); the median PFS and OS were 5.6 and 11.5 months, respectively.

Conclusion: Results from phase I of this study demonstrate that metronomic FABLOx treatment is feasible for patients with MPC. Preliminary data suggest promising antitumor activity with the regimen. NCT02620800.

P – 156 Effectiveness and costs of FOLFIRINOX in the treatment of advanced pancreatic cancer in a Portuguese oncology center

H Magalhães[1], J Lima[2], M Cassiano Neves[1], M Fontes e Sousa[1], M Machado[1]
[1]IPO-Porto, Porto, Portugal, [2]Hospital de Braga, Braga, Portugal

Introduction: Approximately 80% of patients with pancreatic cancer have advanced disease at the time of diagnosis. Despite its poor prognosis, systemic treatment with FOLFIRINOX (combination of oxaliplatin, irinotecan, fluorouracil and leucovorin) when compared to gemcitabine favored a selected population in terms of survival.

Methods: This is a retrospective analysis of a consecutive series of patients with locally advanced non-resectable or metastatic pancreatic adenocarcinoma who received first line chemotherapy with FOLFIRINOX between June 2011 and December 2016. Survival was calculated with Kaplan-Meier method considering the time difference between date of first cycle and death or last observation. We evaluate the total costs per cycle and per patient and estimate the cost of hospital stay for each patient during and after treatment with FOLFIRINOX.

Results: A total of 66 patients were included, with a median age of 59 (range: 35-71); most of them were male (62,1%, n = 41). Median overall survival was 9,87 months (CI 95%: 8,378- 11,362 months). Time till progression was 6.41 months (range: 0,67- 20,27 months). The rate of disease control (partial response and stable disease) was 65,1%. Median treatment duration was 5,18 months and 54,5% of patients experienced adverse events grade ≥3, mainly hematologic and gastro-intestinal. There was 1 treatment related death due to septic shock. Considering economic outcomes, the cost per cycle was 497,21€. The total costs of FOLFIRINOX regimen in our sample was

273465,50€, with 4143,41€average cost per patient. About 68% patients had hospital admission during treatment, with 12 average days of stay and 2000€of cost.

Conclusion: Despite the small size of our population, the demographic characteristics were similar to the phase III trial. Our results in overall survival, as well as rate of disease control and time to progression, were similar to the results of the phase III randomized trial that gave the approval of FOLFIRINOX. In terms of safety profile, it was documented a high incidence of adverse effects grade 3 or 4, mainly hematologic with 7.5% of patients experiencing febrile neutropenia and there was one treatment-related death due to septic shock. In our retrospective study, we were not able to apply cost-effectiveness analysis, since we didn't have access to data regarding quality of life in this population. Besides, we can't employ cost-effectiveness analysis to one intervention; we need a treatment group comparator like gemcitabine-based combination to take conclusions, so this is another limitation of our work. Therefore, we can only analyze this therapeutic intervention economically. Our costs values reflected the drugs costs only, and didn't consider treatment related costs, utilities, etc. The majority of patients had at least one hospital admission during treatment, and maybe total costs were underestimated, as we didn't take into account the exams performed, number of days of antibiotic administered, intravenous fluid therapy, among other considerations. In conclusion, in this single institution, effectiveness of FOLFIRINOX was in harmony with the results of the phase III Prodige trial, at the expense of high incidence of toxicity that should be not forgotten in terms of costs and patients' quality of life.

P – 157 Gemcitabine/nabpaclitaxel efficacy in elderly patients with metastatic or locally advanced pancreatic adenocarcinoma

V Michalaki[1], A Poydorou[2], G Frangulidis[2], A Vezakis[3], E Karvouni[4], C Papadimitriou[5]

[1]Areteion Hospital University of Athens, Athens, Greece, [2]Areteion Hospital 2nd Department of Surgery, Athens, Greece, [3]Department of Surgery Areteion Hospital, Athens, Greece, [4]Histopathology Department, Athens, Greece, [5]Oncology Unit Areteion Hospital University of Athens, Athens, Greece

Introduction: Pancreatic cancer is a major health concern worldwide and, despite the attempts at management, the prognosis of patients remains poor, with a median survival of a few months. Gemcitabine/nabpaclitaxel is an active regimen currently used as first-line treatment of patients with metastatic pancreatic adenocarcinoma and a good performance status (PS). but few data are available in elderly patients. Aim of this analysis is to evaluate outcomes and toxicities of gemcitabine/nabpaclitaxel in a cohort of elderly patients.

Methods: Clinical records of advanced pancreatic cancer patients receiving nabpaclitaxel 125 mg/m2 and gemcitabine 1000 mg/m2on days 1,8 and 15 of a 28 day cycle as first line chemotherapy were reviewed, investigating activity, efficacy (Progression Free Survival, PFS and Overall Survival, OS) and safety. Analysis was then performed in $\geq$ 70 years group of pts. OS and PFS were estimated with Kaplan-Meyer method with 95% CI. Cox-regression model was applied to the data with univariate and multivariate approach.

Results: Twenty eight patients with a median age of 72 years (range: 70-78) were included in this analysis: PS2: 5 (18%); primary location: head 15 (54%); biliary stent:10 (35%). Overall response rate (ORR) was 35.2%; median progression-free survival (PFS) was 7.4 months (95% CI 5.54-9.26) and median overall survival (OS) was 12.8 mo (95% CI 10.9-15.24). Treatment was well tolerated. No grade 4 toxicity was reported. Grade 3 toxicity included neutropenia in 3 pts (11%), peripheral neuropathy in 1 pts (3.5%), thrombocytopenia in 2 pts (7%), diarrhea in 3 pts (11%), nausea and vomiting in 1 pt (3.5%), and fatigue in 3 pts (11%). Finally, pain control was achieved in 21 of 28 patients (75%) with a performance status improvement of 15% according to the Karnofsky scale.

Conclusion: These data suggest that patients aged $\geq$ 70 may benefit of first-line gemcitabine plus nab-paclitaxel combination, as well as younger ones, both in terms of response and survival experiencing a tolerable, toxicity profile. Identifying elderly patients who will benefit from combination chemotherapy for pancreatic cancer remains a significant clinical challenge.

P – 158 Correlation of neutrophil lymphocyte ratio, platelet lymphocyte ratio and rate of change of CA 19.9 in predicting outcome for metastatic pancreatic cancer

A Dean[1], D Higgs[1], A Das[2], M Rogers-Seeley[2], S Fennessy[2], C McGarvey[2], M McNulty[2]

[1]St John of God Hospital Subiaco, Subiaco, Australia, [2]St John of God Hospital Subiaco, Perth, Australia

Introduction: CA19.9, NLR and PLR have all been proposed as prognostic in pancreatic cancer. We analysed correlation between NLR, PLR and rate of change of CA19.9.

Methods: A total of 63 metastatic pancreatic cancer patients were identified from our database and evaluated retrospectively for blood count, NLR, PLR and serial CA19.9 levels during treatment. Daily Rate of Change of CA19.9 levels were calculated for the first 90 days (DRC90) of the patient's treatment. Kaplan Meir curves, univariate and multivariate Cox regression analyses were calculated to assess the effects of these 3 markers on overall survival.

Results: In a univariate analysis, PLR > 240, NLR > 5 and DRC90 > 0.4% were all significantly associated with deceased overall survival. The Cox proportional hazards model showed that NLR < 5 (HR 0.475, 95% CI 0.259 to 0.873, P = 0.017), PLR < 240 (HR 0.444, 95% CI 0.229 to 0.861, P = 0.016), and a DRC90 < 0.4% (HR 0.294, 95% CI 0.102 to 0.851, P = 0.024) were independent predictors of good prognosis (22.6 months vs. 9.6 months, 22.3 months vs 12.4 months and 23.9 months vs. 9.3 months respectively). In multivariate analysis, only a DRC90 < 0.4% was independently associated with a longer survival (HR 0.239, 95% CI 0.076 to 0.752, P = 0.014). The formula (F) {PLR + (NLRxNLR) + (DRC90 x 100)} was predictive for survival, as patients with F > 190 (HR 3.295, 95% CI 1.232 to 8.807, P = 0.017), having a significantly lower survival rate than patients with F < 190 (25.1 months vs. 10.6 months, logrank P = 0.009).

Conclusion: These findings indicate the prognostic utility of the rate of CA 19.9 decline measured as a standardised daily percentage change in value over 90 days. Our data validates daily rate of change of CA 19.9 over 90 days as an independent variable that correlates with prognosis, independent of PLR and NLR. We also identified a novel formula PLR + (NLRxNLR) + (DRC90 x 100) as being predictive for survival. We would like to increase the sample size to further validate our initial findings and investigate possible relationships in combining these variables for better prognostication in metastatic pancreatic cancer.

P – 159 Analysis of early tumor shrinkage and depth of response in metastatic pancreatic cancer patients treated with first-line modified FOLFIRINOX or gemcitabine + nab-paclitaxel

C Vivaldi[1], C Cappelli[2], F Donati[3], L Fornaro[4], G Musettini[1], G Pasquini[5], I Pecora[2], S Catanese[1], M Lencioni[6], F Salani[7], P Boraschi[3], A Falcone[8], E Vasile[1]

[1]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [2]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, [3]Department of Diagnostic Imaging - Pisa University Hospital, Pisa, Italy, [4]U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [5]Department of Oncology, University Hospital, Pisa, Italy, [6]Azienda Ospedaliero-Universitaria di Pisa, Pisa, Italy, [7]Unit of Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [8]University of Pisa, Pisa, Italy

Introduction: Early Tumor Shrinkage (ETS) and Depth of Response (DoR) can help in predicting favourable outcome in metastatic colorectal cancer. Combination chemotherapy such as FOLFIRINOX or gemcitabine+nab-paclitaxel (GemNab) represents the main options for fit metastatic pancreatic cancer (PC) patients (pts). Data about the role of ETS and DoR in PC are lacking. The aim of the present analysis is to investigate the putative prognostic role of these parameters in PC.

Methods: One hundred thirty nine metastatic PC pts treated in a single center with modified FOLFIRINOX (mFOLFIRINOX) or GemNab (81 and 57, respectively) and evaluable for response were enrolled. Best response according to RECIST criteria, ETS and DoR were analyzed. ETS was defined as a $\geq$ 20% reduction in the sum of longest diameters of RECIST target lesions after 8 weeks of treatment compared to baseline. DoR was defined as the percentage of shrinkage in the sum of longest diameters of RECIST target lesions observed at the nadir compared to baseline; pts with appearance of new lesions were excluded from the analysis regarding DoR. Association of ETS and DoR with progression-free survival (PFS) and overall survival (OS) was assessed by univariate and multivariate Cox models.

Results: Main pts characteristics were: male/female, 51.4%/48.6%; median age, 64 years (range 41-76); PS 0/1, 60.8%/39.2%; previous resection of primary tumor, 26.8%, median number of metastatic sites, 2 (range 1-5), median Ca19.9 value, 471 U/mL (range 0.6-100000). In the whole population median OS was 10.9 months (11.5 in mFOLFIRINOX and 10.6 in GemNab) and median PFS was 6.2 months (6.4 in mFOLFIRINOX and 6.2 in GemNab). Fourty-seven (34%) pts achieved partial response, of whom 35.8% in mFOLFIRINOX group and 32.2% in GemNab group. ETS was achieved in 49 pts (35.5%), 39.5% of mFOLFIRINOX and 29.8% of GemNab group, respectively (p = 0.280). Median ETS was 23% with mFOLFIRINOX and 13% with GemNab (p = 0.029). Considering the entire population, ETS was significantly associated with better PFS (8.0 vs. 4.8 months, p < 0.001) as well as OS (13.2 vs. 9.7 months, p = 0.001). Median DoR was 27.5% (29.4% with mFOLFIRINOX and 21.4% with GemNab, p = 0.016). DoR was significantly associated with better PFS (9.0 vs 6.7 months, p < 0.001) and OS (14.3 vs 11.1 months, p = 0.031). Multivariate analysis didn't confirm the association of ETS with PFS and OS (p > 0.05). The association of DoR with PFS was confirmed in multivariate analysis stratified for other prognostic variables (p = 0.005), while a trend toward association with OS was observed (p = 0.079).

Conclusion: In our retrospective cohort, ETS and DoR can help in predicting favorable outcome in PC treated with first-line combination chemotherapy; these parameters should be integrated as secondary endpoints in future prospective clinical trials.

P – 160 Quality of life of patients with metastatic pancreatic adenocarcinoma initiating first-line chemotherapy in routine practice

A García Velasco[1], T Macarulla[2], C Bugés Sánchez[3], M Martín[4], C García[5], C Pericay[6], S Merino[7], L Visa[8], T Martín[9], M Pedraza[10], B Carnero[11], R Guardeño[1], L Pellín[12], D Vilanova[12], B Laquente[13]

[1]Institut Català d'Oncologia (ICO), Girona, Spain, [2]Hospital Universitari Vall d'Hebrón, Barcelona, Spain, [3]Institut Català d'Oncologia (ICO) – Hospital Germans Trias i Pujol, Badalona, Spain, [4]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [5]Complejo Hospitalario de Burgos, Burgos, Spain, [6]Corporació Sanitaria Parc Taulí, Sabadell, Spain, [7]Hospital Sant Joan de Reus, Reus, Spain, [8]Hospital del Mar, Barcelona, Spain, [9]Hospital Universitario de Salamanca, Salamanca, Spain, [10]Complejo Asistencial Universitario de León, León, Spain, [11]Hospital del Bierzo, Ponferrada, Spain, [12]Celgene S.L.U., Madrid, Spain, [13]Institut Català d'Oncologia, L'Hospitalet de Llobregat, Spain

Introduction: Considering the physical decline of patients with metastatic pancreatic adenocarcinoma (mPAC), the assessment of quality of life (QoL) becomes a matter of major concern. We aimed to assess the QoL of mPAC patients treated with first-line chemotherapy in routine practice.

Methods: This observational, prospective, multicenter study included mPAC patients who were prescribed first-line chemotherapy between 2014 and 2015 in 12 Spanish centers. Treatment and clinical characteristics were recorded at chemotherapy start (baseline). Patients' QoL, ECOG, and Karnofsky index (KI) were measured at baseline, at days 15 and 30, and every 4 weeks up to 6 months of chemotherapy. QoL was measured using the EORTC QLQ-C30 global health status (QLQ) and EQ-5D questionnaires. Other endpoints included treatment response, overall survival (OS), and progression-free survival (PFS).

Results: The study sample included 116 patients with a median age of 65 years (range 37-84). Metastases were mostly hepatic (75%). mPAC was recurrent in 22% of patients and de novo in 78%. At baseline, 33 patients (44.6%) presented > 10% weight loss in the last 3 months. ECOG was 0-1 and 2 in 82% and 18% of patients, respectively, and KI was 70-80 and 90-100 in 48% and 52% of patients, respectively. Median OS was 9.0 months (95% CI 6.5-11.1) and median PFS was 6.0 months (95% CI 4.6-7.8); the objective response rate (ORR) was 32%, and 38% of patients had stable disease. At all follow-up visits ≥46.8% of patients showed better QoL than at baseline: 65.5% of patients improved their QoL in at least one visit, 17.2% showed a decline in all visits, and 17.2% a decline or a stable score. Patients with either KI 70-80 or ECOG 2 showed a significant trend towards a greater improvement of the QoL than the corresponding groups with higher performance status (PS) score ($p \leq 0.01$ for both PS scales). From 2nd month on, QLQ scores of patients with baseline KI 70-80 and patients with baseline ECOG 2 were comparable to those with KI 90-100 and ECOG 0-1, respectively. Within the first 3 months, patients with either partial/complete response or stable disease had higher QLQ scores than those who progressed ($p = 0.008$). The analysis of each item of the QLQ scale revealed an improvement in pain, appetite, and sleep disturbance throughout treatment. Median OS and PFS were higher in patients with baseline QLQ ≥50 (OS 10.6 [95%CI 8.2-14.9] and PFS 7.8 [4.6-8.4]) than those with QLQ <50 (OS 5.5 [2.7-9.7] and PF 4.8 [2.3-5.5]). No significant relationships were observed regarding the EQ-5D score.

Conclusion: The EORTC QLQ-C30 questionnaire is suitable for measuring the QoL of mPAC patients undergoing chemotherapy and its baseline score is associated with OS and PFS. Most patients with poor PS at baseline improved their QoL during the first month of chemotherapy, reaching a QLQ score comparable with patients with higher PS scores at 2nd month and following.

P – 161 FOLFIRINOX versus gemcitabine plus nab-paclitaxel for treatment of metastatic pancreatic cancer: a single-center cohort study

I Cho[1], H Kang[2], J Jo[2], H Lee[3], M Chung[4], J Park[2], S Park[5], S Song[4], M Park[6], C An[6], S Jung[7], S Bang[8]

[1]Department of Internal Medicine, International St. Mary's Hospital, Catholic Kwandong University, Incheon, Republic of Korea, [2]Department of Internal medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Division of Gastroenterology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, [4]Division of Gastroenterology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, [5]Yonsei University College of Medicine, Seoul, Republic of Korea, [6]Department of Radiology, Yonsei University College of Medicine, Seoul, Republic of Korea, [7]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [8]Yonsei University, Seoul, Republic of Korea

Introduction: Pancreatic cancer demonstrates a dismal prognosis and is one of the main causes of cancer-related death worldwide and Korea. Unlike other cancers, progress in the treatment outcomes of metastatic pancreatic cancer has remained stagnant. Recently, two effective regimens were introduced through large-scale clinical trials. FOLFIRINOX and gemcitabine plus nab-paclitaxel (Gem+nabPTX) improved the prognosis of metastatic pancreatic cancer patients. However, treatment efficacy and safety were not validated in the Asian population and there was also lack of data that compared the efficacy and safety of the two regimens. Therefore, the purpose of this study was to compare the efficacy, safety, and economic aspects of FOLFIRINOX and Gem+nabPTX in the treatment of metastatic pancreatic cancer in Korean population.

Methods: Metastatic or recurrent pancreatic cancer patients treated with FOLFIRINOX (n = 86) and Gem+nabPTX (n = 81) as the first-line chemotherapy from January 2015 were identified using the Severance Hospital Pancreatic Cancer Cohort Registry. Treatment efficacy, treatment-related adverse events, and economic aspects were analyzed and compared between two groups.

Results: The median follow-up period was 7.9 (range, 1.5-23.4) months. Patients in the FOLFIRINOX group were significantly younger (65 vs. 54 years-old; $p < 0.001$) and had better performance status at diagnosis. Chemotherapy duration (Gem+nabPTX: 154 vs. FOLFIRINOX: 138 days; $p = 0.249$) and treatment efficacy were not significantly different between the two groups. Median overall survival, median progression-free survival and objective response rate were 12.1 months, 8.4 months and 46.9% in Gem+nabPTX group and 10.7 months ($p = 0.157$), 8.0 months ($p = 0.134$) and 33.7% ($p = 0.067$) in FOLFIRINOX group. Neurologic adverse events (AEs) were more common in Gem+nabPTX group. Grade ≥3 neuropathy occurred in 18.5% of Gem+nabPTX group and 3.5% in FOLFIRINOX group ($p = 0.002$). On the other hand, Grade ≥3 neutropenia and gastrointestinal AEs were more common in FOLFIRINOX group. The anticancer drug cost was similar between the two groups. However, in terms of the potential cost burden, the FOLFIRINOX regimen seems to have some disadvantages because FOLFIRINOX group patients must be hospitalized to receive the chemotherapy and showed higher rates of hematologic AE which can cause severe infection. So, total treatment cost was slightly cheaper in Gem+nabPTX group than FOLFIRINOX.

Conclusion: There was no significant difference in the treatment efficacy of both regimens. However, considering the cost and side effects, Gem+nabPTX is more favorable for metastatic pancreatic cancer patients.

P – 162 Second line in pancreatic cancer: Resuming our experience and looking for prognostic factors

B Anton[1], F Longo Muñoz[2], D Gutierrez Abad[1], M De Torres Olombrada[1], I Juez Martel[1], B Losada Vila[3], J Letéllez[1], J Guerra Martínez[1], A Fernñandez Román[1]

[1]Hospital Universitario Fuenlabrada, Fuenlabrada, Spain, [2]Hospital Universitario Ramón y Cajal, Madrid, Spain, [3]Hospital de Fuenlabrada, Fuenlabrada, Spain

Introduction: Pancreatic tumours are a systemic disease with early metastatic spread and poor survival rates. In the past years we have experienced a transition where FOLFIRINOX and Gemcitabine plus NAB-paclitaxel have settled as first line therapy. There is some controversy about second line, with no standard regimen. The challenge of using more than one systemic treatment is based on patients' clinical conditions since they are not always fit to withstand a systemic treatment. Most of studies described and stratify patients according to the presence of metastases, performance status or progression free survival to first-line. Clearly those patients with better nutritional status, lower burden of disease or less comorbidity hope to present better response to chemotherapy in terms of lower toxicity, although this does not always translate into tumour response. We review the patients with pancreatic cancer in our working area last 10 years that have received second-line systemic chemotherapy (including locally advanced or metastatic), describe survival according to different therapies and assess clinical markers that can be related to best tolerance and prognosis.

Methods: We selected all patients with pancreatic tumours (n = 108) diagnosed since January 2007 until December 2017 and selected all that have received SECOND LINE chemotherapy. We search at clinical history notes about tumor stage, location, performance status (ECOG), tumour stage, biliary stent, albumin and Ca 19.9 rates, radiotherapy and thromboembolic disease. These factors are chosen based on published literature and clinical criteria. Primary end point: Median survival (Kaplan Meier estimation) based on chemotherapy regimens, stratify by most frequent therapies and monotherapy (capecitabine or gemcitabine) and doublet (FOLFOX or gemcitabine plus nab-paclitaxel). Secondary end point: we practiced both uni and multivariate analysis between tumor location, ECOG, Ca19.9 level, thrombosis and previous radiotherapy.

Results: Gemcitabine plus nab-paclitaxel first and FOLFOX are two systemic therapies with acceptable tolerance in symptomatic patients with better survival in our database. Our Kaplan-Meier estimation shows discrete benefit initially although those patients with response to monotherapy, especially with gemcitabine, can have extended survival (Figures 4, 5 and table 2). However, our population do not show improved survival with doublet in terms of overall survival(figure 5) although it is noted that FOLFOX and gemcitabine plus nab-paclitaxel presented benefit initially. The characteristics at the first table are consistent with the literature (gender equality, thromboembolic events near 30%, performance status at the beginning of second line 0 and 1 and any patient being treated with ECOG3) (Table 1). We carried out both uni and multivariate analysis in this case. Only performance status (ECOG) seems to have in our population prognostic reflection with survival. It is determined that if we increase ECOG, it is more likely to use monotherapies.

Conclusion: Gemcitabine plus nab-paclitaxel is a systemic treatment well-tolerated as second-line chemotherapy in our database with optimal responses in terms of overall survival. Chemotherapy based in doublet does not improved overall survival in our population although there seems to be some clinical benefit at the beginning of second-

line. ECOG status is a strong prognostic factor in or database which correlates with better survival rates.

P – 163 Observational study of comparative effectiveness of nab-paclitaxel plus gemcitabine vs gemcitabine plus cisplatin or gemcitabine alone for the first-line treatment of metastatic pancreatic adenocarcinoma in the University Hospital Centre Zagreb

J Prejac[1], I Goršić[1], M Vidović[2], H Golem[1], D Kekez[1], N Librenjak[1], S Pleština[1]
[1]University Hospital Center Zagreb, Zagreb, Croatia, [2]University Hospital Centre Zagreb, Zagreb, Croatia

Introduction: The goal of this non-randomized, retrospective, and observational study was to assess the efficacy of three different first-line chemotherapy regimens in the treatment of metastatic pancreatic cancer.

Methods: Data were retrieved on 139 patients (pts) who were treated for metastatic pancreatic cancer in the University Hospital Centre Zagreb between January 1st, 2015 and March 1st, 2018. Pts were treated with nab-paclitaxel plus gemcitabine (Nab-Gem), gemcitabine plus cisplatin (Cis-Gem), or gemcitabine alone (Gem). Median age at the time of the beginning of therapy was 62 yrs in the Nab-Gem group (n = 45), 64.4 yrs in the Cis-Gem group (n = 19), and 70 yrs in the Gem group (n = 75).

Results: The median duration of treatment for Nab-Gem, Cis-Gem, and Gem regimens was 23.1, 24.7, and 12.9 weeks (w), respectively. Multivariate analyses tested influence of prognostic factors on treatment duration. In accordance with previous studies, for the pts treated with Nab-Gem the duration of treatment was negatively correlated with age ($p < 0.05$). The same age-dependent relationship was not observed in the Cis-Gem and Gem groups. Pts treated with Nab-Gem showed significant difference in terms of time to failure of treatment when analyzed for the two age groups separately, <65 and >65 yrs of age. The <65 group received chemotherapy for the median duration of 57.1 w compared to the >65 group which was treated with Nab-Gem for median of 21.5 w. No significant sex-dependent difference was found in regard to duration of treatment in any of the three treatment regimen groups.

Conclusion: With regards to the above limitations of the study, we conclude that, for pts younger than 65 y, Nab-Gem is an effective chemotherapy regimen with significant clinical effect. Furthermore, for selected patients, a combined use of Cis-Gem is superior to Gem alone in the first-line treatment for metastatic pancreatic cancer.

P – 164 Gemcitabine plus nab-paclitaxel versus modified FOLFIRINOX as first line chemotherapy in metastatic pancreatic cancer: A comparison of toxicity and survival

V Pacheco-Barcia[1], T France[2], G Zogopoulos[3], N Bouganim[2], O Donnay[1], T Alcindor[4], R Mondéjar Solís[1], K Guo[2], E Martin[5], R Colomer[1], J Asselah[6]
[1]Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria La Princesa, Madrid, Spain, [2]McGill University Health Center, Cedars Cancer Centre, Montreal, Quebec, Canada, [3]McGill University Health Centre, Montreal, Quebec, Canada, [4]McGill University Health Centre, Montréal, Quebec, Canada, [5]Hospital Universitario La Princesa, Madrid, Spain, [6]McGill University Royal Institution, Montreal, Quebec, Canada

Introduction: Gemcitabine plus nab-paclitaxel and modified FOLFIRINOX have been established as first line chemotherapy in metastatic pancreatic cancer, but there is no conclusive data on their comparison. The aim of our study is to evaluate survival and toxicity profile of metastatic pancreatic cancer patients treated with these therapies.

Methods: Retrospective review of 85 metastatic PC diagnosed between January 2014 and January 2018 at two tertiary hospitals. Differences in treatment-related toxicity were assessed by the Chi-square test, progression-free survival (PFS) and overall survival (OS) with the log-rank test.

Results: 46 patients were included: 25 Gemcitabine plus Nab-Paclitaxel and 21 received modified FOLFIRINOX. Median age was 63 years. Demographic and baseline characteristics were similar as follows (gemcitabine plus nab-paclitaxel/mFOLFIRINOX): Gender (male): 72%/71%, comorbidities: 16%/14%, liver metastasis: 72%/63%, jaundice that required stent insertion: 32%/48% and thromboembolic events: 56%/62%. The population of elderly patients (> 70y) was similar between both cohorts (36% vs. 42%, $p = 0.2$) but, 48% of patients treated with gemcitabine plus nab-paclitaxel showed ECOG PS > 1 compared to 4% of patients treated with mFOLFIRINOX ($p = 0.01$). Similar toxicity profile between both treatments was observed (36% vs 28%, $p = 0.67$). Incidence of grade 4 neutropenia was similar in both cohorts (12% vs 10%, $p = 0.7$), probably due to an increased use of G-CSF in patients receiving mFOLFIRINOX. Also, peripheral neuropathy (5% vs 7%, $p = 0.8$) and diarrhea (3% vs 2.1%, $p = 0.6$) were similar between groups. No differences were observed in median PFS of mFOLFIRINOX compared to gemcitabine plus nab-paclitaxel (8 months vs 4 months, $p = 0.26$). However, median OS was significantly longer in patients treated with mFOLFIRINOX (14 months vs 7 months, $p = 0.02$).

Conclusion: Metastatic pancreatic cancer patients treated with mFOLFIRINOX showed increased survival compared to gemcitabine plus nab-paclitaxel, with a similar toxicity profile. These results raise the issue of appropriately selecting patients with poor ECOG PS who can benefit from gemcitabine plus nab-paclitaxel for an adequate control of disease.

P – 165 Clinical outcomes for modified FOLFIRINOX chemotherapy for pancreatic cancer

D Holyoake[1], C Lo[2], H Stubbings[1], T Roques[1]
[1]Norfolk and Norwich University Hospital, Norwich, UK, [2]Norfolk and Norwich University Hospital, Norwich, UK

Introduction: FOLFIRINOX chemotherapy improves overall survival in pancreatic ductal adenocarcinoma (PDAC) when compared to gemcitabine in clinical trials (Conroy et al., 2011). We aimed to examine the delivery and outcomes for this treatment in routine clinical practice.

Methods: We identified all patients treated with a FOLFIRINOX regimen since its introduction at a university teaching hospital. Doses were modified from the published regimen to reduce toxicity (irinotecan 135 mg/m2, oxaliplatin 85 mg/m2, folinic acid 400 mg/m2, and 5-fluorouracil 2400 mg/m2 as an infusion over 48 hours). Treatment was given every 14 days, for up to 12 cycles. All patients received prophylactic supportive medications including atropine, G-CSF, antibiotics, steroids, anti-diarrhoeal and anti-emetic medications. We analysed treatment delivery and outcomes for patients with a minimum of 6-months follow-up since treatment commenced. Survival estimates (from time of commencing FOLFIRINOX) were calculated using Kaplan-Meier.

Results: Thirty-eight patients with PDAC commenced treatment with FOLFIRINOX between July 2016 and February 2018. Of these, twenty-five had at least six-months duration of follow-up. Thirteen patients were male, and twelve female. Median age was sixty-seven years (range thirty-five to seventy-six). All patients were ECOG performance status 0-1. FOLFIRINOX was being used as first-line therapy for advanced disease in all but one patient. Median number of cycles administered was nine (range one to twelve). Five patients discontinued treatment early due to disease progression, after a median of five cycles (range 2 – 8), and eight due to toxicity (after a median 6 cycles, range 1 – 10). Fourteen patients had a dose reduction (including two patients starting treatment at reduced dose), with the commonest reason being symptomatic toxicity (most frequently diarrhoea, nausea/vomiting, or neuropathy). Five patients had total treatment deferrals of three weeks or more, most frequently due to deranged blood test results, symptomatic toxicity or patient choice. CTCAE grade-3 toxicities were seen in seven patients (28%) and comprised non-neutropaenic sepsis (rate 12%), nausea/vomiting (8%), and diarrhoea (8%). No febrile neutropaenia was observed, nor any grade-4 toxicity, and no patients died of treatment-related complications. One patient died within 30 days of receiving chemotherapy, and this was attributed to progressive disease. Thirteen patients (52%) had an objective disease response (complete response or partial response), and five further patients had stable appearances on imaging during treatment (20%). Median progression-free survival (PFS) was 8.4 months (95% confidence interval 6.3 – 10.6 months) and overall survival (OS) was 13.2 months (95% CI 7.6 – 18.8 months). Five patients subsequently received second-line palliative chemotherapy. Conroy et al. (2011) reported an objective response rate of 31.6%, and stable disease in 38.6% of patients, with PFS 6.4 months and OS 11.1 months.

Conclusion: A modified FOLFIRINOX regimen has been implemented in routine clinical practice and observed outcomes compare favourably to published clinical trial data. This protocol may be as efficacious as the published protocol but with less toxicity, and universal administration of G CSF may have contributed to lack of febrile neutropaenia.

P – 166 Questions of resolving cholestasis in metastatic cancer of the hepatobiliary system

S Khoshimov
Tashkent Medical Academy, Tashkent, Uzbekistan

Introduction: To clarify the indications for decompression of the biliary tract (BT) by proximal access and to determine the possibilities of its long-term drainage in patients with mechanical jaundice (MJ) caused by metastatic cancer of the hepatobiliary system.

Methods: In the last 10 years, 178 patients were at the Scientific Center of the Liver and Biliary Diseases and the Department of Oncology and Radiology of the Tashkent Medical Academy of Metastatic Liver Cancer and in the zone of the hepatoduodenal ligament. In 69 (38.6%) of them developed MF. There were 41 women (60.1%), men - 28 (39.9%). The cause of metastatic lesion of the hepatobiliary zone was tumors of the following localization: stomach - 23 (33.3%), pancreas - 19 (27.5%), colon and rectum - 24 (35.0%), genitalia - 2 (2, 8%), lungs - 1 (1.4%). Localization, number, sizes of metastases in the liver and in the zone of the hepatoduodenal ligament, as well as the degree of dilatation of BT, the level of its obstruction was established with the help of radiation diagnostic methods: ultrasound, CT, MRI. When planning PTC, the method of 3D modeling of the biliary system, portal and caval vessels according to spiral CT and MRCP was used.

Results: Favorable conditions for transhepatic drainage of BT were found in 49 (71.1%) patients, relatively favorable - in 17 (24.6%), unfavorable - in 3 (4.3%). In the

last 3 cases, it was not possible to carry out PTC, the attempt to perform PTC in 4 (23.5%) observations with relatively favorable conditions was also not effective. In the nearest postoperative period, complications were present in 6 (9.6%) patients from 62 patients who managed to decompress BT by proximal access. In 2 cases, catheter prolapse occurred, and its reinstallation was performed. In 4 cases, hemobiology was noted, which was stopped conservatively. Outer internal drainage of the BT was accomplished in 5 (8.1%) cases. In the near postoperative period there were no lethal outcomes. The period of drainage of BT to 3 months was 95.1% of patients, up to 9 months - 8.0%, up to 1 year no patient survived.

Conclusion: With the development of MJ in patients with metastatic cancer of the hepatobiliary system, it is necessary to find out the conditions for performing decompression of BT and, if they are available, to establish a catheter in BT proximal access. Elimination of jaundice, although not for a long time, improves the quality of life and somewhat prolongs the life of the patient.

P – 167 Symptoms reported at initial diagnosis of (metastatic) pancreatic adenocarcinoma ([m]PAC) in routine clinical practice and variation in frequencies across Europe

D Melisi[1], B Westphalen[2], àMellbring[3], A Carrato[4], J Taieb[5], G Prager[6], T Macarulla Mercadé[7], N D'Esquermes[8], A Ferreras[9], F de Jong[10]

[1]Medical Oncology, University of Verona, Verona, Italy, [2]Comprehensive Cancer Center München, Klinikum der Universität München, Munich, Germany, [3]Shire Sweden AB, Kista, Sweden, [4]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain, [5]Sorbonne Paris Cité, Paris Descartes University, Hôpital Europeen Georges Pompidou, Paris, France, [6]Clinical Division of Medical Oncology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria, [7]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [8]Genactis, Chateauneuf, France, [9]Genactis, Antibes, France, [10]Shire International GmbH, Glattpark-Opfikon, Switzerland

Introduction: PAC is projected to become the second leading cause of cancer death by 2030. It is typically diagnosed late in the course of the disease, amongst other reasons due to lack of screening tests, limited understanding of risk factors, and any clear symptoms typically only appearing late. Systemic treatment options applied in advanced disease vary and recent data on choices and outcomes outside clinical trials are scarce. The goal of this pan-European project was to generate data on diagnosis, treatment patterns and outcomes from the records of patients who completed first-line metastatic PAC treatment across Europe.

Methods: In this observational chart review, physicians completed a retrospective electronic record from initial diagnosis onwards for patients with the following minimal inclusion criteria: completed first-line (m)PAC treatment between 07/2014-01/2016 and ≥18 years. In each country, respondents were recruited across different regions and settings (university and general hospitals, cancer and reference centers, office-based specialists) to ensure a balanced selection. Physicians were encouraged to enter as many second-line metastatic patients as possible. Study endpoints included initial/subsequent treatments, dose modifications, and treatment outcomes. We report here on selected patient and tumor characteristics and incidences of reported symptoms (including variation across countries) at initial PAC diagnosis. Data are descriptive.

Results: A total of 2,565 online patient records were completed by 225 physicians (9 countries; n = 500-504 for France/Germany/Italy/Spain/UK). At diagnosis, 89.5% of patients had advanced disease, median age was 64 years, and 57.7% was male. Primary tumor location was head/head+body/body/body+tail/tail in 40.2%/16.3%/23.2%/9.6%/10.1%. Tumor grade was 1/2/3/unknown in 5.3%/39.5%/38.1%/17.2%. Median CA19-9/albumin/bilirubin levels were 387U×mL-1/34.0g×L-1/1.8mg×dL-1. WHO performance status was 0/1/2/3/unknown in 20.4%/55.8%/21.9%/1.6%/0.4%. At initial diagnosis, on average 3.14 symptoms were reported per patient from 15 pre-listed symptoms. Averages for France/Germany/Italy/Spain/UK varied with -6.3%/+18.9%/-18.4%/+12.3%/-6.7%. Symptoms in decreasing order were: abdominal pain_65.0%; weight loss_61.5%; jaundice_31.1%; nausea_28.3%; mid-back pain_26.8%; bloating_19.0%; vomiting_18.1%; dark urine_12.7%; itching_12.3%; cachexia_8.6%; deep vein thrombosis (DVT)_8.1%; steatorrhea_7.0%; depression_5.9%; diarrhea_5.9%; and recent unexpected diabetes_3.4%. Variation was highest for more frequently reported symptoms (mid-back pain, nausea, weight loss, and bloating). Absolute differences of ≥|10%| versus the mean were identified for nausea (+14.6%_Germany), mid-back pain (+12.5%_Germany), and weight loss (-11.1%_Italy). Absolute differences between countries (highest versus lowest) were greatest for nausea (Δ22.1%: Germany_42.9% versus France_20.8%), mid-back pain (Δ18.7%: Germany_39.3% versus UK_20.6%), and weight loss (Δ18.3%: Germany_68.7% versus Italy_50.4%). Relative differences of ≥|50%| versus the mean were reported for depression (+142.4%_Spain; -72.9%_UK), steatorrhea (+90.0%_Spain; -57.1%_France), cachexia (+59.3%_Spain), DVT (+56.8%_Germany), diabetes (+52.9%_France), and nausea (+51.6%_Germany). Relative differences (highest versus lowest) were greatest for depression (8.9×: Spain_14.3% versus UK_1.6%), steatorrhea (4.4×: Spain_13.3% versus France_3.0%), and DVT (2.8×: Germany_12.7% versus UK_4.6%).

Conclusion: In this European retrospective chart-review, the average number of symptoms at initial diagnosis of (m)PAC reported by treating physicians varied between countries. Most frequently symptoms reported were abdominal pain, weight loss, jaundice, nausea, and mid-back pain. Substantial variation was seen for individual symptoms. Appropriate awareness of and attention to symptoms in the general public and by health care providers may help improve (m)PAC diagnosis, care and outcomes.

P – 168 Multiple dose pharmacokinetics of erlotinib when combined with gastric acid reducing agents: A comparison with a physiologically based pharmacokinetic model

A Sahmanovic Hrgovcic[1], A Gruber[1], C Dittrich[2], M Kitzmueller[1], P Buchner[1], N Kirchbaumer Baroian[1], M Czejka[1]

[1]Department of Clinical Pharmacy and Diagnostics, University of Vienna, Vienna, Austria, [2]Ludwig Boltzmann Institute for Applied Cancer Research (LBI-ACR VIEnna), Kaiser Franz Josef-Spital, 3rd Medical Department – Centre for Oncology and Haematology, Vienna, Austria

Introduction: Erlotinib selectively inhibits the EGFR tyrosine kinase activity and consequently the tumour cell growth in patients. The drug is administered orally and being a weak base, its solubility is strongly dependent upon the acidic pH in the gastric fluid. Gastric acid reducing agents (ARAs), such as proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs), increase the pH of the stomach (pH > 4) and cause a physicochemical drug-drug interaction. The secretion of H+ is drastically reduced by PPIs due to an irreversible binding to the H/K-ATPase pump. H2RAs have a shorter elimination half-life and competitively inhibit histamine action of H2 receptors, on gastric parietal cells. Our objective was to evaluate the plasma concentrations of erlotinib when given alone or in combination with different groups of ARAs (PPIs and H2RAs) and to simulate the erlotinib plasma concentration using a physiologically based pharmacokinetic (PBPK) model to evaluate possible physicochemical interactions from ARA co-medication.

Methods: Three groups of each 8 patients, suffering from pancreatic cancer, received 100 mg erlotinib daily as fixed dose (control group), combined with PPI pantoprazole (PPI group) or combined with H2RA famotidine (H2RA group). Blood samples were collected on day 1 (pre-dose,1,2,3,4,6,8 and 24 hours after administration) and on days 2-7 (pre-dose and 4 hours after administration). Erlotinib samples were stored at -80 °C and were quantified by a HPLC assay. Pharmacokinetic parameters were calculated by a noncompartmental method for extravascular input using WinNonlin 6.0(Phoenix Inc.). The PBPK model was built with the software Gastro Plus™(Simulations Plus Inc.) to simulate plasma concentrations of erlotinib in a population of 25 Caucasian patients.

Results: The PBPK model output corresponds well to the mean observed erlotinib plasma concentrations of the control group. The observed Cmax and AUC0-24 of erlotinib on day 1 were consistent with the predicted concentrations by Gastro Plus™(Cmaxobserved=0.78 µg/mL vs. predicted=0.76 µg/ml, AUC0-24observed=10.7 hr*µg/mL vs. predicted=11.8 hr*µg/ml). The mean trough and peak concentrations showed a high inter-patient variability over the whole investigated period in all patient groups. The co-administration of PPIs decreased the erlotinib trough and peak concentrations as well as the AUC0-24 about 50% compared to the control and H2RA group. The mean trough concentration in the PPI group on day 7 was 0.36 µg/mL and therefore below the necessary threshold concentration of 0.5 µg/mL to inhibit the tyrosine kinase activity. On the contrary, the pharmacokinetic parameters of erlotinib did not differ significantly in presence of the H2RAs. The mean trough and peak concentration of erlotinib in the H2RA group on day 7 were 0.671 and 1.78 µg/mL and thus similar to the values of the control group (Ctrough=0.950 µg/mL, Cpeak=1.76 µg/mL). In the H2RA and control group all measured plasma concentrations exceeded the threshold.

Conclusion: Co-administration of H2RA drugs instead of PPIs is strongly recommended during erlotinib treatment. H2RAs are given 12 hours before erlotinib administration and therefore show no influence on erlotinib plasma concentrations. PBPK is a useful tool to simulate plasma concentration-time curves of a drug and model possible interactions based on patient observations, physicochemical properties and drug classifications.

P – 169 Gemcitabine induced hemolytic uremic syndrome: Underestimated?

E Una Cidon[1], P Alonso[2]

[1]Oncology Department, Royal Bournemouth Hospital, NHS Foundation Trust, Bournemouth, UK, [2]Clinical University Hospital, Valladolid, Spain

Introduction: Thrombotic microangiopathy (TMA) is characterized by inflammation of the arterioles and capillaries wall, detachment of endothelial cells, accumulation of proteins, cellular debris and platelet thrombi that occlude the vessels. It mainly affects the kidney. The clinical signs are called hemolytic-uremic syndrome (HUS). This includes non-immune hemolytic anemia, thrombocytopenia and acute kidney injury. Gemcitabine is an antineoplastic agent with many uses in oncology. HUS is an infrequent toxicity although it could be easily underdiagnosed as many cases may go unrecognized due to difficulties in diagnosis. The true incidence is difficult to estimate. It varies from 0.078% in clinical trials to 0.008% in standard practice. However, some authors have documented 2.2%. We carried out a retrospective review to know the

incidence of gemcitabine induced HUS in our population of pancreatic cancer patients receiving adjuvant treatment and to ascertain potential risk factors.

Methods: We reviewed 187 patients on adjuvant gemcitabine for pancreatic carcinoma. We collected data about haemoglobin, platelets, white cells count, creatinine clearance before each cycle. We calculated the maximum drop between baseline and minimum level of haemoglobin and creatinine clearance for all these patients.

Results: We found that two patients developed HUS (1.06%). 185 patients developed a maximum drop in haemoglobin of 22% (18-27%) and around 19% in creatinine clearance (10-45%). The HUS patients had a drop in haemoglobin of 37% and 34% and a drop in creatinine clearance of 41% and 31%. We carried out a logistic regression analysis. This showed that a drop in haemoglobin >25% and in creatinine clearance >30% from baseline, increased significantly the chances of developing HUS (p 0.0001).

Conclusion: Our data point to a significant drop in hemoglobin and creatinine clearance as two significant risk factors to develop HUS induced by gemcitabine. We recommended that in cases with high index of suspicion, gemcitabine should be stopped or delayed until we receive the results of extra tests such as haptoglobin, lactate dehydrogenase, test de Coombs, to confirm or rule out this diagnosis.

P – 170 Management of patients with unresectable HCC: A simulation-based assessment of medical oncologists' practice choices

T Herrmann[1], A Carothers[1], G Littman[1], M Warters[1], C Cason[1], T Bekaii-Saab[2]
[1]Medscape Education, New York, New York, USA, [2]Mayo Clinic, Phoenix, Arizona, USA

Introduction: For the first time in a decade the hepatocellular carcinoma (HCC) treatment algorithm is undergoing significant change, challenging oncologists to assimilate evidence into practice.

Methods: A CME certified virtual patient simulation (VPS) was made available via a website dedicated to professional development. The VPS consisted of 2 cases presented in a platform that allows oncologists to assess the patients and choose from an extensive database of diagnostic and treatment possibilities matching the scope and depth of actual practice. Clinical decisions were analyzed using a sophisticated decision engine, and instantaneous clinical guidance (CG) employing evidence-base and faculty recommendations was provided after each decision. Oncologists were allowed to revise each decision point post-CG, if desired. Rationales for clinical decisions were also collected in real time. Data were collected between 11/27/2017 and 2/21/2018.

Results: At the time of initial assessment, 76 oncologists, 76% of whom practiced in the community setting, fulfilled the participation criteria for completing the simulation. Assessment of their practice choices revealed: In a patient with newly diagnosed unresectable HCC, only 52% ordered an appropriate regimen. CG led to a 26% increase in evidence-based treatment orders ($P = 0.004$). Sorafenib remained the systemic treatment of choice, with only 10% choosing a different regimen. In a patient whose disease has progressed on sorafenib after 6 months of therapy, only 36% of oncologists prescribed an appropriate regimen. CG resulted in a 36% improvement in evidence-based treatment orders ($P < 0.001$). The primary rationale for the selected treatment differed based on the chosen regimen, disease characteristics (22%) with use of nivolumab to better efficacy for this patient profile (33%) for regorafenib. Less than 50% of oncologists initially ordered side effect counseling in each case. CG resulted in a 14% ($P = 0.091$) and 25% ($P = 0.013$) improvement in case 1 and case 2, respectively.

Conclusion: This study, using an immersive VPS, provides access to unique insights into oncologists' real world clinical practices in an evolving HCC treatment landscape and identifies a lack of clarity about identification of the most appropriate regimen for these patients. Our findings demonstrate a continued need to educate oncologists about how to select and prescribe the most appropriate regimen for a patient with HCC.

P – 171 Analysis of echoendoscopic punctures of a solid pancreatic lesions in a private institution in Brazil

T Pessoa[1], A Pessoa[2], P Aguiar[2], R Pessoa[3], A Moura[4], D Ferreira[5], F Távora[3], F Pessoa[6], R Pessoa[5]
[1]Laboratory of Molecular Biology and Development, University of Fortaleza, Fortaleza, Brazil, [2]University of Fortaleza, UNIFOR, Fortaleza, Brazil, [3]Federal University of Ceará, Fortaleza, Brazil, [4]University of Fortaleza, UNIFOR, Fortaleza, Brazil, [5]SOBED, São Paulo, Brazil, [6]State University of Ceará, Fortaleza, Brazil

Introduction: In the last 10 years echoendoscopy has been consolidated as a major weapon for the diagnosis of pancreatic diseases. The improvement in radiological exams (tomography and MRI) increases the number of nodules detected in asymptomatic patients. And it is important to establish diagnoses by cytology or histology. Echoendoscopy is better than conventional ultrasound to guide puncture because of the retroperitoneal localization. This study aimed to analyze the result of punctures performed in solid lesions in pancreas.

Methods: It is a retrospective study, quantitative, carried out in a private clinic in Northeast of Brazil, comprising 99 patients who underwent pancreatic puncture during the years 2016 and 2017 using a single needle (22 gauge), Fanning maneuver and technique by Negative pressure and capillarity, depending on the doctor's choice, without rose. GraphPad software was used for the statistical analysis efficiency of the punctures, the lesions (size and location), confirmation of the form of collection and degree of similarity of the results with those described in the literature. We divided the size of the lesions in three groups: less than 1 cm; 1 to 3 cm and larger than 3 cm. 5% significance was adopted.

Results: In 86.86% of the cases, the final pathologic diagnosis confirmed the clinical suspicion. Ninety nine (99) pancreatic punctures were performed, 65.66% in the head of the pancreas; 23.24% in the body; 8.08% in the tail and 3.02% in the uncinate process. The major part of the punctures (54.55%) had 1 to 3 cm; 37.37% were greater than 3cm and 8.08% less than 1 cm. Sixty three percent (63.07%) of the punctures of head nodules were positive. 68.29% of them had between 1 to 3cm; 24.40% were greater than 3cm and 9.75% less than 1cm. Eighty two percent of the punctured in the body were positive, 68.42% of them had between 1 to 3 cm; 21,05% was greater than 3cm and 10.52% less than 1cm. In the tail, 50% of the punctures were positive, 62.50% of them were greater than 3cm and 37.50% (1 to 3 cm). In uncinate process, punctures were positive in 66.66%, and 66.67% were greater than 3 cm, while 33.33% had between 1 to 3 cm. Of the 13.13% negative nodules, 56.92% were in the head (1 to 3 cm); 20.01% in the Body (83.24% -1 to 3 cm and 16.76% greater than 3cm); 7.69% in the Tail (1 to 3 cm) and 15.38% in the uncinate process (greater than 3cm).

Conclusion: It is concluded that our study coincided with the literature as we had 86.86% of sensitivity and 100% of specificity. The negative results were more frequent in lesions in the head of the pancreas and smaller than 1 cm.

P – 172 Epidemiology, treatment modalities and prognostic factors of pancreatic cancer: A retrospective study

W Khechine[1], I Belaid[2], F Ezzairi[1], A El Ghali[3], A Bedioui[4], N Bouzid[5], F Bouzaiene[6], M Ben Mabrouk[7], Y Bencheick[8], I Chabchoub[1], M Hochlaf[9], L Ben Fatma[1], S Ben Ahmed[1]
[1]Department of Medical Oncology, Farhat Hached Hospital, Sousse, Tunisia, [2]Medical Oncology Unit, Ibn El Jazzar Hospital, Kairouan, Tunisia, [3]Department of General Surgery, Farhat Hached University Hospital, Sousse, Tunisia, [4]Department of Pathology, Farhat Hached University Hospital, Sousse, Tunisia, [5]Farhat Hached Sousse Hospital, Department of Radiotherapy, Sousse, Tunisia, [6]Department of Radiology, Farhat Hached University Hospital, Sousse, Tunisia, [7]Department of General Surgery, Sahloul University Hospital, Sousse, Tunisia, [8]Department of Radiology, Sahloul University Hospital, Sousse, Tunisia, [9]Department of Medical Oncology, Fathat Hached Hospital, Sousse, Tunisia

Background: Pancreatic cancer is considered a challenge in digestive cancers. Even with early diagnosis, mortality rates are high explaining why, despite the low incidence, it ranks eighth in the world listing of cancer mortality. The aim of this study was to report the epidemiologic profile of patients with pancreatic cancer, to see the different modalities of treatment of this pathology and to identify prognostic factors.

Methods: A single-center series of 130 patients treated between January 2001 and December 2016 in a department of Medical Oncology in Tunisia was retrospectively investigated.

Results: Median age was 58.7 years [32-81] and sex ratio was 1.8. A family history of cancer was found in 4% of the patients. 38.5% had diabetes, 10% were obese and 2% had a chronic pancreatitis. 39 % of patients were smokers and alcohol consumption was noted in 20% of the cases. Most common complaints at diagnosis were abdominal pain (55%) and jaundice (33%). Tumors were mainly located in the head of the pancreas (59%). 30 % of the patients had a localized tumor, 28.5% patients had a locally advanced disease and 41.5% were metastatic at diagnosis. The liver was the main site of metastases (67%). 32% of the patients had a curative surgery while 23% underwent palliative surgery. 14% had an adjuvant chemotherapy. Neoadjuvant chemotherapy was administered in 15% but it did not lead to surgery in any of the patients. 52% of the cases received palliative chemotherapy for a metastatic disease. 8.5% patients were unfit for chemotherapy and received best supportive care. Response rates after first and second line chemotherapy were respectively 14% and 11%. Relapse rate after curative treatment was 27 % with a mean time to relapse of 12.6 months. 63% received a palliative chemotherapy for their relapse. Median overall survival was 6 months and median progression-free survival was 4 months. A ten-year survival rate was 10%. Prognostic factors significantly related to better survival rates were: female gender ($p=0.013$), performance status WHO (0-1) ($p<0.0001$), localization of tumor in the head of the pancreas ($p=0.054$), localized stage at diagnosis ($p<0.0001$), curative surgery ($p<0.0001$), adjuvant chemotherapy ($p<0.0001$) and palliative chemotherapy ($p<0.0001$).

Conclusion: Pancreatic cancer remains one of the deadliest tumors. Etiology of pancreatic cancer remains elusive. Our study confirms that smoking, diabetes, obesity, alcohol consumption and chronic pancreatitis are associated with an increased risk of pancreatic cancer. Chemotherapy is the mainstay of therapy in the majority of the patients whereas resection is the only chance of cure but not usually possible. Curative surgery in localized stage and adjuvant chemotherapy are correlated with better survival rates.

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P – 175 Clinical implication of inflammation markers for identifying radiotherapy candidates in inoperable locally advanced pancreas cancer

W Cho[1], J Yu[1], H Park[1], D Lim[1], J Park[2], S Kim[1], Y Park[1]

[1]Samsung Medical Center, Seoul, Republic of Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Introduction: Several nutrition and inflammation markers are identified to have association with survival in pancreas cancer. This study intended to figure out promising candidates for local radiotherapy among the patients with inoperable locally advanced pancreas cancer (LAPC) using the various inflammation markers.

Methods: We retrospectively reviewed the medical records of 142 patients who are diagnosed as inoperable LAPC and initiated concurrent chemoradiotherapy (CCRT) with curative intent in our institute from January 2000 to December 2012. The prognostic impact of the factors including prognostic nutritional index (PNI), sarcopenia, pretreatment level of CA 19-9, albumin, lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) on locoregional recurrence free survival (LRRFS), distant metastasis free survival (DMFS), and overall survival (OS) were investigated using univariate and multivariate analysis.

Results: The median LRRFS, DFS, and OS of all patients were 9.2 (2.0∼117.5), 10.6 (0.8∼135.0), and 14.2 (2.1∼135.0) months, respectively. For the LRRFS, PNI < 45 ($p = 0.014$), NLR > 3 ($p = 0.020$), sarcopenia ($p = 0.001$), and no use of maintenance chemotherapy ($p = 0.006$) were unfavorable factors in multivariate analysis. Unfavorable factors for DMFS were sarcopenia ($p = 0.006$) and no use of maintenance chemotherapy ($p = 0.040$) and those for OS were PNI < 45 ($p = 0.032$), NLR > 3 ($p = 0.014$), sarcopenia ($p < 0.001$), no use of maintenance chemotherapy ($p = 0.038$), and radiation therapy (RT) dose less than 50 Gy ($p = 0.032$). When the patients were stratified by the number of following risk factors: PNI < 45, NLR > 3, and sarcopenia, the median OS of the patients having no risk factor ($N = 82$), one risk factor ($N = 47$), and two or more risk factors ($N = 13$) were 15.9 (2.6∼135.0), 13.2 (2.1∼30.2), and 6.3 (2.4∼21.6) months, respectively ($p < 0.001$).

Conclusion: In patients with inoperable LAPC, those having two or more risk factors including NLR < 3, PNI < 45, and sarcopenia have dismal survival. The addition of local RT can be considered exclusively in patients having less than two risk factors.

P – 176 Analysis of various clinical and pathological factors affecting survival in patients diagnosed with pancreatic adenocarcinoma: Single institute study

A Nagy

Ain Shams University, Cairo, Egypt

Introduction: Worldwide, pancreatic cancer ranks 13th in incidence but is the 8th cause of cancer related death. Unfortunately even with early diagnosis, mortality rates are high. The collective median overall survival for all patients ranges from 4-6 months. The initial symptoms of the disease are often vague and nonspecific abdominal pain and weight loss which are subtle in onset and most patients present in an advanced stage.

Methods: This is a retrospective study aiming at evaluating the clinic-epidemiological and pathological factors affecting overall survival (OS) in patients diagnosed with pathologically proven pancreatic adenocarcinoma and received treatment at Ain Shams University Department of Clinical Oncology in the period from 1-1-2008 till 1-1-2012. Data collected from files of patients included age, gender, residence, smoking status, medical history of viral hepatitis, family history of cancer, clinical presentation, total bilirubin at presentation, stage, pathology, grade, offered treatment and overall survival (OS). The collected data was revised, coded, tabulated and introduced to PC using statistical package for social science (SPSS 20.0 for windows; SPSS Inc, Chicago, IL, 2001). Numerical data were summarized as means and standard deviations (SD) or medians and ranges as appropriate. While qualitative data were described as frequencies and percentages. The Chi square test was used for comparisons of the categorical variables. Overall survival estimates were calculated using Kaplan-Meier method. Overall Survival (OS) was calculated from the time of diagnosis to date of death or last follow up.

Results: The study included 109 patients (Males 83.5%) where the median age was 58 years (±6.522, range 45-68) and the majority of the patients were of urban residence (74.3%) and most were smokers (71.6%). Positive family history of cancer was reported in about 20% of the studied patients and the most common presentation was jaundice (48.6%). The median overall survival (OS) was 7.5 months (±3.721, range 3-17). The OS was statistically significantly higher in non-smokers 15 months (95% CI 10.627-19.373) versus 7.5 (95% CI 6.973-8.027) months in smokers ($p<.0001$). Patients who presented with total bilirubin more than 10 mg/dL had a OS of 5 months (95% CI4.253-5.747) which was statistically lower than other patients($p<.0001$). The presence of viral hepatitis (HBV and HCV) had a negative effect on survival where positive patients had a 5 month OS (95%CI 4.433-5.567) versus 9 months (95%CI 8.458-9.542) in viral hepatitis free patients ($p<.0001$). Other factors which significantly affected survival negatively were metastatic presentation (6.9 months, 95%CI 5.906-7.894) and

grade 3 pathology (5 months, 95%CI 3.852-6.148). The other observed variables were not associated with a statistically significant effect on survival.

Conclusion: Pancreatic carcinoma still poses a significant clinical challenge, however the eradication of certain predisposing factors like smoking and viral hepatitis could greatly affect the outcome of treatment.

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P – 178 Clinical characteristic of pancreatic cancer

B Abdelkader El Hakim[1], N Caid[2], L Saoudi[2], R Benemla[2], R Ramoul[2], S Rekkache[2], F Smaili[3]

[1]Saad Dahlab Univerity, Blida, Algeria, [2]University of Blida, Blida, Algeria, [3]Societe of Oncologie Medicale, Blida, Algeria

Introduction: Unfortunately, the majority of cases are diagnosed at an advanced stage, where palliative chemotherapy can be administered to alleviate the symptoms and prolong life. Although pancreatic carcinogenesis has not yet been explained, familial aggregation, tobacco smoking, and hypercaloric intake are associated with pancreatic carcinogenesis. Till date, either prevention or screening programs could yet be proposed.

Methods: This is a retrospective study for patients following in medical oncology department of anti-cancer center Blida between January 2010- December 2015. The aims of study are to reported the epidemiologic profile for patients with pancreatic cancer. Although pancreatic carcinogenesis has not yet been explained, familial aggregation, tobacco smoking, and hypercaloric intake are associated with pancreatic carcinogenesis. Till date, either prevention or screening programs could yet be proposed.

Results: 110 patients were following in the department, the median age was 60.8 years [21-80], and sex ratio was 2. Family history of cancer was 13.7%, 30.7% Had diabetes in their antecedents, tobacco smoking was present in 46.8% of cases, 32% of obesity, the most common reasons for consultation were pain in 49.2% and jaundice in 18% with an average consultation time of 03 months. The histological type was adenocarcinoma in 95.7% of patients, stage IV and III in 78.5% and 16.3% at diagnosis.

Conclusion: As the cancer of the pancreas becomes symptomatic the diagnosis is made with a late stage, which testifies to the gravity of this cancer, to improve this situation prevention keeps an important place by acting on the risk factors such as smoking and the obesity. Around the world significant efforts are being made in order to better understand pancreatic cancer. Detailed epidemiological analyses of pancreatic cancer trends and further analytical epidemiological researches will help guide future cancer control strategies.

P – 179 Surgical management of pancreatic tumors in children

A Lukashenko[1], Y Ostapenko[2], O Kolesnik[1], N Chorna[2]

[1]National Cancer Institute, Kiev, Ukraine, [2]National Cancer Institute of Ukraine, Kiev, Ukraine

Introduction: Pancreatic tumors in children are relatively uncommon. The data of their presentation accrues mostly through institutional case series. The very limited experience along with the broad histological heterogeneity have made it difficult to identify possible prognostic factors and develop treatment protocols. The aim of the presented research was to improve surgical treatment of pancreatic tumors in children.

Methods: Retrospective review of medical records and pathology reports of children who were undergone surgery at National Cancer Institute was conducted from 1990 to 2017. Over the whole period there were 19 patients under the age of 18 with surgical treatment due to pancreatic tumors.

Results: Radical (R0) surgical resection was achieved in 18 patients (94,7%). In 12 (63,1%) cases distal pancreatic resection were performed accordingly to localization of the tumor in pancreatic body or tail. Pancreatoduodenectomy (PD) was performed in 4 (21%) cases. Organ-preserving approach was used for 3 patients: enucleations of tumor of pancreatic tail in 1 case (5,2%), spleen preserving distal pancreatectomy in 2 (10,5%) cases. There was no postoperative mortality, but postoperative complications occurred in 2 patients (10,5%) and was treated conservatively. The median follow-up was 126 months (range 16-292 months). No patients were observed with postoperative pancreatic exocrine or endocrine insufficiencies. All patients are still alive so far.

Conclusion: Conclusion: Pancreatic tumors in children have more favorable outcomes in comparison with adults. Surgical treatment is the prominent method for young patients under the age of 18 with pancreatic tumors. Pancreatic resection of pancreatic tumors in children should performed in high-experience surgical center.

P – 180 Neo-adjuvant FOLFIRINOX in borderline-resectable/locally advanced pancreatic adenocarcinoma: An updated analysis

S Temraz[1], M Salim Hammoud[1], M Zorkot[2], W Albonji[2], H Dbouk[3], F Farhat[4], M Charafeddine[2], D Mukherji[1], A Shamseddine[1]

[1]American University of Beirut Medical Center, Beirut, Lebanon, [2]American University of Beirut, Beirut, Lebanon, [3]Nabih Berri Governmental University Hospital, Nabatieh, Lebanon, [4]Hammoud Hospital University Medical Center, Saida, Lebanon

Introduction: Trials examining FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) significantly improved the response rate and median survival in patients with locally advanced/borderline resectable pancreatic cancer and showed promising results for neoadjuvant use. There is currently limited experience with neoadjuvant FOLFIRINOX (nFOLFIRINOX) in borderline resectable and locally advanced pancreatic cancer.

Methods: This is a prospective cohort study launched at the American University of Beirut Medical Center (AUBMC) and Hammoud Hospital University Medical Center (HHUMC), between November 2013 and February 2018. Forty one patients confirmed to have borderline resectable or locally advanced pancreatic adenocarcinomas were enrolled and received nFOLFIRINOX therapy. Our primary outcome was to assess the conversion of the tumor to a surgically resectable disease. The secondary outcomes were progression free survival (PFS) and overall survival (OS).

Results: The total number of patients was 41, with a mean age at diagnosis 63 years; 25 (61%) were males and 16 (39%) were females. Locally advanced unresectable cases were 27 (65.9%) while borderline resectable cases were 14 (34.1%). The tumor was located in the head 17 (41.4%), body 14 (34.1%), and tail 10 (24.4%) in decreasing order. The median number of completed cycles was 10.Upon receiving nFOLFIRINOX, 7 (17.1%) had a stable disease, yet 11 (26.8%) had progression of the disease, and 3 patients (7.3%) still didn't reach the time of initial assessment. 20 (48.8%) patients showed partial response to treatment, among which 40% (8/20) underwent surgical resection of the pancreatic tumor and 40% (8/20) received stereotactic body radiation therapy (SBRT).Therefore, the percentage of patients converted to a resectable state was 19.5% (8/41). Our study sample had a median progression free survival (PFS) of 12 months and a median overall survival (OS) of 21 months. Patients who underwent surgical resection had an improved PFS (p value =0.029) and OS (p value = 0.043). The PFS at 12 months was 85.7% in patients who underwent surgical resection compared to 30.1% in those who did not while the PFS at 24 months was 57.1% compared to 22.6%. As for the OS, it was not obtained at 12 months for patients who had surgical resection but was 67.1% compared to 26.1% in patients who didn't undergo surgery at 24 months. Dose modifications were applied to 15 (36.6%) cases due to FOLFIRINOX adverse effects with the most dose limiting one being grade III neuropathy in 8 (19.5%) of cases.

Conclusion: Our study supports that FOLFIRINOX administered in the neoadjuvant setting aids in enhancing conversion to resectability as surgical resection offers the best possibility for cure in patients with pancreatic cancer. It also shows beneficial effects on the PFS and OS in borderline resectable/unresectable pancreatic cancer patients. The protocol was well tolerated with mild increase in adverse events noted.

P – 181 Pancreatic head resections: Impact factors, perioperative morbidity, mortality and long-term survival

B Ilijevec, S Potrc
University Medical Center Maribor, Maribor, Slovenia

Introduction: One of the toughest procedures for pancreatic surgeon is the resection of the head of the pancreas. The procedure is accompanied by high morbidity and complications. Better patient selection, advancements in perioperative care and in surgical technique have improved perioperative mortality. The main goal of this study was to identify potential impact factors for perioperative morbidity and mortality as well as consequences of perioperative morbidity on long-term survival in pancreatic head resections.

Methods: A retrospective study of clinical-pathological factors of 240 patients which were divided into two chronological groups (period 1 (P1): from January 1, 2008 to December 31, 2012 (96 pts); and period 2 (P2): from January 1, 2013 to March 31, 2017 (144 pts)) and underwent pancreatic head (PD) or total pancreatic (TP) resection were analyzed for correlations with morbidity, 30- and 90-day mortality, and long-term survival. Complications were graded according to Clavien-Dindo classification, grade II and more being defined as overall complications (OAC). Clinical-pathological factors were correlated with OAC, all surgical (ASC), general (AGC) and specific types of complications including leaks from the pancreatoenteric anastomosis (PEA) or pancreatic fistula (PF, type A, B and C), leaks from other anastomoses (OL), bleeding (BD) and abscesses (AA).

Results: In the 9-year period, altogether 240 patients (131 men and 109 women, mean age 66,04 years) had pancreatic resection. The incidence of OAC was 37.1%, ASC 29.2% and AGC 15.8%. ASC were presented as PL, OL, BD and AA in 19% (of 208 PD), 5.8%, 5.8%, and 2.5% respectively. Age, ASA score, amylase on drains, and pancreatic fistulas B and C correlated significantly with various types of complications. Overall 30- and 90-day mortality were 5 and 7.9%, with 7,3 and 11,5% in P1 and decreased to 3.5 and 5% in P2.

Conclusion: Most subtypes of complications did not compromise the long-term survival in analyzed cohort of patients. Exceptions were correlated with PLs and BDs. Independent indicators of morbidity were high amylase on drains and consequently PF B and C, OAC, PL and BD. PL and BD were shown to be an independent predictor for 30-day mortality, and OAC and PF C for 90-day mortality.

P – 182 Efficacy and safety of tislelizumab, an anti-PD-1 antibody, versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma in a phase 3, randomized, open-label, multicenter study - Trial in progress

S Qin[1], R Finn[2], M Kudo[3], T Meyer[4], A Vogel[5], M Ducreux[6], T Macarulla[7], G Tomasello[8], F Boisserie[9], J Hou[10], C Li[11], J Song[12], A Zhu[13]
[1]People's Liberation Army (PLA) 81 Hospital, Nanjing, China, [2]University of California Los Angeles, Los Angeles, California, USA, [3]Kindai University School of Medicine, Osaka, Japan, [4]Royal Free Hospital, University College London, London, UK, [5]Hannover Medical School, Hannover, Germany, [6]Gustave Roussy Cancer Campus Grand Paris, Villejuif, France, [7]Vall d'Hebrón Institute of Oncology, Barcelona, Spain, [8]Department of Medical Oncology, Azienda Istituti Ospitalieri di Cremona, Cremona, Italy, [9]BeiGene USA, Inc, Fort Lee, New Jersey, USA, [10]Beigene USA, Inc, Emeryville, California, USA, [11]BeiGene (Beijing) Co., Ltd., Beijing, China, [12]Beigene USA, Inc., Fort Lee, New Jersey, USA, [13]Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA

Introduction: Unresectable hepatocellular carcinoma (HCC) accounts for 70% of diagnosed HCC. Tislelizumab (previously known as BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for programmed cell death receptor-1 (PD-1). Furthermore, tislelizumab was specifically engineered to minimize FcgR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors, including HCC. A recommended phase 3 dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been established for tislelizumab.

Methods: This global, phase 3, randomized, multicenter study (NCT03412773) was designed to evaluate the efficacy and safety of tislelizumab compared with sorafenib as a first-line treatment of unresectable HCC. Adult patients, aged $\geq$18 years, with unresectable, histologically confirmed HCC, an ECOG score $\leq$1, Child-Pugh A classification, BCLC Stage C disease or BCLC Stage B disease that has relapsed after loco-regional therapy, and who have not received prior systemic therapy, are being enrolled. Approximately, 640 patients from 100 international centers will be randomized (1:1) to receive tislelizumab 200 mg IV Q3W or sorafenib 400 mg orally BID. The primary outcome of this non-inferiority study is overall survival (OS) of patients treated with tislelizumab compared with OS of patients treated with sorafenib; secondary outcomes include objective response rate, progression-free survival, duration of response, time to progression, and quality-of-life outcomes. Safety/tolerability assessments include monitoring adverse events (AEs), including immune-related AEs, as well as physical examinations, vital signs, and electrocardiograms. Exploratory endpoints include assessment of potential predictive biomarkers, characterization of the tislelizumab pharmacokinetic profile in patients with HCC, and to determine host immunogenicity against tislelizumab.

P – 183 A pilot trial of PEGPH20 (Pegvorhyaluronidase alfa) in combination with avelumab (anti-PD-L1 MSB0010718C) in chemotherapy resistant pancreatic cancer (PDAC) - Trial in progress

L Medina Rodriguez[1], C Guillén-Ponce[2], J Feliu[3], M Hidalgo[4]
[1]Hospital de Fuenlabrada, Fuenlabrada, Spain, [2]H. Universitario Ramón y Cajal, IRYCIS, Madrid, Spain, [3]University Hospital La Paz, Madrid, Spain, [4]Centro Nacional de Investigaciones Oncológicas, Madrid, Spain

Introduction: PDAC is characterized by excessive hyaluronan (HA) accumulation in the tumor microenvironment, elevating interstitial pressure, resulting in tumor vascular collapse, hypoxia, blocking chemotherapeutic agent perfusion and immune cells. Consequently, checkpoint inhibitors and immunotherapy strategies have failed in PDAC. PEGPH20 targets tumors that accumulate HA. Enzymatically depleting HA from the extracellular matrix (ECM), resulting in decompression of intratumoral blood vessels and increased penetration of antitumor agents. In preclinical models, depletion of HA in the tumor microenvironment has been shown to inhibit the growth of tumors characterized by accumulation of HA. PEGPH20 has been evaluated in a phase II trial in combination with gemcitabine and nab–paclitaxel (PAG) versus gemcitabine plus nab–paclitaxel (AG). For patients with high HA expression on baseline biopsies, the combination arm with PEGPH20 increased progression-free survival (PFS) by 4 months (9.2 vs. 5.2 months; HR 0.51; $p = 0.048$). Our study tests the hypothesis that elimination of HA in tumor microenvironment by PEGPH20 will result in stromal remodeling and may facilitate the activity of checkpoint inhibitors like avelumab, by at least two mechanisms including increase in drug delivery and increasing immune infiltrate.

Methods: A pilot, open label, multicenter, pharmacodynamics, safety, and efficacy study of PEGPH20 in combination with avelumab in chemotherapy resistant advanced or locally advanced PDAC. PEGPH20 3 microg/Kg dose will be administered on days 1, 4, 8, 11, 15, 18 during the first cycle (28 days) and days 1 and 15 thereafter. Avelumab at dose of 10 mg/Kg will start on day 15 after 4 doses of PEGPH20 and continued to be administered every 2 weeks during the study. Enoxaparin will be administered to all subjects to minimize the risk of thromboembolic events (TE) associated to PEGPH20 administration. Pharmacokinetics (Pk) samples for PEGPH20 will be collected. Other assessments: serum CA 19-9 and tissue biomarkers (including collagen content, cancer associated fibroblasts [CAF], and immune infiltrate). Objectives: Primary: To determine the objective response rate (ORR) as per RECIST v1.1 criteria. Secondary: To determine the overall survival (OS), progression free survival (PFS) and CA19-9 tumor marker response. Exploratory: To determine the effect of PEGPH20 in HA content in plasma and paired tumor biopsies. Key inclusion criteria: progression to first line treatment for locally advanced or advanced disease, life expectancy $\geq$ 3 months and no clinical evidence of prior TE within 12 months or other known TE during the screening.

P – 184 CanStem111P trial: A Phase 3 Study of napabucasin (NAPA) plus nab-paclitaxel (nPTX) with gemcitabine (Gem) in adult patients with metastatic pancreatic adenocarcinoma (mPDAC) - Trial in progress

T Bekaii-Saab[1], T Okusaka[2], D Goldstein[3], B O'Neill[4], J Tabernero[5], C Li[6], M Reni[7], B Jin[8], C Oh[8], L Borodyansky[8], E Van Cutsem[9]
[1]Mayo Clinic Cancer Center, Scottsdale, Arizona, USA, [2]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Chuo-ku, Japan, [3]Prince of Wales Hospital, Sydney, Australia, [4]IU Health University Hospital, Indianapolis, Indiana, USA, [5]Vall d'Hebron University Hospital, Barcelona, Spain, [6]Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Republic of Taiwan, [7]Ospedale San Raffaele, Milan, Italy, [8]Boston Biomedical, Cambridge, Massachusetts, USA, [9]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

Introduction: NAPA is an oral investigational agent, which has been hypothesized to inhibit cancer stemness pathways, including STAT3 pathway implicated in cancer stem-cell viability. Preclinical studies suggest that NAPA may sensitize heterogeneous cancer cells to chemotherapeutic agents, including nPTX and Gem. Encouraging anticancer activity in mPDAC was observed in a phase 1b study (NCT02231723) of 59 patients (pts), reporting 92% (46/50) disease control rate (DCR) and 56% (28/50) overall response rate (ORR), with 2 complete and 26 partial responses in pts who had a RECIST evaluation. Maturing median progression-free survival (mPFS) and median overall survival (mOS) were 7.06 and 9.59 mo, respectively. On the basis of these data, a phase 3 trial is being conducted in North America, Europe, Australia and Asia.

Methods: This randomized, open-label, multicenter study (NCT02993731) will assess the efficacy of NAPA + nPTX + Gem vs nPTX + Gem in pts with mPDAC ($n = 1132$). Pts must not have received systemic treatment for mPDAC. Pts will be randomized in a 1:1 ratio to receive NAPA 240mg PO twice daily continuously plus IV nPTX 125mg/m

2 + Gem 1000mg/m 2 weekly for 3 of every 4 weeks or nPTX + Gem weekly for 3 of every 4 weeks. Pts will be stratified by geography, Eastern Cooperative Oncology Group performance status, and presence of liver metastases. Treatment will continue until disease progression or another discontinuation criterion. The primary endpoint is OS in the general study population (HR 0.80 for OS improvement from 8.5 to 10.63 months); secondary endpoints include ORR, DCR, and PFS. In addition, OS, PFS, ORR, and DCR will be evaluated in the biomarker positive sub-population. Study enrollment is ongoing with >30% of patients enrolled to date.

P – 185 PANOVA-3: A phase 3 study of Tumor Treating Fields combined with nab-paclitaxel and gemcitabine for front-line treatment of locally-advanced pancreatic adenocarcinoma - Trial in progress

U Weinberg[1], O Faber[1], M Giladi[2], Z Bomzon[2], G Lavy-Shahaf[2], E Kirson[2]
[1]Novocure, Root D4, Switzerland, [2]Novocure, Haifa, Israel

Introduction: Tumor Treating Fields (TTFields) are a non-invasive, regional antimitotic treatment modality that predominantly acts by disrupting the formation of the mitotic spindle during metaphase. TTFields are delivered at specific frequencies (150 to 200 KHz) to the tumor region through transducer arrays placed on the skin surface. TTFields (200 KHz) are approved for the treatment of patients with recurrent and newly diagnosed glioblastoma. The effectiveness of TTFields has been demonstrated in multiple preclinical models of pancreatic cancer. TTFields in vitro showed a significant decrease in pancreatic adenocarcinoma cell count, an increase in cell volume and reduced clonogenicity. TTFields in vivo studied either alone or in combination with gemcitabine and paclitaxel in hamsters bearing syngeneic, orthotopic pancreatic tumors significantly reduced tumor volume. The Phase 2 PANOVA study [NCT01971281], the first trial of TTFields (150 KHz) in pancreatic cancer patients, demonstrated the safety of TTFields when combined with nab-paclitaxel and gemcitabine in both metastatic and locally advanced pancreatic cancer (LAPC). Dermatitis was seen below the arrays: Grades 1-2 and 3-4 in 15% and 10% of patients respectively. The median progression-free survival (PFS) with TTFields + gemcitabine + nab-paclitaxel was 12.7 months (95% CI 5.4, NA). The Phase 3 PANOVA-3 trial (NCT03377491) is designed to test the efficacy and safety of adding TTFields to nab-paclitaxel and gemcitabine combination in LAPC.

Methods: Patients (N = 556) with unresectable, LAPC (per NCCN guidelines) will be enrolled in this prospective, randomized trial. Patients will have an ECOG score of 0-2 and no prior progression or treatment. Patients, stratified based on their performance status and geographical region will be randomized 1:1 to TTFields plus nab-paclitaxel and gemcitabine or to nab-paclitaxel and gemcitabine alone. Chemotherapy will be administered at standard dose of nab-paclitaxel (125 mg/m2) and gemcitabine (1000 mg/m2 once weekly). TTFields at a frequency of 150 kHz will be delivered at least 18 hours/day until local disease progression per RECIST Criteria V1.1. Transducer arrays are placed on the back and front of the patient to deliver the highest field intensities to the abdominal region. Follow up to be performed q8w, will include a CT scans of the chest and abdomen. Following local disease progression, patients will be followed monthly for survival. Overall survival will be the primary endpoint. PFS, objective response rate, rate of resectability, quality of life and toxicity will all be secondary endpoints. Sample size was calculated using a log-rank test comparing time to event in patients treated with TTFields plus chemotherapy with control patients on chemotherapy alone. PANOVA-3 is designed to detect a hazard ratio 0.75 in overall survival. Type I error is set to 0.05 (two-sided) and power to 80%.

P – 186 Chemotherapy for patients with advanced or metastatic pancreatic cancer (AMPC)

B Abdelkader El Hakim[1], F Braneci[2], N Caid[2], L Saoudi[2], R Ramoul[2], R Benemla[2], S Rekkache[2], F Smaili[3]
[1]Saad Dahlab Univerity, Blida, Algeria, [2]University of Blida, Blida, Algeria, [3]Societe of Oncologie Medicale, Blida, Algeria

Introduction: Pancreatic cancer is a common, highly lethal disease that is rising in incidence. Chemotherapy based on 5-fluorouracil (5-FU) has been shown to prolong survival in advanced pancreatic cancer. Gemcitabine improves major symptoms and survival outcomes compared with bolus 5-FU. Many novel small molecules are being widely and actively researched. These compounds are based on classical mechanisms of action as well as biological therapies targeting novel cellular survival pathways.

Methods: The primary objective of this retrospective analysis is to evaluate overall survival; the secondary objective is to evaluate progression-free survival and toxicity of gemcitabine-cisplatin in AMPC after 4 cycles. Inclusion criteria were histologically proven pancreatic carcinoma, no prior chemotherapy (adjuvant chemotherapy allowed if more than 6 month before), no other serious concomitant illness ECOG PS < 2, adequate renal and liver function, good marrow reserve.

Results: From 01/2010 to 12/2015, 90 patients were enrolled in this study. Median age 57.8 ± 1.5 years old (21-80), with a total 410 cycles were administrated, median = 4 (4- 8). All patients were evaluated for efficacy and toxicity. Median of overall survival was 7.1 months[3-17 months]; median of progression free survival was 3.4 months, the overall response rate was 10% and disease control rate was 32% including 10% partial response, 22% had stable disease. Grade ¾ toxicities evaluated were asthenia 3%, leucopenia 1%, neutropenia 2%, anemia 1.5%, vomiting 1.5%, thrombopenia 1%, mucositis 1%.

Conclusion: Gemcitabine-cisplatin is moderately effective and well tolerated as first line treatment for AMPC with a correct quality of life. The results of chemotherapy in metastatic or advanced pancreatic cancer remain poor; they must be improved by other therapeutic combinations.

P – 187 Erythrocyte membrane fatty acids as the potential biomarkers for detection of early-stage and progression of colorectal cancer

M Kruchinina[1], A Gromov[1], Y Prudnikova[1], M Shashkov[2], A Sokolova[3], V Kruchinin[4]
[1]Research Institute of Internal and Preventive Medicine - Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russian Federation, [2]Boreskov Institute of Catalysis Siberian Branch of Russian Academy of Sciences SB RAS, Novosibirsk, Russian Federation, [3]N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry Of Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russian Federation, [4]Rzhanov's Institute of Semiconductor Physics Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russian Federation

Introduction: Colorectal cancer (CRC) is the third most common cancer in the world. Clinical data show that 5-year survival rate of early-stage CRC postoperative patients is around 90%. However, most of CRC patients were diagnosed at advanced stage due to its asymptomatic and poor diagnostic techniques. Early screening is an effective way to reduce the morbidity and mortality. So, it is necessary to develop low-cost, less invasive, high-sensitivity, and high-specificity screening methods for early diagnosis of CRC and its progression. The study aims to assess erythrocyte membrane fatty acids (FA) as the potential biomarkers for detection of early-stage from healthy controls and progression of colorectal cancer (CRC).

Methods: Erythrocyte membrane FA from 95 patients (56 + 8 years old) with colorectal adenocarcinoma and 28 healthy people (the control group) were measured using an accelerated solvent extraction and analyzed by GC/MS system triple quad Agilent 7000B (USA). Tumors were further classified into early stage (stage I or II, n = 44) and advanced stage (stage III or IV, n = 51) based on TNM classification.

Results: Erythrocyte membrane levels of C14:0 ($p < 0.03$), C15:0 ($p < 0.04$), C17:0 ($p < 0.02$), the sum of saturated FA ($p < 0.03$), C16:1 ($p < 0.04$), the sum of monounsaturated FA ($p < 0.01$), C18:2 ($p < 0.01$), omega-6/omega-3 ($p < 0,01$) in early stage CRC patients were significantly decreased compared with healthy controls, whereas the levels of C20:0 ($p < 0.01$), C20:2, ($p < 0.01$), C20:3 ($p < 0.001$), C20:4 ($p < 0.001$), C22:4 ($p < 0.001$), C22:5 ($p < 0.001$), C22:6 ($p < 0.001$) and the sum of all unsaturated FA ($p < 0,03$) were significantly higher than those from the controls. CRC progression was accompanied by decrease in the content of saturated, monounsaturated as well as by increase polyunsaturated fatty acids ($p < 0.001$-0.05). Elevated levels of polyunsaturated fatty acids as structural components of membranes reflect a high level of their instability, which is probably associated with the process of tumor proliferation. In contrast, a decrease in the level of saturated fatty acids may be due to their consumption as an energy substrate for rapid metabolism which is necessary for tumor growth. As saturated FA do not require creation of a double bond within the beta-oxidation process it allows them for an accelerated energy production. The panel, containing the FA - C17:0, C16:1, C18:2, C20:4, C22:5, C22:6 - achieved an excellent diagnostic performance when comparing early stage patients with healthy controls with an AUC of 0.959, a sensitivity of 86.5%, and a specificity of 96.2%. A combination of C16:0, C18:1;t9, C18:3, C20:2, C20:4, C20:5, C22:5, C22:6 showed the best diagnostic ability when comparing the late stage CRC patients with early stages (AUC 0.871, sensitivity of 82.7%, specificity of 80.8%.

Conclusion: Erythrocyte levels of the fatty acids should be considered as the promising biomarkers for detecting of early stages of CRC and the progression of the disease.

P – 188 LncRNA-ZFAS1 contributes to colon cancer progression through the miR-150-5p/VEGFA axis

X Chen, S Wang
Medical College, Southeast University, Nanjing, China

Introduction: Increasing long noncoding RNAs (lncRNAs) have been reported to play key role in the development and progression in many types of malignancies. ZNFX1 antisense RNA1(ZFAS1) has been reported to be aberrant expression and suggested as a tumor suppressor or oncogene in many cancers. However, the biological role and underlying molecular mechanism of ZFAS1, especially the miRNA sponge role of which in colon cancer remain largely unknown.

Methods: Quantitative PCR was employed to evaluate the level of ZFAS1, miR-150-5p and VEGF-A mRNA expression in colon cancer tissues and cell lines. CCK-8, colony

formation, wound-healing, transwell chamber and tube formation assays were used to detect the effects of ZFAS1 on colon cancer cell proliferation, migration, invasion and angiogenesis, respectively. Luciferase reporter assays were applied to confirm the miR-150-5p target genes, and RIP assay was used to determine whether ZFAS1 binds to miR-150-5p in an AGO2-dependent manner. In vivo tumor growth and metastasis were conducted in nude mice, and in vivo tumor angiogenesis was conducted using chicken chorioallantoic membrane model. The markers of metastasis and angiogenesis-VEGFA, CD31, MMP-9, E-cadherin, N-cadherin and Vimentin, VEGFR2, Akt, mTOR and phosphorylation of VEGFR2(p-VEGFR2), phosphorylation of Akt (p-Akt), phosphorylation of mTOR(p-mTOR) were detected by using immunohistochemistry and western blot analysis.

Results: In our study, by using TCGA database, we identified a group of differentially expressed lncRNAs in human colon cancer, including ZFAS1, which mainly located in the cytoplasm with RNA-FISH. We found that ZFAS1 expression was higher in colon cancer tissues, where it was associated with TNM stage, pTstage, distant metastasis and poor overall survival. Moreover, ZFAS1 and VEGF-A are target genes of miR-150-5p, while ZFAS1 binds to miR-150-5p in an AGO2-dependent manner. Additionally, ZFAS1 knockdown significantly suppressed colon cancer cell proliferation, migration, invasion, EMT and angiogenesis in vitro, and also inhibited tumor growth, metastasis and angiogenesis in vivo. While antagomiR-150-5p or VEGF-A could reverse ZFAS1 knockdown- induced suppressing of proliferation, metastasis and angiogenesis both in vitro and in vivo. Lastly, ZFAS1 knockdown could markedly reduce the expression of VEGF-A, p-VEGFR2, p-Akt and p-mTOR, VEGFR2 inhibitor Ki8751 could obviously decrease the expression of p-VEGFR2, p-Akt and p-mTOR and inhibited colon cancer cell proliferation, metastasis and angiogenesis. Based on above data, we could conclude that ZFAS1 promoted colon cancer growth, metastasis and angiogenesis via activating VEGFA/VEGFR2 and downstream Akt/mTOR signaling pathway.

Conclusion: ZFAS1 promoted tumor progression by upregulating VEGF-A via competitively binding to miR-150-5p, which acts as a tumor suppressor by targeting VEGF-A in colon cancer. Furthermore, we verified that ZFAS1 promoted colon cancer cell proliferation, metastasis, angiogenesis and EMT process via activated VEGFA/VEGFR2/Akt/mTOR signaling pathway in colon cancer.

P – 189 Retinoic acid-induced 2 (RAI2) is a potential tumor suppressor and RAI2 promoter methylation is a poor prognostic marker in colorectal cancer

W Yan[1], K Wu[2], Y Yang[1], M Guo[3], G Dai[4]

[1]Department of Oncology, Chinese PLA General Hospital, Beijing, China, [2]Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, [3]Chinese PLA General Hospital, Beijing, China, [4]The General Hospital of the People's Liberation Army, Beijing, China

Introduction: Retinoic acid (RA) plays an important role in development, adult hematopoiesis and cell differentiation. Retinoic acid induced 2 (RAI2) was originally discovered to be induced by retinoic acid in embryonal carcinoma cells. Low retinoic acid induced 2 (RAI2) expression was found in breast cancer as an independent poor prognostic factor, promoting early hematogenous dissemination of human breast cancer cells to bone marrow. The expression of Retinoic acid induced 2 (RAI2) was found reduced in colorectal cancer (CRC) by searching The Cancer Genome Atlas (TCGA) database. The regulation and function of RAI2 in human cancer remain unclear. In this study, we focused on the epigenetic regulation and function of RAI2 in colorectal cancer (CRC).

Methods: Eight CRC cell lines, 237 cases of primary colorectal cancer samples and 15 cases of normal colorectal mucosa were analyzed in this study. Semi-quantitative RT-PCR, methylation specific PCR (MSP), Immunohistochemistry, Western Blot, flow cytometry, cell viability detection assay, trans-well migration assay and invasion assay and xenograft mouse model technique were employed to study the epigenetic regulation and the function of RAI2 in CRC.

Results: The promoter region of RAI2 was completely methylated in RKO, LoVo and HCT116 cells, partially methylated in HT29 cells and unmethylated in SW480, SW620, DLD1 and DKO cells. The expression of RAI2 was regulated by promoter region methylation. RAI2 was methylated in 53.6% (127/237) of primary colorectal cancer samples. Methylation of RAI2 was significantly associated with gender ($P < 0.001$), TNM stage ($P < 0.001$) and lymph node metastasis ($P < 0.001$). Analysis using the Kaplan–Meier method demonstrated that methylation of RAI2 was significantly associated with poor 5-years overall survival (OS) ($p = 0.0035$) and 5-years relapse-free survival (RFS) ($p = 0.0062$). According to Cox proportional hazards model analysis, RAI2 methylation was an independent prognostic marker for poor 5-years OS after adjusting for TNM stage, tumor differentiation and lymph node metastasis ($p = 0.029$). RAI2 suppressed cell proliferation, migration and invasion and induced cell apoptosis in CRC. In addition, RAI2 inhibited AKT signaling in CRC cells and suppressed human CRC cell xenograft growth in mice.

Conclusion: RAI2 is frequently methylated in human CRC, and the expression of RAI2 is regulated by promoter region methylation. Methylation of RAI2 is an independent poor prognostic marker of CRC. RAI2 suppresses CRC cell growth both in vitro and in vivo. RAI2 may serve as a tumor suppressor by inhibiting AKT signaling in CRC.RAI2 is frequently methylated in human CRC, and the expression of RAI2 is regulated by promoter region methylation. Methylation of RAI2 is an independent poor prognostic marker of CRC. RAI2 suppresses CRC cell growth both in vitro and in vivo. RAI2 may serve as a tumor suppressor by inhibiting AKT signaling in CRC.

P – 190 The influence of GSTM1-null, TS-del6bp, XRCC1-A751C gene polymorphisms on overall survival in colorectal cancer patients related to the TNM parameters: A Romanian single-center study

L Procopciuc[1], G Osian[2], M Iancu[3]

[1]University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania, [2]3rd Surgery Clinic, Cluj-Napoca, Romania, [3]Department of Medical Informatics and Biostatistics,"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Introduction: Sporadic colorectal cancer (CRC) can be caused by different polymorphisms located in genes associated with methylation defects (thymidylate synthase-TS), genes implicated in carcinogen metabolism (glutathione S-transferase Mu 1-GSTM1), and genes involved in the DNA repair process (XRCC1). The objective of this study was to investigate: i) the associations between clinical factors: Duke's stages and certain parameters of TNM classification such as tumor extension (pT), distant metastases (M), lymph nodes (N), grade of cancer cells (G) and survival in colorectal cancer patients; ii) the influence of the studied gene polymorphisms stratified by TNM parameters.

Methods: This was a prospective study on 75 patients who were genotyped for GSTM1-null, thymidylate synthase enhancer region (TSER) double and triple tandem repeats (TSER-2R, TSER-3R), TS3'-UTR (1494del6), and XRCC1-A751C using PCR-RFLP. The Kaplan–Meier method, log-rank test and univariate Cox regression were used to analyze differences in survival time based on genetic and clinical factors. The magnitude of association was quantified by hazard ratio (HR) and 95% confidence level for HR. All statistical tests and calculations were performed in R-software, v.4.3.0.

Results: We analyzed survival data in a sample of 75 colorectal cancer patients with a mean age of 65.3±9.7 years. The GSTM1, TS-del6bp, XRCC1-A751C variant genotypes were observed in 46 (61.3%), 44 (58.7%) and 41 (54.7%) patients. The distribution of Duke's stages was as follows: A (20%), B (24%), C (48%), D (8%), and the tumor characteristics were: pT1 (16%), pT2/pT3 (58.7%), pT4 (25.3%), N0 (42.7%), N1/pN2 (57.3%), M0 (42.7%), M1 (57.3%), G1/G2 (77.3%), G3/G4 (22.7%). The mean survival times (months) of Duke's stages (A, B, C and D) were 45.4, 43.4, 26.9 and 37.5, respectively ($p < 0.001$). Patients with Duke's C stage of CRC had a poor survival rate compared to Duke's A stage ($HR = 16.4$, $p = 0.006$). The pT and N parameters were significant predictors with a negative effect on overall survival (pT2/pT3 vs. pT1: $HR = 4.7$, $p = 0.136$, pT4 vs. pT1: $HR = 15.9$, $p = 0.008$ and N1 vs. N0: $HR = 3.2$, 95% HR: 1.4-7.6), while M and G were not significant predictors of survival time. The results of stratified survival analysis by the presence of distant metastases (M) showed that TS-del6bp gene polymorphism was a significant predictor with a negative effect on overall survival only for CRC patients with M1 ($p = 0.009$, $HR = 7.32$, 95% CI: 1.63-32.94). Stratification by grade of cancer cells evidenced that XRCC1-A751C gene polymorphism was a significant predictor with a positive effect on survival for patients with G1/G2 ($p = 0.005$, $HR = 0.27$, 95%CI: 0.10-0.66), while GSTM1 gene polymorphism tended to be a predictor with a positive effect on survival for patients with G3/G4 ($p = 0.104$, $HR = 0.30$, 95% CI: 0.07-1.3).

Conclusion: The pT, N parameters and Duke's stages are predictors of poor overall survival. The effect of the studied gene polymorphisms on overall survival of CRC patients was different depending on M and G parameters: TS-del6bp gene polymorphism was a negative predictor of survival only for patients with distant metastases, while XRCC1-A751C gene polymorphism was a significant predictor with a positive effect on survival for patients with G1/G2.

P – 191 Combined analysis of KRAS, NRAS, BRAF mutations and mismatch repair deficiency testing in Indian patients with metastatic colorectal carcinoma: A single centre experience

T Sood[1], A Rauthan[2], P Patil[2], S Kulkarni[1]

[1]Manipal Hospital, Bengaluru, India, [2]Manipal Comprehensive Cancer Center, Manipal Hospital, Bangalore, India

Introduction: Molecular evaluation of KRAS, NRAS and BRAF mutation has become an important part in colorectal carcinoma evaluation as their alterations determine the therapeutic response to anti-EGFR therapy and prognosis. MMR deficiency is important for identification of Lynch syndrome families and it has now become an important biomarker of response to immunotherapy in metastatic CRC. The aim of this study is to investigate the distribution of these mutations by tumor localization and to determine the prevalence of MMR deficiency in metastatic colorectal cancer.

Methods: A retrospective analysis of 149 patients was done who presented between May 2016 to February 2018 with metastatic colorectal cancer. Molecular analysis was done on paraffin blocks of tumour tissue for KRAS, NRAS, BRAF mutations by PCR and Mismatch Repair protein expression was evaluated by immunohistochemistry.

Results: The mean of age for patients at diagnosis was 57.67±13.20 years (range, 28-80 years), 95 patients (63.7%) were male and 54 patients (36.3%) were female. Location of tumour was left sided in 100 patients and right sided in 49 patients. 58 patients (39%) had KRAS mutation and 5 patients (3.3%) had NRAS mutation. Out of 149 patients, 89 underwent BRAF mutation analysis of which 6 patients (6.8%) had mutation (V600E). 51% patients had RAS mutation and 6% had BRAF mutation with tumour localised to right side. 38% patients had RAS mutation and 7.1% had BRAF mutation with left sided disease. BRAF showed no significant difference between prevalence in right and left sided disease. No concomitant mutation of KRAS, NRAS and BRAF mutations was

observed. MMR by IHC revealed deficiency in 12 (17.1%) out of 70 patients evaluated, of which 21.4% were right sided and 14.2% were left sided. All of these had BRAF wild type suggestive of Lynch syndrome.

Conclusion: To our knowledge this is the first study to evaluate MMR deficiency by IHC in Indian patients with tumour localisation. 12 (17.1%) patients with MMR deficiency qualified as likely candidates for immunotherapy and these families would benefit from cancer screening for Lynch syndrome and genetic counselling. The frequency of KRAS mutation was 39% which is similar to worldwide reports and in our study, by evaluating NRAS and BRAF mutants, we were able to classify an additional 10.2% patients as likely non-responders to anti-EGFR therapy. In present therapeutic landscape, it is imperative to test genetic biomarkers for colorectal cancer patients.

P – 192

P – 193 RAS status in Algerian metastatic colorectal cancer

A Bensalem

EH Didouche Mourad, Medecine Faculty, University 3 Constantine, Constantine, Algeria

Introduction: The identification of genetic anomalies within the cancerous cells today constitutes very valuable information to guide the diagnosis, the classification, the choice and the monitoring of the treatment for a growing number of cancers. Mutations in the gene RAS are found in meadows of half of the colorectal cancers and their research is therefore of paramount importance for the therapeutic care and the choice of a targeted therapy appropriate.

Methods: It is a retrospective study, from records of patients followed in Medical Oncology Department, for a metastatic colorectal cancer, based on the study of bio molecular RAS status; from March 2016 to November 2017. 89 cases were collected; the parameters studied were: age, histological type, location, status NRAS, KRAS and the degree of tumor infiltration.

Results: Of the 89 cases studied, the average age of discovery was 59 years old (40-77). The histological type adenocarcinoma represented 100% (n = 89) of cases. In 36.92% (n = 24) of the cases the localization was colic; 9.23% (n = 6) of cases were rectal and 3.06% (n = 2). The KRAS wild was in 51.68% (n = 46) of cases, in 19.10% (n = 17) at the level of exons 2, 3, 4 and at the level of the: codon 12 in 19.10% (n = 17), codon 13 in 17.97% (n = 16. The NRAS was wild in 46,06% (n = 41) of cases; in 17.97% (n = 16) at the level of exons 2, 3, 4 and posted in 3.37% (n = 3) of the cases, at the level of: the exon 2.4 in 2.24% (n = 2) and the exon 3 in 1.12% (n = 1).The average of the tumor infiltration was 66% (40% - 90%). The response to treatment was different (right versus left) and patients achieved treatment in more than 80% of cases. DISCUSSION: It is necessary to raise the percentage of the wild character at the beginning for the KRAS and the interest of the anti-EGFR. The development of the technique of the research of the NRAS has regained less wild suggesting that some of the non-responses to anti-EGFR are probably due to this difference in the determination of the Full RAS; deserving all the interest of the clinician in the support of adequate patients.

Conclusion: The targeted therapies constitute a major evolution in digestive cancer. Before the effects very promising of these drugs, other molecules of the same therapeutic classes (anti-VEGF, anti EGFR) are in course of development and will probably to further the therapeutic effects.

P – 194 Transcribed ultraconserved regions Uc160 and Uc346 in colon cancer progression

A Kottorou, C Sirinian, F Dimitrakopoulos, A Antonacopoulou, T Makatsoris, H Kalofonos

Clinical and Molecular Oncology Laboratory, Division of Oncology, Medical School, University of Patras, Patras, Greece

Introduction: Expression of Transcribed Ultra Conserved Regions (Transcribed Ultra Conserved Regions, T-UCRs) is often deregulated in many types of cancer, including colorectal cancer (CRC). Our previous results showed that T-UCRs Uc160 and Uc346 are methylated in CRC. Additionally, their tumor methylation is associated with time to disease progression (TTP) and appears to be a promising biomarker for CRC. However, their role in CRC progression has not been elucidated to date.

Methods: Aim of the study was to investigate the role of Uc160 and Uc346 in proliferation, motility and migration in colon cancer cells. For that purpose, Uc160 and Uc346 were cloned into plasmids and three colon cancer cell lines (HT-29, Caco-2 and DLD-1) were transiently transfected. After overexpression of Uc160 and Uc346, proliferation (MTT assay), motility (scratch wound healing assay) and migration (transwell migration assay) rates were evaluated.

Results: Proliferation rates, 48h after overexpression, were higher in the transfected cell in all cell lines, compared with the control cells (mock transfected). The most significant differences in proliferation rates were noticed for Uc160 overexpression in Caco-2 ($p = 0.008$) and Uc346 overexpression in DLD-1 cells ($p = 0.033$). Similar results were observed in motility assay, with cells overexpressing Uc160 or Uc346 having higher motility rates compared to control cells in all cell lines. More specifically, most significant differences in motility rates were observed in HT-29 and DLD-1 cells overexpressing Uc160 or Uc346 ($p = 0.017$, $p = 0.041$ and $p = 0.023$, $p = 0.004$ respectively). Further analysis of DLD-1 cells migration confirmed the above results, with higher number of Uc160 or Uc346 overexpressing cells migrating compared to the control cells ($p = 0.005$ for both T-UCRs).

Conclusion: T-UCRs Uc160 and Uc346 appear to affect the proliferation, motility and migration rates of colon cancer cells, implicating a complex role in CRC progression.

P – 195 Cost of illness for colorectal cancer at low middle income countries Egypt case

A Abotaleb

World Health Organization (WHO), Cairo, Egypt

Introduction: According to international statistics colorectal cancer (CRC) is the third most common cancer. Two-thirds of all colorectal cancers occur in the more developed regions of the world. Egypt with the population with 100 million people (CRC) may represent a pressure on health care system and developing some questions need answers like: Are the polices for CRC treatment efficient for the health care system? Does health care system need new treatments? What is the outcome for present treatment polices? The objective of this study is to estimate the total medical cost of illness (CRC) to improve understanding of the economic consequences of different health-care policies from the payer prospective for the last 3 years with analysis of treatments used.

Methods: Data from patients aged (18 -60 years) for the last 3 years including direct and indirect health care costs for conventional treatment as it was not including (cost of treatment, complications including, Rehabilitation. Metastatic, outpatients costs). The total (n) of patients enrolled in the national database =20389 weighted average method was used for calculations for cost and consequences. The value of lost productivity using Egyptian estimates for the value of a statistical life year (VSLY). Outcomes was calculated in form of QALY. Several methods were employed to reach an average. Value for a QALY: lost production represented by actual per capita annual proEarnings based on the average national salary and VSLY. Lost production: annual productivity was calculated by dividing the gross domestic product (GDP) by the labour force (ages 20–65). GDP in 2012 came from the World Bank, and the labour force came from CAPMAS. Lost earning: average annual salary was calculated from CAPMAS for the year 2012, and adjusted by the annual salary increase. VSLY: The value of a statistical life (VSL) in Egypt was calculated from the average of the following methods: (a) Examining the ratio between GDP per capita in Egypt to countries with published GDP and VSLductivity of the labour force, lost Uncertainty Analyses: To test the stability of

our results to variation in the estimates of the input model parameters, one-dimensional sensitivity analyses were performed.

Results: Mean direct cost for CRC is amounted (610) Dollar per patient per year 80% of total expenditures where chemotherapy, surgery represent 4.7% of expenditures and radio therapy represents 1.7%. Costs increase in the metastatic phase than primary phase QALY gained for metastatic patients receiving biological treatment was 1.9 QALY versus .4 QALY with conventional chemotherapy.

Conclusion: Reforming treatment polices for CRC in Egypt become a need the new polices should include Early detecting programs reimbursement for of Biological products after establishing treatment guidelines based on multiple criteria including (socio-economic impact, economic values, efficacy parameters).

P – 196 Anti-angiogenic action of leukotriene-C4 induced 15-hydroxyprostaglandin dehydrogenase in colon cancer cells is a TNF-α dependent phenomenon

S Satapathy, A Sjolander
Lund University, Malmö, Sweden

Introduction: Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide. Cyclooxygenase-2 (COX-2), which plays a key role in the biosynthesis of prostaglandin E2 (PGE2), is often up-regulated in CRC and in other types of cancer. PGE2 induces angiogenesis and tumor cell survival, proliferation and migration. The tumor suppressor 15-hydroxyprostaglandin dehydrogenase (15-PGDH) is a key enzyme in PGE2 catabolism, converting it into its inactive metabolite 15-keto-PGE2 and is often down-regulated in cancer. Interesting enough, CRC patients expressing high levels of Cysteinyl leukotriene receptor 2 (CysLTR2) have a good prognosis and therefore, we investigated a potential link between CysLTR2-signaling and the tumor suppressor 15-PGDH in colon cancer cells. In the other hand, TNF-α is considered as the main regulator of COX-2 and mPGES-1 that contribute to the increased synthesis of PGE2, which is inhibited by overexpressed 15-PGDH. Level of the pro-tumorigenic PGE2 is increased in CRC, previously attributed to increased production via TNF-α mediated COX-2 up-regulation but more recently attributed to decreased catabolism due to down-regulation of 15-PGDH.

Methods: HT-29 and Caco-2 cells were employed for this study. Unstimulated and LTC4 stimulated cells were compared for various markers through qRT-PCR as well as immunoblotting analysis. Vibrant-DiI labeled HT-29 cells were used for the zebrafish metastasis model. Visualization of the metastatic spread was observed using the light sheet microscopy (SPIM) and tissue sections were analyzed by immunohistochemistry for specific markers. Conditioned media from the unstimulated and LTC4 stimulated HT-29 cells were used to analyze the endothelial tube formation in HUVEC.

Results: Elevation of 15-PGDH expression by leukotriene C4 (LTC4), a CysLTR2 ligand, exhibited anti-tumor activity in colon cancer cells with significant phosphorylation of β-catenin and down-regulation of anti-apoptotic marker Bcl-2 with concurrent activation of CASPASE-3 expression. We also observed a dramatic down-regulation of TNF-α on mRNA level and NF-κβ on both mRNA as well as protein level with LTC4 induced 15-PGDH in a TNF-α dependent manner. Moreover, TNF-α regulated anti-angiogenic action of 15-PGDH in HT-29 and Caco-2 colon cancer cells by depleting the mRNA level of MMP-2 and MMP-9 and protein level of VEGFR-1. Furthermore, we also observed disrupted tube formation in HUVEC with LTC4 induced 15-PGDH which is also governed by TNF-α. The angiogenesis study in transgenic zebrafish, Tg(fli1a: EGFP) embryo model suggested significant decrease in early and late metastasis with distinct disruption in the intersegmental vessel in the LTC4 induced 15-PGDH treated group. IHC analysis of Ki-67 exhibited decrease with LTC4 and very interestingly CASPASE-3 showed increase in the stimulated group which supported our in vitro observation.

Conclusion: Hence, restoration of 15-PGDH expression through CysLTR2-signaling promotes the anti-angiogenic action against colon cancer cells, indicating an anti-tumor as well as the anti-metastatic efficacy of CysLTR2-signaling.

P – 197 Repurposing ponatinib for the treatment of colorectal cancer

F Tan[1], T Putoczki[2], F Hollande[3], R Luwor[4]
[1]Peter MacCallum Cancer Centre, Melbourne, Australia, [2]Walter and Eliza Hall Institute for Medical Research, Parkville, Australia, [3]The University of Melbourne, Melbourne, Australia, [4]The University of Melbourne, Parkville, Australia

Introduction: Colorectal cancer (CRC) is the 4th most common cancer globally. Despite, targeted agents producing advances in some CRC patients, tumour progression is still frequently observed. Further research is urgently needed to realise the potential of targeted therapies for CRC. A key transcription factor to potentially target is Signal Transducer and Activator of Transcription 3 (STAT3). In over 50% of human CRC tissue, STAT3 is hyper-activated, and considerable evidence demonstrates that STAT3 is critical for CRC progression. Inhibiting STAT3 is therefore a crucial step in advancing CRC treatment. But the matter is complicated by the fact that key receptors such as the Epidermal growth factor receptor (EGFR), Interleukin-6 receptor (IL-6R), and Interleukin-11 receptor (IL-11R) all activate STAT3. We and others have shown that blocking one receptor is not sufficient in inhibiting STAT3 activity, as other uninhibited pathways can reactivate STAT3, leading to continued tumour growth and refractory outcomes clinically. Therefore, identifying a therapeutic agent that can inhibit STAT3 activity driven by several upstream mediators, including EGFR, IL-6R and IL-11R, is required to reduce compensatory signalling and STAT3 reactivation. As it stands, the discovery of such a therapeutic agent has not been achieved.

Methods: Here we perform a luciferase based screen on a panel of approximately 1200 FDA approved agents to identify inhibitors that can block EGF, IL-6 and IL-11 mediated STAT3 activity. Following a secondary western blot screen, we identified ponatinib as a candidate anti-STAT3 inhibitor. We further validated our results and characterised ponatinib's anti-STAT3 properties using RT-PCR, cell viability, cell migration and animal xenograft models.

Results: Here, we describe an extensive screen for an anti-STAT3 inhibitor from 1167 FDA-approved agents, identifying ponatinib as a lead candidate. Importantly, ponatinib could inhibit STAT3 activity and downstream transcriptional regulation driven from EGF, IL-6 and IL-11, 3 major ligands involved in CRC development and progression. Ponatinib also produced significant inhibition of CRC migration and in vivo tumour growth. Furthermore, ponatinib, displayed superior STAT3 inhibition and anti-proliferative efficacy compared to 5 FDA approved SRC and JAK inhibitors. Finally, long-term exposure of CRC cells resulted in acquired resistance to SRC and JAK inhibitors within 6 weeks, while acquired resistance to ponatinib was only observed after long-term exposure of >4 months. These results identify ponatinib as a broad STAT3 inhibitor that offers a potential therapeutic strategy for CRC and other tumour types.

Conclusion: In summary, we successfully identified a novel mechanism for the currently FDA-approved agent ponatinib with inhibitory properties against STAT3 activity in CRC. Overall, our findings provide proof-of-principle evidence for the re-purposing of ponatinib into the clinical management of CRC patients with tumours harbouring elevated STAT3 activity driven by related growth factors and cytokines.

P – 198 The management of locally advanced and metastatic colorectal cancer: A retrospective study of 77 cases

F Boudinar[1], G Bettache[2], K Wahiba[3], B Larbaoui[1]
[1]Medical Oncology Department, EHSO Emir Abdelkader, Oran, Algeria, [2]Oncology Department, Oran, Algeria, [3]CHU Oran, Oran, Algeria

Introduction: Colorectal cancer is the third most common cause of cancer after lung and breast cancer, with an estimated 1,2 million new cases diagnosed world wide per year and it is the third most common death – related cancer. Liver and lung are the most frequent locations of metastasis.

Methods: Retrospectively, we included 77 patients with locally advanced and metastatic colorectal adenocarcinoma, treated in our medical oncology department between 2014 and 2017.

Results: We have collected 77 patients with 39 women and 38 men, the mean age is 54 years, range (26-77), 66 patients (85,71%) had WHO performance status of 0 or 1 at the of diagnosis. 17% had IMC $<$ 18,5, risk factors: MICI in 2 cases, TOBACCO in 15 cases. We noted abdominal pain in (67,53%, n = 52), proctorrhagia (54,54%, n 42), Adenocarcinoma account for 100% of cases. Rectal location in 41,15% and colon location in 55,84%. 14,28% (n = 11) were stage III, 66 patients (85, 71%) were stage IV. Metastases sites: liver (35,06%, n = 27), lung (11,68%, n = 9), nodes (9,09%, n = 7), other sites (4%, n = 3). RAS test performed in 48%, RAS WILD TYPE in 26%, RAS MUTANT in 21%. Surgery in primary tumor 30%. 85,71% received chemotherapy 1st line, FOLFIRI 40,25%, FOLFOX 35,06%, XELOX 3,89%, CETUXIMAB 35,06%, PANITUMUMAB 5,19%, BEVACIZUMAB 37,66%. Most common gastrointestinal toxicity (nausea, vomiting, diarrhea). Hematologic toxicity was more frequent in patients receiving FOLFOX regimen. Cutaneous rash noted in patients receiving cetuximab and panitumumab. Evaluation after 1st line progression 22,07%, CR 6,49%, PR 15,58%, ST 11,68%. Chemotherapy 2nd line 29,87%. Chemotherapy 3rd line 11,68%, REGORAFENIB in 5,19%.

Conclusion: The multidisciplinary approach at all stages of the process requires the involvement of various specialties in order to give the patient an optimal quality of care.

P – 199 Colorectal cancer screening in Flanders: Advances in personalised screening

W van de Veerdonk[1], G Van Hal[1,3], M Peeters[1,2], I Brabander[4], G Silversmit[4], S Hoeck[1,3]
[1]University of Antwerp, Antwerp, Belgium, [2]Antwerp University Hospital, Edegem, Belgium, [3]Centre for Cancer Detection, Bruges/Antwerp, Belgium, [4]Belgian Cancer Registry, Brussels, Belgium,

Introduction: The quantitative faecal immunochemical test (FIT) is used in the Flemish colorectal cancer screening programme to detect precancerous lesions and colorectal cancer (CRC). Current CRC screening programmes are based upon a binary FIT result. However, a substantial part of the positive FITs followed up by colonoscopy are found negative (normal). And several participants are not followed up by colonoscopy within 6 months after a positive FIT. Therefore, this study evaluates the possibility of establishing a risk profile based upon a combination of the quantitative FIT, age

and gender to gain more insight into tailored risk prediction and communication of risk to general practitioners (GPs) and/or participants.

Methods: In this retrospective study, data was used of 57,421 participants who underwent a colonoscopy after a positive FIT in the Flemish CRC screening programme between October 2013 until July 2016. Analyses were performed with multinomial logistic regression to predict the probability of normal or noncancerous lesions, precancerous lesions, in situ or invasive cancers. Additionally, odds ratios (OR) were established to visualize the magnitude of the differences between risk profiles within a population with positive FIT, based upon a combination of the quantitative FIT, age and gender.

Results: The amount of false positive FIT results followed up by colonoscopy is ~27%, where ~20% are not followed up at all by colonoscopy within 6 months after a positive FIT. Based on our risk profile calculation, we found a significant difference between the risk of having a normal outcome, a precancerous lesion, an in situ or an invasive cancer. For example, the detection of invasive cancer was 58 (OR) times more likely in a male of 74 years old with a FIT result of $\geq$ 1,000 ng/ml compared to a woman of 56 years old with a FIT result of 75 ng/ml.

Conclusion: The differences in precancerous lesions or CRC according to our calculated risk profiles, justifies an approach where participants with a positive FIT are not all treated in the same way, based on a binary FIT. Participants and/or their GPs should be informed about individual risks. This will promote informed decision to an extent where participants and/or professionals can make decisions on follow-up. How to communicate this personalised information to participants needs to be discussed and tested. Contrary to the participant, professionals such as GPs should be provided with extra insight in the risk differences per patient, which supports their clinical decision making. The approach above could be extended by adding simple risk factors such as BMI, diet, alcohol intake, family history etc., creating the opportunity to more accurately discriminate between participants with a normal outcome, precancerous lesion, in situ or invasive cancer. Colonoscopy follow up based upon the quantitative FIT, combined with age, gender and additional risk factors instead of upon a binary FIT result only, will probably increase accuracy.

P – 200 Risk factors of colorectal cancer in Linxian, China: A nutrition intervention trial with 30 years follow-up

H Keskin[1], A Etemadi[2], P Taylor[2]

[1]Istanbul Medeniyet Uni., Istanbul, Turkey, [2]Metabolic Epidemiology Branch, the National Cancer Institute (NCI), the National Institutes of Health (NIH), Bethesda, Maryland, USA

Introduction: Colorectal cancer (CRC) is one of the most common cancers in the world. Epidemiological and experimental studies have shown that some dietary factors and vitamins/minerals are associated with the risk of CRC. The Nutrition Intervention Trial (NIT) tested whether daily multivitamin/mineral supplements could reduce the incidence and mortality rate of esophageal/gastric cardia cancer. The current study evaluated the CRC risk factors at the NIT population.

Methods: After over than 30 years follow-up, 179 CRC cases were identified. Risk factors were evaluated for the development of CRC among 29,594 adults supplemented for 5.25 years according a 24 fractional factorial study design between 1986 and 1991 [factor A (5000 IU vitamin A and 22.5 mg zinc oxide), factor B (3.2mg riboflavin and 40 mg niacin), factor C (120 mg ascorbic acid and 30 ug molybdenum), and factor D (50 ug selenium, 30 mg alpha-tocopherol, and 15 mg beta-carotene)]. Using this large cohort with 30 years of follow-up that was initially established as a randomized controlled trial of upper gastrointestinal cancer and multivitamin/mineral intake conducted in rural Linxian, China, we evaluated whether demographic characteristics, food items, and intake of vitamins/minerals are associated with the risk of CRC development.

Results: When the effects of four different intervention factors were assessed in the total cohort, no associations were observed. However, subgroup analyses showed that CRC was decreased by 38% in females who received Factor D (selenium/alpha-tocopherol/beta-carotene) (RR = 0.62, 95% CI = 0.43-0.92, P = 0.015) compared to females who did not get Factor D.

Conclusion: This study showed that increased risk of CRC was associated with age, height, and weight. Furthermore, piped water, increased consumption of food cooked in oil, eggs, fresh vegetables, and fruits were associated with increased risk of CRC. However, higher intake of selenium, alpha-tocopherol, and beta-carotene were protective factors for CRC risk. Some of these associations were dependent on the age and gender subgroups. To account for the racial/ethnic differences of the intervention effect we were not able to find similar multivitamin intervention studies' information from the Chinese population, therefore we had to review other studies of immigrants or other countries. This is one of the largest and most comprehensive evaluations of CRC risk factors in rural Chinese people to date by the prospective design randomize clinical intervention cohort study.

P – 201 Evaluation of the prognostic value of lymph-node ratio in patients with colon cancer in the oxaliplatin era

B Bird[1], D Connell[2], D O'Connor[1]

[1]Bon Secours Hospital Cork, Cork, Ireland, [2]University College Cork, Douglas, Ireland

Introduction: N stage for colon cancer is based on the absolute number of cancer-positive lymph nodes removed at surgery. Lymph node ratio (LNR) is the ratio of the number of cancer-positive nodes to the total number of lymph nodes removed. In patients receiving adjuvant 5-fluorouracil (5-FU), LNR has been shown to be a more accurate prognostic indicator than N stage. However, a combination of adjuvant oxaliplatin and 5-FU has now become the new standard of care. There is limited evidence to show LNR retains its prognostic significance in this setting. The aim of this project is to determine if LNR retains its prognostic significance for colon cancer when patients are treated with oxaliplatin.

Methods: Data was collected for all patients with stage 3 colon cancer treated with adjuvant oxaliplatin at a single institution between 2000 and 2015. End points were overall survival and disease-free survival. Based on previous work patients were stratified into three groups according to LNR (LNR1 < 0.11; LNR2 0.11 - 0.27; LNR3 >0.27). These categories were related to the endpoints using Kaplan-Meier curves and Cox regression analysis.

Results: 142 patients met the inclusion criteria. Using LNR1 as the reference category, the hazard ratios for overall survival were 1.54 (p = 0.26) for LNR2 and 0.53 (p = 0.23) for LNR3. The hazard ratios for disease-free survival were 1.95 (p = 0.68) and 1.12 (p = 0.79) for LNR2 and LNR3, respectively. The Kaplan-Meier curves did not show a statistically significant relationship between LNR and overall survival (p = 0.10) or disease-free survival (p = 0.13). The hazard ratios for N2 compared to N1 were 0.8 (p = 0.578) and 1.65 (p = 0.124) for overall survival and disease-free survival, respectively. The Kaplan-Meier curves did not show a statistically significant relationship between N stage and overall survival (p = 0.58) or disease-free survival (p = 0.12).

Conclusion: LNR is not a useful prognostic indicator for colon cancer treated with 5-FU and oxaliplatin.

P – 202 Competing risks analysis of microsatellite instability as a prognostic factor in colorectal cancer

K Spring[1], J Toh[2], P Chapuis[3], L Bokey[4], C Chan[3], O Dent[5]

[1]Ingham Institute/University of Western Sydney, Sydney, Australia, [2]Westmead Hospital, Sydney, Australia, [3]Concord Hospital, Sydney, Australia, [4]Liverpool Hospital, Sydney, Australia, [5]University of Sydney, Sydney, Australia

Introduction: Despite an extensive literature suggesting that high microsatellite instability (MSI-H) enhances survival and protects against recurrence after colorectal cancer (CRC) resection such effects remain controversial as many studies show no or only a weak bivariate association or no multivariable association. This study examined the association between MSI-H and recurrence and death due to CRC adjusting for death due to other cause as a competing risk.

Methods: Data were drawn from a prospective hospital registry of consecutive resections for CRC, which contains detailed clinical, operative, pathology, adjuvant therapy and follow-up information. The cumulative incidence of recurrence and CRC-specific death were evaluated by competing risks regression.

Results: Among 1009 patients who had a resection between August 2002 and December 2008 and were followed to at least December 2013 there were 114 (11.3%) with MSI-H. After potentially curative resection and adjustment for 19 other prognostic variables and accounting for non-CRC death as a competing risk there was no association between MSI-H and recurrence (HR 0.8 95% CI 0.42-1.57) or CRC-specific death (HR 0.73 CI 0.39-1.35). For palliative resections there was no association between MSI-H and CRC-specific death (HR 0.65, CI 0.21-2.04). For both curative and palliative resections MSI-H had a bivariate association with non-CRC death (HR 1.55 CI 1.04-2.30 and HR3.80 CI 1.32-11.00 respectively) but this disappeared in multivariable models.

Conclusion: These results contradict the suggested protective association between MSI-H and recurrence or survival reported in other studies. MSI status may not be an independent prognostic variable for CRC.

P – 203 Survival and prognostic factors of non metastatic rectal adenocarcinoma: Analytic multifactor review of 91 cases

K Darif[1], Z Benbrahim[2], M Benhami[3], I Ahalli[4], R Boujarnija[4], H Erraichi[4], R Elhazzaz[5], H Ouahbi[2], L Amaadour[6], K Oualla[2], F El M'rabet[3], S Arifi[7], N Mellas[7]

[1]Hassan II University Hospital Fez, Fez, Morocco, [2]Medical Oncology Department, Hassan II University Hospital, Fez, Morocco, [3]Department of Medical Oncology, University Hospital Center Hassan II, Fez, Morocco, [4]Hassan II University Hospital, Fez, Morocco, [5]UHC Fez, Fez, Morocco, [6]University Hospital of Hassan II Oujda, Fez, Morocco, [7]Department of Medical Oncology, Hassan II University Hospital, Fez, Morocco

Introduction: Rectal cancers are the second most common cancers in human and major public health problems worldwide. Prognostic factors have a pivotal role in

clinical oncology. They are helpful in the selection of treatment; provide insights into the disease process and the therapeutic response. This study attempts to observe the survival of rectal adenocarcinoma and to find prognostic factors and other variables potentially associated with outcome of operated rectal adenocarcinoma.

Methods: It's a retrospective study based on 91 patients with operated rectal adenocarcinoma collected at the Medical Oncology Department of Hassan II University Hospital for a period of 4 years between January 2014 and June 2017. Various prognostic factors had been identified through univariate (Kaplan-Meier) then multivariate (Cox) analyze, namely: age, sex, tumor localization, degree of differentiation, stage, tumor recurrence, ACE level, neoadjuvant therapy and adjuvant chemotherapy.

Results: The mean age was 59 years (± 14.14) with extremes "24-86". These were 40% men and 60% women. At endoscopic examination the tumor was located: in the middle rectum in 30.8%; 36.3% in the lower rectum and 33% in the upper rectum. Histologically, the biopsy showed that liberkunian adenocarcinoma was well differentiated in 56%, moderately differentiated in 42% and in 2% poorly differentiated. The carcinoembryonic antigen revealed a rate greater than 5 ng/ml in 25% of patients. Neo-adjuvant treatment with concomitant radiochemotherapy was performed in 61.5% and radiotherapy for 24%. Histopathological examination classified the patients according to the TNM classification with: 7% of patients in stage I, 30% in stage II, 54% in stage III and 9% in stage IV. After surgery 78 patients (86%) received adjuvant chemotherapy. Average overall survival was 25 months. In addition, 23% of patients had a recurrence, median-free survival was 29-month. Adjuvant therapy was the only prognostic factor influencing survival: mean survival in the group receiving adjuvant chemotherapy was 32 months vs 14 months in the surveillance group with a very significant difference ($p = 0.006$).

Conclusion: In our series adjuvant therapy was an important prognostic factor influencing overall survival, our results correlate with those in the literature.

P – 204 Prognostic value of neo-adjuvant treatment in localized rectal cancer about 78 cases

K Darif[1], Z Benbrahim[2], M Benhami[3], I Ahalli[4], R Boujarnija[4], H Erraichi[4], R Elhazzaz[5], H Ouahbi[2], L Amaadour[6], K Oualla[2], F El M'rabet[3], S Arifi[7], N Mellas[7]

[1]Hassan II University Hospital Fez, Fez, Morocco, [2]Medical Oncology Department, Hassan II University Hospital, Fez, Morocco, [3]Department of Medical Oncology, University Hospital Center Hassan II, Fez, Morocco, [4]Hassan II University Hospital, Fez, Morocco, [5]UHC Fez, Fez, Morocco, [6]University Hospital of Hassan II Oujda, Fez, Morocco, [7]Department of Medical Oncology, Hassan II University Hospital, Fez, Morocco

Introduction: The frequency of colorectal adenocarcinoma continues to increase, which is the leading cause of cancer deaths in developed countries. Unlike colon cancer, there is currently no compelling evidence for the value of adjuvant chemotherapy in rectal cancer. Preoperative chemoradiotherapy has become the standard for middle and low rectum tumors, improving local control without improving survival without metastatic relapse and overall survival.

Methods: It's a retrospective study based on 78 patients with non metastatic rectal adenocarcinoma who received adjuvant chemotherapy, collected at the Medical Oncology Department of Hassan II University Hospital for a period of 4 years between January 2014 and June 2017. The aim of the study is to determine the place of neoadjuvant treatment as a prognostic factor using a univariate study (Kaplan-Meier survival analysis).

Results: The average age of patients was 56 +/- 14, 42% men and 75% women. The tumor was located in the middle rectum in 28%; 34% in the lower rectum and 37% in the upper rectum. Histologically, the biopsy showed that the lieberkuhnian adenocarcinoma was well differentiated in 53%, moderately differentiated in 45% and in 2% poorly differentiated. Most patients (86%) received neo-adjuvant therapy: radiochemotherapy (RCC) was performed in 63% and short cycle radiotherapy alone for 23%. Histological examination classified the patients according to the TNM classification with 30% at stage II, 61% at stage III and 9% at stage IV. The mean overall survival was 31 months (95% CI). 32% of patients had a recurrence within an average of 12 months. The analysis of neo-adjuvant treatment did not show a significant improvement in overall survival, and the mean non-relapse-free survival was 12 months in the group that received the neo-adjuvant treatment versus 7 months (group not received neoadjuvant treatment), but the difference was statistically insignificant.

Conclusion: Despite the progress made in diagnostics and therapeutics, particularly with adjuvant treatments and resection of metastases, five-year survival does not exceed 25%.

P – 205 Preoperative short course of radiotherapy in selected high risk patients

M Caro Gallarín[1], H Rosales González[2], J Jové Teixidó[1], E Luguera Sánchez[1], I Planas Toledano[1], Y Luis Dorta[2], G Antelo Redondo[2], E Baena González[2], A Álvarez Gracia[1], C Bugés Sánchez[3], I Camps Ausàs[2], S Villà Freixa[1]

[1]ICO Badalona, HUGTiP, Badalona, Spain, [2]Hospital Germans Trias I Pujol, Badalona, Spain, [3]Institut Català d'Oncologia (ICO) – Hospital Germans Trias i Pujol, Badalona, Spain

Introduction: Preoperative short course radiotherapy (SCRT) is considered a standard treatment in the management of locally advanced rectal cancer. However, in southern European countries, preoperative chemoradiotherapy is the preferred option, leaving SCRT only for those patients not suitable for combined treatment. Our aim was to retrospectively analyze the outcome of patients who have been treated with SCRT in our Institution.

Methods: From 2006 to 2017, 68 patients (p) (50 men and 18 women) with a proven biopsy of adenocarcinoma of the rectum were treated with SCRT in our Department. The median age at diagnosis was 74 years (42-86). All patients were evaluated in a multidisciplinary tumor board and the reasons to indicate SCRT were: age> 80 years (25p), presence of synchronous metastases at diagnosis (21p), heart disease (7p), synchronous intestinal tumors (12p), unknown reason (3p). Dose delivered was 25 Gy in 5 fractions of 5 Gy, administered in prone position by 3D-conformal radiotherapy (3DCRT), with photons of 6-18 MV. In 65 (95.5%) patients, surgery was performed in the week following the end of 3DCRT.

Results: With a mean follow up of 40 months, no acute or chronic toxicity was observed. Median overall survival (OS) was 42 months, median specific cancer survival (SCS) was 59 months and median disease-free survival (DFS) was 56 months. The 5 years OS, SCS and DFS was 43.5%, 59.6%, and 48.7% respectively. Only 2 local recurrences were observed, one of them in a patient who refused surgery once 3DCRT was finished. In the univariate data analysis, no significant difference was observed in the SCS or OS nor in the analysis of the SCRT indication subgroups, neither in the location of the tumor (lower 31%, middle 47%, upper 20% or unknown 2%). According to the staging we did not observe any differences in survival. However, for patients with T4 tumors median survival was 16 months, versus no T4 patients, in whom median was not reached ($p < 0.001$). In patients with a positive margin in the surgical specimen, the median survival was 43 months compared with negative margin patient subgroup in which median survival was not reached, with trend to significance (p 0.056). Adjusted to the state of the surgical margin, only T4 tumor was an independent factor in multivariate analysis for worse survival, with an estimated risk of death 5 folds higher than the rest of the stages (p 0.022).

Conclusion: Despite being a group of selected patients with poor vital prognosis (due to age, metastasis or heart disease), we obtain a median overall survival of 59 months and only 2 local recurrences, with an excellent profile of acute and chronic toxicity, for all subgroups of patients and all tumor locations. In our analysis only T4 was a predictor for worse results.

P – 206 Intensive first line FIr-C/FOx-C association of triplet chemotherapy plus cetuximab in RAS wild-type metastatic colorectal cancer patients: Preliminary phase II data and individual limiting toxicity syndromes prediction by pharmacogenomic biomarkers

G Bruera[1], S Massacese[2], F Pepe[3], U Malapelle[3], A Dal Mas[4], E Ciacco[2], G Calvisi[4], P Marchetti[5], G Troncone[3], M Simmaco[6], E Ricevuto[1]

[1]Oncology Territorial Care, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy, [2]Pharmacy Unit, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, L'Aquila, Italy, [3]Department of Public Health, University Federico II, Naples, Italy, [4]Pathology, S. Salvatore Hospital, Oncology Network ASL1 Abruzzo, L'Aquila, Italy, [5]La Sapienza University, Sant'Andrea Hospital, Rome, Italy, [6]Advanced Molecular Diagnostics, S. Andrea Hospital, Rome, Italy

Introduction: Intensive triplet chemotherapy/bevacizumab significantly increased MCRC outcome. Phase II study investigated safety/activity of FIr-C/FOx-C triplet/cetuximab (CET) in first line RAS wild-type and prediction of individual limiting toxicity syndromes by pharmacogenomic biomarkers.

Methods: Simon two-step design: p0 70%, p1 85%, power 80%, α 5%, β 20%; projected objective response rate (ORR) I step 14/19. FIr-C/FOx-C: 5-fluorouracil (5-FU) 12h-timed-flat-infusion 900 mg/m2 days (d)1-2,8-9,15-16,22-23; alternating irinotecan (CPT-11) 160 mg/m2 d1,15, oxaliplatin 80 mg/m2 d8,22; CET loading 400 then 250 mg/m2 d1,8,15,22; every 28d. Toxicity, individual limiting toxicity syndromes (LTS) evaluated, compared by chi-square test; activity/efficacy by log-rank. 5-FU/CPT-11 pharmacogenomic biomarkers, 5-FU degradation rate (5-FUDR), SNPs ABCB1, CYP3A4, DYPD, UGT1A1 evaluated in patients with LTS and at recommended dose.

Results: Enrolled: 29 patients 80%; G3-4 toxicities: diarrhea 23%, asthenia 15%, vomiting 8%, hypertransaminasemy 8%; LTS 19 patients (65.5%), 83% yE. LTS prevalently multiple (ms) vs single site (59 vs 7% p 0.006). Reduced FUDR 56%, SNPs CYP3A4 22%, UGT1A1 71%, >2 positive pharmacogenomics biomarkers 78% prevalently in patients with gastrointestinal LTS.

Conclusion: Intensive first-line FIr-C/FOx-C at recommended doses is tolerable, highly effective in RAS wild-type. Reduced FUDR, CYP3A4, UGT1A1 SNPs may predict individual LTS-ms to select fit patients. Prospective studies personalized by toxicity biomarkers will confirm efficacy.

P – 207 Clinico-pathological and molecular characterization of BRAF mutant metastatic colorectal cancer (mCRC): Are all mutations created equal?

M Schirripa[1], P Biason[2], F Cortiula[3], M Pino[4], F Urbano[5], C Antoniotti[6], S Corallo[7], F Gelsomino[8], A Orlandi[9], S Lonardi[1], F Bergamo[10], G Munari[11], U Malapelle[12], M Rugge[13], C Mescoli[14], L Reggiani Bonetti[15], G Lanza[16], A Dei Tos[17], G De Maglio[18], V Zagonel[19], F Loupakis[1], M Fassan[14]

[1]Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [2]Oncologia Medica 1, Istituto Oncologico Veneto IRCCS, Padua, Italy, [3]Oncologia, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy, [4]Medical Oncology, Ospedale Santa Maria Annunziata, Bagno a Ripoli, Italy, [5]Department of Radiological, Oncological and Anatomopathological Sciences, Sapienza University of Rome, Rome, Italy, [6]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [7]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [8]Modena Cancer Centre, Department of Oncology/Haematology, University of Modena and Reggio Emilia, Modena, Italy, [9]Università Cattolica del Sacro Cuore - Oncologia Medica, Rome, Italy, [10]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [11]Istituto Oncologico Veneto, IRCCS, Padua, Italy, [12]Department of Public Health, University Federico II, Naples, Italy, [13]Department of Medicine, Pathology and Cytopathology Unit, University of Padova, Padua, Italy, [14]Department of Medicine (DIMED), Pathology Unit, University of Padua, Padua, Italy, [15]Department of Laboratory Integrated Activities, Anatomic Pathology and Legal Medicine, University of Modena and Reggio Emilia, Modena, Italy, [16]Universitry of Ferrara, Ferrara, Italy, [17]Department of Pathology, General Hospital of Treviso, Treviso, Italy, [18]University Hospital Udine, Udine, Italy, [19]Oncologia Medica 1, Istituto Oncologico Veneto - IRCCS, Padua, Italy

Introduction: Functional studies on preclinical models (Yao et al. Nature 2017) identified 3 classes of BRAF mutations: activating RAS -independent BRAF mutations signaling as monomers (class 1- BRAF V600E) or as dimers (class 2-codons 601/597) and RAS -dependent BRAF mutations with impaired kinase activity (class 3-codons 594/596). While clinico-pathological and molecular features of class 1 mutation are well known, limited data are available with regard to class 2 and 3 mutations, due to their rarity in CRC.

Methods: Clinico-pathological, molecular and outcome data from BRAF mutated (codons 594, 596, 597, 600, 601) mCRC patients were collected. A group of BRAF wild-type patients was included as control. IHC analyses were performed to determine the consensus molecular subtypes (CMS). Clinical features were compared by chi-square or fisher's exact test. PFS and OS were evaluated by Kaplan-Meier and log-rank test.

Results: Class 1, 2 and 3 included 92, 12 and 13 patients respectively. BRAF wild-type patients were 540. No clinico-pathological differences were observed comparing class 1 to class 2 BRAF mutated. Conversely, BRAF class 3 mutated were more frequently left sided ($p = 0.0028$), well differentiated ($p = 0.0120$), pN0 ($p = 0.0159$), and with no peritoneal metastases ($p = 0.0176$) compared to class 1. With regard to CMS, class 2 and 3 tumors were all assigned to CMS2-3. Class 1 tumors were assigned to CMS1, 2-3 and 4 in 39%, 44% and 17% of cases. Median OS for BRAF wt, BRAF mutant class1, 2 and 3 were 42.2, 21, 23.4 and 44.5 months respectively. HR for OS was 2.38 (95% CI 1.61-3.54) for class 1, 1.90 (95% CI 0.85-4.26) for class 2 and 0.93 (95% CI 0.51-1.69) for class 3, compared to BRAF wt ($p < 0.0001$). Median PFS for BRAF wt, BRAF mutant class1, 2 and 3 were 10.1, 7.3, 7.0 and 13.8 months respectively. HR for PFS was 2.02 (95% CI 1.39-2.94) for class 1, 2.49 (95% CI 0.92-6.74) for class 2 and 0.85 (95% CI 0.47-1.54) for class 3, compared to BRAF wt ($p < 0.0001$).

Conclusion: Our data confirm previous findings describing specific features associated with BRAF rare mutations. For the first time clinico-pathological characteristics and outcome data are reported according to the 3 classes categorization of BRAF mutations. In particular, class 1 and 2 share similar features and worse outcome compared to class 3 and wild type patients

P – 208 Autophagy (A) related proteins evaluation represents an independent survival factor of colorectal cancer (CRC) patients (pts)

M Karamouzis[1], A Saetta[2], E Koustas[1], I Chatziandreou[2], I Giannopoulou[2], M Michelli[2], C Giaginis[3], A Papavassiliou[1], S Theoharis[2]

[1]Molecular Oncology Unit, Department of Biological Chemistry, Medical School, National and Kapodistrian University of Athens, Athens, Greece, [2]Department of Pathology, Medical School, National and Kapodistrian University of Athens, Athens, Greece, [3]Department of Food Science & Nutrition, University of the Aegean, Lemnos, Greece

Introduction: A holds a bimodal role during carcinogenesis. Before tumorigenesis, A promotes normal cells survival and suppress carcinogenesis, while after cancer development A induces cancer cells survival. The aim of this study is to assess the impact of A related proteins in the survival of CRC pts.

Methods: The data of 68 CRC pts treated at our Department from January 1st to December 31st, 2016 were studied. KRAS, NRAS and BRAF status was evaluated with polymerase chain reaction, while MSI, p62 and LC3B with immunohistochemistry (IHC). IHC scoring of A related proteins was based on both the percentage of positive tumor cells and staining intensity. Statistical analysis was done using SPSS for Windows Software.

Results: Patients' characteristics are shown in Table 1. Sixty-eight pts aged 34-81 years (median 66.4 years) were included. All pts were treated with chemotherapy (adjuvant or metastatic setting). By the time of the data evaluation (December 2017) 8 pts (11.8%) had died due to their disease. In cross-tabulation, p62 expression did not shown any significant association with clinicopathological parameters. Moreover, higher LC3B expression was more frequently observed in KRAS-positive CRC pts compared to KRAS-negative ($p = 0.0550$), whereas no correlation between LC3B expression and clinicopathological parameters was recorded. In univariate analysis, CRC pts having high p62 expression showed significantly better overall survival (OS) compared to those with low expression (24.8 vs 15.9 months; $p = 0.008$). In addition, CRC pts having high LC3B expression showed significantly better OS compared to those with low expression (24.9 vs 16.1 months; $p = 0.007$). In multivariate analysis, both p62 and LC3B expression were identified as independent prognostic factors of OS ($p = 0.012$ and $p = 0.019$, respectively), independently of tumor grade, disease stage and mutational status. CRC pts with high p62 expression also showed mildly better recurrence-free survival (RFS) compared to those with low expression (43.1 vs 34.8 months; $p = 0.115$), whereas high LC3B expression was not associated with better RFS (39.7 vs 38.4 months; $p = 0.714$).

Conclusion: Overall, these results indicate that the evaluation of A related proteins expression in paraffin specimens might represent an independent survival factor of CRC pts. The biological rationale could be the blockade of autophagy by chemotherapy resulting in high expression and accumulation of p62 and LC3B proteins. Further testing of other A related proteins (Beclin-1 and RAB7) is ongoing and will be presented.

P – 209 P 53 abnormal expression might influence global outcome through EGFR modulation in RAS/BRAF wild type metastatic colorectal cancer patients receiving later-line irinotecan cetuximab

M Puzzoni[1], L Demurtas[1], P Ziranu[1], E Lai[2], R Giampieri[3], L Faloppi[4], A Mandolesi[5], C Cremolini[6], G Masi[6], F Gelsomino[7], S Mariani[1], A Cubeddu[1], L Casula[1], N Liscia[1], V Pusceddu[1], C Antoniotti[6], C Loretelli[8], F Meriggi[9], A Zaniboni[10], A Falcone[11], S Cascinu[12], M Scartozzi[13]

[1]Departments of Medical Oncology, University of Cagliari, University Hospital 'Duilio Casula', Cagliari, Italy, [2]Departments of Medical Oncology, University of Cagliari, University Hospital 'Duilio Casula', Cagliari, Italy, [3]Clinica Oncologica, AOU Ospedali Riuniti, Ancona, Italy, [4]Medical Oncology Unit, Macerata General Hospital, ASUR Marche AV3, Macerata, Italy, [5]Departments of Institute of Pathology, AO Ospedali Riuniti-UNIVPM, Ancona, Italy, [6]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [7]Modena Cancer Centre, Department of Oncology/Haematology, University of Modena and Reggio Emilia, Modena, Italy, [8]Department of Biomedical and Clinical Sciences, Milan, Italy, [9]Medical Oncology Unit, Fondazione Poliambulanza, Brescia, Italy, [10]Fondazione Poliambulanza, Brescia, Italy, [11]University of Pisa, Pisa, Italy, [12]Azienda Ospedaliera-Università di Modena, Modena, Italy, [13]Medical Oncology, University of Cagliari, University Hospital, Cagliari, Italy

Introduction: Preclinical data suggest that loss of p53 might influence epidermal growth factor receptor (EGFR) promoter activity in different tumour types. The clinical role of p53 status in colorectal tumours, however, is still controversial. In the present study we assessed the role of p53 abnormal expression in patients with colorectal tumours treated with anti-EGFR therapy.

Methods: Tumour samples from RAS/BRAF WT patients with colorectal tumours treated with second-third line irinotecan-cetuximab were analysed for the immunohistochemical expression of p53. Aim of the present study was to evaluate the correlation of p53 abnormal expression with clinical outcome in terms of OS, PFS, ORR. Tumour sidedness, EGFR promoter methylation and EGFR GCN were evaluated as covariates. The association between categorical variables has been estimated with the chi-squared test. Statistical analysis has been performed with the MedCalc package. Survival distribution has been estimated by the Kaplan–Meier method. Comparison of survival curves has been performed with log-rank test. Logistic regression analysis has been used to assess the independent role of variables resulted significant at univariate analysis.

Results: Eighty-eight patients were included in the study, 36/88 (40.9%) had abnormal expression of p53 (abnormal p53), 52/88 (59.1%) had normal expression of p53 (normal p53). Abnormal p53 status was more frequent in left sided tumours (88.9% vs 16.7% of abnormal p53 for left sided and right sided tumours respectively) whereas it was less frequent in EGFR promoter methylated tumours (19.4% vs 71.2% of abnormal p53 for methylated and unmethylated respectively) and in EGFR GCN<2.12 tumours (5.6% vs 57.7% of abnormal p53 for EGFR GCN≥2.12 and EGFR GCN<2.12 respectively). Median PFS was 8,00 (95% CI: 6,98 to 8,10) vs 3,00 (95% CI: 2.90 to 3,63) months in patients with abnormal p53 tumours and in patients with normal p53 tumours respectively (HR 0.36; $p < 0.0001$). Median OS was 18 (95% CI:) vs 8 (95% CI: 6.98 to 8.10) months in patients with abnormal p53 tumours and in patients with normal p53 tumours respectively; HR: 0.21; $p < 0.0001$). ORR was 61.1%VS 3.8% in patients with abnormal p53 tumours and in patients with normal p53 tumours respectively ($p < 0.0001$). In multivariate analysis, EGFR promoter methylation and p53 expression maintained their independent role for OS (p:0.0003, Exp(b):0.21 and

p:0.01, Exp(b):2.82 respectively) whereas only EGFR promoter methylation resulted independently correlated with PFS (p:0.025, Exp(b):3.03 and p:0.056, Exp(b):0.51 for EGFR promoter methylation and p53 expression respectively).

Conclusion: The crosstalk between p53 and EGFR represents a poorly understood issue which could be significant in clinical practice. Our findings suggest a potential prognostic/predictive role of p53 status in patients with colorectal cancer treated with anti EGFR therapy. Further studies are needed to better understand the clinical role of p53 status in this setting.

P – 210 Unexpected discordance in 5-year OS rates between Nx colon cancer patients and those in stages II plus III

I Tonev[1], N Conev[2], A Petrov[1], I Donev[2]

[1]Complex Cancer Center Plovdiv, Plovdiv, Bulgaria, [2]Medical University of Varna, Varna, Bulgaria

Introduction: One of the most commonly diagnosed types of cancer among men and women is colon cancer. Pathological stage at surgery is one of the most important prognostic features in that type of cancer. The number of lymph nodes found during surgery and the presence of nodal metastases is determining for prognosis and further adjuvant treatment decisions. Unknown nodal status is defined as Nx and the results from an analysis performed by Surveillance, Epidemiology, and End Results Program show that 14% of colon cancer patients are defined as Nx. The prognosis in the Nx group of patients is not known. Theoretically, the overall survival (OS) in Nx subgroup should be equal to OS in N0+N1+N2 patients. The potential benefit of chemotherapy in Nx patients is not known.

Methods: A total of 1187 patients with colon cancer that underwent surgery at the Complex Cancer Center Plovdiv from 01.2004 to 12.2011 (734 stage II, 329 stage III and 124 Nx patients) were analyzed retrospectively. Studied data included date of surgery, age, gender, tumor location, lymph node status and tumor differentiation. All stage III patients, Nx patients and 21.9% of stage II patients underwent adjuvant chemotherapy. Survival analysis was performed using Kaplan-Meier method and Cox regression model.

Results: For stage II, III and Nx cancer patients, overall survival rates at five years after surgery were 92.4%, 88.3% and 33.9%, respectively. Moreover, the patients with Nx lymph node status were associated with higher risk of death HR- 1.44 (95% CI, 1.028-2.022; p = 0.03).

Conclusion: This study shows an unexpected discordance in 5-year overall survival rates between Nx colon cancer patients and patients in stages II plus III. Further investigations are needed to confirm that Nx lymph node status is an independent negative prognostic marker for colon cancer patients.

P – 211 Serum angiogenesis associated proteins and clinical outcome in metastatic colorectal cancer patients receiving bevacizumab

G Marisi[1], E Scarpi[2], A Passardi[2], O Nanni[3], F Pagan[3], M Valgiusti[4], A Casadei Gardini[5], C Molinari[2], G Frassineti[2], D Amadori[4], P Ulivi[1]

[1]Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [2]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [3]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [4]Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy, [5]IRST-IRCCS, Meldola, Italy

Introduction: Bevacizumab (B) plus chemotherapy (CT) is a common choice for first-line treatment of metastatic colorectal cancer (mCRC). Molecular predictors of B efficacy have not been identified yet. Previous studies have assessed circulating levels of pro- and anti-angiogenic factors at baseline and during therapy in relation to B response with conflicting results. We analyzed the potential role of 22 angiogenesis associated proteins (FGF-basic, HGF, sTIE-2, sVEGFR-1, sVEGFR-2, Ang-2, EGF, IL-6, IL-8, PLGF, VEGF-A, VEGF-C, VEGF-D, PDGF-bb, Ang-1, SDF-1alpha, MDC, Galectin, TSP-1, Endocan, eNOS, HIF-1alpha) in relation to patient outcomes.

Methods: Serum samples collected at different times (baseline, first clinical evaluation and disease progression) were available for 58 patients treated by CT (FOLFOX4/FOLFIRI) with B out of the 176 patients enrolled in the randomized multicenter ITACa trial (NCT01878422). Levels of all serum proteins were determined using a Bio-Plex 200 array reader, based on Luminex X-Map Technology. Baseline marker expression levels and their modulation during therapy were correlated with objective response (OR), progression-free survival (PFS) and overall survival (OS).

Results: Higher baseline vascular endothelial growth factor C (VEGF-C) levels and macrophage-derived chemokine (MDC) levels were associated with higher OR rate (Odd Ratio=7.69, 95% CI 2.13-27.78, p = 0.002 and Odd Ratio=3.58, 95% CI 1.12-11.37, p = 0.031, respectively). Baseline IL-8 levels were associated with PFS and OS, in particular patients with IL-8 <145 pg/mL showed a better median PFS and OS compared to those with higher levels (12.6 vs 6.5 months; Hazard Ratio [HR] 5.09, 95% CI 2.00-12.97, p < 0.001 and 28.8 vs 8.7 months, HR 6.06, 95% CI 2.12-17.37, p < 0.001, respectively). Moreover, patients with thrombospondin-1 (TSP-1) levels ≥12000 ng/mL showed a better median OS compared to those with lower levels (34.5 vs 13.1 months, HR 0.43, 95% CI 0.23-0.8, p = 0.007). Regarding serum proteins modulation during therapy, patients with a > 20% reduction from baseline to first clinical evaluation in IL-8 levels showed a better PFS and OS compared to those with a < 20% reduction or an increase (HR 0.41, 95% CI 0.22-0.77, p = 0.005 and HR 0.43, 95% CI 0.23-0.79, p = 0.007, respectively).

Conclusion: Our data suggest that baseline IL-8 and TSP-1 levels could represent potential prognostic markers in patients with mCRC receiving B-based chemotherapy and that IL-8 modulation from baseline to the first clinical evaluation may indicate better clinical outcomes.

P – 212 CDX2 immunohistochemistry as a prognostic biomarker for colorectal cancer

A Fatimilehin[1], C Mikropoulos[1], J Summers[2], L Rajakumar[1], M Hill[1]

[1]Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK, [2]Maidstone & Tunbrudge Wells NHS Trust, Maidstone, UK

Introduction: The caudal-type homeobox transcription factor 2 (CDX2) gene is expressed in intestinal epithelial cells. The encoded protein regulates genes involved in cell growth and differentiation. We performed a retrospective study to assess the impact of loss of expression of CDX2 in our cohort of patients at Kent Oncology Centre diagnosed with colorectal cancer on outcomes.

Methods: Results from all histology samples with CDX2 immunohistochemistry testing performed between January 2011 and November 2013 were obtained. 147 samples were initially included. Duplicate samples and patients with insufficient data on outcomes were subsequently excluded, leaving a total of 78 patients. Data collected included age at diagnosis, tumour stage, performance status, tumour location, KRAS and BRAF status, CDX2 status, time to relapse and time to death.

Results: Our 78-patient cohort had a median age of 70.5. 57.7% had a performance status of 2 or better, 24.4% had no performance status recorded. 48.7% of patients had left sided tumours, 48.7% had right sided tumours. 1.3% had disseminated disease, and 1.3% had unknown primary. 15 (19.2%) patients had CDX2 negative samples, and 58 patients (74.4%) were CDX2 positive. We were unable to obtain CDX2 test results for 5 patients (6.4%). 34 patients (43.6%) had metastatic disease on presentation compared to 44 (56.4%) patients without metastases. 34 patients (43.6%) were KRAS wild type, 8 (10.3%) were KRAS mutant. 36 patients (46.2%) had unknown KRAS status. 24 patients (30.8%) were BRAF wildtype, 12 (15.4%) were BRAF mutant. 42 (53.8%) had unknown BRAF status. For all stages of CRC the median overall survival was 27.8 months in CDX2 negative patients compared to 36.4 months in CDX2 positive patients. The hazard ratio for death in the CDX2 negative group compared to the positive group was 1.27 (95% CI 0.59 – 2.71 p = 0.5608). In the metastatic colorectal cancer group, there were 34 patients in total, 8 (23.5%) of who were CDX2 negative. In this subgroup, the median overall survival in the CDX2 negative group was 4 months. In contrast, the mean survival in the CDX2 positive group was 13.8 months. The hazard ratio for death in this subgroup was 2.40 (95 CI 0.85 -6.81, p = 0.0210).

Conclusion: mCRC CDX2 negative patients have a poorer prognosis. This was not confirmed in early stage CRC.

P – 213 An evaluation of the clinical utility of a panel of variants in DPYD and ENOSF1 for predicting common capecitabine related toxicities

C Palles[1], S Fotheringham[2], L Chegwidden[3], M Lucas[4], G Mozolowski[5], I Tomlinson[3], D Kerr[4]

[1]Insitute of Cancer and Genomic Sciences, Birmingham, UK, [2]Oxford Cancer Biomarkers, na, Alabama, USA, [3]Institute of Cancer and Genomic Sciences, Birmingham, UK, [4]Oxford University, Oxford, UK, [5]Oxford, Oxford, UK

Introduction: 5-Flurouracil (5-FU) based adjuvant chemotherapy, including the 5-FU oral prodrug capecitabine, is commonly used as it is extremely effective in increasing survival of stage III colorectal cancer patients and patients with resectable gastric or breast cancer. Its use is however limited by the concomitant toxicities that arise in some patients. ~ 50% of patients experience dose limiting toxicity when treated with capecitabine as a single agent and this percentage increases when given in combination e.g. with oxaliplatin. We have tested the diagnostic accuracy of a panel of toxicity associated/DPYD deficiency alleles at predicting patients risk of Capecitabine-related toxicity.

Methods: Genetic markers were included if they met one of the following criteria: Minor allele frequency (MAF) < 1%, identified in patients with DPYD deficiency. 3 of these markers were also associated with toxicity at P < 0.05. MAF >1% and associated with global Capecitabine-related toxicity with an odds ratio > 1.5 at pathway level significance and associated with an individual toxicity at genome wide significance. DPYD genotype based dosing guidelines have been published. These were incorporated in a simple genotype guided risk classification system with the following grades: critical risk, high risk, standard risk and standard risk with high risk of hand foot syndrome (HFS). Dose reductions based on DPYD haplotype B3 have been recommended. Whilst this variant didn't meet inclusion criteria for the panel we have evaluated the clinical utility of including the variant. In order to test the clinical utility of the panel the markers selected were genotyped in 888 participants of the QUASAR2 trial for

whom DNA and CTCAE graded toxicity data on gastrointestinal toxicities (Diarrhoea, Mucositis/Stomatitis, Vomiting), haematological toxicities (Neutropenia/Thrombocytopenia) and HFS were available.

Results: 17 DPYD low function/no function alleles, 1 common (MAF>1%) polymorphism mapping to DPYD and one common polymorphism mapping to ENOSF1 were selected for inclusion in the panel. The test has high sensitivity and specificity when toxicity induced death or grade 4 haematological toxicities are the outcome of interest (100% sensitivity, 98% specificity, negative predictive value (NPV) 1.0, positive predictive value (PPV) 0.1 (death); 75% sensitivity, 98% specificity, NPV 1, PPV 0.14 (haematological toxicities). Two deaths occurred during QUASAR2 which were attributable to Capecitabine administration. Both patients would have been highlighted by the test as high risk and a 50% reduction in starting dose would have been recommended. Whilst the sensitivity and specificity of the common markers included to provide a measure of risk of HFS are only moderate (83% sensitivity, 31% specificity, NPV 0.87, PPV 0.25), explanation by an oncologist of ways to mitigate the impact of this side effect on quality of life may enable participants to continue with treatment for longer. Inclusion of HapB3 in the panel was not supported as evidenced by reduced area under the curve and reduced sensitivity/specificity.

Conclusion: A panel of no function/low function DPYD alleles has clinical utility for the prediction of the most serious capecitabine related adverse events. Inclusion of two HFS associated markers may assist clinicians and patients in the management of this side effect.

P – 214 Bevacizumab combined with 1st line chemotherapy in elderly patients with metastatic colorectal cancer: Are there good prognostic indicators?

C Borges[1], J Simões[1], C Lemos[2], C Fernandes[1], C Sarmento[3], M Damasceno[3], D Almeida[1]

[1]Hospital S. João, Porto, Portugal, [2]IPV, Viseu, Portugal, [3]Hospital de S. João, Porto, Portugal

Introduction: As population ages, the incidence of metastatic colorectal cancer (mCRC) amongst elderly patients (>65 years old) rises. However, the geriatric population is a heterogeneous subset of patients, ranging from very fit to very frail, and often underrepresented in clinical trials. Studies suggest that elderly patients may benefit from target therapies as their younger counterparts, but careful clinical and analytical geriatric assessment is necessary in order to individualize treatment approach. The aim of our study is to evaluate the prognostic value of tumor markers and markers of systemic inflammation, in senior patients with mCRC, treated with anti-VEGF in 1st line palliative systemic treatment.

Methods: Retrospective analysis of 52 patients, over 65 years old, treated with bevacizumab in 1st line palliative chemotherapy between 2008 and 2017. Pretreatment CEA and CA 19.9 concentrations were ascertained, as well as the following inflammation markers: modified Glasgow prognostic score (mGPS), neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR) and platelet/lymphocyte ratio (PLR). Progression free survival (PFS) and overall survival (OS) analysis was calculated using Kaplan-Meier method and Cox hazard regression, with a significance level of 0,05.

Results: Our population's median age was 69 years (CI 95% 65-76). Mean PFS was 16 months, 10 months and 19 months, for patients aged < 70 years, 70 to 75 years and over 75 respectively. Mean OS was 26 months, 18 months and 36 months, for patients aged < 70 years, 70 to 75 years and over 75 respectively. The patient age was not significantly associated with either PFS or OS. There was no significant survival difference between right and left side (p = 0,569 for PFS; p = 0,330 for OS) and between KRAS wt/mut (p = 0,986 for PFS; p = 0,140 for OS). Over 50% had liver metastasis and 37% underwent liver metastasectomy. Concomitant chemotherapy protocol was irinotecan-based in 63,5%, oxaliplatin-based in 30,8% and capecitabine monotherapy in 5,8% of patients. Mean CEA value was 11,75 ng/mL (CI95% 1,79-3457,85) and CA 19.9 was 32 U/mL (CI95% 0-6259). Patients with elevated CEA concentrations had a significantly worse PFS than regular concentrations (median 10.8 vs 18.7 months, p = 0.047), but not OS. Multivariate analysis confirmed the findings for PFS (HR 1,39, CI95% 0,59-3,26, p = 0,030). Four percent had elevated mGPS, 50% elevated NLR, 34,6% reduced LMR and 53,8% elevated PLR. OS and PFS analysis failed to demonstrate a prognostic role for inflammatory markers. However, multivariate analysis suggested that the presence of three or more inflammatory criteria was associated with a trend towards worse OS (HR 0,45, CI95% 0,20-1,05, p = 0.066) and worse PFS (HR 0,79, CI95%, 0,38-1,29, p = 0,098).

Conclusion: We concluded that CEA concentration may be a valuable negative prognostic marker for PFS, in elderly patients treated with bevacizumab. Concomitant presence of elevated mGPS, elevated NLR, reduced LMR and/or elevated PLR was associated with a trend towards worse outcomes. However, further prospective studies might lead to better risk stratification.

P – 215

WITHDRAWN

P – 216 Primum non nocere: Screening patients for fluoropyrimidine-related toxicity risk: The most effective method

M Boisdron-Celle[1], J Metges[2], O Capitain[1], R Faroux[3], C Stampfli[4], M Ferec[5], P Laplaige[6], T Lecomte[7], T Matysiak-Budnik[8], H Senellart[9], M Campone[10], A Morel[1], E Gamelin[1]

[1]Institut de Cancérologie de l'Ouest Paul Papin, Angers, France, [2]CHU de Brest – Hôpital Morvan, Brest, France, [3]C.H.U. La Roche sur Yon, La Roche sur Yon, France, [4]C.H. Laval, Laval, France, [5]CHU Morlaix, Morlaix, France, [6]Polyclinique de Blois, La Chaussée st Victor, France, [7]Hôpital Trousseau, Tours, France, [8]C.H.U. Hôtel Dieu, Nantes, France, [9]Institut de cancérologie de l'Ouest René Gauducheau, St-Herblain, France, [10]Institut de Cancerologie de l'Ouest, Angers, France

Introduction: Fluoropyrimidines carry a 3% to 5% risk of grade 3 or higher early toxicities and a 0.2% risk of death linked to dihydropyrimidine dehydrogenase (DPD) deficiency, related to genetic and epigenetic factors.

Methods: 462 patients were tested after the first or second cycle: 254 because of grade 3 or greater toxicities, among them, 27 deaths, and 208 after grade 2 or lower toxicity. Patients were treated with several regimens. Colorectal cancer patients received fluoropyrimidines using the protocols LV5FU2, FOLFIRI, or FOLFOX over 46 hours, with or without EGFR or VEGF monoclonal antibodies. Breast cancer patients were treated by either FEC50, FEC100, or capecitabine. Head & neck cancer, and pediatric cancer patients were treated by continuous infusion of fluoropyrimidines over 96 hours along with cisplatin. Toxicity evaluation was performed after the first or second chemotherapy cycle and given a Common Terminology Criteria for Adverse Events (CTCAE) grade according to the National Cancer Institute adverse reactions to cancer drugs. Six methods were compared: genotyping DPYD*2 alone, four SNPs, uracil plasma levels, dihydrouracil/uracil ratio, GPCP-RNPGx and multiparametric approach.

Results: All six methods yield a high specificity. However, when the sensitivity is considered, it is markedly insufficient to test only for the DPYD*2 mutation. Screening for the four selected mutations was more sensitive; nonetheless, 66% of patients had a DPD deficiency which did not involve any of the four selected DPYD SNPs. The UH2/U ratio alone was more sensitive but not sufficient either. The multiparametric algorithm, combining all of these approaches was clearly the best method with 96% sensitivity. Interestingly, all the methods yield a reasonable positive predictive value (probability that patients with a positive screening test truly will experience an adverse reaction), but all, except the multiparametric algorithm have a low negative predictive value (probability that patients with a negative screening test truly will not have an adverse reaction). Comparing the positive likelihood ratio (LR+, which is the probability of an individual with the condition having a positive test result divided by the probability of an individual without the condition having a positive test result) for all four methods shows that although the multiparametric algorithm was not better than the UH2/U ratio, it is close. The negative likelihood ratio (LR-) is defined as the probability of a patient having a high risk of a toxic response divided by the probability of a patient

at low risk having a negative test. Once again, the algorithm, which considered multiple parameters, gave the most accurate prediction of the four approaches.

Conclusion: Finally, the high value (610) of the diagnostic odds ratio for the multiparametric test confirms it is the superlative method for predicting a patient's risk of having a toxic reaction to fluoropyrimidines.

P – 217 ABCG2 and TOP-1 as predictive biomarkers and targets for therapy in colon cancer

N Brünner[1], J Stenvang[1], V Popovici[2], E Budinska[3]

[1]University of Copenhagen and Scandion Oncology, Copenhagen, Denmark, [2]RECETOX, Faculty of Science, Masarykova Univerzita, Brno, Czech Republic, [3]2. RECETOX, Faculty of Science, Masarykova Univerzita, Brno, Czech Republic

Introduction: There is a need for new and innovative solutions in the medical treatment of colon cancer since many of these patients eventually develop resistance to currently used drugs leading to untreatable cancer disease and death of the patients. We have by using our DEN50-R cell line based screening platform (isogenic pairs of drug sensitive and drug resistant human cancer cell lines), followed by testing in the PETACC-3 prospective randomized clinical study, identified ABCG2 and TOP1 mRNA expression as significant predictive biomarkers for irinotecan (a topoisomerase 1 inhibitor) resistance in the adjuvant treatment of colon cancer. Moreover, we have identified a new drug (SCO-101) that reverses irinotecan resistance in preclinical experiments (the DEN50-R platform). Here we present the clinical data with the biomarkers and data on SCO-101 including the clinical development plans for the drug.

Methods: Biomarker studies: The study included 580 patients with mRNA expression data profiled from stage III colon cancer samples obtained from patients enrolled in the PETACC-3 study, which randomized patients to 5FUL +/- irinotecan. The primary end-points were recurrence free survival (RFS) and overall survival (OS). Median ABCG2 and the 75 percentile TOP-1 mRNA expression data were used to allocate patients into one of two groups: One with high ABCG2 expression (above median) and low TOP-1 expression (below 75 percentile) ("resistant") (n = 216) and another group including all other combinations of these two genes ("sensitive") (n = 364). Cox proportional hazards regression was used to estimate the hazard ratios and the association between variables and end-points and log-rank tests to assess the statistical significance of differences in survival between groups. Kaplan-Meier estimates of the survival functions were used for visualization and estimation of survival rates at specific time points. Reversal of irinotecan resistance: SCO-101 is a small molecule that as an oral formulation has passed 4 clinical phase 1 studies as monotherapy. SCO-101 is well tolerated with limited toxicity and a good PK profile. SCO-101 was tested alone and together with chemotherapy in the DEN50-R platform

Results: Biomarker studies: Significant differences were found for both RFS (HR: 0.63 (0.44-0.92); p = 0.016) and OS (HR: 0.60 (0.39-0.93); p = 0.02) between the two biomarker groups when the patients received FOLFIRI. When considering only the MSS patients (n = 470), the differences were even more pronounced (RFS: HR: 0.57; 95% CI: 0.37-0.85; p = 0.006) and (OS:HR: 0.57, 95% CI: 0.35-0.92; p = 0.02). In contrast, no significant differences were observed between the groups when patients received 5FUL alone. Reversal of irinotecan resistance: In irinotecan (SN38) resistant colorectal cancer cell lines with upregulation of ABCG2, SCO-101 reversed the resistance and subsequent analyses showed that SCO-101 effectively blocked ABCG2 mediated drug efflux from the cancer cells.

Conclusion: We will now initiate a clinical phase Ib study with the combination of SCO-101 and irinotecan in irinotecan resistant and ABCG2 high metastatic colorectal cancer patients.

P – 218 Biomarkers of oxidative stress in patient with colorectal cancer

H Haddouche

Université Abou-Bekr Belkaid Tlemcen, Algerie, Laboratoire de Biologie Moléculaire Appliquée et d'Immunologie, Tlemcen, Algeria

Introduction: The number of colorectal cancer increases regularly every year in Algeria and precisely in Tlemcen. It is a disease involving several genetic, hormonal, professional, environmental, but also behavioral factors, namely nutrition, the objective is to evaluate the nutritional and lipid profile on the one hand and some oxidative parameters of and to determine the relationship that may exist between nutritional factors and oxidative stress in patients with this type of cancer.

Methods: Thirty-three patients with newly diagnosed colorectal cancer were recruited from the Department of Gastroenterology, C.H.U. (CL, HDL-LC, LDL-CL, TG) and the oxidative status (ORAC, Catalase, Vitamin C, MDA) of Tlemcen and thirty-five healthy controls.

Results: A very significant difference was observed for patients with liver cancer compared to ORAC controls (1, 143 ± 0.121) (0, 4197 ± 0.0456) p < 0.000; MDA (0, 2400 ± 0.0492) (0, 083 ± 0.0275) P < 0.008; Catalase (1.385 ± 0.162) (0, 588 ± 0.219) p < 0.008; LDL-CHOL (0.4300 ± 0.0239) (1. 0692 ± 0.0627 p < 0.000, on the other hand no difference was observed for Vitamin C (0.221 ± 0.0465) (0, 1947 ± 0.0889) p < 0.615 HDL-CHOL (0.4300 ± 0.0322) (0.466 ± 0.031) p < 0.355

Conclusion: The balance of the oxidizing/antioxidant status is a primary factor in oncology. The free radicals can lead to the appearance of mutations and, conversely. Oxidative stress, colorectal cancer.

P – 219 Colorectal neuroendocrine carcinoma and colorectal mixed adeno-neuroendocrine carcinoma: A population-based study of the surveillance, epidemiology, and end results registry

M Liu[1], H Zhang[1], Y Yang[2], X Fu[1], K Nan[1], T Tian[1]

[1]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, [2]Shaanxi Provincial People's Hospital, Xi'an, China

Introduction: Neuroendocrine carcinoma (NEC) is defined as poorly differentiated neuroendocrine neoplasms. Mixed adeno-neuroendocrine carcinoma (MANEC) is a really new pathological diagnosis. It was defined as tumors with both neuroendocrine and epithelial components. Both NEC and MANEC belong to NEN. Up to now, the most published literatures about MANEC are case reports and small case studies. Research about the differences between colorectal NEC and colorectal MANEC is missing.

Methods: In this study, we collected patients from Surveillance, Epidemiology, and End Results Registry (SEER) database-18. We analyzed the demographic and clinical pathological characteristics of colorectal MANEC and compared colorectal MANED with colorectal NEC. Then we analyzed the prognosis factors and survival rate of these two types of pathology in colorectum.

Results: The results revealed that the age of diagnosis, the most frequency primary site, median survival time, the 5-year survival rate and the prognosis factors were different between colorectal MANEC and colorectal NEC. Next, we analyzed the survival curve in different subgroups and we found that 5-year survival rate of distance metastasis or stage IV patients of colorectal MANEC was significant less than that of colorectal NEC. Finally, we analyzed surgical operation and radiotherapy in colorectal MANEC and NEC and we found that colorectal MANEC patients with tumors located in colon or who were older than 50 years old or in TNM Stage III/IV could benefit from surgical operation. All colorectal NEC patients could benefit from surgical operation except patients with distance metastasis. Colorectal MANEC patients could not benefit from radiotherapy. Well for colorectal NEC patients, receiving radiotherapy meant shorter overall survival.

Conclusion: Our study found that the median survival time of colorectal MANEC was longer than colorectal NEC, but the rapid progress of advanced colorectal MANEC resulted in the lower 5-year survival rate than colorectal NEC. Operation is a best choice for both MANEC patients and NEC patients.

P – 220 MTHFR, TSER and DPYD gene mutation is associated with toxicity and response in pre-operative chemo-radiotherapy for local advanced rectal cancer

S Mancarella, O Potì, D De Giorgi, M Schirinzi

ASL Lecce, Galatina, Italy

Introduction: Radiotherapy and 5 FU based chemotherapy is the most common pre-operative regimen used for cT3-T4, N1 rectal cancer (RC). Evaluation of predictive markers of response and toxicity to radio-chemotherapy is a challenging approach for patients (pts) and drug selection. In the present experience we have analyzed the predictive role of the genetic polymorphisms (MTHFR, TSER and DPYD) on toxicity and response to pre-operative radio-chemotherapy.

Methods: We have enrolled eighteen patients with locally advanced RC treated with pre-operative radiotherapy and fluoropyrimidines based chemotherapy. Genetic polymorphisms of MTHFR C677T, MTHFRA 1298C, DPYD IVS 14 + 1G>A, DPYDA 2846T, DPYD T 1679 G, TSER 28 bp VNTR were analyzed by PCR and pyrosequencing of genomic DNA extracted from peripheral blood samples. Genetic markers were correlated with toxicity to treatment (chemotherapy and radio-chemotherapy) and clinical response.

Results: Patients characteristics were: male 15 pts, female 3 pts, median age 66 years, ECOG PS 0-1 all pts. We found DPYD IVS 14 + 1 G>A G/G homozygous wild type, DPYD A2846T, T/T homozygous wild type and DPYD T1679 g, T/T homozygous wild type in 100% of pts, homozygous wild type MTHFR C677T in 10% of pts, MTHFR C677T homozygous mutated in 50% of pts, heterozygous MTHFR A1298C in 60% of pts and homozygous wild type MTHFR A 1298C in 40% of pts. Adverse events G-3 (diarrhea, neutropenia, asthenia, mucositis) were observed in 60% of pts with heterozygous MTHFR A 1298C and in 10% of pts with homozygous mutated MTHFR C 677t treated with chemo radiotherapy combination. DPYD homozygous wild type was not associated with severe toxicity. Rectal surgery with TME/TEM will be performed 8 weeks after the end of pre-operative chemo-radiotherapy. We obtained 9 pathological complete response and 9 partial pathological response. Adjuvant chemotherapy was well tolerated without G3-G4 adverse events. Five pts with pathological complete response were treated with Transanal Endoscopic Microsurgery (TEM) and they are alive without recurrence to twelve months after surgery.

Conclusion: Concomitant assessment of genetic polymorphisms of MTHFR and DPYD is promising to predict severe toxicity during preoperative chemo-radiotherapy

approach for pts with locally advanced rectal cancer. This result does not exclude the need to consider other non-genetic factors that might influence the individual enzyme activities.

P – 221 Regorafenib or trifluridine/tipiracil in refractory metastatic colorectal cancer: The optimization of pharmacological costs

J Giuliani[1], A Bonetti[2]

[1]Department of Oncology - Mater Salutis Hospital - Az. ULSS 9 Scaligera - Legnago (VR), Legnago, Italy, [2]U.O. Oncologia - Mater Salutis Hospital - Az. ULSS 9 Scaligera - Legnago (VR), Legnago (VR), Italy

Introduction: The introduction of active new agents for refractory metastatic colorectal cancer (mCRC), such as regorafenib and trifluridine/tipiracil, is associated with a relevant increase of costs and it might be interesting to make a balance between the costs of treatment and the added value represented by the improvement of the clinical parameters of interest such as OS (overall survival).

Methods: Pivotal phase III randomized controlled trials (RCTs) of regorafenib and trifluridine/tipiracil in refractory mCRC were considered. Differences in OS (expressed in months) between the different arms were calculated and compared with the pharmacological costs (at the Pharmacy of our Hospital) needed to get one month of OS. The costs of drugs are at the Pharmacy of our Hospital and are expressed in euros (€). We assumed the following costs: 2299 € for 1 month of therapy with regorafenib at dose of 160 mg daily, 1160 € for 1 month of therapy with trifluridine/tipiracil at dose of 35 mg per square meter twice daily. Calculations were based on an "ideal patient" (BSA 1.8 sqm; weight 70 Kg). The dosage of drugs were considered according to those reported in each RCT. We have subsequently applied the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) to the above phase III RCTs.

Results: Three phase III RCTs (RECOURSE, CORRECT and CONCUR trials), including 1764 patients, were considered. ESMO-MCBS reached grade 3 for the CONCUR trial, grade 2 for the RECOURSE trial and grade 1 for the CORRECT trial. Combining the costs of therapy with the measure of efficacy represented by the OS, we get the costs for obtaining the advantage in OS, for each arm of the analyzed trials. Trifluridine/tipiracil (RECOURSE trial) resulted the less expensive, with 967 € per month OS-gained towards the CONCUR trial and CORRECT trial, with 2207 € and 2956 € per month OS-gained, respectively, mainly due to the increase in OS difference compared to placebo.

Conclusion: Combining pharmacological costs of drugs with the measure of efficacy represented by the OS, trifluridine/tipiracil is a cost-effective treatment for patients with refractory mCRC.

P – 222 Is the PEG-G-CSF useful as the prevention for the severe neutropenia in metastatic colorectal cancer patients treated with FOLFOXIRI plus bevacizumab?

H Osumi[1], E Shinozaki[1], T Wakatsuki[2], M Suenaga[1], T Ichimura[3], M Ogura[4], Y Ota[5], I Nakayama[3], D Takahari[3], K Chin[1], K Yamaguchi[6]

[1]Department of Gastroenterology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Japan, [2]Cancer Institute Hospital Department of Gastroenterology, Koto-ku, Japan, [3]Cancer Institute Hospital, Koto-ku, Japan, [4]Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Japan, [5]Cancer Institute Hospital, Japanese Foundation of Cancer Research, Tokyo, Japan, [6]Department of Gastroenterology Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-ku, Japan

Introduction: FOLFOXIRI plus bevacizumab (Bev) significantly improved both the progression free survival (PFS) and the overall survival (OS) of patients with metastatic colorectal cancer (mCRC). However, as the frequency of grade 3/4 neutropenia is very high, we often require the dose adjustment in the clinical practice. The Polyethylene glycol conjugated granulocyte colony-stimulating factor (PEG- G-CSF), which is characterized by an increased circulating half-life, has the potential to shorten the duration and severity of neutropenia. However, there is a few evidences to evaluate the efficacy of the PEG-G-CSF for the neutropenia in mCRC. This study aimed to evaluate treatment outcomes, safety and the efficacy of the PEG-G-CSF for neutropenia in mCRC patients treated with FOLFOXIRI plus Bev.

Methods: We retrospectively analyzed mCRC patients who received FOLFOXIRI plus Bev between December 2015 and December 2017 at the Cancer Institute Hospital. Bev was given as a 5 mg/kg intravenous dose. FOLFOXIRI consisted of a 165 mg/m2 intravenous infusion of irinotecan for 60 min, followed by an 85 mg/m2 intravenous infusion of oxaliplatin given concurrently with 200 mg/m2 leucovorin for 120 min, followed by a 3200 mg/m2 continuous infusion of fluorouracil for 48 h. We evaluated the overall response rate (ORR) according to the RESICT ver 1.1, PFS, OS, adverse events by CTCAE ver 4.0 and the efficacy of the PEG-G-CSF for the neutropenia. PFS and OS were estimated using the Kaplan-Meier method and compared using the log-rank test.

Results: A total of 26 patients (13 male, 13 female) with a median age of 53.5 (27-74) were included. The median follow up time of the study was 24.2 months. Among all the patients, 18 patients (69.2%) had the ECOG PS of 0. 8 of 26 patients (30.8%) had right-sided primary tumor location. 23 of 26 patients (88.5%) had the RAS mutant tumor. UGT1A1 status were wild type (26.9%), *6 (23.0%), *28(7.7%), Unknown (42.4%), respectively. The ORR rate was 65.3%, the median PFS was 9.6 months (7.2–16.9), and the median OS was 24.2 months (13.6–NA). Grade 3/4 neutropenia occurred in 53.8% of patients and the febrile neutropenia occurred in 7.7%. The PEG-G-CSF was used in 76.9% of patients. In the patients who used the prophylactic PEG-G-CSF (n = 9), 7 of 9 patients (77.7%) didn't require the dose adjustment. In the patients who used PEG-G-CSF after grade 3/4 neutropenia (n = 11), no one experienced grade 3/4 neutropenia again. 2 of 26 patients (7.2%) required the dose adjustment due to non hematologic adverse events.

Conclusion: The PEG-G-CSF is useful to prevent a severe neutropenia and to keep dose intensity in mCRC patients treated with FOLFOXIRI plus Bev.

P – 223 NORTH/HGCSG1003: A phase II study evaluating the safety and efficacy of FOLFOX as adjuvant chemotherapy for patients with stage III colon cancer: Comparison with medical oncologists and surgeons

S Yuki[1], Y Komatsu[2], Y Kawamoto[3], H Nakatsumi[3], N Takahashi[4], T Shichinohe[5], H Okuda[6], A Ishiguro[7], K Harada[8], I Iwanaga[9], K Hatanaka[10], K Oomori[11], M Nakamura[12], N Senmaru[13], K Iwai[14], M Koike[15], T Shinohara[16], K Miyashita[17], Y M. Ito[18], A Taketomi[19], S Hirano[5], N Sakamoto[20]

[1]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [2]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [3]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [4]Department of Surgical Center, Hokkaido University Hospital, Sapporo, Japan, [5]Department of Gastroenterological Surgery II, Hokkaido University Hospital, Sapporo, Japan, [6]Department of Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan, [7]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan, [8]Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan, [9]Department of Medical Oncology, Japanese Red Cross Kitami Hospital, Kitami, Japan, [10]Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan, [11]Department of Surgery, Keiwakai Ebetsu Hospital, Ebetsu, Japan, [12]Department of Gastroenterology, Sapporo City General Hospital, Sapporo, Japan, [13]Department of Surgery, Steel Memorial Muroran Hospital, Muroran, Japan, [14]Department of Surgery, Oji General Hospital, Tomakomai, Japan, [15]Department of Surgery, KKR Sapporo Medical Center, Sapporo, Japan, [16]Department of Gastroenterological Surgery, Hokkaido Cancer Center, Sapporo, Japan, [17]Department of Gastroenterology, Aiiku Hospital, Sapporo, Japan, [18]Department of Biostatistics, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [19]Department of Gastroenterological Surgery I, Hokkaido University Hospital, Sapporo, Japan, [20]Department of Gastroenterology and Hepatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Introduction: The efficacy of oxaliplatin containing regimens were confirmed in large randomized phase III trials in which they were superior to fluorouracil and leucovorin as adjuvant setting for patients with stage III colon cancer. In Japan, not only medical oncologists but also surgeons practice chemotherapy. In this analysis, we investigated differences in safety and efficacy between surgeons and medical oncologists from NORTH/HGCSG1003 study.

Methods: NORTH/HGCSG1003 is a multicenter phase II study. This study enrolled patients with resected stage III colon cancer. Patients received FOLFOX4 or mFOLFOX6 repeated every 2 weeks for 12 cycles. Primary endpoint is disease-free survival, and secondary endpoints were overall survival, safety, RDI and so on. In this analysis, pts characteristics and safety were compared using Fisher's exact test. Dose intensity was compared using Student's t-test, and DFS and RFS using log-rank test.

Results: From September 2010 to March 2013, 273 patients at 28 institutions were enrolled. In the eligible population (n = 264), 159 patients were treated with chemotherapy by medical oncologists (group O) and 105 patients by surgeons (group S). Patients' characteristics between two groups were well balanced except for bowel obstruction before surgery (8.8% in group O vs 23.8% in group S; p = 0.001). Median RDI (group O vs group S) of oxaliplatin was 0.631 vs 0.751 (p

Conclusion: RDI of oxaliplatin and bolus 5-FU were significantly lower in group O than group S. The frequency of platelet count decreased (all grade) was significantly less in O. This was presumed to be because the relative dose intensity of oxaliplatin was significantly lower in O. However, there was no significant difference in the frequency of peripheral sensory neuropathy. There was no significant difference in efficacy between O and S.

P – 224 Analysis of clinical outcomes of two antiEGFR antibodies, cetuximab and panitumumab, in the 1st line chemotherapy of RAS wild metastatic colorectal cancer, by neutrophil-to-lymphocyte ratio (NLR) kinetics

D Manaka[1], R Nishitai[1], S Konishi[1], T Ota[1], Y Nishikawa[2], R Kudo[1], K Kawaguchi[1], H An[2], S Hamasu[1]

[1]Department of Surgery, Gastrointestinal Center, Kyoto Katsura Hospital, Nishikyo-ku, Japan, [2]Department of Surgery, Gastrointestinal Center, Kyoto Katsura Hospital, Nishikyo-ku, Japan

Introduction: mFOLFOX6+antiEGFR antibody is a standard-of-care in the 1st line chemotherapy of metastatic colorectal cancer. Two molecular targeted drugs, i.e. cetuximab (Cet) and panitumumab (Pani), are the choices of antiEGFR antibody, but the proper use of these drugs are not clarified yet. Cet, IgG subclass1 antibody, is demonstrated to have ADCC activity and other immune, inflammatory functions. Differences of the activities of these two antibodies could be analyzed from this standpoint using the kinetic evaluations of neutrophil-to-lymphocyte ratio (NLR), which is the indicator of cancer-related immune and inflammatory activities.

Methods: 50 pts with RAS wild metastatic colorectal cancer were enrolled and treated with mFOLFOX6+antiEGFR antibody (25 pts with Cet, 25 pts with Pani). NLR was measured at the points of pre-treatment (preT), early-tumor-shrinkage (ETS) and progression of disease (PD). The associations of NLR and clinical outcomes were evaluating by Spearman's rank correlation coefficient, and two-sample Mann-Whitney U tests were performed with several variants between Cet and Pani pts.

Results: The median follow-up time for censored cases was 28 months (m) (IQR, 14-52). Progression free survival (PFS) and overall survival (OS) were 10.9m (95% C.I;7.9-12.6) and 30.0m (95% CI; 20.4-41.2), respectively. PFS and OS of Cet and Pani pts were not different significantly different [PFS: 12.0m (95% CI; 7.2-16.2) vs 9.5m (95% CI; 7.8-12.1), $p = 0.23$; OS: 30.0m (95% CI; 21-49.9) vs 33.1m (95% CI; 13-41.9), $p = 0.202$]. NLR at preT and PD were significantly correlated with OS, -0.291($p = 0.0422$) and -0.347 ($p = 0.0413$), respectively. Correlation of PFS with NLR at ETS and with the difference of NLR between preT and ETS, were -0.415 ($p = 0.0391$) and -0.355 ($p = 0.0816$) in Cet pts, whereas there were no significant trends of correlation in Pani pts, 0.272 ($p = 0.209$) and 0.598 ($p = 0.002$), respectively.

Conclusion: Our results suggest that NLR kinetics could reflect the treatment outcomes and kinetic analysis would lead to the stratification of clinical use of Cet and Pani. Cet, rather than Pani, might have more immune and inflammatory associations in the 1st line chemotherapy of RAS wild metastatic colorectal cancer. Clinical trial information: UMIN000031535.

P – 225 The role of maintenance therapy in the first line treatment of metastatic colorectal cancer

D Gridnev[1], A Popov[1], E Vozny[1], V Makarov[1], D Islamova[1], A Kudryavtseva[2], A Zhevelyuk[1], M Trandofilov[1]

[1]City Hospital Named After Pletnev D.D., Moscow, Russian Federation, [2]Engelhardt Institute of Molecular Biology RAS, Moscow, Russian Federation

Introduction: The first line of chemotherapy is decisive in the treatment of colorectal cancer. Choosing the right one allows you to increase PFS and improve long-term results. Surgical treatment and maintenance therapy (MT) increase PFS and OS, as they can be prescribed at any stage of treatment.

Methods: The analysis included 100 patients diagnosed with mCRC who received treatment between 2014 and 2018. The average age of the patients was 62.4 years. At the beginning of treatment, the overall condition of all patients was ECOG1. Primary mCRC had 67 (67%) patients. In 33 (33%) patients, locally advanced disease was first diagnosed, which were included in the study after progression. Only 27 (82%) of the patients received adjuvant therapy. PFS and OS for all patients were calculated from the start of the 1-line. Localization of the primary tumor in 19 patients (19%) was in the right part of the colon, and in the left part - in 81 (81%). Among the patients with primary metastatic disease 41 (61%) had isolated metastases, the remaining 26 (39%) had 2 or more localizations. Different types of surgical treatment of metastases in the liver received 20 (20%) patients. MT was performed in 58 (58%) patients by de Gramont regimen. The remaining 42 (42%) did not receive MT and made a comparison group. Evaluation of the effect was performed using RECIST criteria, at intervals of 3 months or the appearance of clinical symptoms of progression. The treatment was carried out before the progression. At the time of analysis, 39 patients are alive and continue to receive treatment. MT was provided in the second and subsequent chemotherapy lines.

Results: In the general population in the group of patients receiving MT in the first line (group A) PFS-10 months that twice exceeds the same figure in the control group (group B) 5 months. OS in both groups was 29.6 months. When the primary tumor was localized in the left parts of the large intestine in group A (44 patients), PFS-10.5 months, OS-29.3 months VS group B (38 patients) PFS-6 months, OS-30.4 months. When the primary tumor was localized in right in group A (14 patients), PFS-9 months, OS-20.8 months VS group B (5 patients) PFS-4 months, OS-27.8 months. At metastatic lesion of only a liver in group A (41 patients) PFS-10 months, OS-29.0 months VS group B (33 patients) PFS-6 months, OS-31.0 months. With metastatic lesion of more than one organ in group A (17 patients) PFS-11 months, OS-27.4 months VS group B (9 patients) PFS-4 months, OS-9.3 months. In the presence of the primary disseminated disease in group A (44 patients) PFS-10.5 months, OS-25.8 months VS group B (23 patients) PFS-6 months, OS-14.2 months. With the progression of initially locally advanced disease in group A (14 patients) PFS-9 months, OS-33.0 months VS group B (19 patients) PFS 5 months, OS-34.3 months. Pre-existing chemotherapy (adjuvant) patients in group A (13 patients) PFS-8 months, OS-34.5 months VS group B (14 patients) PFS-10 months, OS-32.5 months. Untreated chemotherapy patients in group A (45 patients) PFS -11 months, OS-25.3 months VS group B (28 patients) PFS-6 months, OS-22.6 months.

Conclusion: PFS increases with the inclusion of MT on the first line, without increasing the OS. A significant increase in PFS and OS during MT in the first line is observed in the group of those who did not receive chemotherapy before the first line. The appointment of MT in the first line is important for patients who have not received previous chemotherapy.

P – 226 HGCSG 1301: A Multicenter, Double-Blind, Randomized control phase II trial comparing Hange-shashin-to versus placebo to prevent diarrhea in patients with metastatic colorectal cancer under IRIS/Bev second-line treatment

M Nakamura[1], Y Komatsu[2], T Muranaka[3], M Yagisawa[3], Y Kawamoto[3], H Nakatsumi[3], S Yuki[4], T Saiki[5], A Ishiguro[5], M Tateyama[6], Y Kobayashi[7], T Miyagishima[8], T Takahata[9], A Sato[9], M Dazai[10], H Okuda[11], K Fujikawa[12], K Eto[13], S Muto[14], K Hatanaka[15], T Amano[16], Y Sakata[17]

[1]Department of Gastroenterology, Sapporo City General Hospital, Sapporo, Japan, [2]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [3]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [4]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [5]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan, [6]Department of Internal Medicine, Tomakomai Nisshou Hospital, Tomakomai, Japan, [7]Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan, [8]Department of Internal Medicine, Kushiro Rosai Hospital, Kushiro, Japan, [9]Department of Medical Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, [10]Department of Gastroenterology, Sapporo Medical Center NTT EC, Sapporo, Japan, [11]Department of Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan, [12]Department of Gastroenterology, Hokkaido Cancer Center, Sapporo, Japan, [13]Department of Gastroenterology, Tomakomai City Hospital, Tomakomai, Japan, [14]Department of Gastroenterology, Hokkaido Medical Center, Sapporo, Japan, [15]Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan, [16]Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan, [17]Misawa City Hospital, Misawa, Japan

Introduction: S-1 plus irinotecan (IRIS) showed non-inferiority to fluorouracil and folinic acid plus irinotecan (FOLFIRI) by FIRIS study. Therefore, IRIS is widely used with bevacizumab (IRIS/Bev) as the second-line chemotherapy in patients with colorectal cancer. The most frequent non-hematological adverse event shown at the study was diarrhea. Baicalin contained within Hange-shashin-to is a potent competitive inhibitor of beta-glucuronidase which cleaves conjugated SN-38-glucuronide to SN-38 which causes cytotoxic diarrhea as an active metabolite from irinotecan. We conducted to evaluate the usefulness of prophylactic administration of Hange-shashin-to to prevent diarrhea in patients receiving IRIS/Bev.

Methods: This trial was designed as a multicenter, randomized, double-blind, placebo-controlled study. We administrated Hange-shashin-to 2.5g or placebo PO t.i.d. until 3 months from the first treatment cycle of IRIS/Bev. The primary endpoint is proportion of Grade 3 or worse diarrhea assessed by CTCAE v4.0. This study is registered with UMIN-CTR, number UMIN000012276.

Results: Between Jan 1, 2014 and Mar 31, 2017, 59 patients with colorectal cancer in need of second-line chemotherapy from 11 institutes in japan were randomly assigned to receive Hange-shashin-to ($n = 28$, Group H) or placebo ($n = 29$, Group P). The patients' characteristics were well-balanced. The median relative dose intensities of S-1, irinotecan and bevacizumab were 0.89 vs 0.89, 0.89 vs 0.89 and 0.89 vs 0.86 in group H vs group P. The proportions of Grade 3 or worse diarrhea were 10.7% (3 of 28) in Group H and 13.8% (4 of 29) in Group P ($p = 1.00$). Those of any grade diarrhea were 64.3% (18 of 28) in Group H and 72.4% (21 of 29) in Group P ($p = 0.58$). The other major adverse events (grade 3 or worse) were fatigue (3.6% vs 10.3%), anorexia (14.3% vs 10.3%), nausea (0.0% vs 3.4%) in Group H vs Group P. The overall response rate in group H vs group P was 13.6% vs 7.7% ($p = 0.65$), and the disease control rate was 86.4% vs 80.8% ($p = 0.71$), respectively.

Conclusion: Our study to examine the diarrhea control effect by Hange-shashin-to induced by IRIS/Bev did not show any significant difference between two groups.

P – 227 Analysis of the benefit of the adjuvant chemotherapy in stage II colon cancer according to the presence of classic poor risk factors: Our experience in Ramon y Cajal Hospital

C Saavedra Serrano[1], M Villamayor Delgado[2], E Corral de la Fuente[1], A Barquín García[1], J Serrano Domingo[3], R Martín Huertas[1], O Martínez Saez[2], F Longo Muñoz[4], P Reguera Puertas[5], V Pachón Olmos[5], M Rodriguez Garrote[5], M Vaz[4], R Fuentes[1], A Carrato[6], R Ferreiro Monteagudo[5]

[1]Ramón y Cajal Hospital, Madrid, Spain, [2]Ramón y Cajal Univsersity Hospital, Madrid, Spain, [3,4]Hospital Universitario Ramón y Cajal, Madrid, Spain, [5]Ramón y Cajal University Hospital, Madrid, Spain, [6]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain

Introduction: Despite surgery is a curative treatment for colon cancer (CC), recurrence is common. The role of adjuvant chemotherapy (AC) in stage II CC is controversial. Classically, certain factors have been associated with poor prognostic outcomes and they are widely considered in the decision making algorithm for stage II CC.

Methods: We conducted an unicentric retrospective study. Patients with resected stage II CC between 2009 and 2014 were identified. Univariate analysis were performed for classic high risk factors (CRF), and those which obtained a $p < 0.05$ were incorporated in a multivariate model. In addition, we analyzed the relapse free survival (RFS) and overall survival (OS) rates according to the presence of at least one risk factor. Finally, we studied the benefit of AC in patients depending on the presence or absence of risk factors. Cox regression was employed for the analysis.

Results: 282 patients were identified. 60% were men. Median age at diagnosis was 74 years. The most were right sided (55%) and stage IIA (86%). 62% had at least one CRF. 30% of all patients received AC, most of them having at least one risk factor (82%). Median follow up was 60,2 months. Median 5-year RFS was 67,3% and the 5-year OS rate was 76,8%. In the univariate analysis for OS: T stage, the presence of perforation or obstruction and positive margins were significant prognostic factors (HR 2.1, 2.3, 2.8 and 2.9 respectively). In the multivariate model: obstruction, perforation and positive margins were independent risk factors for OS (HR 3.1, 1.9 and 3.2 respectively). The same analysis for RFS was performed: T stage, lymphovascular infiltration, perforation or obstruction, positive margins and presurgical CEA elevation were significant risk factors in the univariate analysis (HR 2.1, 2, 2.1, 2.6, 2.3 and 2.4, respectively). Presurgical CEA elevation and lymphovascular infiltration were the only prognostic factors in the multivariate model (HR 3.6 and 4.6, respectively). Having at least one CRF represented a detrimental factor for OS (HR 1.9, $p = 0{,}015$) and RFS (HR 2.2, $p = 0.022$). According to risk factors identified in our analysis, similar results were found for OS (HR 2.99, $p < 0.001$) and RFS (HR 1.8, $p = 0.008$). In addition, patients with at least one CRF receiving AC had benefit in OS (HR 0.27, $p < 0.001$) and RFS (HR 0.49, p 0.012), while there was not benefit in patients without any CRF neither for OS or RFS. However, stratifying patients only according to risk factors identified in our analysis, does not discriminate accurately which patients benefit from AC.

Conclusion: Adequate selection of patients with stage II colon cancer who can benefit from AC is essential for avoid overtreatment and for improve prognosis of those patients with higher risk. In this way, CRF seems to stratify properly patients who benefit from an AC and those who need closer surveillance. However, more precise information is needed and including molecular biomarkers could help to accurate decision making in the near future.

P – 228 VOLTAGE: Multicenter phase Ib/II study of nivolumab monotherapy and subsequent radical surgery following preoperative chemoradiotherapy (CRT) with capecitabine in patients with locally advanced rectal cancer (LARC)

H Bando[1], Y Tsukada[2], K Inamori[2], S Fukuoka[3], T Sasaki[2], Y Nishizawa[2], M Wakabayashi[4], M Kojima[5], Y Togashi[3], S Yuki[6], Y Komatsu[7], S Homma[8], Y Hatanaka[9], Y Matsuno[10], M Uemura[11], T Kato[11], A Sato[12], H Nishikawa[3], M Ito[2], T Yoshino[13]

[1]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [2]Department of Colorectal Surgery, National Cancer Center Hospital East, Kashiwa, Japan, [3]Division of Cancer Immunology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center Hospital East, Kashiwa, Japan, [4]Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, [5]Division of Pathology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center Hospital East, Kashiwa, Japan, [6]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [7]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [8]Department of Gastroenterological Surgery, Hokkaido University Hospital, Sapporo, Japan, [9]Research Division of Genome Companion Diagnostics, Hokkaido University Hospital, Sapporo, Japan, [10]Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan, [11]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [12]Clinical Research Support Office, National Cancer Center, Kashiwa-city, Japan, [13]National Cancer Center Hospital East, Kashiwa, Japan

Introduction: Fluoropyrimidine-based Chemoradiotherapy (CRT) and subsequent radical surgery is widely accepted as the standard treatment for patients with Locally Advanced Rectal Cancer (LARC). Higher pathological complete response (pCR) rates are associated with good clinical outcomes. Recently, improved therapeutic effects have been reported in patients with various types of cancer by combining an immune checkpoint inhibitor with radiotherapy (RT). The purpose of this study is to investigate safety, efficacy and proof-of-concept (POC) of nivolumab monotherapy plus subsequent radical surgery following preoperative CRT with capecitabine, in patients with LARC. Here, we present the results of the phase Ib and the preliminary results of phase II part.

Methods: The Phase Ib part was designed to determine the recommended phase II dose (RP2D) in a "3 + 3" cohort-based design of nivolumab (240mg every 2 weeks, maximum of 5 times) and subsequent radical surgery. The Phase II part was designed to evaluate the efficacy and safety of RP2D of nivolumab and surgery for both primary and locally recurrent LARC, respectively. Patients with T3–4 Nany M0 primary LARC or locally recurrent LARC treated with 50.4Gy of RT plus 1,650 mg/m2 of capecitabine were enrolled. The primary endpoint is the pCR rate of primary non-MSI-H LARC by independent central assessment. Disease-free and overall survival, and treatment-related adverse events, are evaluated as secondary endpoints. Totally 52 patients including 5 primary MSI-H (high-level microsatellite instability), 37 primary non-MSI-H, and 10 locally recurrent LARC will be enrolled.

Results: Three patients primary LARC were enrolled in phase Ib part. All 3 patients received the full, planned administration of nivolumab without dose modification, as well as radical surgery. During nivolumab treatment, only a single grade 1 pruritus event was observed. During surgery, one grade 2 gastritis, one grade 1 nausea, one grade 1 pain and one grade 1 extrapyramidal disorder were observed, none of which was related to the surgery. No dose limiting toxicities (DLTs) were observed in phase Ib part. Preliminary efficacy assessment of phase Ib/II by local pathologists demonstrated 4 pCR of the 7 patients with primary LARC, including 2 of 3 in phase Ib and 2 of 4 in phase II part, respectively. As of February 2018, 13 patients who received the RP2D were enrolled in the phase II part.

Conclusion: Nivolumab monotherapy and subsequent radical surgery following preoperative CRT were safely performed in patients with LARC. According to the preliminary efficacy assessment, promising pCR rate was observed.

P – 229 Long-term clinical outcomes in large colorectal polyps with indefinite or positive resection margin after endoscopic resection

D Kang[1], H Kim[1], C Choi[1], S Park[1], S Kim[1], H Nam[1], D Ryu[1], J Ko[1], H Kim[1], B Kwon[1], K Lee[2], J Lee[2], J Lee[2]

[1]Pusan National University Yangsan Hospital, Yangsan, Republic of Korea, [2]Pusan National University Yangsan Hospital, Yangsan-si, Republic of Korea

Introduction: Large colorectal polyps are often incompletely resected during colonoscopy, and incomplete resection might contribute to the recurrence after endoscopic resection. In indefinite or positive resection margin in pathology after complete endoscopic resection, local recurrence was not well known. We evaluated the long-term clinical outcomes in large, sessile or flat colorectal polyps with indefinite or positive resection margin after complete endoscopic resection.

Methods: Patients with large size ($\geq$10 mm), sessile or flat shape, indefinite or positive resection margin in pathologic report, and more than 24 months of follow-up intervals were enrolled. Associations between local recurrence and polyp location, size, resection methods, piecemeal resection, complications, and histology were retrospectively analyzed.

Results: Of 125 neoplastic polyps (105 patients; 70.5% males; mean age, 53.9 years) were resected, 82 (65.6%) were indefinite and 43 (34.4%) were positive in resection margin, respectively. During follow-up periods (24~86 months, mean 42.7), recurrence occurred in 2.4% (3/125). Mean time to recurrence was 41.7 months. All recurrent lesions were low-grade adenomas and successfully treated endoscopically. In univariate analysis and multivariate analysis, $\geq$30 mm size (OR 67.87, $p = 0.006$; OR 24.37; $p = <0.001$), $\geq$3 pieces of resection (OR 83.63, $p = 0.004$; OR 28.95, $p = <0.001$), and perforation (OR 147.0, $p = 0.004$; OR 41.13, $p = <0.001$) were significantly related with recurrence, respectively.

Conclusion: Following resection with indefinite or positive resection margin after complete endoscopic resection in large colorectal polyp, recurrence rate was lower than expected. Short-term follow-up colonoscopy in these conditions may be not required.

P – 230 Second line FOLFOX4 and bevacizumab for metastatic colorectal cancer: Real life efficacy and predictive factors

T Lewandowski, R Biernacka, M Chmielowiec, M Gryziak

Maria Skłodowska-Curie Cancer Centre Institute Warsaw, Warsaw, Poland

Introduction: Bevacizumab with chemotherapy is one of valid options in second line treatment for patients with mCRC. According to clinical trials it improves overall survival (OS) and time to progression (TTP) for approximately 2 and 2.5 months compared to chemotherapy alone. However, it is still uncertain what predictive and prognostic factors are useful to select patient who may benefit from that therapy.

Methods: We analysed 82 unselected patients treated between 2012-2015 in single-institution with FOLFOX4 regimen and bevacizumab after first-line treatment with FOLFIRI. All of them presented ECOG 0-1. None of them was previously treated with bevacizumab, oxaliplatin or anti-EGFR. The RECIST 1.1 criteria were used to evaluate treatment response. Following factors were investigated to have impact on response

rate (ORR), TTP, and OS: RAS (KRAS/NRAS) mutational status, primary tumour location and metastases site, efficacy of first-line treatment, sex, age, body mass index, lactate dehydrogenase (LDH), alkaline phosphatase, CEA, lymphocytes and haemoglobin level at the time of beginning second line treatment. Median follow-up was 35 months.

Results: In whole group median TTP was 5.1 months and OS – 12.9. Response rates: CR -1%, PR – 18%, NC – 40%, PD – 40%. For patients who achieved ORR (CR or PR) median TTP and OS was 7.8 and 19.3 months while for patients with PD – 2.8 and 9.9. Hepatic location of metastases was associated with the highest rate of ORR, while peritoneal with the lowest: 46% and 0% ($p = 0.041$) respectively. Median TTP for patients who gained CR, PR or NC (DCR - disease control) while first-line treatment was 6.7 compared with 3.3 months for patients with PD ($p < 0,0001$). TTP under/equal 6 months and PD during first-line treatment were associated with shorter OS: 12.9 vs 15.3 months ($p = 0.049$) and 9.9 vs 14.2 months ($p = 0.007$). Age over 70 and BMI $\geq$25 were good prognostic factors with OS 19.6 months vs 10.4 ($p = 0.01$) and 18.4 months vs 9.1 ($p = 0.039$) respectively. There was no difference between patients in terms of KRAS and NRAS mutational status. For wild type and mutant tumours it was 6.6 months vs 6.1 ($p = 0.098$) and 17.9 vs 12.9 ($p = 0.183$) respectively in TTP and OS. Right-side primary tumours were associated with worse DCR, TTP and OS compared to left-side primary; 45%, 2.3 months and 11.2 months vs 61%, 4.9 months and 12.8 months, but the differences were not statistically significant. Other factors did not occur relevant. Sixteen patients (20%) discontinued treatment due to adverse events. There were no toxic deaths.

Conclusion: Positive prognostic impact on second-line treatment with bevacizumab and FOLFOX4 in mCRC have: first-line treatment response, hepatic site of metastases, age over 70 and BMI $\geq$25. Worse prognosis was observed in group of patients with peritoneal metastases and poor response for first-line chemotherapy. RAS mutational status seemed to not influence prognosis in the analysed cohort. Location of the primary tumour in the right side of the colon was not proven to be a negative prognostic factor.

P – 231 Clinical significance of microsatellite instability in gender-dependent patients with right-sided colorectal cancer

J Choi[1], J Kim[2], S Han[1], M Park[1], S Park[3]

[1]Kosin University, College of Medicine, Busan, Republic of Korea, [2]Kosin University College of Medicine, Busan, Republic of Korea, [3]Kosin University, Busan, South Korea

Introduction: Colorectal cancer (CRC) with microsatellite instability (MSI) are known to have better prognosis compared to those with microsatellite stable (MSS). Recent studies reported that there are biological differences according to tumor location in CRC. In this study, we aimed to identify the clinical significance of MSI in patients with right-sided CRC.

Methods: Between October 2004 and December 2016, medical records from a total of 1,009 patients with CRC were retrospectively reviewed. Patients with MSI testing were included in the analysis. We assessed the long-term outcomes of MSI according to the tumor location using the Kaplan-Meier curves and Cox regression models.

Results: The median follow-up duration was 25 months (interquartile range, 15 - 38). The patients with MSI were 124 (12.3%) and those with right-sided CRC were 250 (24.8%). The patients with MSI who have right-sided CRC showed better disease free survival (DFS) than those with MSS in Log-rank test (p=0.013). And these results were prominent in female (p=0.035), but not in male who have right-sided CRC. In multivariate Cox regression analysis, MSS was significant risk factor predicting poor DFS in patients with right-sided CRC (HR 3.21, 95% CI 1.13 - 9.14, p=0.029), and these results were found only in female patients (HR 4.83, 95% CI 1.06 - 21.95, p=0.042).

Conclusion: In this study, we identified that MSI is a useful factor to predict DFS in patients with right-sided CRC, especially in female patients.

P – 232 Efficacy of adjuvant chemotherapy for elderly patients with colon cancer

M Villamayor Delgado[1], C Saavedra Serrano[2], E Corral de la Fuente[2], A Barquín García[2], O Martínez Saez[1], R Martín Huertas[2], J Serrano Domingo[3], J Molina Cerrillo[4], F Longo Muñoz[5], V Pachón Olmos[4], M Rodriguez Garrote[4], P Reguera Puertas[4], M Vaz[5], A Carrato[6], R Ferreiro Monteagudo[4]

[1]Ramón y Cajal Univsersity Hospital, Madrid, Spain, [2]Ramón y Cajal Hospital, Madrid, Spain, [3,4]Ramón y Cajal University Hospital, Madrid, Spain, [5]Hospital Universitario Ramón y Cajal, Madrid, Spain, [6]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain

Introduction: The benefit of adjuvant chemotherapy (fluoracil or capecitabine with or without oxaliplatin) has been well established in the adjuvant setting for node-positive colon cancer (stage III). The extent to which older adults benefit from adjuvant chemotherapy was not well established in the different trials (MOSAIC, NSABP C-07, N016968) given that there was no participation of patients older than 75 years old. However, in the latest published systematic reviews there are contradictory results on the efficacy of adjuvant chemotherapy in this population.

Methods: We retrospectively included patients with stages II and III colon cancer that underwent surgical treatment between 2009 and 2014 at the University Hospital Ramón y Cajal (Madrid). We calculated DFS and OS at 48 months and we performed a univariate and multivariate Cox model analysis to estimate the benefit of chemotherapy for different age groups (cut-off point 70 years) and stage at diagnosis. The model was further adjusted by including the following confounding factors: ECOG-PS, grade, number of resected nodes, CEA before surgery, colon side location, stage and presence of obstruction/perforation. A covariate was considered a confounding factor if the difference between the adjusted and unadjusted chemotherapy coefficient varied> 10%. Stata 13.1 was used to analyse the data.

Results: 551 patients were identified (166 patients <70 years old and 385 patients $\geq$ 70 years old). 281 were stage II (51%) of which 220 were older than 70 years old and 270 were stage III (49%) of which 165 were older than 70 years old. In addition, 220 had ECOG-PS: 0 but 331 had ECOG-PS greater than 0 (43%, 1). 248 received chemotherapy and 303 did not. The median follow-up in the entire cohort was 49 months. The median DFS and OS were not reached at the moment of the analysis. DFS and OS at 48 months were both 78.5%. Globally, chemotherapy did not improve DFS (HR 0, 72, p 0, 43) but OS was significantly better (HR 0, 36, p 0,005). By stage, chemotherapy did not improve DFS in stage II (HR: 0, 67, p: 0.2) nor OS (HR 0.4, p: 0.085). In stage III, chemotherapy showed a trend to improve DFS (HR de 0, 23, p 0, 58) and did clearly improve OS (HR 0,071, p 0,002). Nevertheless, the univariate analysis of the global population shows benefit in both DFS (HR 0,657 p 0,031) and OS (HR 0,257 (IC: 0,149 – 0,445) p 0,002) probably affected by confounding factors (ECOG-PS, presence of obstruction/perforation and number resected nodes).

Conclusion: The multivariable analysis showed benefit of chemotherapy in patients older than 70 years old with stage III colon cancer, with a 77% reduction in the risk of recurrence and a 29% in the risk of death. However, in stage II patients these benefits were not found either in PFS or OS. More prospective studies in this population group are needed to confirm these findings.

P – 233 Trifluridine/tipiracil vs regorafenib as salvage-line treatment in patients with metastatic colorectal cancer: A multicenter retrospective study

M Kotaka[1], M Ogata[2], T Ogata[2], Y Hatachi[3], H Yasui[4], T Kato[5], A Tsuji[6], H Satake[7]

[1]Department of Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan, [2]Kobe City Medical Center General Hospital, Kobe, Japan, [3]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [4]Department of Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [5]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [6]Department of Medical Oncology, Kagawa University Hospital, Kida-gun, Japan, [7]Department of Medical Oncology, Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan

Introduction: Trifluridine/tipiracil (TAS-102) and Regorafenib (REG) have shown promising activity in patients with heavily pretreated metastatic colorectal cancer (mCRC). The aim of this study was to compare the efficacy and safety of TAS-102 and REG alone in patients with mCRC refractory to standard chemotherapies.

Methods: From May 2014 to December 2017, 135 patients with mCRC were treated with TAS-102 or REG as salvage-line therapy. Efficacy, safety and clinical outcomes were retrospectively evaluated. Inclusion criteria were histologically confirmed colorectal adenocarcinoma; refractory or intolerant to fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy and anti-EGFR antibody (for tumours with wild-type RAS); measurable or evaluable lesion; age $\geq$ 20 years; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2; and written informed consent. The clinical outcomes were evaluated using the Cox's proportional hazard models.

Results: Among 135 patients, 77 received TAS-102 (median age 77 y, male 49%, ECOG PS 0 62%, RAS wt 43%) and the other 58 received REG (median age 66 y, male 53%, ECOG PS0 64%, RAS wt 51%). With a median follow-up of 5.8 months (range, 1.5 to 19.0), median progression-free survival was statistically longer in the TAS-102 group than in the REG group (TAS-102 2.9 vs REG 2.0 months; $HR = 0.591$, $p = 0.0035$). No significant difference in overall survival between TAS-102 and REG (TAS-102 10.4 vs REG 9.2 months; $HR = 1.14$, $p = 0.57$) was observed.

Conclusion: TAS-102 and REG showed equivalent survival benefit in the treatment of mCRC which had progressed after standard therapies.

P – 234 Phase 1b open-label study evaluating the safety, pharmacokinetics, and preliminary efficacy of ABT-165 plus FOLFIRI in patients with second-line (2L) colorectal cancer (CRC)

Z Wainberg[1], J Strickler[2], M Gordon[3], M Barve[4], L Wang[5], H Yue[5], M Motwani[6], S Kasichayanula[7], L Naumovski[5], E Hamilton[8]

[1]Ronald Reagan UCLA Medical Center, Los Angeles, California, USA, [2]Duke University Medical Center, Durham, North Carolina, USA, [3]Pinnacle Oncology Hematology/HonorHealth Research Institute, Scottsdale, Arizona, USA, [4]Mary Crowley Medical Research Centers, Dallas, Texas, USA, [5]Oncology Early Development, AbbVie Inc., Redwood City, California, USA, [6]Oncology Early Development, AbbVie Inc., North Chicago, Illinois, USA, [7]Clinical Pharmacology and Pharmacometrics, AbbVie Inc., Redwood City, California, USA, [8]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee, USA

Introduction: ABT-165 is a first-in-class dual-variable domain immunoglobulin with specificity for both vascular endothelial growth factor and delta-like ligand 4 (DLL4) that has demonstrated encouraging preliminary clinical antitumor activity as monotherapy. As part of a phase 1 trial, we evaluated an expansion cohort of ABT-165 plus FOLFIRI in patients with 2L CRC previously treated with a fluoropyrimidine/oxaliplatin regimen with or without bevacizumab.

Methods: Patients with 2L CRC (≥18 years; Eastern Cooperative Oncology Group performance status 0–2) eligible to receive FOLFIRI were included (NCT01946074). Patients received ABT-165 (2.5 mg/kg) plus FOLFIRI (irinotecan: 180 mg/m 2; leucovorin: dl-400 (or l-200) mg/m 2; fluorouracil bolus: 400 mg/m 2, infusion: 2400 mg/m 2) intravenously on days 1 and 15 in 28-day cycles until disease progression or intolerable toxicity. Assessments (tumor and cardiac imaging) were performed every 2 cycles. Primary objectives were to evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of the ABT-165 plus FOLFIRI combination therapy.

Results: As of 05 Jan 2018, 16 patients with 2L CRC (KRAS mutation status: 4 wildtype, 9 mutated, 3 unknown) have been enrolled (median age [range]: 64 years [42–81]). Pharmacokinetic data illustrated that the overall exposure, as demonstrated by maximum plasma concentration and area under the curve of ABT-165, were not altered by FOLFIRI administration. All patients with 2L CRC experienced a treatment-related adverse event (TRAE). The most common TRAEs (≥50%) were fatigue (81%), diarrhea, nausea (each 63%), anemia (56%), dehydration, and neutropenia (each 50%). Pulmonary hypertension (19%) and gastrointestinal perforation (6%) were also noted. Anemia, neutropenia, and hypertension (each 25%) were the most common grade ≥3 TRAEs. Three of 16 2L CRC patients (19%) had a partial response, 1 of whom was on treatment for 10 cycles with progression-free survival of 8.2 months. Median time on treatment was 16.0 weeks (range: 0.1–40.1). Treatment is ongoing in 2 patients. Evaluation of DLL4 expression, angiogenesis signatures, and molecular profile in archival tissue is in progress, and correlations with outcomes will be presented.

Conclusion: Combination therapy with ABT-165 2.5 mg/kg and FOLFIRI was well tolerated and demonstrated encouraging preliminary clinical efficacy in patients with 2L CRC. Further clinical studies are ongoing in this patient population with significant unmet need (NCT03368859).

P – 235 Adjuvant chemotherapy for colorectal cancer using oxaliplatin induced irreversible sinusoidal obstruction syndrome

K Hara, T Yamada, M Koizumi, S Shinji, Y Yokoyama, G Takahashi, M Hotta, T Iwai, K Takeda, H Yoshida

Nippon Medical School Department of Digestive Surgery, Bunkyo-ku, Japan

Introduction: Oxaliplatin reduces the recurrence rate after curative surgery in high risk stage II and stage III colorectal cancer. However, it can cause hepatic sinusoidal obstruction syndrome (SOS). SOS can cause an adverse effect associated with chemotherapy or morbidity after liver resection at the time of recurrence. Conventionally, SOS is diagnosed using liver biopsy which is invasive. We have reported that the 10% increase in splenic volume (SV) indicate SOS (Journal of Surgical Oncology 2017). In this retrospective study, we evaluated SOS caused by adjuvant chemotherapy by measuring SV.

Methods: High-risk stage II and stage III patients with colorectal cancer who received complete resection at our hospital between January 2011 and December 2016 were retrospectively analyzed in the current study. All patients received mFOLFOX6, CapeOX or UFT/UZEL as adjuvant chemotherapy. We excluded patients with recurrence within 1-year after finishing adjuvant chemotherapy, and patients whose age were over 80. Patients treated with oxaliplatin (mFOLFOX6 or CapeOX) belong to group 1 and patients treated with UFT/LV belong to group 2. We measured SV three times; before surgical treatment, after finishing adjuvant chemotherapy, and 1-year after finishing adjuvant chemotherapy. SV was calculated by using a volume calculator SYNAPSE VINCENT v3.0® (Fujifilm, Japan) base on Computed tomography images taken in 5-mm slices. We defined that the cut off volume increasing is 10%.

Results: This study included 148 patients (High risk stage II: n = 25, stage III: n = 123). All patients received adjuvant chemotherapy after curative surgery. Group 1 included 53 patients (FOLFOX: n = 42, CapeOX: n = 11), and group 2 included 95 patients (UFT/LV: n = 95). 83% of the patients in group 1 and 92% of the patients in group 2 completed chemotherapy. In group 1, SV after chemotherapy was significantly higher than that before surgery ($P < 0.001$), and SV 1-year after finishing chemotherapy returned to the same level with before surgery. In 84% of the patients, SV increased after chemotherapy and did not recover in 47% 1-year after finishing chemotherapy. Conversely, there was no significant difference in SV between before and after or 1 year after chemotherapy in group 2. In 13% of the patients, SV increased after chemotherapy and did not recover in 12% 1-year after finishing chemotherapy. No patients treated with FOLFOX less than 8 course experienced SV increasing.

Conclusion: In 80% of patients treated with oxaliplatin, SV increased after adjuvant chemotherapy. SV did not recover in half of these patients within 1 year after finishing chemotherapy.

P – 236 Clinical and pathological features in colorectal cancer associated to Lynch syndrome

O Higuera[1], A Rodriguez[2], N Rodriguez-Salas[3], L Ruiz-Giménez[4], A Gallego[4], I Ghanem[4], A Custodio[4], D Sanchez[5], L Ostios[5], J Miranda Poma[6], J Feliu[4]

[1]University Hospital La Paz, Madrid, Spain, [2]Universidad Autónoma de Madrid, Madrid, Spain, [3]University Hospital La Paz, Madrid, Spain, [4]University Hospital La Paz, Madrid, Spain, [5]Universitary Hospital La Paz, Madrid, Spain, [6]Hospital Universitario La Paz, Madrid, Spain

Introduction: Lynch syndrome (LS) is the most common cause of inherited colorectal cancer (CRC) and accounts for approximately 3 percent of newly diagnosed cases of CRC. Lynch syndrome is an autosomal dominant disorder that is caused by a germline mutation in one of several DNA mismatch repair genes (MLH1, MSH2, MSH6 and PMS2) or loss of expression of MSH2 due to deletion in the EPCAM gene (previously called TACSTD1). It is characterized by an increased risk for colorectal cancer (CRC) and cancers of the endometrium, stomach, ovary, small bowel, hepatobiliary tract, urinary tract, brain, and skin. CRCs in Lynch syndrome differ from sporadic CRCs.

Methods: We performed a descriptive, retrospective study of individuals and families referred to the multidisciplinary heredofamilial cancer unit (HFCU) of the Hospital Universitario La Paz between September 2008 and December 2017. We collected data on patient histories, tumor phenotypes, and results of germline DNA sequencing of patients registered in our database. The objective of the study is to describe the germline mutations in the MMR genes and to analyze the clinical and histological features of the CCRs associated with lynch syndrome. Data were analyzed using the statistical package for the social sciences 22.0 (SPSS Inc., Chicago, IL, USA).

Results: We identified 75 patients from 65 different families attended by our HFCU with germline mutation in the MMR genes. 27 subjects had mutations in MSH2, being the most prevalent variant; 26 in MSH6, 20 in MLH1 and 1 in PMS2. In addition, one individual had an EPCAM deletion. Among individuals with MSH2 mutations, 3 had Muir-Torre syndrome (a variant of Lynch syndrome). 48 patients (65.7%) were referred from oncology, 20 (26.6%) from gastroenterology, 3 (4.0%) from gynecology and 4 from patient's own request. 44% of patients have a personal history of cancer, being CRC in the 82% of cases. The median age at diagnosis of colorectal cancer was 42.3 years. At diagnosis, 4 patients had synchronous CCR whereas 6 patients who had undergone segmental resection for the first CCR developed a metachronous CRC. Regarding to the location, 47% of them arises in the right side. Concerning to the pathological features, 26% of subjects had ganglionar involvement; 31% had a brisk lymphocytic infiltrate with an intense lymphoid reaction and 36% were mucinous and poorly differentiated. At the time of the analysis, only three patients developed metastases. The 47% of patients had a personal history of malignancy related to LS, being the endometrial cancer the most frequent. In six of these with a double primary endometrial and colorectal cancer, the uterine one was diagnosed first.

Conclusion: Lynch syndrome is the most common cause of inherited colorectal cancer. Germline mutation in MSH2 was the most prevalent detected in our database. Less than a half of patients had a personal history of cancer being the CRC the most frequent malignancy and it has distinct histologic features.

P – 237 Development of a new clinical nomogram including velocity rate of disease progression to predict outcome in metastatic colorectal cancer patients treated with bevacizumab beyond progression: A subanalysis from tribe trial

E Dell'Aquila[1], F Pantano[1], D Rossini[2], M Stellato[3], S Lonardi[4], G Masi[2], M Schirripa[4], F Marmorino[2], C Antoniotti[2], S Murgioni[4], G Tomasello[5], M Ronzoni[6], P Racca[7], B Vincenzi[1], G Allegrini[8], F Urbano[9], A Buonadonna[10], M Banzi[11], G Tonini[1], C Cremolini[2], A Falcone[12], D Santini[1]

[1]Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy, [2]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [3]Department of Medical Oncology, Campus Biomedico University of Rome, Rome, Italy, [4]Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [5]Department of Medical Oncology, Azienda Istituti Ospitalieri di Cremona, Cremona, Italy, [6]Department of Oncology, Istituto Scientifico San Raffaele, Milan, Italy, [7]Medical Oncology Department, University San Giovanni Battista Istituto di Totino- Molinette, Turin, Italy, [8]Department of Medical Oncology, Ospedale F. Lotti, Pontedera, Italy, [9]Department of Radiological, Oncological and Anatomopathological Sciences, Sapienza University of Rome, Rome, Italy, [10]Department of Medical Oncology, Centro di Riferimento Oncologico, Aviano, Italy, [11]Department of Medical Oncology, Nuova Azienda Ospedaliera, Reggio Emilia, Italy, [12]University of Pisa, Pisa, Italy

Introduction: In metastatic colorectal cancer (mCRC) there is the unmeet clinical need to predict outcome to second line therapy. Our aim was to test if a new nomogram including the velocity rate of disease progression (VRPD), a new dynamic marker, can predict outcome in terms of second line progression free survival (PFS) in mCRC patients (pts) enrolled in TRIBE trial.

Methods: Continuous variables are presented as mean and median and 95% CI of the mean and median respectively and dichotomous parameters as frequencies and percentages. The normal distribution of continuous variables was explored with the Shapiro-Wilk normality test. The prognostic value in term of second line Progression Free Survival was explored using Cox Regression in continuous variables and Log-Rank Test in dichotomous variables. Variables demonstrated to be statistically significant at univariate analysis were evaluated in multivariate fashion using Cox proportional hazard regression model. Variables demonstrated to be statistically significant at univariate analysis were also selected to be included in nomogram construction. To avoid loss of statistical power, missing data in baseline characteristics were handled using a multiple imputation technique based on Predictive Mean Matching Algorithm. We applied a Penalized Cox Regression Model based on least absolute shrinkage and selection operator (lasso) penalized estimation method with the penalty parameter selected by 10-fold cross-validation with λ selection rule set at minimal. The model with minimum cross-validated error included 8 variables: primary cancer located in Right Colon; PS at baseline; presence of metastasesother than liver, lung, peritoneum, bone or CNS at baseline; LDH levels at the time of first disease progression; VRPD; BRAF Mutation; Alkaline Phosphatase at baseline; WBC count at baseline. The nomogram was evaluated in terms of discrimination and calibration. Discrimination was assessed with the area under the curve (AUC) at receiver operating characteristics analysis (with values ranging from 0.5 for no discrimination to 1.0 for perfect discrimination). To assess potential changes with time of the model discrimination performance, time-dependent AUC values were analyzed every 3 months from the month 3 to month 12 of follow-up using inverse-probability- of-censoring weights method. Calibration was investigated by plotting the predicted and observed probabilities of events at 9 months. All discrimination and calibration measures were internally validated using Repeated Cross Validation (Repeated cross-validation fold number:10; Repeated Times: 20). All analyses were conducted with R statistical software (version 3.3.2) equipped with the "glmnet," "hdnom," and "mice" packages. Alltests were 2-tailed and a p value <0.05 was considered statistically significant.

Results: The nomogram included 8 variables: right colon; baseline Performance Status (PS); presence of metastases other than liver, lung, peritoneum, bone or CNS at baseline; LDH levels at first disease progression; VRPD; BRAF status; baseline Alkaline Phosphatase; baseline WBC count. The nomogram was internally validated using Repeated Cross Validation showing a good performance in terms of discrimination and calibration.

Conclusion: This nomogram, including VRPD and other consolidated parameters, can be used to predict second line PFS in mCRC pts. Further studies are needed to test VRPD in a larger validation set.

P – 238 Analysis of classical high risk factors in stage III colon cancer: Experience at University Hospital Ramon y Cajal (UHRyC)

J Serrano Domingo[1], R Martín Huertas[2], A Barquín García[2], E Corral de la Fuente[2], C Saavedra Serrano[2], M Villamayor Delgado[3], O Martínez Saez[3], F Longo Muñoz[4], V Pachón Olmos[5], M Rodriguez Garrote[5], M Vaz[4], P Reguera Puertas[5], R Fuentes[2], A Carrato[6], R Ferreiro Monteagudo[5]

[1,2]Ramón y Cajal Hospital, Madrid, Spain, [3]Ramón y Cajal Univsersity Hospital, Madrid, Spain, [4]Hospital Universitario Ramón y Cajal, Madrid, Spain, [5]Ramón y Cajal University Hospital, Madrid, Spain, [6]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain

Introduction: In colon cancer (CC), surgery is a curative treatment but, because of recurrence risk factors, postoperative adjuvant chemotherapy (AC) is widely accepted, at least for stage III. However, the benefit in stage II remains uncertain and indication of AC is based on risk factors. Nevertheless, the role of these high-risk factors (HRF) in stage III it is not clear.

Methods: We conducted an observational unicentric retrospective study. Patients with stage III resected CC between 2009 and 2014 were identified, and data was collected for predefined variables including patients and tumor characteristics, treatment procedures and oncological outcomes. Univariate analyses were performed for classic stage II HRF in patients with stage III CC, and those with a $p < 0.05$ were incorporated in a multivariant model. We analyzed the relapse free survival (RFS) and overall survival (OS) rates according to the presence of at least one classic HRF. Finally, we studied the benefit of AC on patients depending on the presence or absence of risk factors. Cox regression was employed for the analysis. Stata 13.1 was used for the statistical analysis.

Results: 268 patients with stage III CC were identified. 53.16% were men. Median age was 77 years (range 28-97). Most patients received AC (65.43%) most of them with oxaliplatin (78.86%). 71.38% had at least one HRF. In univariate analysis for RFS the perineural infiltration and the KRAS mutation (KRASm) were significant (hazard ratio (HR) 1.88 and 2.1 respectively). We incorporated them in a prognostic multivariate model were KRASm was identified as an independent risk factor for stage III (HR 3.17). On the other hand for OS, no HRF were significant. For RFS, patients with at least one HRF receiving AC had benefit (HR 0.43, $p < 0.001$), whereas there was no benefit in those without HRF (HR 0.7, 95% CI 0.26-1.86, p 0.48). For OS, both patients with at least one HRF and those without any of them, obtained benefit with AC (HR 0.16, $p < 0.001$ and HR 0.21, p 0.008). Oxaliplatin based chemotherapy showed benefit in terms of RFS in those patients with at least one risk factor (HR 0.38 p 0.006) whereas no benefit was obtained in those without any HRF (HR 1.69, 95% CI: 0.37-7.73, p 0.497). For OS, the addition of oxaliplatin to fluoropyrimidines had benefit in patients with any HRF (HR 0.25, p 0.02), and there is a trend to improve OS in those with none of the HRF (HR 0.12, p 0.085).

Conclusion: Patients with at least one HRF, benefit from AC in terms of RFS and OS, especially those receiving oxaliplatin based treatment. In those without HRF, the role of AC is not clear in reducing the risk of relapse even with the addition of oxaliplatin. In these patients, there is benefit in terms of OS with AC, but oxaliplatin does not seem to be a determinant.

P – 239 Impact of adding oxaliplatin to fluoropyrimidines in the adjuvant therapy in stage II in colon cancer: Experience in Ramon y Cajal Universitary Hospital

R Martín Huertas, J Serrano Domingo, E Corral de la Fuente, A Barquín García, M Villamayor Delgado, C Saavedra Serrano, O Martínez Saez, F Longo Muñoz, V Pachón Olmos, M Rodriguez Garrote, M Vaz, A Carrato, P Reguera Puertas, R Fuentes, R Ferreiro Monteagudo

Ramón y Cajal Univsersity Hospital, Madrid, Spain

Introduction: The addition of oxaliplatin to fluorouracil and leucovorin as adjuvant chemotherapy (AC) for patients with stage II and III colon cancer (CC) has been analyzed in two large, randomized trials, MOSAIC and C-07 trials. The updated results of these studies showed that the addition of oxaliplatin enhances overall survival by approximately 5% in patients with stage III disease but has no effect in patients with stage II disease.

Methods: We retrospectively included patients with stage II CC that were operated between 2009 and 2014 in the Ramon y Cajal University Hospital. We perform a multivariable Cox model analysis to estimate the benefit of the chemotherapy stratifying by oxaliplatin. We have analyzed whether receiving AC improves the relapse free survival (RFS) and overall survival (OS) and has been stratified according to the presence of at least one classic high risk factor (HRF). Additionally, it has been evaluated whether the addition of oxaliplatin improves the results.

Results: 246 were identified. 151 were men (61%). 117 patients had at least one HRF (47%), 52 received AC (44%) of which 33 with oxaliplatin (63%). Patients without any HRF, 27 received AC (21%) of which 19 with oxaliplatin (70%). The median follow-up was 58.2 months. Globally, adjuvant chemotherapy (either with some HRF or without any) showed no benefit in RFS (Hazard ratio (HR) of 1.48 and 1.36, respectively). The benefit in OS was significant for patients with at least one HRF (HR 0.33, p: 0.007) but not in those patients without any HRF (HR 0.52, p: 0.54). Patients with stage II treated with oxaliplatin and fluoropyrimidines showed no benefit in terms of RFS neither with any HRF (HR 0.58, p: 0.33) nor without any (HR 1.11, p 0.936). In terms of OS, there is only benefit in those patients with some HRF (HR 0.16, p: 0.03).

Conclusion: The AC in patients with stage II show benefit in OS in those patients with at least one HRF, especially with the addition of oxaliplatin. In those patients without any HRF, there is no benefit with AC, even with addition of oxaliplatin.

P – 240 Benefit of the addition of oxaliplatin to 5-FU/leucovorin or capecitabine in adjuvant therapy for stage II/III colorectal cancer in elderly patients: Experience in Ramon y Cajal University Hospital.

E Corral de la Fuente[1], C Saavedra Serrano[1], M Villamayor Delgado[2], A Barquín García[1], R Martín Huertas[1], J Serrano Domingo[3], O Martínez Saez[2], V Pachón Olmos[4], M Rodriguez Garrote[4], F Longo Muñoz[5], P Reguera Puertas[4], C Guillén-Ponce[6], A Carrato[7], R Ferreiro Monteagudo[4]

[1]Ramón y Cajal Hospital, Madrid, Spain, [2]Ramón y Cajal Univsersity Hospital, Madrid, Spain, [3,4]Ramón y Cajal University Hospital, Madrid, Spain, [5]Hospital Universitario Ramón y Cajal, Madrid, Spain, [6]H. Universitario Ramón y Cajal, IRYCIS, Madrid, Spain, [7]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain

Introduction: Oxaliplatin-based combination chemotherapy is considered standard of care for patients with stage III colorectal cancer disease. However, the benefit of the addition of oxaliplatin to adjuvant chemotherapy in elderly patients (aged 70 years or older) is not well established, because elderly patients are underrepresented in clinical trials. A post hoc analysis of outcomes in the MOSAIC trial, reported in Journal of Clinical Oncology by Tournigand et al. as well as, a recent report from the ACCENT database, suggested that there was no benefit in overall or disease-free survival with the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years or older, compared to the use of single agent fluoropyrimidines.

Methods: We retrospectively included patients with stage II and III colorectal cancer that underwent surgical treatment between 2009 and 2014 in the Ramon y Cajal University Hospital. We performed a multivariate Cox model analysis to estimate the benefit of chemotherapy stratifying patients older than 70 years old by chemotherapy regimen received (with or without oxaliplatin). The model was further adjusted by including the following confounders: ECOG-PS, number of removed nodes, perforation, obstruction, grade, localization and age. A covariate was considered a confounder factor if the difference between the adjusted and unadjusted coefficient of chemotherapy varied>10%. Stata 13.1 was used to analyze the data.

Results: 551 patients were identified (a total of 385 were aged 70 or older and 166 were younger than 70 years). Overall, 259 received chemotherapy and 292 did not. 281 were stage II (51%) of which 220 were aged 70 or older and 270 were stage III (49%) of which 165, were aged 70 or older. Among the younger patients, 11 received single agent fluoropyrimidines (5-FU/leucovorin or capecitabine) and 115 oxaliplatin-based combination chemotherapy. Among the patients aged 70 years or older, 53 received single agent fluoropyrimidines and 78 the combination with oxaliplatin. The median follow-up in the entire cohort was 49 months. For elderly patients, oxaliplatin based chemotherapy did improve OS (hazard ratio (HR) 0.277, p = 0.001, 95% CI, 0.12 to 0.59) and disease-free survival (DFS) (HR 0.14, p = 0.013, 95% CI, 0.02 to 0.66).

Conclusion: The results from this multivariate analysis show that for elderly patients, the addition of oxaliplatin in the adjuvant treatment of stage II/III in elderly patients could be beneficial in terms of disease-free survival and overall survival.

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P – 242 International prospective multi-center clinical trial with adherence to surgical and pathological quality measures: Influence of body mass index (BMI) on outcome in colon cancer

M Protic[1], A Bilchik[2], A Nissan[3], S Usaj Knezevic[4], B Kukic[4], M Kresoja[4], R Veljkovic[5], M Zivojinov[5], A Stojadinovic[6]

[1]University of Novi Sad-Faculty of Medicine and Oncology Institute of Vojvodina, Novi Sad, Serbia, [2]John Wayne Cancer Institute, Santa Monica, California, USA, [3]Chaim Sheba Medical Center, Tel Hashomer, Israel, [4]Universisity of Novi Sad - Faculty of Medicine and Oncology Institute of Vojvodina, Novi Sad, Serbia, [5]University of Novi Sad-Faculty of Medicine and Clinical Center of Vojvodina, Novi Sad, Serbia, [6]Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA

Introduction: Various prognostic factors significantly influence oncological outcomes across various stages of colon cancer (CC). The prognostic influence of BMI for CC remains incompletely defined. We hypothesized that BMI significantly influences outcomes in node-negative (NN) CC.

Methods: Patients with non-metastatic CC were prospectively enrolled in a trial with strict adherence to quality metrics (ClinicalTrials.gov: NCT00949312; UECC Trial), and stratified according to nodal status (NN and N+). Patients were stratified according to WHO BMI classification to assess the prognostic influence of BMI using univariate and multi-variate analyses.

Results: Of 456 patients 285 were NN and 171 N+. Number of NN patients by WHO BMI classification was: BMI<18.5: 2 (2.1%); BMI 18.6-24.9: 123 (43.2%); BMI 25-29.9: 102 (35.8%); and, BMI>30: 54 (18.9%); in N+ patients the distribution was: 2.9%, 35.7%, 46.2%, 15.2%, respectively. NN patients with normal BMI (18.5-24.9) had significantly more right sided (65.5%; p = 0.02) and fewer low grade tumors (26.1%; p = 0.015), more examined nodes (20.9; p = 0.003), lower recurrence rate (2.5%; p = 0.036) and higher DFS (96.1 mos.; p = 0.033). These factor and outcome differences were not seen in N+ patients. BMI and number of nodes were significantly associated with DFS in the NN group. In the multivariate model BMI and total number of nodes were independent predictors of DFS. Tumor size and number of positive nodes were associated with DFS in the N+ group, and # positive nodes were an independent predictor of DFS.

Conclusion: This is the first prospective trial to show BMI-associated differences in CC when surgical and pathological quality standards are strictly adhered to. Normal BMI is associated with improved DFS in node-negative CC. Normal BMI and number of resected nodes are independent predictors of DFS in Stage I/II CC. Further studies are needed to determine how and why BMI influences colon cancer biology.

P – 243 Phase II study of third-line panitumumab rechallenge in patients with metastatic wild-type KRAS colorectal cancer who achieved a clinical benefit in response to first-line panitumumab plus chemotherapy

A Tsuji[1], M Nakamura[2], T Watanabe[3], D Manaka[4], H Matsuoka[5], M Kataoka[6], M Takeuchi[7], W Ichikawa[8], M Fujii[9]

[1]Department of Medical Oncology, Kagawa University Hospital, Kida-gun, Japan, [2]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan, [3]Department of Surgery, Japanese Red Cross Society Himeji Hospital, Himeji, Japan, [4]Department of Surgery, Gastrointestinal Center, Kyoto Katsura Hospital, Nishikyo-ku, Japan, [5]Gastroenterological Surgery, Fujita Health University, Toyoake, Japan, [6]Department of Surgery, Nagoya Medical Center, Nagoya, Japan, [7]Department of Clinical Medicine (Biostatistics), Kitasato University School of Pharmacy, Minato-ku, Japan, [8]Division of Medical Oncology, Showa University Fujigaoka Hospital, Yokohama, Japan, [9]Department of Digestive Surgery, Nihon University School of Medicine, Itabashi-ku, Japan

Introduction: Cetuximab rechallenge has been reported to be promising (Santini D et al. Ann Oncol 2012 and Tsuji A et al. Annals of Oncology, Volume 27, Issue suppl_6, 2016, 510P,).On the other hand, usefulness of panitumumab for cetuximab is expected (WJOG6510G, ASCO-GI 2017). We performed a multicenter phase II prospective study panitumumab rechallenge in Japan.

Methods: The study cohort comprised patients with metastatic wild-type KRAS colorectal cancer who achieved a clinical benefit (confirmed stable disease for at least 6 months or clinical response) in response to first-line panitumumab plus chemotherapy, then had disease progression and received second-line chemotherapy, and finally had a clear new progression of disease. Patients received bi-weekly irinotecan (150 mg/m2) combined with panitumumab (8 mg/m2 bi-weekly). The primary endpoint was the 3-month progression-free rate. The required sample size was estimated to be at least 30 patients, assuming a 3-month progression-free rate of less than 15% as the null hypothesis versus a 3-month progression-free rate of higher than 35% as the alternative hypothesis, a power of 80%, and an alpha value of 0.05.

Results: A total of 25 patients were recruited. One patients were excluded: one did not receive the study treatment because of poor condition at the time scheduled for treatment. 22 of 25 patients received bevacizumab combined therapy before this trial. The 3-month progression-free rate of 54.2% (95% confidence interval: 34.2-74.1) met the primary endpoint, with a median progression-free survival time of 3.8months and an overall survival time of 8.9 months. The overall response rate and disease-control rate were 8.3% and 50.0%, respectively. The most frequent grade 3 to 4 adverse event was neutropenia (8.3%), and skin toxicities (all grade) occurred in 91.7% of all patients, as expected.

Conclusion: Third-line panitumumab rechallenge may be clinically beneficial treatment before regorafenib and TAS102, with manageable toxicity. Clinical trial identification: Trial protocol number: UMINUMIN000011440, UMIN release date: 2018/01/17.

P – 244 Dose finding phase Ib study of triplet plus cetuximab for patients with wild-type RAS gene metastatic colorectal cancer (TRICETSU study)

H Satake[1], T Kotake[2], Y Okita[2], Y Hatachi[2], H Yasui[3], M Kotaka[4], T Kato[5], A Tsuji[2]

[1]Department of Medical Oncology, Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan, [2]Department of Medical Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [3]Department of Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [4]Department of Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan, [5]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan

Introduction: The aim of this study was to determine the recommended dose of FOLFOXIRI plus cetuximab (Cmab) as first-line treatment for patients (pts) with RAS wild-type metastatic colorectal cancer.

Methods: The eligibility criteria included pts with unresectable colorectal adenocarcinoma, age 18 years or more, ECOG PS 0 or 1, wild-type or heterozygous UGT1A1 *28 or *6, no history of prior chemotherapy, and adequate organ function. Patients received the combination of Cmab (initiation dose of 400 mg/m2, followed by weekly infusion of 250 mg/m2 on day 1) with FOLFOXIRI (irinotecan (CPT-11), oxaliplatin (L-OHP) 85 mg/m2, and folinate (LV) 200 mg/m2 on day 1, followed by fluorouracil (5-FU) 3200 mg/m2 infused as a 46-hour continuous infusion starting on day 1) repeated every 2 weeks. Three dose levels of CPT-11 were planned as follows: Level 1: CPT-11 165 mg/m2, Level 0 as starting dose: CPT-11 125 mg/m2, and Level -1: CPT-11 95 mg/m2. The dose-limiting toxicity (DLT) was evaluated in the first cycle. This trial was registered with the University Hospital Medical Information Network (number UMIN000016009).

Results: From May 2014 to June 2017, we enrolled a total of 8 pts (4 pts in the Level 0 and 4 pts in the Level 1). The pts characteristics were as follows: median age, 50.4 (range, 38-64); male, 3; ECOG PS 0, 6; and all left sided primary. All were assessed for safety and seven were assessed for efficacy. No treatment related death was observed. The grade 3 or 4 toxicities were neutropenia (n = 2). Among 7 pts who had at least once tumor evaluation, three (43%) were converted to the surgical resection. With a median follow-up period of 33.1 months, the time to protocol treatment failure, the medina progression-free and median overall survival was 7.8 months, 8.0months and not reached, respectively.

Conclusion: The recommended phase II dose was determined to be standard dose of Cmab with FOLFOXIRI (CPT-11 165 mg/m2, L-OHP 85 mg/m2, and LV 200 mg/m2 on day 1, followed by 5-FU 3200 mg/m2 infused as a 46-hour continuous infusion).

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WITHDRAWN

P – 246 Rechallenge with oxaliplatin and peripheral neuropathy in colorectal cancer patients

M Martínez-Villacampa[1], S Besora Tavera[2], C Santos Vivas[3], C Izquierdo[4], J Bruna[5], R Velasco[6]

[1]Department of Medical Oncology, Institut Català d'Oncologia - IDIBELL, L'Hospitalet de Llobregat, Spain, [2]Bellvitge Hospital, Hospitalet, Spain, [3]Translational Research Laboratory and Department of Medical Oncology, Institut Català d'Oncologia-IDIBELL, L'Hospitalet de Llobregat, Spain, [4]Bellvitge Hospital, L'Hospitalet de Llobregat, Spain, [5]Bellvitge Hospital, Spain, [6]Bellvitge Hospital, Hospitalet de Llobregat, Spain

Introduction: Oxaliplatin (OXA) is a cornerstone in the treatment of colorectal cancer (CRC). Retreatment with OXA is frequently considered as salvage treatment. OXA-induced neuropathy (OIN) is the most frequent and feared long-term side-effect.

Methods: CRC patients receiving at least twice OXA-based chemotherapy lines at our institution between June 2000 and July 2016 were reviewed. The aim of this study was to investigate whether retreatment with OXA increases the risk of developing new or worsening previous neuropathy. OIN was assessed by National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI), Total Neuropathy Score©(TNS) and nerve conduction studies.

Results: 106 patients were included in the analysis. Median age at OXA-based retreatment was 61.5 [20-83] years. After the first OXA-based chemotherapy treatment, 60.3% of patients developed OIN, 29.2% and 8.4% grade 2 and grade 3, respectively after a median of 11 [1-17] cycles. After 30 [11-90] months of median to retreatment with a median of 8 [1-14] OXA cycles, 39.6%, 22.6% and 0% of patients developed grade 1, 2 and 3 OIN, respectively. Worsening of previous OIN was observed in one third (31.1%) of all patients. OXA cumulative dose was independently associated with greater risk of worsening OIN ($p < 0.001$). Non-significant trend towards higher TNSc© scores after retreatment were observed (5 [0-11] vs 6 [3-13], $p = 0.083$).

Conclusion: Retreatment with OXA in CRC patients is a feasible option even in patients who previously developed moderate or severe OIN. One third of patients experienced a worsening of their previous OIN. Neurological monitoring of patient candidates to retreatment with OXA should be considered.

P – 247 Adding oxaliplatin (OX) do neoadjuvant therapy of locally advanced rectal cancer (LARC): Still promising option?

W Rogowski[1], L Wyrwicz[2], V Sulzyc-Bielicka[3]

[1]The Cardiological-Oncological Hospital Magodent, Warsaw, Poland, [2]Centrum Onkologii-Instytut im. M. Sklodowskiej Curie, Warsaw, Poland, [3]Pomeranian Medical University, Szczecin, Poland

Introduction: Fluoropyrimidine (5-fluorouracil or capecitabine, FU)-based regimens and radiation are standard-of-care in neoadjuvant treatment of patients with LARC. Meta-analysis (2012) showed, that adding OX to FU significantly improved pathologic complete response (pCR), and reduced peri-operative metastases with significantly higher toxicity rate. The aim of study was to review a literature published after 2012, assessing the role of OX in neoadjuvant treatment of LARC and to consider meta-analysis feasibility.

Methods: We searched PubMed, EMBASE, and Cochrane library after 2012 to select the studies with neoadjuvant OX. We also searched trial registries and conference proceedings with variably combined key words.

Results: We identified 66 different studies with numerous phase II and III trials, including more than 3000 patients in total. They evaluated adding OX to existing chemotherapy (CHT) regimens (mFOLFOX6), combinations with drugs from other class (antiangiogenic – bevacizumab) or new drugs (S-1), and also combination with radiotherapy (RTH) with CHT given prior to, concomitant with, or following g RTH. Other category includes studies with combination with surgical treatment. Unfortunately, there are very different endpoints analyzed: resection rate, sphincter rate, pCR, downstaging, local-regional tumor event rate, local-regional tumor recurrence, DFS, OS. Results from elected studies are contradictory; some studies show that: adding OX to mFOLFOX6 is safe, effective and reasonable option; increasing of proportion of patients eligible for invasive treatment; significant improvement of DFS. On the other hand, others show that adding OX does not improve local-regional disease control, DFS, and OS.

Conclusion: Variety of studies published since 2012 till date will be presented and discrepancies regarding their results will be also discussed. We will also present some assumptions as regard to further up-dated meta-analysis.

P – 248 G8 screening tool for treatment decision-making in elderly colorectal cancer patients

J Marín[1], G Soler[2], M Martínez-Villacampa[3], S Vázquez[4], C Santos Vivas[5], N Mulet Margalef[6], A Teule[2], R Salazar[7]

[1]Catalan Institute of Oncology, L'Hospitalet de Llobregat, Spain, [2]Department of Medical Oncology, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Spain, [3]Department of Medical Oncology, Institut Català d'Oncologia - IDIBELL, L'Hospitalet de Llobregat, Spain, [4]Servei d'Oncologia Mèdica, Institut Català d'Oncologia, Hospital Duran i Reynals, Barcelona, Spain, [5]Translational Research Laboratory and Department of Medical Oncology, Institut Català d'Oncologia-IDIBELL, LHospitalet de Llobregat, Spain, [6]Institut Catala d'Oncologia de l'Hospitalet, Hospitalet de Llobregat, Spain, [7]Translational Research Laboratory and Department of Medical Oncology, Institut Catala d'Oncologia-IDIBELL, LHospitalet de Llobregat, Spain

Introduction: Colorectal cancer (CRC) is the third most common cancer worldwide. It is mostly diagnosed in elderly people, with a median age at diagnosis of 70 years. The aim of our study is to explore whether G8 questionnaire may be helpful to decide the best treatment for older colorectal cancer patients.

Methods: From October 2015 to June 2017, we prospectively screened 137 ≥75-years-old patients diagnosed with CRC who were referred for chemotherapy. In our center, these patients underwent oncogeriatric screening for a comprehensive geriatric assessment. Screening is positive in ≥ 85-years-old patients or 75-85-years-old patients with 2 of the following criteria: G8 scale,14, Pfeiffer test >2, Barthel index <90 and positive TIRS social risk scale. In addition, age, comorbidity and ECOG performance status were taken into account for final treatment decision. We hypothesize G8 vulnerability score correlates with toxicity and may help guiding treatment decisions.

Results: The median age of screened patients was 80.44 years (75.1-88.9). The most frequent diagnosis was colon cancer (71.8%) followed by rectal cancer (28.2%). 47.4% of patients had metastatic disease. G8 detected vulnerability (<14 score) in 62% of patients. Chemotherapy was more frequently dismissed in these fragile patients (45.9% of G8<14 patients vs 28.6 of G8≥14 patients). Overall, 67 patients received chemotherapy (capecitabine 70.1%, FOLFOX 19.4%, FOLFIRI 1.5%, clinical trial treatment 9%). Interestingly, for those patients who initiated treatment at full-dose intensity, a dose reduction was needed afterwards in 76% of G8<14 patients vs 28.6% of G8≥14 patients ($p = 0.032$). Tolerance of chemotherapy also significantly differed, with any grade 3/4 toxicity seen in 50% vs 20% of patients respectively ($p = 0.041$), and a higher risk ratio of presenting such toxicity for G8<14 patients (Risk ratio 4, 95% CI 0.995-16.074). Definitive interruption of treatment due to toxicity was needed in 15.2% vs 6.7% of patients respectively ($p = 0.43$). There were no toxic deaths.

Conclusion: G8<14 score correlates with a greater probability of presenting relevant toxicity. In addition, G8 questionnaire identifies a group of patients who more likely need dose-reduction during treatment. For this reason, G8 appears to be a helpful screening tool for treatment decision-making in elderly colorectal cancer patients.

P – 249 A SEER analysis of increasing disparities in age-related cause specific survival (CSS) among patients with colorectal cancer

T Mehmood

Northwest General Hospital and Research Centre, Peshawar, Pakistan

Introduction: Survival for patients with colorectal cancer (CRC) has improved over the past decades. However, it is unclear whether older patients have benefited to the same extent as younger patients.

Methods: The Surveillance, Epidemiology, and End Results (SEER) 9 registries database was queried for patients diagnosed with colorectal cancer from 1975 to 2009. Patients were categorized by age as being ≤54, 55-64, 65-74, 75-84, and ≥85 years. We presented yearly data for survival with overlying loess smoothing lines across all age groups. Another cohort was created using the SEER 18 registries database for patients diagnosed with CRC from 1973 to 2014. Survival analyses for the periods of 1973-1979, 1980-1989, 1990-1999, and 2000-2012 were conducted. Yearly data for surgery-performed rate and stage proportion were performed with overlying loess smoothing lines across all age groups.

Results: In the analysis of the SEER 9 registries database, 5-year CSS of patients aged ≤54, 55-64 and 65-74 years showed robust increase since 1975; however, survival of patients aged 75-84 years remained low despite of modest improvement, and patients aged 85 or older even showed no survival gains since 1990. Same trend exists after stratifying the disease as localized, regional and distant. In the analysis of the SEER 18 registries database, there has been a steady increase in the survival of patients aged ≤54, 55-64, 65-74 and 75-84 years as time period advanced; however, of CRC patients aged 85 years and older, the survival curves of period 1990-1999 and 2000-2012 couldn't be distinguished from each other and presented with a negligibly small gap from the survival curve of 1980-1989.

Conclusion: The strong interaction between age and year of diagnosis implies that older patients have benefited less over time than younger patients, especially for patients aged ≥85 years. Further studies are needed to determine the cause for these trends and identify potential strategies.

P – 250 Capecitabine, irinotecan, and bevacizumab in patients with previously untreated metastatic colorectal cancer: Experience of the oncology department of the university hospital of Oran, Algeria

Z Behourah[1], A Bousahba[2], L Djellali[1]

[1]University Hospital, Oran, Algeria, [2]University Hospital of Oran, Oran, Algeria

Introduction: This study aims to investigate the effectiveness of the associated chemotherapy based on capecitabine and irinotecan (CARIPI) with anti-VEGF, the bevacizumab, in terms of progression free survival (PFS), objective response rate (ORR) and overall survival (OS), in a way to evaluate the clinical benefit and tolerance to patients with mCRC in first line.

Methods: A prospective observational study was conducted in the Oncology department of the University Hospital of Oran between March 2012 and May 2015. Eligible patients were aged over 18 years, with non-pre-treated mCRC and performance status HWO ≤ 2. Patients were treated with capecitabine 1000 mg/m2 (800mg/m2 for patients over 65 years old) morning and evening during 14 days associated with irinotecan 240mg/m2 and bevacizumab 7.5mg/kg to D1 every three weeks. Stable or responder patients could receive a maintenance treatment by capecitabine-bevacizumab until the progression of the disease.

Results: Fifty-two patients with mCRC were included in the study. The ratio-sex was about 2.05 with a mean age of 57.4 ±1.7 years. 84.6% of patients showed a conserved performance status (HWO of 0-1). A total of 395 cycles was administered with an average of 7.6± 0.4 cycles (CI 95%) [3-16]. Twenty-tree patients (44.2%) received a maintenance treatment by capecitabine–bevacizumab with an average of 11.6 ± 2.2 cycles (CI 95%) [3-41]. After median follow up of 40 months (CI 95%: 42-49), the median PFS in intention to treat (ITT) was about 11 months (95% CI: 7.8 to 14.2) with a PFS rate estimated to 12 months of 44.2%. The ORR in ITT was 39.2% (95% CI: 27.5 to 52.2) and the Disease Control Rate (DCR) was 82.3%. The median OS was 20.8 months (95% CI: 16.5 to 25.1) with an OS rate at 2-year of 39.2%. The main grade 3-4 toxicities were represented by diarrhea (26.9%), neutropenia (13.5%), asthenia (7.7%), vomiting (7.7%), hand-food syndrome (5.8%). Toxicity given to bevacizumab was mainly moderate and representing by thromboembolic events (7.7%), blood pressure (32.7%; G3: 1.9%) and hemorrhagic events (G3:1.9%). Dose reductions of capecitabine and irinotecan were required in 36.5% and 28.8% of patients respectively, due to toxicities.

Conclusion: CAPIRI–bevacizumab in first line treatment of the mCRC is really efficient with an acceptable tolerance profile after doses adaptation of capecitabine and irinotecan.

P – 251 The prognostic ad predictive value of primary tumor sidedness in the mCRC pts

E Sezer[1], K Eser[2], A Onder[3], B Ozturk[3], V Ercolak[4], Z Oruc[5]

[1]Mersin University Medical Faculty, Department of Medical Oncology, Mersin, Turkey, [2]Mersin university Medical Faculty, Department of Medical Oncology, Mersin, Turkey, [3]Health Sciences University, Antalya Education and Research Hospital, Division of Medical Oncology, Antalya, Turkey, [4]Mersin University Medical Faculty Dept. of Medical Oncology, Mersin, Turkey, [5]Mersin City Hospital, Division of Medical Oncology, Mersin, Turkey

Introduction: The prognostic and predictive value of primary tumor sidedness in the pts with metastatic colorectal cancer (mCRC) is well known today. Right-sided primary was associated with high mutational burden, microsatellite instability, worse prognosis, more BRAF mutation rates and poor anti-EGFR response. We aimed to investigate the effects of tumor sidedness on survival, RAS-RAF mutation rates and responses to biologic agents in the pts with mCRC.

Methods: A retrospective study with mCRC pts performed in two different centers. Tumor sides were categorized as left (from rectum to splenic flexura) and right (from caecum to hepatic flexura) sided. The effects of tumor sidedness on treatment responses and survival rates and RAS-RAF status of mCRC pts were investigated using the log rank test. The Kaplan- Meier survival estimates were calculated.

Results: A total of 317 (F/M=127/190) pts were included to study. Median age was 61±12 (range: 23-89) years. Primary tumor was categorized as right-sided in 72 (23.2%) pts, and left-sided in 231 (74.5%). Initial tumor stages were 66 (%22) pts were stage I-II, 115 (36%) were stage III and 135 (42%) were stage 4. 38 (18.1%) pts have two or above metastatic site. Approximately a half of pts was at stage 4. Liver, peritoneum and locoregional relapses were most common sites. Metastasectomy rate was 23%. Kras, nras and braf mutation rates were 31.7, 5 and 6.3%, respectively. Median follow-up was 22 (range: 1.3-274) months. Kras mutation rates were similar between right and left sided tumors, braf mutation rates were significantly increased in right-sided tumors (40.6 vs 7.7%, $p < 0.0001$). Median PFS (12.9 vs. 12.2 months) and OS (27.5 vs. 22.5 months) were similar between left and right-sided tumors. First line biologic agent and chemotherapy regimens were similar between two groups. Bevacizumab and anti-EGFR usage were 75 and 23%, respectively. Median PFS with first-line bevacizumab was 13.4 and 12.3 months, with Anti-EGFR was 12.5 and 16.9 months in the pts with right and left-sided tumors, respectively. Median OS with first line bevacizumab was 16.9 and 28.8 months, with anti-EGFR 23.9 and 39.3 months in right and left-sided tumors, respectively. Median PFS and OS differences were not reached statistically significance. Median OS was similar between braf wild and mutant tumors (27.2 vs 19.2 months). There was no significant surival difference between kras wild (29.1 months) and mutated (24.7 months) groups.

Conclusion: In concordance with literature, right sided primary was associated with higher BRAF mutation rates and poor survival. RAS and RAF mutation rates were

similar to literature. However, most of old cases, we can obtain ras mutation status after first line therapy, so in the ras wild type tumors, first line anti-EGFR usage was lower than the current practice. Despite of low-percentage of anti-EGFR usage at first line, our results showed that the pts with left-sided primary, with first line anti-EGFR treatment, median OS was 39.3 months. In the pts with right sided primary, the OS difference between first line anti-EGFR and anti-VEGF treatments were not significant.

P – 252 The evaluation of liver resection for colorectal cancer liver metastases

M Ogawa[1], K Haruki[2], A Horiuchi[2], H Shiba[3], Y Mitsuyama[2], M Kusumoto[4], S Eto[4], M Ishiyama[5], T Hasegawa[5], K Yoshida[5], K Yanaga[6]

[1]Katsushika Medical Center, The Jikei University School of Medicine, Katsushika-ku, Japan, [2]Department of Surgery, The Jikei University of Medicine, Tokyo, Japan, [3]Jikei University School of Medicine, Minato-ku, Japan, [4]Department of Surgery, Katsushika Medical Center, The Jikei University of Medicine, Tokyo, Japan, [5]Department of Surgery, Katsushika Medical Center, The Jikei University School of Medicine, Tokyo, Japan, [6]Department of Surgery, The Jikei University School of Medicine, Minato-ku, Japan

Introduction: In colorectal cancer chemotherapy, FOLFOX from 2004.4.1, molecular targeted agents from 2009.9.1, has been covered by insurance reimbursement in Japan. In addition, our department expanded the surgical indications from 2004, and actively enforced liver resection. We retrospectively examined the treatment outcome of liver resection for colorectal cancer liver metastases (CRLM) to verify the efficacy of the method and strategy of the new treatment.

Methods: In our department,132 cases of first liver resection were performed for CRLM from April 2004 to December 2015, and 123 cases traceable for data analysis. The group that underwent liver resection (first resect able cases) defined as group A, chemotherapy performed at the time of define diagnosis of metastasis and underwent conversion therapy of liver resection, as group B and compared the survival outcomes between the two groups. Unilateral metastasis group (group C) and bilateral metastasis group (group D) were compared in the same manner, also in comparison due to the presence or absence of post-operative chemotherapy.

Results: ①5-year recurrence-free survival rate (5YRFSR) of liver resection of all 123 cases is 28.7%, the 5-year survival rate (5YSR) was 52.7%. In the multivariate analysis, in 5RFSR, extra hepatic lesions, metastatic cite, was an independent factor. In regard to 5YSR, N factor, post-operative chemotherapy was an independent factor. ② There was no significant difference in 5YRFSR (31.4%) of group A ($n = 91$) and in group B ($n = 32$) ($p = 0.477$), and no significant difference in 5YSR (57.3%) of group A ($n = 86$) and in group B ($n = 37$) ($p = 0.063$). ③ There was no significant difference in 5YSR of group C ($n = 88$) and in group D ($n = 35$) ($p = 0.135$). ④ 5YSR for the first time resect able cases ($n = 70$) in group C, was 65.2%, but no significant difference compared with the conversion cases ($n = 18$) was not observed ($p = 0.057$). ⑤ 5-year survival rate for the first resect able cases ($n = 21$) of the D group 34.0% and compared with the conversion cases ($n = 14$) was not significant difference ($p = 0.64$). ⑥ In comparison due to the post-operative chemotherapy in group C and group D, significant difference in 5YSR was not observed ($p = 0.145$, $p = 0.140$).

Conclusion: 5YSR of 52.7% by liver resection was obtained and had a favorable outcome, and the conversion cases had an equal prognosis compared to the cases of first resection. Post-operative chemotherapy was a prognostic factor of colorectal cancer liver metastases.

P – 253 A phase I/II study of panitumumab combined with TAS-102 in patients (pts) with RAS wild-type (wt) metastatic colorectal cancer (mCRC) refractory to standard chemotherapy: APOLLON study

K Yamazaki[1], H Yasui[2], K Yamaguchi[3], Y Kagawa[4], Y Kuboki[5], T Yoshino[6], M Gamoh[7], Y Komatsu[8], H Satake[9], M Goto[10], H Tanioka[11], E Oki[12], M Kotaka[13], A Makiyama[14], T Denda[15], J Soeda[16], K Shibya[16], M Iwata[16], K Oba[17], T Kato[18]

[1]Department of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun, Japan, [2]Shizuoka Cancer Center, Sunto-gun, Japan, [3]Department of Gastroenterology Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-ku, Japan, [4]Department of Gastrointestinal Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [5]National Cancer Center Hospital East, Kashiwa-city, Japan, [6]National Cancer Center Hospital East, Kashiwa, Japan, [7]Department of Medical Oncology, Osaki Citizen Hospital, Osaki-shi, Japan, [8]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [9]Department of Medical Oncology, Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan, [10]Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki, JAPAN, [11]Department of Medical Oncology, Okayama Rosai Hospital, Okayama, Japan, [12]Department of Surgery, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Japan, [13]Department of Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan, [14]Japan Community Healthcare Organization Kyushu Hospital, Department of Hematology/Oncology, Kitakyushu, Japan, [15]Chiba Cancer Center, Chiba, Japan, [16]Takeda Pharmaceutical Company Limited, Chuo-ku, Japan, [17]Department of Biostatictics, The University of Tokyo, Tokyo, Japan, [18]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan

Introduction: APOLLON is an open-label, single-arm phase I/II study investigating the efficacy and safety of Pmab in combination with TAS-102 (trifluridine/tipiracil) in pts with RAS (KRAS/NRAS) wt mCRC refractory to standard chemotherapy. The recommended phase II dose (RP2D) of this combination was reported in ASCO-GI 2017 as Pmab at 6 mg/kg on Days 1 and 15, every 4 weeks (Q4W) and TAS-102 at 35 mg/m^2 twice daily on Days 1–5 and 8–12, Q4W, and was well tolerated without dose-limiting toxicities. Here, we present the efficacy and safety data for pts treated with Pmab with TAS-102 at the RP2D.

Methods: Eligible pts were aged 20–74 years (y); ECOG PS 0–1; with RAS wt mCRC; refractory or intolerant to fluoropyrimidines, irinotecan, oxaliplatin and anti-angiogenesis therapy; and had no prior treatment with any anti-EGFR antibody, TAS-102 nor regorafenib. Primary endpoint was investigator-assessed progression-free survival (PFS) rate at 6 months in RP2D treated pts treated at the RP2D (including seven pts in phase I). Secondary endpoints included PFS, response rate (RR), disease control rate (DCR), overall survival (OS) and safety. Using an exact single-stage binomial design, 47 pts were required, with a 6-month PFS rate of 48% deemed promising and 29% unacceptable (one-sided $\alpha = 0.05$; $\beta = 0.2$).

Results: From 2015 to 2017, 56 pts (30 male) with a median age of 64 y (range: 38–74 y) were enrolled. Median follow-up was 10.4 months. PFS rate at 6 months ($n = 54$) was 33.3% (90% CI: 22.8–45.3; $p = 0.2414$). Median PFS, RR and DCR were 5.8 months (95% CI: 4.5-6.5), 37.0% (95% CI: 24.3-51.3) and 81.4% (95% CI: 68.57-90.75), respectively ($n = 54$). Median OS was not reached. In subgroup analysis with primary tumour location, left-sided tumors (LT, $n = 47$) were relatively associated with longer PFS (6.1 vs. 2.9 months) than right-sided tumors (RT, $n = 7$). RR in LT and RT were 38.3% and 28.6%, respectively. The most common grade (G) 3/4 treatment-emergent adverse events ($n = 55$) included neutropenia (G3: 30.9%, G4: 16.4%), febrile neutropenia (G3: 10.9%), stomatitis (G3: 9.1%), dermatitis acneiform (G3: 9.1%), fatigue (G3: 3.6%) and hypomagnesemia (G3: 3.6%). There were no treatment-related deaths or unexpected safety signals.

Conclusion: The first phase II study of Pmab with TAS-102 at the RP2D showed favourable antitumor activity with an acceptable safety profile for pretreated pts with RAS wt mCRC, although the primary endpoint of PFS rate at 6 months did not meet the prespecified threshold.

P – 254 Ultrasonic monitoring of liver metastasis after radiofrequency thermoablation

S Khoshimov

Tashkent Medical Academy, Tashkent, Uzbekistan

Introduction: To determine the possibility of ultrasound scanning for the choice of treatment methods and postoperative dynamic observation of patients with colorectal liver metastases.to determine the possibility of ultrasound scanning for the choice of treatment methods and postoperative dynamic observation of patients with colorectal liver metastases.

Methods: In our clinic since 2014, radiofrequency thermoablation (RFT) of colorectal liver metastases was performed in 44 patients aged 47 to 75 years. There were 30 men (68.2%), women - 14 (31.8%) people. Most often noted bilobar liver damage, the tumors were intraparenchymatous. The metastases varied from 1 to 4 cm in diameter. Electrosurgical apparatus for radiofrequency ablation of Valleylab Cool-Tip RF was used. Visualization of the process was provided by ultrasonic monitoring in real time. Ultrasound studies were carried out on GE Medical Systems Vivid 3, Logiq Book XP in B-mode and duplex scanning.

Results: The algorithm for preoperative research consisted of a set of measures: ultrasound, MRI, biopsy followed by histological examination. To select the RFA method (percutaneous under ultrasound or intraoperative), ultrasound scanning was the determining factor. In 3 patients, RFT was performed intraoperatively in connection with the bilobar, subcapsular location of the foci. Ultrasonic monitoring was performed on the first, seventh and thirtieth days after the operation. Early studies (the first and seventh days) revealed complications after manipulation. Dynamic observation noted: on the first day - increased echogenicity of the liver; on the seventh - a marked increase in echogenicity, increased clarity of borders and a violation of blood flow in the foci. A month later, when visualizing the location of RFT, all patients noted a decrease in the size of the focus by 10-30%, a lack of blood flow in it.

Conclusion: Ultrasound scanning should be considered the optimal screening method for monitoring patients after RFT for metastatic liver damage in the immediate postoperative period.

P – 255 Immediate and long-term results of liver resections with metastatic lesion

S Lukmonov[1], O Usmanov[1], M Ismailov[2], K Madatov[1], U Kurbankulov[1], U Allazarov[1]

[1]Tashkent Medical Academy, Tashkent, Uzbekistan, [2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Introduction: To evaluate the effectiveness of surgical treatment of metastatic liver damage.

Methods: The analysis of the results of 29 liver resections performed on the basis of the Department of Oncology and Radiology of the Tashkent Medical Academy, performed for metastatic liver damage from 2002 to 2012 inclusive, is presented. Patients were

distributed as follows: with metastases of colorectal cancer - 22 (75.86%), non-cortical - 7 (24.14%). The study included 11 (38%) men, the average age was 56.4 ± 8.4 years, and 18 (62%) women, the average age was 61.8 ± 7.9 years. A total of 21 (72.4%) large resection of the liver and 8 (27.6%) of small ones, including anatomical resections: segmentectomy - 1; bisegmentectomy - 2; atypical - 5.

Results: Early postoperative lethality (during the first 30 days after surgery) during surgical treatment of patients with metastases of colorectal cancer in the liver was 9.1%, non-cortical - 22%. The incidence of postoperative complications is 27.6%. According to the analysis of cumulative survival by the Kaplan-Mayer method, the median survival in the group of patients with colorectal cancer metastases in the liver is 24 months, non-cortical cancer is 12 months, the three-year survival is 27.5 and 0%, respectively, the five-year survival is 9.1%.

Conclusion: Liver resection is the only radical treatment for patients with metastatic lesions, improving the prognosis and providing a five-year survival rate of up to 9.1%. Improving the results of liver resections in patients with metastatic lesions implies the need to improve technique and the desire to perform anatomical resections in order to reduce early postoperative lethality and specific complications.

P – 256 Treatment efficacy and survival analysis of extremely elderly (80 years of age or older) patients with metastatic colorectal cancer: Single institute retrospective study

Y Liang[1], C Wei[2], J Tsai[3], Y Jeng[4], K Chen[1], A Cheng[5], K Yeh[6]

[1]Graduate Institute of Oncology, National Taiwan University; National Taiwan University Cancer Center; Department of Oncology, National Taiwan University Hospital, Taipei, Republic of Taiwan, [2]Department of Oncology, National Taiwan University Hospital, Hsin-Chu Branch, Hsinchu City, Republic of Taiwan, [3]Pathology, National Taiwan University Hospital, Taipei, Republic of Taiwan, [4]Graduate Institute of Pathology, College of Medicine, National Taiwan University, Taipei, [5]Department of Oncology and Internal Medicine, National Taiwan University Hospital, Taipei, Republic of Taiwan, [6]National Taiwan University Hospital, Taipei, Republic of Taiwan

Introduction: With improvement of public health and general medicine, the proportion of elderly cancer patients in daily practice keeps growing. Indeed, the evidence of systemic targeted therapy and chemotherapy to extremely elderly (80 years of age or older) patients remain limited.

Methods: This was a single institute, retrospective study. Extremely elderly patients (80 years of age or older) with diagnosis of metastatic colorectal cancer at National Taiwan University Hospital, Hsinchu branch between July 1st, 2014 and June 30th, 2016 were enrolled. Patients received less than 2 cycles of systemic treatment were excluded. The last follow-up date was at August 31st, 2017

Results: In total 19 patients enrolled, sixteen (84.2%) patients were men. Median age was 82.0 years-old (range: 80.1-88.0). Eleven (57.9%) patients had initial diagnosis of metastatic disease. Only four (21.1%) patients had right-sided colon cancer. Seven (46.2%) patients had wile type RAS tumors and all are wild type BRAF tumors. Eight (42.1%) patients had liver-confined metastatic disease and only two (10.5%) patients had peritoneal metastases. Thirteen (68.4%) patients received chemotherapy doublet as first line treatment. Eleven (57.9%) patients received first line chemotherapy in combination with targeted therapy, which mainly comprised by bevacizumab (eight patients). The median progression-free survival (PFS) of first line therapy was 8.2 months (95% confidence interval [CI]: 5.8-10.6 months). Fourteen (73.7%) patients received second line systemic therapy. The median overall survival (OS) was 22.5 months (95% CI: 15.9-29.2 months). In Univariate and multivariate Cox proportional hazards analysis revealed no any independent prognostic factor for longer PFS or OS.

Conclusion: Extremely elderly patients with metastatic colorectal cancer who had fair performance status to receive systemic therapy have comparable survival under regular medical care.

P – 257 Improvement of metastatic colorectal cancer patient survival: Single institution experience

E Fenocchio[1], F Colombi[2], M Calella[1], R Filippi[3], I Depetris[1], P Lombardi[1], D Marino[4], C Cagnazzo[4], R Ferraris[5], M Vaira[2], M Aglietta[4], F Leone[1]

[1]Department of Oncology, Candiolo Cancer Institute - FPO - IRCCS - University of Turin Medical School, Candiolo, Italy, [2]Department of Oncology, Candiolo Cancer Institute - FPO - IRCCS, Candiolo, Italy, [3]Institute for Cancer Research and Treatment, IRCCS Candiolo (TO), Candiolo, Italy, [4]Department of Medical Oncology, University of Turin Medical School, Candiolo Cancer Institute, FPO, IRCCS, Candiolo, Italy, [5]Department of Oncology, Candiolo Cancer Institute - FPO - IRCCS, Candiolo, Italy

Introduction: The outcome of patients with metastatic colorectal cancer (mCRC) has significantly improved over the last two decades, reaching a median overall survival (mOS) of around 30 months, more than double that 20 years ago. Both surgery and a more aggressive systemic approach may have contributed to this result. The aim of this study is to describe the evolution of survival of mCRC patients followed at a single institution over the past 17 years, investigating the possible influence of tumour characteristics, as well as the changes in treatment practice through the years.

Methods: We retrospectively collected data from 788 mCRC patients treated from 2001 to 2016. As molecular targeted agents were introduced in clinical practice in 2007, in order to detect survival changes, patients were divided into two groups according to the year of metastatic disease diagnosis: Cohort A (between 2001 and 2006) and Cohort B (between 2007 and 2014).

Results: 788 patients with a minimum follow-up period of two years were analyzed (365 in Cohort A and 423 in Cohort B). The mOS was 32.0 months (95% CI; 28.8 to 35.3 months). Patients' survival in Cohort B was significantly longer compared to Cohort A (median 33.5 months vs 29.2 months respectively, HR 0.832; 95% CI 0.697-0.992; $p = 0.041$). Surgical procedures increased from 42% in Cohort A to 58% in Cohort B, $p < 0.009$: particularly extra-hepatic surgery (from 21.4% to 33.9%; $p < 0.005$). No differences in survival of patients who underwent surgery – in addition to a systemic treatment – were detected between Cohorts (median 58.9 months vs 58.2 months, HR 1.033; 95% CI, 0.779-1.369; $p = 0.822$). Similarly, we failed to demonstrate a survival improvement in patients treated with systemic treatment alone (with or without targeted agents): mOS 18.9 months in Cohort A vs 20.7 months in Cohort B (HR 1.0 - IC 95% 0.799-1.271; $p = 0.948$). At the multivariate analysis, a right-sided primary tumour and synchronous metastatic disease were found independent unfavorable prognostic factors. In these subgroups, survival improved in Cohort B. In particular, in patients with right-sided tumours, median survival was 18.5 months in Cohort A and 25.8 months in Cohort B ($p = 0.041$).

Conclusion: The results of our studies suggest that in current clinical practice, unless patients are classified as unfit for therapy, the therapeutic strategy is moving towards intensive treatment where at least two cytotoxic therapies are combined together with biological agents, and a multimodal approach where surgery of metastatic sites is considered feasible. This approach seems appropriate to increase patient survival. In particular, it is likely that poor prognostic subgroups of mCRC patients would benefit from an integration of medical and surgical treatments in a 'continuum of care' strategy.

P – 258 HGCSG1503: A retrospective cohort study evaluating the safety and efficacy of TAS-102 in patients with metastatic colorectal cancer: Analysis of cases of prior regorafenib

Y Shindo[1], S Yuki[2], M Yagisawa[3], Y Kawamoto[3], Y Tsuji[4], K Hatanaka[5], Y Kobayashi[6], S Kajiura[7], A Ishiguro[8], T Honda[9], M Dazai[10], K Eto[11], M Nakamura[12], M Koike[13], S Ota[14], A Sato[15], K Kato[16], A Ueda[17], A Fukunaga[18], M Sekiguchi[19], Y Sakata[20], Y Komatsu[21]

[1]Department of Gastroenterological Surgery, Nakadori General Hospital, Akita, Japan, [2]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [3]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [4]Department of Medical Oncology, Tonan Hospital, Sapporo, Japan, [5]Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan, [6]Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan, [7]Department of Gastroenterology and Hematology, Faculty of Medicine, University of Toyama, Toyama, Japan, [8]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan, [9]Division of Clinical Oncology Center, Nagasaki University Hospital, Nagasaki, Japan, [10]Department of Gastroenterology, Sapporo Medical Center NTT EC, Sapporo, Japan, [11]Department of Gastroenterology, Tomakomai City Hospital, Tomakomai, Japan, [12]Department of Gastroenterology, Sapporo City General Hospital, Sapporo, Japan, [13]Department of Surgery, KKR Sapporo Medical Center, Sapporo, Japan, [14]Department of Surgery, Akita City Hospital, Akita, Japan, [15]Department of Medical Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, [16]Department of Gastroenterology, Iwamizawa Municipal General Hospital, Iwamizawa, Japan, [17]Department of Medical Oncology, Toyama Red Cross Hospital, Toyama, Japan, [18]Department of Surgery, Asahikawa City Hospital, Asahikawa, Japan, [19]Data Center, Hokkaido Gastrointestinal Cancer Study Group (HGCSG), Sapporo, Japan, [20]Misawa City Hospital, Misawa, Japan, [21]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan

Introduction: The J003 trial and RECOURSE trial revealed the safety and efficacy of TAS-102 for patients with metastatic colorectal cancer (mCRC). In March 2014, TAS-102 was approved in Japan. However, in these pivotal trials, there were few cases in which regorafenib was administered as prior treatments, and also there were few reports on the effectiveness and safety of TAS-102 after administration of regorafenib.

Methods: We retrospectively analyzed the clinical data of 411 patients who received TAS-102 in the multi-institutional retrospective study (HGCSG1503). This study was analyzed by CTCAE v4.0 for adverse events (AEs), RECIST v1.1 for response rate (RR)/disease control rate (DCR). To compare patients who received regorafenib before TAS-102 (Prior REG) and those did not receive regorafenib (No prior REG), Fisher's exact test was used in terms of patient characteristics, AE, RR/DCR, and Log-rank test was used in terms of TTF, PFS and OS.

Results: No prior REG and Prior REG were 285 and 126, respectively. The patient' characteristics between No prior REG and Prior REG were generally balanced except for lung metastasis (56.8% in No prior REG, 67.5% in Prior REG; $p = 0.049$), prior oxaliplatin administration (95.1% in No prior REG, 99.2% in Prior REG; $p = 0.045$), prior irinotecan administration (90.5% in No prior REG, 100% in Prior REG; $p < 0.001$) and patients over 18 months since diagnosis of metastasis (63.2% in No prior REG, 84.1% in Prior REG; $p < 0.001$). The AEs between No prior REG and Prior REG were also generally balanced. RR/DCR were 0.8/37.5% in No prior REG and 0/36.5% in Prior REG ($p = 1.000/0.908$). Median PFS was 2.3 months in No prior REG and 2.1 months in Prior REG (HR 1.157, $p = 0.185$). Median OS was 8.1 months in No prior REG and 5.7 months in Prior REG (HR 1.355, $p = 0.007$).

Conclusion: In this analysis, No prior REG population contained lung metastasis, and short interval from diagnosis of metastasis. The adverse events, detail of administration,

RR/DCR, and PFS were no significant difference regardless of the administration history of REG. The OS was significantly extended with No prior REG population. This is presumed because 30% of No prior REG population received REG for post TAS-102 therapy.

P – 259 Variability of current global practice patterns in the management of metastatic colorectal cancer

T Bekaii-Saab[1], K Marcello[2], G Fisher[3], S Kopetz[4], J Strickler[5], A Venook[6], K Obholz[2]

[1]Mayo Clinic Cancer Center, Scottsdale, Arizona, USA, [2]Clinical Care Options, Reston, Virginia, USA, [3]Stanford University School of Medicine, Palo Alto, California, USA, [4]UT MD Anderson Cancer Center, Houston, Texas, USA, [5]Duke University Medical Center, Durham, North Carolina, USA, [6]University of California, San Francisco, California, USA

Introduction: Therapeutic options for mCRC have changed dramatically in recent years, greatly increasing the complexity of therapeutic decision-making. Treatment guidelines may limit flexibility to individualize patient care. The aim of this analysis was to assess "real world" global practice patterns for metastatic colorectal cancer (mCRC) compared with recommendations from US experts based on patient cases entered by clinicians into an online decision support tool designed to provide specific, patient-individualized expert recommendations.

Methods: A panel of 5 experts provided treatment recommendations for 311 unique case scenarios across 1st- (1L), 2nd- (2L), and 3rd-line (3L) settings for mCRC. Individual scenarios were defined by key patient and disease characteristics including mutation status, microsatellite instability (MSI), sidedness of primary tumor, and previous therapy. To use the tool, clinicians entered their patient and disease factors and were surveyed about their intended treatment plan for that case. The expert treatment recommendations for that specific case were then provided to the clinician.

Results: Analysis includes 755 cases entered by healthcare practitioners (HCPs) globally, comprising 30% Europe, 29% US, and 41% rest of the world (ROW). Practice pattern highlights: in the 1L setting, 100% of experts chose a VEGF inhibitor for patients with right-sided, RAS/BRAF wild type (WT) mCRC vs 56% of HCPs surveyed in the tool. In left-sided RAS/BRAF WT mCRC, 80% of experts selected an EGFR inhibitor in 1L and 100% in 2L (in patients who received prior VEGF inhibitor) vs 41% and 44% of HCPs, respectively. In patients with RAS-mutated (MT) tumors who had received prior irinotecan and oxaliplatin, as well as a VEGF inhibitor, 60% of experts selected regorafenib and 40% selected TAS-102 in this 3L setting vs 33% and 22% of HCPs, respectively. In patients with BRAF V600E -MT mCRC, 100% of experts selected a VEGF inhibitor (bevacizumab) as the biologic agent in 1L and 60% selected vemurafenib/cetuximab in 2L, whereas 64% of HCPs selected a VEGF inhibitor in 1L and only 7% planned to use vemurafenib/cetuximab in 2L. In patients with MSI-high tumors, 1 of 5 experts would use an immune checkpoint inhibitor in 1L vs 43% of HCPs. In both 2L and 3L, 100% of experts would use immune checkpoint inhibitors for MSI-high patients vs 62% of HCPs in 2L and 54% in 3L.

Conclusion: Planned treatment by global HCPs for mCRC show a substantial variance from the US expert treatment recommendations for the same cases, particularly treatment based on the site of the primary tumor and BRAF V600E mutation status, and for patients with MSI-high tumors. A detailed analysis of expert treatment selections vs planned treatment of HCPs, including a comparison of trends by region (US vs Europe vs ROW) and the overall impact of the recommendations from US-based experts on global practice will be presented.

P – 260 Quality-of-life in patients with metastatic colorectal cancer (mCRC) treated with aflibercept and FOLFIRI: Interim results of the non-interventional AIO study QoLiTrap

M Zahn[1], F Scholten[2], R von Moos[3], J Thaler[4], R Hofheinz[5]

[1]Onkologie/Hämatologie Goslar, Goslar, Germany, [2]Klinikum Frankfurt Hoechst GmbH, Frankfurt am Main, Germany, [3]Kantonsspital Graubuenden, Chur, Switzerland, [4]Dept Internal Medicine, Wels, Austria, [5]University Hospital Mannheim, Mannheim, Germany

Introduction: The anti-angiogenic fusion protein aflibercept targets VEGF-A, VEGF-B and PlGF. Aflibercept is approved in combination with FOLFIRI for treatment of mCRC that is resistant or has progressed after oxaliplatin-containing therapy.

Methods: QoLiTrap (AIO-LQ-0113) is a multinational (D, A, CH) ongoing non-interventional study with a recruitment target of 1500 patients. Primary goal is to evaluate Quality-of-life (QoL) in mCRC patients treated with aflibercept+FOLFIRI using the EORTC-QLQ C30 questionnaire at baseline and before every cycle.

Results: This interim analysis (data cut-off: 05 December 2017) includes 702 patients (mean age: 64.8 ± 9.9 years; 65.0% male, 50.9% with documented RAS mutation, ECOG 0-1: 86.0) who completed the baseline and at least 2 post-baseline EORTC-QLQC30 questionnaires. Aflibercept was administered for 7 cycles in median (range: 1-65). Median global health score at baseline was 58.3 and decreased moderately (mean change -4.4, $p < 0.0001$) within the first 18 weeks of therapy with no significant worsening in gastrointestinal, dyspnea, and sleep disturbance symptom scales. Reduction was greater in patients with RAS mutation compared to RAS wild-type. 91.9% of patients received prior palliative therapy or prior therapy during metastatic stage. Mainly, study treatment was given as 2nd line treatment, followed by 3rd and 4th line treatment. 64.3% of these patients were pretreated with bevacizumab and 13.7% with anti-EGFR (cetuximab or panitumumab) alone or in combination with chemotherapy. Previous 1st line therapy was primarily oxaliplatin-containing regime with bevacizumab for RAS mutant and with anti EGFR for RAS wildtype. As prior 2nd line therapy bevacizumab was given nearly equally in combination with oxaliplatin or irinotecan for RAS mutant and wildtype; anti-EGFR was combined approximately equal with irinotecan or oxaliplatin for RAS wildtype, too. Evaluable patients pretreated with anti-EGFR and/or bevacizumab receiving study therapy as 2nd line treatment had 13.8% documented CR + PR and 31.5% SD as best response to aflibercept. Sidedness of CRC and RAS mutation status had an impact on best response in these patients. Median PFS of patients pretreated with biologics was 8.3 months (95% CI 7.0- 9.3) and 7.8 months (95% CI 6.4-10.6) for study treatment as 2nd line and 3rd line, respectively. Patients treated with prior anti-EFGR or bevacizumab independent of therapy line had a median PFS of 9.4 months (95% CI 5.9-.) and 7.3 months (95% CI 6.0 – 8.3), respectively; pretreatment with both substance groups yielded a median PFS of 5.7 months (95% CI 5.0 – 8.1). These results corresponded to ORR of 14.6%, 11.0% and 6.3% for patients pretreated with anti-EFGR, bevacizumab or both. No statistically significant differences for median PFS were observed for patients with RAS wildtype or RAS mutation. Toxicity was in line with the known safety profile of the study medications.

Conclusion: The current interim analysis showed encouraging effectiveness results for mCRC patients treated with aflibercept+FOLFIRI under routine conditions even for patients with prior anti-EGFR antibody and/or bevacizumab therapy. Best efficacy results were obtained for patients with study treatment as 2nd line. Global health status declined moderately without clinical relevance during study treatment. This study is supported by Sanofi-Aventis Deutschland GmbH.

P – 261 HGCSG1503: A retrospective cohort study evaluating the safety and efficacy of TAS-102 in patients with metastatic colorectal cancer: Analysis of GERCOR index

K Hatanaka[1], S Yuki[2], S Nakano[2], K Sawada[3], K Harada[4], H Okuda[5], T Ando[6], K Ogawa[7], K Furukawa[8], S Minami[9], T Saiki[10], T Ohta[11], T Kato[12], J Nakajima[13], T Sasaki[14], S Saitoh[15], Y Shindo[16], M Tateyama[17], S Kato[18], H Nagai[19], Y Sakata[20], Y Komatsu[21]

[1]Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan, [2]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [3]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [4]Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan, [5]Department of Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan, [6]Department of Gastroenterology and Hematology, Faculty of Medicine, University of Toyama, Toyama, Japan, [7]Department of Gastroenterology, Kouseiren Takaoka Hospital, Takaoka, Japan, [8]Department of Gastroenterology, Niigata City General Hospital, Niigata, Japan, [9]Department of Gastroenterology, Oji General Hospital, Tomakomai, Japan, [10]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan, [11]Department of Gastroenterology, Sapporo Higashi Tokushukai Hospital, Sapporo, Japan, [12]Department of Internal Medicine, Wakkanai City Hospital, Wakkanai, Japan, [13]Department of Gastroenterology, Obihiro Kosei Hospital, Obihiro, Japan, [14]Department of Internal Medicine, Hokkaido Gastroenterology Hospital, Sapporo, Japan, [15]Department of Internal Medicine, Misawa City Hospital, Misawa, Japan, [16]Department of Gastroenterological Surgery, Nakadori General Hospital, Akita, Japan, [17]Department of Internal Medicine, Tomakomai Nisshou Hospital, Tomakomai, Japan, [18]Department of Gastroenterology, Sapporo Hokuyu Hospital, Sapporo, Japan, [19]Data Center, Hokkaido Gastrointestinal Cancer Study Group (HGCSG), Sapporo, Japan, [20]Misawa City Hospital, Misawa, Japan, [21]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan

Introduction: In the treatment for metastatic colorectal cancer (mCRC), it is essential for understanding the prognosis of each individual patient. GERCOR index (GI) based on performance status and serum LDH has been previously proposed. However, in the later line setting, the validity of GI has not been reported in patients treated by TAS-102.

Methods: 411 patients with mCRC treated by TAS-102 were retrospectively registered from 28 centers in Japan. Selection criteria for this analysis were: (1) ECOG performance status 0-2, (2) presence of serum LDH before the start of TAS-102, and (3) presence of KRAS mutational status. Univariate and multivariate analysis for overall survival (OS) and progression-free survival (PFS) were performed using patient characteristics. Survival analyses were performed with Kaplan-Meier method, log-rank test and Cox proportional hazards model.

Results: In 389 patients, all data were available for prognostic categorization. Median OS and PFS were 7.4 and 2.2 months in this analysis set. The distribution of GI were Low risk (L: n = 64), Intermediate risk (I: n = 158), and High risk (H: n = 167). The median OS of L, I, and H were 13.5, 8.4, and 5.3 months, respectively. For OS, there were significant difference between L and H ($p < 0.001$), I and H ($p < 0.001$), and L and I ($p = 0.003$). The median PFS of L, I, and H were 2.8, 2.6, and 1.9 months, respectively. For PFS, there were significant difference between L and H ($p < 0.001$), I and H ($p = 0.015$), and L and I ($p = 0.007$). In Cox multivariate analysis, GI showed an independent prognostic (L vs I; HR 1.566, $p = 0.008$/L vs H; HR 2.476, $p < 0.001$) and predictive impact(L vs I; HR 1.427, $p = 0.022$/L vs H; HR 1.932, $p < 0.001$).

Conclusion: In this analysis, GI might be a predictive and prognostic factor in later line treatment with TAS-102 for patients with mCRC. The prospective evaluation is needed for the further validation.

P – 262 Trial-level analysis of early tumor shrinkage and disease control rate as intermediate end points of first-line medical treatment in randomized studies of metastatic colorectal cancer

G Colloca, A Venturino, D Guarneri
G. Borea Hospital, Sanremo, Italy

Introduction: Early tumor shrinkage (ETS) is a response-related end point (EP), defined as a radiologic dimensional reduction of at least 20% after 8 weeks of chemotherapy, and it has been shown to be predictive of overall survival (OS) in studies of metastatic colorectal cancer (mCRC). From the available studies and a patient-level meta-analysis it appears that ETS correlates better than overall response rate (ORR) with OS [Sommereir 2014, J Clin Oncol 32:3538]. However, a trial-level pooled analysis concluded that ETS predicted progression-free survival (PFS) but not OS. Disease control rate (DCR) by RECIST appeared as a good intermediate end point of OS from a previous analysis of 11 randomized trials of patients with mCRC who underwent first-line treatment with chemotherapy plus bevacizumab vs. chemotherapy alone, reporting a better performance than PFS [Colloca 2016, Clin Oncol 28:e155-64]. The aim of the present study is to perform a trial level analysis to verify if DCR and ETS after a first-line chemotherapy are related to OS in patients with mCRC receiving various regimens.

Methods: After a systematic search of randomized trials reporting ETS, randomized clinical trials (RCTs) were selected whenever they evaluated PFS, ETS, ORR and DCR in relation to OS. Two arms per trial were selected, and the differences in the results of these two arms for every EP (Δ, delta) were calculated. The nonparametric Spearman ρ (r) was used as a measure of correlation between the difference in each end point and the difference in OS. The analysis evaluated the treatment effects on ΔPFS, ΔETS, ΔORR or ΔDCR and on ΔOS, by separate linear regressions for every EP, and the proportions of variability explained (R2trial) on OS for the four EPs (PFS, ETS, ORR and DCR) have been calculated.

Results: The systematic review of the literature led to the selection of 12 RCTs (7 phase-3, 5 phase-2). Despite the limitations and possible bias related to the limited number of patients with an ETS report for each study (in total 3117/4327 patients; 72%), ETS have a different performance in the whole sample vs. phase-3 trials (R2trial = 0.172 vs. 0.842), similarly to ORR (R2trial = 0.349 vs. 0.740). Of the response-related EPs DCR is the most closely related to OS (R2trial = 0.541 vs. 0.816). PFS was significantly related to OS when all trials are included but not when phase-3 trials only are considered (R2trial = 0.586 vs. 0.466).

Conclusion: In phase-3 trials response-related end points are more accurate in OS prediction and performs better than PFS. However ETS needs a prospective validation, considering its retrospective determination in all available trials. DCR is a very interesting intermediate EP also in studies with chemotherapy plus EGFR-inhibitors or chemotherapy alone and should be explored at pre-established time points.

P – 263 Survival analysis of a multicentre, randomized phase 3 study on the optimization of the combination of bevacizumab with FOLFOX/OXXEL in patients with metastatic colorectal cancer (mCRC)

A Avallone[1], G Nasti[2], G Rosati[3], C Carlomagno[4], C Romano[5], D Bilancia[6], A De Stefano[5], L Silvestro[5], A Ottaiano[5], A Cassata[5], F Bianco[5], F Izzo[7], P Delrio[5], E De Gennaro[5], R Casaretti[8], S Tafuto[5], V Albino[5], U Pace[5], S Lastoria[5], C Gallo[9], A Budillon[5], M Piccirillo[5]

[1]Abdomen Medical Oncology, Istituto Nazionale Tumori - IRCCS - Fondazione G. Pascale, Naples, Italy, [2]Dipartimento di Oncologia Medica, Istituto Nazionale per lo Studio e la Cura dei Tumori Fondazione G. Pascale, Naples, Italy, [3]Medical Oncology, San Carlo Hospital, Potenza, Italy, [4]Azienda Ospedaliera Universitaria Federico II, Naples, Italy, [5]IRCCS Fondazione G. Pascale, Naples, Italy, [6]S. Carlo Hospital, Potenza, Italy, [7]IRCCS Fondazione G. PAscale, Naples, Italy, [8]Istituto Tumori - Fondazione Pascale, Naples, Italy, [9]Università Vanvitelli Napoli, Naples, Italy

Introduction: Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, approved in combination with chemotherapy in the treatment of mCRC. It is proposed that its schedule of administration might be critical and that anticipating bevacizumab to chemotherapy might improve treatment efficacy.

Methods: mCRC patients, ≤ 75 years, ECOG PS ≤ 1 were randomized (1:1) to receive standard (S) administration of bevacizumab (5mg/kg d1 Q14) with chemotherapy (mFOLFOX/OXXEL regimen for 12 cycles) vs experimental (E) bevacizumab given 4 days before chemotherapy (same dose), at each cycle. Patients could receive maintenance bevacizumab until disease progression or unacceptable toxicity. Primary end point was the objective response rate (ORR). With 80% power and 2-tailed alpha 0.05, an expected 20% increase in response rate, 230 patients were planned. With 163 events, the study also had 80% power to detect a 0.64 hazard ratio (HR) of progression-free survival (PFS). Analyses were based on intention to treat. Correlative studies on biomarkers and FDG-PET were also planned.

Results: From May 2012 to Dec 2015, 230 patients were randomised to E (n = 115) and S (n = 115) arm. Median age was 62 (IQ range 53-68), 79% were PS 0, 93% were not pretreated, 53% had a single metastatic site, 71% had a left primary site; RAS-mutant tumors were less frequent in the S vs E arm (54/108 [47%]vs 71/108 [57%]). ORR was 54% in both arms (p = 0.89). With a median follow-up of 42 months, 209 PFS events and 150 deaths were reported. Median PFS was 10.5 and 11.7 months (HR 0.80, 95% CI: 0.61-1.06; multivariate adjusted p = 0.12) and median OS was 23.8 and 29.1 months (HR 0.70, 95% CI: 0.51-0.97; multivariate adjusted p = 0.03), in the S and E arm, respectively. Rate of patients receiving treatment after progression was similar in the two arms.

Conclusion: Although anticipating bevacizumab to chemotherapy does not improve ORR, its association with a significant longer OS suggests that the schedule of administration of bevacizumab in combination with chemotherapy could be critical to improve treatment efficacy in mCRC patients. Supported by the Italian Ministry of Health. CT.gov NCT01718873.

P – 264 HGCSG1401: A retrospective cohort study evaluating the safety and efficacy of regorafenib in patients with metastatic colorectal cancer: Analysis of risk factors for liver dysfunction

T Honda[1], S Yuki[2], T Muranaka[3], H Nakatsumi[3], Y Tsuji[4], T Miyagishima[5], S Yoshida[6], K Hatanaka[7], T Sasaki[8], A Ishiguro[9], O Muto[10], H Ohnuma[11], S Kato[12], A Sato[13], M Abe[14], K Kato[15], K Onodera[16], K Eto[17], M Tateyama[18], T Amano[19], Y Sakata[20], Y Komatsu[21]

[1]Division of Clinical Oncology Center, Nagasaki University Hospital, Nagasaki, Japan, [2]Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan, [3]Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [4]Department of Medical Oncology, Tonan Hospital, Sapporo, Japan, [5]Department of Internal Medicine, Kushiro Rosai Hospital, Kushiro, Japan, [6]Department of Gastroenterology, The University of Tokyo Hospital, Tokyo, Japan, [7]Department of Gastroenterology, Hakodate Municipal Hospital, Hakodate, Japan, [8]Department of Internal Medicine, Hokkaido Gastroenterology Hospital, Sapporo, Japan, [9]Department of Medical Oncology, Teine Keijinkai Hospital, Sapporo, Japan, [10]Department of Medical Oncology, Japanese Red Cross Akita Hospital, Akita, Japan, [11]Department of Medical Oncology and Hematology, Sapporo Medical University, Sapporo, Japan, [12]Department of Gastroenterology, Sapporo Hokuyu Hospital, Sapporo, Japan, [13]Department of Medical Oncology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan, [14]Department of Medical Oncology, Sapporo-Kosei General Hospital, Sapporo, Japan, [15]Department of Gastroenterology, Iwamizawa Municipal General Hospital, Iwamizawa, Japan, [16]Department of Gastroenterology and Hepatology, Sapporo Medical University, Sapporo, Japan, [17]Department of Gastroenterology, Tomakomai City Hospital, Tomakomai, Japan, [18]Department of Internal Medicine, Tomakomai Nisshou Hospital, Tomakomai, Japan, [19]Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan, [20]Misawa City Hospital, Misawa, Japan, [21]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan

Introduction: Regorafenib (REG) prolongs overall survival (OS) and progression-free survival (PFS) for patients (pts) with metastatic colorectal cancer (mCRC) in RCTs. However, there is a problem with REG-induced severe liver dysfunction (≥Grade 3) which occurs in 5-11% of treated Japanese pts. Therefore, we analyzed the incidence, therapeutic efficacy, and potential risk factors for REG-induced severe liver dysfunction in a community-based retrospective study (HGCSG1401) of pts treated with REG.

Methods: 173 pts treated with REG were retrospectively registered from 22 centers in Japan. Survival analyses were performed with Kaplan-Meier method. Log-rank test and Cox-proportional hazard model were used to compare Grade 0-2 and 3-5. To identify risk factors for REG-induced severe liver dysfunction, a multivariate analysis was performed using the logistic regression analysis with backward elimination for variables with $p < 0.10$ in univariate analysis.

Results: In 173 eligible pts, 24 (13.9%) experienced REG-induced severe liver dysfunction. The median PFS of Grade 0-2 and 3-5 were 2.2 and 1.6 months, respectively. The median OS of Grade 0-2 and 3-5 were 6.9 and 3.4 months, respectively. In the analysis of PFS and OS, there were significant difference between Grade 0-2 and 3-5 (PFS: HR 1.578, p = 0.045, OS: HR 1.799, p = 0.010). Univariate analyses showed that high AST, LDH, ALP, and GGT level at baseline were associated with REG-induced severe liver dysfunction. In multivariate analyses, high baseline AST level (≥ 50 U/L) was significantly associated with increased risk of REG-induced severe liver dysfunction (odds ratio=3.458, p = 0.032).

Conclusion: Compared with previous reports, this analysis showed the slightly higher incidence of REG-induced severe liver dysfunction (13.9%). In multivariate analysis, it was inferred that high AST level (≥ 50 U/L) at baseline might be an independent risk factor. REG-induced severe liver dysfunction population significantly showed shorter OS than mild liver dysfunction. It is presumed that this patient population could not receive TAS-102 as post regorafenib therapy. Since this is an exploratory analysis, we consider it necessary to verify in large data set.

P – 265 Treatment choices in metastatic colorectal cancer according to sidedness and RAS/BRAF status: A national survey by the Brazilian Group of Gastrointestinal Tumors (GTG)

R Peixoto[1], R Riechelmann[2], G Prolla[3], R Weschenfelder[4], J Rego[5], G Dos Santos Fernandes[6], G Pereira[7], M de Oliveira[8], D da Rocha Filho[9], A Coutinho[10]

[1]Hospital Alemão Oswaldo Cruz, São Paulo, Brazil, [2]AC Camargo Cancer Center, São Paulo, Brazil, [3]Hospital Mãe de Deus, Porto Alegre, Brazil, [4]Hospital Moinhos de Vento, Porto Alegre, Brazil, [5]Liga Contra o Câncer, Natal, Brazil, [6]Hospital Sirio Libanês, Brasília, Brazil, [7]Centro de Oncologia do Paraná, Curitiba, Brazil, [8]Oncologia DOr, Rio de Janeiro, Brazil, [9]Fujiday, Fortaleza, Brazil, [10]Clínica AMO, Salvador, Brazil

Introduction: Tumor sidedness and RAS/BRAF status have changed the treatment landscape of metastatic colorectal cancer (mCRC). This study was performed to understand the first line choices of Brazilian oncologists for patients with advanced/unresectable metastatic colorectal cancer (mCRC), especially in the emergent context of tumor sidedness and RAS/BRAF V600E status.

Methods: This is a cross-sectional electronic survey composed of 6 questions, which was sent to Brazilian medical oncologists and medical oncology groups by email, Facebook and/or WhatsApp. The survey instrument assessed current practices in terms of first-line treatment choices for fit patients with mCRC, including left-sided wild-type (wt)-RAS/wt-BRAFV600E, right-sided wt-RAS/wt-BRAFV600E and any-side mutated RAS, considering that all drugs were available. The instrument also elicited data about years in practice in Medical Oncology, gender and how much of each oncologist's practice was dedicated to gastrointestinal tumors (GI). Those with at least 75% of their time dedicated to patients with GI malignancies were considered specialists. The questionnaire was open for answers for 12 days.

Results: The survey was completed during a 12-day period by 222 medical oncologists from across the country. Because the survey was not sent to all individual emails, we could not estimate the response rate but for those who responded, the completion rate was 100%. Most oncologists were male (57.2%) and were in Oncology practice for less than 10 years (61.7%). Only 9.4% of the participants were specialists in GI tumors. For left-sided, wt-RAS/wt-BRAFV600E mCRC, most oncologists (81.9%) chose first line chemotherapy (CT) + anti-EGFR therapy, with 53.2% of them preferring FOLFIRI as the CT backbone. Meanwhile, for right-sided, wt-RAS/wt-BRAFV600E mCRC, the majority (71.1%) would offer CT + bevacizumab (53.7% with FOLFOX, 31.6% with FOLFIRI and 14.5% with FOLFOXIRI). For mutated-RAS mCRC, most oncologists (51.8%) decided for FOLFOX + bevacizumab (33.6% for FOLFIRI + bevacizumab and 14.5% for FOLFOXIRI + bevacizumab).

Conclusion: This is the first study conducted among Brazilian oncologists to investigate treatment preferences according to sidedness and RAS/BRAF V600E status. Our survey indicates that tumor sidedness influences the choice of both CT backbone and monoclonal antibody in unresectable wt- RAS mCRC.

P – 266 Retrospective analysis of clinical factors associated with a greater benefit with Trifluridine and Tipiracil in metastasic colorectal cancer

N Rodriguez-Salas[1], M Soriano Segura[2], A Jimenez-Gordo[3], R Molina[4], J Cámara[5], A Lopez Alfonso[6], B Martínez-Amores[7], A Pertejo Fernandez[8], G Reynoso[9], J Miranda Poma[8]

[1]University Hospital La Paz, Madrid, Spain, [2]Hospital Universitario Puerta de Hierro, Madrid, Spain, [3]Hospital de Getafe, Getafe, Spain, [4]Department of Medical Oncology, Principe de Asturias University Hospital, Alcalá University, Alcalá de Henares, Alcalá de Henares, Spain, [5]H. Universitario Fundacion Alcorcón, Alcorcón, Spain, [6]Hospital Universitario Infanta Leonor, Madrid, Spain, [7]Department of Medical Oncology, Principe de Asturias University Hospital, Alcalá University, Alcalá de Henares, Alcalá de Henares, Spain, [8]Hospital Universitario La Paz, Madrid, Spain, [9]Hospital Civil de Guadalajara, Guadalajara, Mexico

Introduction: Colorectal cancer (CRC) is the most incident in Spain, according to Spanish Network of Cancer Registries (REDECAN) and is the second cause of death by cancer in Spain. Although the OS in metastatic setting has increased to 24-30 months, the 5-year OS continues to be less than 12%. The first and second line of treatment are well defined; however, there are few therapeutic options for those patients who have progressed to these standard therapies. After progression to the second line of treatment, the only therapeutic options with approved specific indication are Regorafenib and Trifluridine and Tipiracil. Trifluridine and Tipiracil has shown its efficacy in two randomized clinical trials comparing Trifluridine and Tipiracil versus placebo: a Phase II and a Phase III study (RECOURSE). In the previous Phase II study, the mOS was 9.0 months in the group treated with Trifluridine and Tipiracil, compared to 6.6 months in the placebo group. In the RECOURSE study, among patients treated with Trifluridine and Tipiracil mPFS was 2 months versus 1.7 months among those treated with placebo, and mOS was 10,5 with Trifluridine and Tipiracil vs 7,6 with placebo. We described the clinical characteristic of patients treated with Trifluridine and Tipiracil in seven hospitals from Madrid; identifying and analyzing clinical factors associated with long-term response.

Methods: We collected retrospectively the clinical data of 98 patients who had received treatment with Trifluridine and Tipiracil until January 2018 in seven different hospitals in Madrid.

Results: The mean age at first use of Trifluridine and Tipiracil was 66± 9.45 years, 57.5% were men and 42.3% were women, most of them in good performance status (ECOG 0-1: 71.2%), 27.8% had ECOG ≥2 when started Trifluridine and Tipiracil. All of the patients were diagnosed of metastatic colorectal cancer (73.2% had liver metastases, 58.2% lung metastases and 30.9% peritoneal metastases). Tumor localization was: 73.2% left colon, 24.8% right colon, and only 2% small intestine or 1% two synchronous colonic tumors. KRAS mutations were found in 62.9%, NRAS mutations in 17.4% and BRAF mutations were found in 5.4% patients. The median of prior lines of chemotherapy was three. The median progression free survival was 3 months (95% CI 2.65 – 3.36). The median overall survival was 5 months (95% CI 4.23-5.78). The median duration of treatment was 3 cycles. 23.7% patients had an adverse event that led to treatment withdrawal. The requirement of dose-reduction was associated with longer PFS (4 months vs 3 months, $p = 0.002$) and OS (14 months vs 5 months, $p = 0.017$). The existence of BRAF mutation was also associated with shorter PFS (1 month vs 3 months, $p = 0.002$) and OS (1 month vs 5 months, $p = 0.000$). There was no statistically significant difference of PFS and OS according to primary tumor location.

Conclusion: Trifluridine and Tipiracil is effective in metastatic colorectal cancer (in patients with ≥2 lines of treatment). The OS (5 months) and PFS (3 months) reached in our study in real clinical practice are consistent with findings from previous studies. Mutational status of BRAF was statistically significant associated with shortened PFS and OS. Dose reduction during treatment is associated with Trifluridine and Tipiracil efficacy in terms of prolonged OS and PFS.

P – 267 The prognostic impact of sidedness in RAS wild-type colorectal cancer

N Tavares[1], A Costa[1], D Almeida[1], S Meireles[2], C Fernandes[1], C Rey[3], C Sarmento[2], M Damasceno[2]

[1]Hospital S. João, Porto, Portugal, [2]Hospital de S. João, Porto, Portugal, [3]Centro Hospitalar de São João, EPE, Porto, Portugal

Introduction: Colorectal cancer (CRC) is a heterogeneous disease and sidedness [right colon (RC) vs. left colon (LC)] reflects different clinical, biological and molecular behaviors, which could have a significant prognostic impact. This study tried to evaluate the impact of sidedness on overall survival (OS) and progression-free survival (PFS) in RAS wild-type (RAS-WT) CRC patients treated with anti-EGFR antibodies in first line palliative chemotherapy.

Methods: Retrospective cohort of adult patients with CRC RAS-WT treated with anti-EGFR antibodies in first line palliative chemotherapy between 01/01/2012 and 31/12/2016 in a tertiary university hospital. Differences between groups were determined according to chi-square test; OS and PFS were estimated by Kaplan-Meier method and multivariate analysis according to Cox regression; a significant level of 0.05 was chosen to assess the statistical significance.

Results: We included 65 patients. Fifteen patients had RC tumors (cecum: 5; ascendant: 1; hepatic flexure: 1; proximal transverse: 6) and 50 had LC tumors (splenic flexure: 3; descending: 3; sigmoid: 33; rectum: 11). The median age at diagnosis of metastatic disease was 63 years-old [28-79]. Thirty eight patients (58.5%) were treated with cetuximab and 27 (41.5%) with panitumumab. Concomitant chemotherapy protocol was FOLFIRI in 41 patients (63.1%), FOLFOX in 19 (29.2%) and irinotecan in 5 (7.7%). There were no statistically significant differences between RC and LC groups. The median OS was 33.8 months (CI 95% 19.4-48.3 months). In univariate analysis, patients with RC cancer had an unfavorable OS (RC 26.8 vs. LC 43.4 months, $p = 0.001$). An ECOG performance status ≥1 at metastatic diagnosis, presence of bone metastases, hypomagnesemia during anti-EGFR treatment and irinotecan monotherapy had prognostic impact on OS. In multivariate analysis, ECOG ≥1 (HR 0.323, CI 95% 0.149-0.698, $p = 0.004$), RC (HR 0.322, CI 95% 0.129-0.804, $p = 0.015$), irinotecan monotherapy (HR 0.319, CI 95% 0.097-0.869 $p = 0.027$) and bone metastases (HR 0.220, CI 95% 0.058-0.838, $p = 0.027$) kept their negative prognostic impact in OS. The median PFS was 13.0 months. Patents with RC (RC 7.5 vs. LC 16.3 months, $p < 0.001$) and those who were treated with Irinotecan monotherapy (irinotecan 8.2 vs. FOLFOX/FOLFIRI 13.9 months, $p = 0.003$) also had worse PFS, both in univariate and multivariate analysis.

Conclusion: In our cohort of CRC RAS-WT patients, right-sided tumors demonstrated worse OS and PFS, thus reflecting the significant prognostic impact of sidedness. Growing evidence on sidedness should alert oncologists to RC cancer patients as a group with a more aggressive disease and for which the optimal treatment strategy is still controversial. Performance status, the presence of bone metastases and treatment with irinotecan monotherapy vs. FOLFOX/FOLFIRI also emerged as prognostic factors.

P – 268 Advanced colorectal cancer and risk factors for survival

D Kaidarova[1], K Smagulova[2], S Yesentaeva[3], Y Ishkinin[1], Y Ukolova[1], A Kurmankulova[1]

[1]Kazakh Research Institute of Oncology and Radiology, Almaty, Kazakhstan, [2]Kazakh Science Research Institute Oncology and Radiology, Almaty, Kazakhstan, [3]Kazakh-Russian Medical University, Almaty, Kazakhstan

Introduction: Colorectal cancer (CRC) is one of the most common localizations of malignant tumors. Given the characteristics of the course of this disease and its diagnosis lead to a large prevalence of advanced form. In the Republic of Kazakhstan CRC takes a leading position in the structure of cancer incidence. In 2015 in Kazakhstan

registered 3686 CRC patients and 1840 CRC patients died. Despite the fact that significant progress has been made in the treatment of CRC in recent years, this disease is still one of the leading causes of mortality from cancer pathology.

Methods: Retrospective study of 287 patients with advance colorectal cancer who tested the mutational status of the KRAS gene. 60.2% of patients have negative and 39.8% of patients have positive mutational status of the KRAS gene. The most common forms of mutation are G12D (12.5%), G13D (10.1%) G12V (8.4%). Right side of intestinum lesion was in 42 (14.6%) patients, left side intestinum in 128 (44.6%) patients, rectum in 117 (40.8%) patients. Median of follow- up was 25.1 month. Overall survival (OS) was calculated from the start of treatment to death from any cause or until the date of the last appearance of the patient. Survival was estimated by Kaplan- Meier survival curves, comparison of curves by Log rank test.

Results: OS 24%, median was 24 months, SE 0.9, CI 95% (22.3 – 25.7). Risk factor differences not significant for: gender ($\chi2 = 0.01$ p = 0.9), ethnic group ($\chi2 = 0.19$ p = 0.7), age < 50 survival median was 27-months, age > 50 survival median was 24 months ($\chi2 = 2.46$ p = 0.12). Standard chemotherapy survival median was 24-months, target chemotherapy survival median was 26 months ($\chi2 = 0.25$ p = 0.62). Adenocarcinoma histology type survival median was 25 months, for mucosa histology type survival median was 17 months ($\chi2 = 1.1$ p = 0.29). Positive mutational status of the KRAS gene survival median was 24 months. Positive mutational status of the KRAS gene survival median was 24 months. For T3 category survival median was 26 months for T4 spread was 24 months ($\chi2 = 2.1$ p = 0.15). For new metastasis during treatment survival median was 24 months, for no metastases during treatment survival median was 27 months ($\chi2 = 1.03$ p = 0.31). Differences in OS was significant for: metastasis in regional lymph nodes, survival median was 23 months, N0 survival median was 27,4 months ($\chi2 = 12.1$ p = 0,01). G3 tumor differentiation survival median was 20 months, for G2 survival median was 26 months, G1 survival median was 28 months ($\chi2 = 7.78$ p = 0,02). Intestinum right side OS was 26.2%, survival median 24 months, left side OS was 27.3% survival median 26 months, rectum OS was 19.7% survival median 21 months ($\chi2 = 4.8$ p = 0,04).

Conclusion: Metastasis in regional lymph nodes and G3 tumor differentiation are significant risk factors for advance colorectal cancer.

P – 269 Dynamics of the monoclonal antibodies (MABs) treatment rate and mortality rate in patients with metastatic colorectal cancer (mCRC) in Russia from 2013 to 2016

M Fedyanin, H Elsnukaeva, E Polyanskaya, A Popova, I Pokataev, E Ignatova, A Bulanov, A Tryakin, S Tjulandin

N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation

Introduction: Previously, we revealed inverse significant association between mortality rate from mCRC in 2014 and the irinotecan treatment rate in 2013 in Russian regions (Ann Oncol (2016) 27 (suppl 2): ii15). The aim of this study was to evaluate dynamics of penetration of different chemotherapy drugs and Mabs and mortality rate in a population of patients with mCRC across 82 regions of Russia from 2013 to 2016.**Methods:** We have compared the mortality rate for mCRC patients sourced by the National Russian State Cancer Register in and the Russian Government purchasing published data on hospital tenders for oxaliplatin, irinotecan, capecitabine and MABs (bevacizumab, cetuximab, panitumumab, aflibercept) at regional level across 82 regions within the period of 2013-2016. Given that the expected median overall survival for mCRC patients varies from 18 to 29 months, the correlation was explored between penetration recorded for 2013/2015 and mortality rate recorded for 2014/2016, accordantly. The penetration was defined as a number of mCRC patients that were enrolled on a particular drug treatment divided by the total number of patients suitable for the particular treatment. The mortality rate was defined as percentage of deaths among of all patients with CRC. Regression test was applied. Statistical analyses were performed using Statistical Package for the Social Sciences Version 22.0 (SPSS Inc., Chicago, IL).

Results: We revealed the significant increase of mean number of patients who received chemotherapy in regions from 2013 to 2016: capecitabine (from 51.3 to 56.6, p < 0.01), oxaliplatin (from 67.2 to 88, p = 0.07) and irinotecan (from 31.3 to 45.1, p < 0.01). There was stable level of patients who received MABs from 2013 to 2016: bevacizumab (from 35.1 to 38.9, p = 0.3) and anti-EGFR antibodies (from 18.4 to 18.3, p = 0.2). According to the regression analysis the relationship of penetration for any MABs only (β=-0.09, 95%CI -0.16 - -0.018, p = 0.015) with the mortality decrease has been detected. There weren't any relationship between penetration and mortality rate for oxaliplatin (β=-0.06, 95%CI -0.14 - 0.025, p = 0.16), for irinotecan (β = 0.007, 95%CI -0.067 - 0.081, p = 0.85), for capecitabine (β=-0.037, 95%CI -0.12 - 0.046, p = 0.38), for bevacizumab (β=-0.15, 95%CI -0.12 - 0.024, p = 0.17), for cetuximab (β = 0.018, 95%CI -0.03 - 0.066, p = 0.36), for panitumumab (β=-0.017, 95%CI -0.033 - 0.062, p = 0.54) and for aflibercept (β = 0.046, 95%CI -0.034 - 0.127, p = 0.25).

Conclusion: Emerging penetration for any Mabs in mCRC patients population appear to have a significantly correlation with the mortality reduction. Increase of chemotherapy use in the population of patients with mCRC from 2013 to 2015 led to significant effect of penetration of targeted therapy in 2015 on mortality in 2016 in Russia.

P – 270 Association between duration of oxaliplatin-free interval and effect of reintroduction of oxaliplatin-containing chemotherapy in patients with metastatic colorectal cancer (mCRC)

M Fedyanin, A Tryakin, A Bulanov, A Popova, E Ignatova, O Sekhina, D Chekini, E Polyanskaya, H Elsnukaeva, I Pokataev, S Tjulandin

N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation

Introduction: Reintroduction of chemotherapy and targeted agents is one of the suitable treatment options in patients with mCRC after 3rd line of therapy. The aim of this study was to evaluate association between duration of oxaliplatin-free interval and effect of reintroduction of oxaliplatin-containing chemotherapy.

Methods: Patients who received oxaliplatin-containing regimen (FOLFOX, XELOX, FLOX) at least in two lines were included in the study. Only 47 of 430 (10.9%) patients met the inclusion criteria. The mean age was 58 (min 38 max 81, σ = 9.3), male – 40.4%, right sided tumor was revealed in 29.8%, primary tumor was resected in 91.5% of cases, metastasectomy was performed in 38.3%. The main primary endpoints were progression free survival (PFS) and overall survival (OS). A two-sided significance test with a P value of less than 0.05 was considered significant. Statistical analyses were performed using Statistical Package for the Social Sciences Version 22.0 (SPSS Inc., Chicago, IL).

Results: Reintroduction of oxaliplatin was performed more often in 3rd line, after 1st line oxaliplatin-containing chemotherapy – in 20 (42.6%) patients, after adjuvant chemotherapy – in 4 (8.5%), after 2nd line – in 1 patient. Also, oxaliplatin was administered in the 1st line after adjuvant oxaliplatin-containing chemotherapy in 12 (25.5%) patients, in 2nd line after 1st line or after adjuvant oxaliplatin-containing chemotherapy - in 8 (17%) and 2 (4.3%) of patients, respectively. Median PFS for patients with oxaliplatin-free interval < 6 months (n = 25) was 3 months, 7-23 months (n = 13) – 5 months and ≥ 24 months (n = 9) – 6 months (HR 0.76, 95%CI 0.5-1.0, p = 0.1). Median OS for patients with oxaliplatin-free interval <6 months was 5 months, 7-23 months - 12 months and ≥24 months - 24 months (HR 0.64, 95%CI 0.4-0.9, p = 0.04).

Conclusion: The clinical and statistical significant effect of reintroduction of oxaliplatin-containing chemotherapy on progression free and overall survival was achieved only if the duration of oxaliplatin-free interval was more than 6 months.

P – 271 Prognostic impact of K-RAS mutational status and primary tumour location in patients undergoing resection for colorectal cancer liver metastases: A METHEPAR analysis (multicentre study in Argentina)

J O'Connor[1], E Huertas[2], F Sanchez Loria[2], F Brancato[2], J Grondona[3], M Fauda[4], O Andriani[5], P Sanchez[6], P Barros Schelotto[7], V Ardiles[8], E de Santibañes[9]

[1]Institute Alexander Fleming, Buenos Aires, Argentina, [2]Instituto Alexander Fleming, Caba, Argentina, [3]Sanatorio San Lucas, San isidro, San Isidro, Argentina, [4]Hospital Universitario Austral, Pilar, Argentina, [5]Surgical Department Hospital Austral, Sanatorio Los Arcos, Caba, Argentina, [6]Instituto A Roffo, Caba, Argentina, [7]Fundacion Favaloro, Caba, Argentina, [8]Hospital Italiano Buenos Aires, Caba, Argentina, [9]Hospital italiano Buenos Aires, Caba, Argentina

Introduction: Even though RAS mutations are known to imply aggressive tumour biology, their objective impact on survival is still controversial. The purpose of this study is to determine the impact of KRAS mutational status in the overall survival (OS) and recurrence free survival (RFS) of patients undergoing surgery for colorectal liver metastases (CLM).

Methods: Patients with resected CLM from a multicenter collaborative database (METHEPAR) and known KRAS mutational status were included in the present study. Survival outcomes were compared between patients with mutated KRAS (mt-KRAS) versus wild-type KRAS (wt-KRAS).

Results: From a total of 662 patients evaluated, 174 patients (26,3%) were mt-KRAS, while 488 (73,7%) were wt-KRAS. At a median follow-up of 37 months, patients with mt-KRAS had significantly less RFS than those with wt-KRAS (HR 1,42; 95% c.i. 1,10 – 1,84). Regarding the location of the primary tumour, 73,3% had left tumours and 25,5% had right tumours, and only 1,2% had both, without differences between the two groups. In multivariable analysis, a mt-KRAS along with positive lymph nodes, >1 metastases, >5 cm tumours, synchronic tumours and R1-R2 resections were independently associated with worse survival.

Conclusion: KRAS mutational status seems useful for the prediction of RFS. In our Multicentric Study we couldn't confirm location of the primary tumour, as a prognostic factor in pts. with resected liver metastases. In pts. with CRC after curative resection of CLM, KRAS mutation status may be used to individualize multidisciplinary approach.

P – 272 Understanding of metastatic colorectal cancer (mCRC) in the real world: Initial results from a European survey on the unmet needs of patients living with metastatic colorectal cancer

Z Maravic[1], L Wyrwicz[2], B Karczmarek-Borowska[3], E Espín Basany[4], A Carrato[5], A Horvath[6], àBenedict[7], Z Kapitány[8]

[1]EuropaColon, Salisbury, UK, [2]Centrum Onkologii-Instytut im. M. Sklodowskiej Curie, Warsaw, Poland, [3]Center of Clinical Oncology of Provincial Hospital No. 1, Rzeszów, Poland, [4]Hospital Valle de Hebron, Universitat Autonoma de Barcelona, Barcelona, Spain, [5]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain, [6]Semmelweis University, Budapest, Hungary, [7]Evidera, Budapest, Hungary, [8]Semmelweis University Faculty of Health Sciences, Budapest, Hungary

Introduction: EuropaColon, a European CRC patient organisation, planned and executed a survey in 12 European countries on the Unmet Needs of Patients Living with mCRC. The aim of this patient survey was to understand the challenges and needs of those living with mCRC and their health-related quality-of-life challenges. Recruitment in Hungary, Serbia and Spain was completed. The objective of this paper is to describe basic demographics and patient responses about discovery of the disease in these four countries.

Methods: The survey included sections on demographics, patient discovery of the disease, diagnosis and treatment. The section on patient discovery comprised of 13 questions, including reasons for contacting physicians, symptoms experienced, the delay between first symptoms and seeking clinical help, and misdiagnosis. IRB approval, where needed, was sought for the survey. Clinicians and nurses together with EuropaColon partner organisations recruited patients for the survey. Patients could complete either a paper-based survey or an on-line form. Data entry from the paper surveys was done by EuropaColon.

Results: Altogether 578 surveys were collected and analyzed with 170 from Serbia, 163 from Poland, 112 from Spain and 103 from Hungary. Most surveys were received in paper format (80%). Completion rates varied across responses, but in general were high. Average age of patients across these countries was 70.4, ranging from 63.2 years in Spain to 81.3 in Poland. The sample included 55% men and 45% women. Most patients had a secondary education and were retired (64%). Approximately 50% of patients were diagnosed on a routine exam or due to symptoms not related to CRC, while only 4% were discovered through screening programmes. 56% of patients would have participated in screening if invited. CRC symptom awareness in the analyzed sample was very low – only 26% of patients knew what symptoms may have been associated with CRC. Although 35% of patients waited less than a month from observing symptoms, 33% waited 1-3 months, 14% waited 3-6 months and the rest even longer. Similar delays were observed for diagnosis. Importantly, 23.5% indicated that they were misdiagnosed. Overall, 48% of patients were 'very satisfied' with the process of establishing a diagnosis however, there was large variation across countries – including 35% in Hungary who were 'not satisfied at all'.

Conclusion: The survey captured a large and diverse patient population and is a reflection of patients with recent experiences. Patient awareness of CRC is low, with few respondents recognizing symptoms and seeking help without delay. Misdiagnosis levels are still high. The attitude towards screening programmes is positive among patients, but despite the existence of different types of screening programmes in these countries, awareness and compliance rates are low. The understanding of CRC needs to be improved at patient level and most importantly at clinical diagnosis.

P – 273 Recruitment for a survey on the unmet needs of patients living with metastatic colorectal cancer (mCRC): Lessons from a European study

Z Maravic[1], J Stanisic Trenevski[2], J Bokros[3], A Ruiz Casado[4], C González de Pedro[5], M Méndez Otero[5], J Borràs[6], T Ferro[7], O Rial[7]

[1]EuropaColon, Salisbury, UK, [2]Dom zdravlja Voždovac, Belgrade, Serbia, [3]Semmelweis University, Budapest, Hungary, [4]Hospital Puerta de Hierro-Majadahonda, Majadahonda, Spain, [5]Servicio de Oncología Médica, Hospital Puerta de Hierro - Majadahonda, Majadahonda (Madrid), Spain, [6]ICO l'Hospitalet, Hospitalet de Llobregat, Spain, [7]Catalan Institute of Oncology, L'Hospitalet de Llobregat, Barcelona, Spain

Introduction: Colorectal cancer is still a taboo for many patients and there is little information about the patient's experience in general practice. Much of what is known about their quality-of-life comes from clinical trials – that are not representative of everyday patient experience. To fill this gap, EuropaColon, a European CRC patient organisation, planned and carried out a survey on the Unmet Needs of Patients Living with Metastatic Colorectal Cancer (mCRC). The aim of the survey was to better understand the challenges and needs of those living with mCRC as well as to understand their quality-of-life.

Methods: The English survey was translated into 11 languages (German, Greek, Hungarian, Italian, Dutch, Serbian, Spanish, Polish, Portuguese and Turkish). It covered demographics, the illness (discovery, diagnosis, treatment and support), and health-related quality-of-life instruments: EORTC QLQ-C30 and EORTC QLQ-C29. IRB approval, where needed, was obtained at the local hospital level. Recruitment was planned by directly contacting nurses and clinicians in specific hospitals that volunteered to help recruit for the survey, or through EuropaColon partner groups (Portugal, Serbia and Turkey), or both recruitment strategies were used (Spain, Netherlands, Poland and UK). Healthcare teams were asked to inform patients about the survey and provided them with an information leaflet and patients would need to make an effort to complete the survey by visiting a dedicated web-page (europacolon.com/survey). They could either complete the survey on-line or download it, print it and complete on paper.

Results: After 4 months of recruitment, because of low response alternative strategies for patient recruitment had to be initiated. Different approaches were used in different countries. In Poland, Spain and Hungary, clinicians printed the survey to give paper copies to patients who would then complete on the spot. In Spain, 4 nurses had active roles in patient recruitment. In Serbia, Serbian CRC Patient Association printed and distributed 300 copies by mail to all centers treating mCRC patients with a pre-stamped envelope for the completed survey to be returned. A nurse from the Association made weekly calls to local clinicians in order to motivate them to recruit patients. By the end of February 2018, 719 patients had completed the survey. 202 patients (28%) completed the survey on-line while 517 patients (72%) completed the paper version. The majority of surveys came from Serbia (170), Poland (163), Spain (112) and Hungary (103).

Conclusion: It is possible to reach patients outside of the clinical trial setting and they are interested in expressing their views. Paper versions of the survey were preferred, especially in Central and Eastern Europe. Social media (i.e. Twitter) as a recruitment platform worked only in few Western European countries e. g. Netherlands and UK. This may reflect the access to technology across the elderly population. Patients from Central and Eastern Europe are far better motivated to express their opinion whilst in the Western countries there is greater saturation with this type of research. The recruitment will continue until the number of 1'000 patients is reached.

P – 274 The clinical effectiveness and safety of re-induction oxaliplatin, irinotecan and fluorouracil (FOLFOXIRI regimen) for the treatment of metastatic colorectal cancer after two lines of chemotherapy (oxaliplatin- and irinotecan-based regimens)

E Ledin[1], A Mochalova[1], Y Zaitseva[2]

[1]Clinical Hospital "Medsi", Moscow, Russian Federation, [2]N.N. Petrov National Medical Research Center of Oncology, Saint Petersburg, Russian Federation

Introduction: The choice of antitumor agents used in the treatment of metastatic colorectal cancer (mCRC) is limited, which reduces the therapeutic possibilities. The improvement in survival for mCRC patient led to there is a significant number of patients progressing beyond the second or third line of treatment still suitable for further therapy when enrollment into clinical trial is not possible. In this situation, any rechallenge therapy plays an important role. We evaluated the efficacy and safety of the re-induction of oxaliplatin, irinotecan and fluorouracil (FOLFOXIRI regimen) in the third line of chemotherapy mCRC.

Methods: A total of 22 patients (median age = 62) with mCRC, all of whom had developed progressive disease within at least 3 months of discontinuing two sequential chemotherapy lines (oxaliplatin- and irinotecan-containing regimens), were accrued in this study. The majority (85%) had FOLFOX as first-line chemotherapy and FOLFIRI as second-line chemotherapy. Bevacizumab was added to chemotherapy in 45% (n = 10) of patients. Only one patient was with wild-type KRAS genotype, therefore in the third-line all of other patients couldn't receive cetuximab. Treatment regimen third line was FOLFOXIRI (irinotecan 165 mg/m^2 on day 1, oxaliplatin 85 mg/m2 on day 1, leucovorin 400 mg/m2 on day 1, 5-fluorouracil 2400 mg/m2 46-hours infusion every 14 days). The response evaluation of antitumor treatment was carried out every 2 months on the basis of RECIST 1.1 criteria. The primary end point was progression free survival (PFS), the secondary end point was overall survival (OS), objective response rate (ORR) and safety.

Results: The median number of chemotherapy cycles was seven. The objective response rate (ORR) by intent-to-treat analysis was 23,8% (n = 5), and 61,9% (n = 13) had stable disease. The disease progression at the first follow-up examination was registered in 13,6% of cases (n = 3). The disease control rate was 86,4%. The median progression-free survival and overall survival were 5,2 months (range: 2-17 months) and 7,21 months (range: 4-35 months), respectively. The main hematological toxicity was grade III/IV neutropenia, which occurred in 27,2% of patients (n = 6), including febrile neutropenia in 3,1% (n = 5), while anemia and thrombocytopenia were uncommon. Grade III/IV non-hematological toxicities were asthenia nausea (9%); vomiting (9%), sensory neuropathy (4,5%) and diarrhea (13,6%). No toxic death was observed, one patient with grade IV vomiting after the eighth cycle refused chemotherapy.

Conclusion: The re-induction of oxaliplatin, irinotecan and fluorouracil (FOLFOXIRI) in the third line of mCRC treatment provided a significant antitumor effect. This approach significantly expands the therapeutic possibilities in mCRC and promotes an increase in the life expectancy of patients.

P – 275 Selective internal radiation therapy (SIRT) with yttrium-90 microspheres and peri-procedural FOLFIRI/irinotecan in pre-treated colorectal liver metastases patients: An analysis of outcomes from a UK Cancer Centre between 2009 and 2017

G Wilson[1], D Bentley[1], S Mullamitha[2], M Braun[1], M Nasralla[1], J Bell[1], D Mullan[3], J Hasan[1], M Saunders[4], F Marti[1], C McBain[1], N Alam[1], H Laasch[3], P Najran[1], T Westwood[1], S Jeans[1], J Tipping[1], P Manoharan[1], J Lawrance[1]

[1]The Christie NHS Foundation Trust, Manchester, UK, [2]The Christie Hospital NHS Foundation Trust, Manchester, UK, [3]The Christie Hospital, Manchester, UK, [4]Christie Hospital NHS Foundation Trust, Manchester, UK

Introduction: Selective Internal Radiation Therapy (SIRT) involves hepatic intra-arterial infusion of β-particle emitting Yttrium-90 labelled microspheres. SIRT increases first line response rates (RR) and hepatic progression free survival (hPFS) in liver predominant metastatic colorectal cancer (mCRC) patients treated with oxaliplatin/5FU/folinic acid (FOLFOX). SIRT is often used in pre-treated mCRC patients with peri-procedural FOLFOX to achieve radio-sensitization and control extra-hepatic disease. Since 2009 we have used FOLFIRI as an alternative peri-procedural regimen with SIRT.

Methods: Between 2009 and 2017 we treated 32 mCRC patients with SIRT and peri-procedural irinotecan based chemotherapy followed by further chemotherapy cycles at clinician's discretion. Nine patients also received concurrent cetuximab. Of 32 patients, 20 were KRAS wild type, 12 KRAS mutated. Extra-hepatic disease: 11 patients. Primary in-situ: 7 patients. Average number of metastatic lines of pre-SIRT chemotherapy was 2.1. Not included in the analysis were 4 patients who commenced FOLFIRI up to 2 weeks after SIRT and 11 patients who received FOLFIRI prior to SIRT but not peri-procedurally. 30/32 (94%) patients had prior oxaliplatin+5FU/capecitabine. 28/32 patients (88%) had prior irinotecan, 25 with 5FU/capecitabine. Thirty patients received FOLFIRI (irinotecan 180mg/m2, 5FU 400mg/m2 day 1 and 2400mg/m2 via infuser pump over 46 hrs) and 2 had single agent irinotecan with no 5FU given. In 26 cases SIRT was delivered on FOLFIRI day 2 with 5FU infusion continuing. Eight patients received SIRT within the 2 days prior to chemotherapy. The average number of subsequent cycles of FOLFIRI/irinotecan given after the SIRT+ chemo was 5.2. PET-CT was performed pre-SIRT and 2-3 months later. The median number of subsequent chemotherapy lines was 1 with 4 patients remaining alive at time of censorship. Data was correlated from retrospective case note review using standard statistical techniques to evaluate response, hepatic (h) and extra-hepatic (eh) progression free survival (PFS) and overall survival (OS). Due to the retrospective nature of the analysis, toxicity data was limited but there were no reported cases of neutropenic sepsis or death within 30 days of SIRT, and no cases of Radiation Induced Liver Disease (RILD).

Results: In the treated liver, responses were as follows: CT response rates: PR 28% (n = 9), SD 31% (n = 10) and PD 41% (n = 13); PET response rates: PR 34% (n = 11), SD 34% (n = 11), PD 31% (n = 10). Fourteen patients had PD outside the liver at first assessment. Of those 14 patients, 2 had PR and 2 had SD in the liver at that assessment. Median hPFS (n = 31) was 5.62 months (CI 3.22-6.64 m). Median ehPFS in the group with pre-SIRT known extra-hepatic disease (n = 11) was 2.60 months (CI 1.35-5.22 months). Median OS (n = 32) was 12.58 months (CI 9.07-16.30m).

Conclusion: SIRT with peri-procedural FOLFIRI in pre-treated mCRC patients produces encouraging response rates and survival. RILD was not observed and the treatment seems to be well tolerated. SIRT with FOLFIRI provides an alternative strategy for patients with pre-treated liver predominant mCRC.

P – 276 Raltitrexed as salvage therapy for metastatic colorectal cancer: A multicenter retrospective study

I Ghanem[1], A Viudez[2], E García-Torralba[3], J Torres-Tenor[4], A Carmona[3], R Vera[2], N Rodriguez-Salas[5], F Ayala de la Peña[3], O Higuera[6], J Feliu[1]

[1]University Hospital La Paz, Madrid, Spain, [2]Service of Medical Oncology, Hospital de Navarra, Pamplona, Spain, [3]Morales Meseguer University Hospital, Murcia, Spain, [4]University Hospital la Paz, Madrid, Spain, [5]University Hospital La Paz, Madrid, Spain, [6]University Hospital La Paz, Madrid, Spain

Introduction: Raltitrexed is used as an alternative to fluoropyrimidines (FP) for the treatment of colorectal cancer patients. We previously reported a retrospectively unicentric study analyzing the activity and tolerance of raltitrexed as salvage therapy for advanced colorectal cancer. Here, we report an update and an enlargement of the sample size as a multicenter study.

Methods: From January 2008 to June 2017, 134 metastatic colorectal cancer patients (p) treated with raltitrexed as salvage therapy at three Spanish Hospitals, monotherapy (72p; 54%) or combined with oxaliplatin (29p; 22%), mitomycin (26p; 19%), or other therapies (7p; 5%) were identified. Clinical characteristics, tolerability and efficacy were collected.

Results: One hundred and thirty-four p (70 men; 52%) with a median age of 67 years (range 28-86) and ECOG 0-1 (92p; 69%) or ECOG 2 (42p; 31%) were included. Fifty-seven p (42%) had received adjuvant therapy, 77p (57%) two previous lines for metastatic disease, and 57p (43%) three or more lines. Median time from metastatic diagnosis to first administration of raltitrexed was 24.9 months. All patients were previously treated with FP, irinotecan and oxaliplatin, 121p (90%) antiangiogenic therapy, 61p (45%) anti-EGFR therapy, 11p (8%) mitomycin, 7p (5%) regorafenib and 4p (3%) TAS 102. The most common sites of metastases were liver in 99p (74%) and lung in 95p (71%). Median number of cycles was 3 (1-37) and dose adjustment was done in forty-five p (34%), most of them (27p; 20%) at first cycle. One hundred and thirty-two p were evaluated for toxicity: 122p (91%) presented some adverse event (AE), grade 3-4 AE were observed in 35 p (26%). The most frequent AE were asthenia in 99 p (74%) and anemia in 79 p (59%). One p (0.7%) presented complete response, 2p (1.5%) partial response, 16p (12%) stable disease, 96 p (72%) progressive disease, and 19p (14%) were not evaluated. The median progression free survival and median overall survival were 2.4 (95% CI, 2.15 to 2.64) and 5.1 months (95% CI, 4.02 to 6.18) respectively.

Conclusion: Despite acceptable tolerance, in our multicenter retrospective study, raltitrexed does not seem to have activity as salvage therapy for metastatic colorectal cancer.

P – 277 Real world data in colorectal cancer: A retrospective analysis of overall survival in metastatic colorectal cancer patients between 2011-2015 treated in Spain, preliminary results (RWD-ACROSS study)

C Pericay[1], J Gallego[2], A Fernandez Montes[3], H Oliveres[4], H Asensio-Martínez[5], J Garcia-Gómez[6], J Fernandez-Plana[7], M Marín-Alcalá[8], M Ballester-Espinosa[5], M Salgado[9], I Macías Declara[10], L Gómez-González[5], L Iglesias-Rey[6], I Cirera[11]

[1]Hospital de Sabadell, Corporació Sanitaria Parc, Taulí-Institut Universitari, Sabadell, Spain, [2]Hospital General Universitario de Elche, Elche, Spain, [3]Complexo Hospitalario Universitario de Ourense, Ourense, Spain, [4]Parc Tauli Hospital-Sabadell, Sabadell, Spain, [5]Hospital General de Elche, Elche, Spain, [6]Hospital de Ourense, Ourense, Spain, [7]Hospital Mutua de Terrassa, Terrassa, Spain, [8]Parc Tauli, Sabadell, Spain, [9]Complejo Hospitalario Universitario de Ourense, Orense, Spain, [10]Corporació Sanitaria Parc Taulí, Sabadell, Spain, [11]Mutua Terrassa, Terrassa, Spain

Introduction: Colorectal cancer is a global problem due the incidence and prevalence. Clinical trials do not represent treatment of real life population effectiveness, so real world data trials are needed. Aim: We present preliminary results based on a registry for Spanish metastatic colorectal cancer (mCRC) patients.

Methods: Cohort study including 4 hospitals in Spain. Inclusion criteria: Aged≥18 years(y), histological confirmation mCRC, at least 1 cycle of chemotherapy(CT) administered, mCRC diagnosed between 01/2011-12/2015. Overall survival(OS) was calculated from time of mCRC diagnosis to death or date of last contact. Kaplan-Meier curves were used to estimate median survival and survival rates. The study was approved by Ethics Committees.

Results: 804pts were analyzed. Median age: 65.7y. Ratio male/female: 64.9%/35.1%. Synchronous or metachronous tumors: 5.7%. RAS-mutations were seen in 50.1%, BRAF-mutations in 1.6% and RAS/BRAF-wild type in 48.3% of pts. MSI (Microsatellite Instability) was in 3.4%. Ratio left/right: 73.4%/26.1%. Metastatic site location at diagnosis: liver 36.6%, lung 8.6%, peritoneal 8.7%, liver+lung 10.1% and liver+peritoneal 6.1%. 63.8%pt received 2 lines, 28.5% 3 lines and 9.1% 4 or more lines. In the cohort analysed, 74.8%pt had died. Relation of lines of therapy and drugs used are shown in Table1. Chemotherapy 1st line: alone 51.6%, plus antibody 48.4% (EGFR 46.0%, VEGF 53.2%), oxaliplatin 55.3%, irinotecan 27.4%, 5FU 12.4%. Chemotherapy 2nd line: alone 51.5%, plus antibody 48.5% (EGFR 38.8%, VEGF 60.7%), oxaliplatin 26.3%, irinotecan 57.5%, 5FU 9.0%. Chemotherapy 3rd line: alone 59.2%, plus antibody 40.8% (EGFR 36.3%, VEGF 49.5%), oxaliplatin 23.6%, irinotecan 32.5%, 5FU 20.2%. mOS: 23.4 months(m). mPFS (Progression free survival): 1stline: 9.6m, 2ndline: 7.6m and 3rdLine: 6.7m. OS left/right: 25.2m vs 18.0m (HR:0.634, P <.001). The probability of surviving beyond 12m was 73.3%, beyond 24m was 48.2%, beyond 36m was 30.7% and beyond 48m was 21.1%.

Conclusion: The RWD-ACROSS study is the first data-base for mCRC patients in Spain including information on CT, biologics, OS, PFS, and prognostic and predictive factors. Funded by Merck, S.L. (Merck KGaA, Darmstadt, Germany).

P – 278 Prognostic factors in metastatic colorectal cancer

M Silva, I Guerreiro, S Abreu, D Marques

IPO-Porto, Porto, Portugal

Introduction: In addition to the predictive value of RAS complex status in metastatic colorectal cancer (MCRC), the impact of several clinicopathological characteristics in the outcome has been described, although the practice recommendations have not yet clearly separate algorithms. The purpose of this study is to identify features that affect natural history of disease in our population. Furthermore, we aim to analyze the difference between prognosis of mCRC according with the choice of initial biologic agent.

Methods: This is a retrospective analysis of consecutive series of patients who presented with unresectable synchronous or metachronous mCRC, proposed for systemic first-line treatment combining chemotherapy with EGFR or VEGF-targeted therapy, between January 2014 and June 2015. Descriptive statistics were used to describe demographics and clinicopathological variables. Survival estimates were performed using Kaplan Meier method, and comparisons accomplished using log-rank, and association between nominal variables with person's correlation.

Results: A total of 80 cases were included, with median age at diagnosis of mCRC 61 years (min 33, max 79 years), of whom 58 (72,5%) were males. Most patients had stage IV disease (n = 50, 62,5%), and 20 patients (25,1%) had stage III disease. Eastern

Cooperative Oncology Group Performance Status was considered 0 or 1 in most patients (n = 78, 97,5%). In 44 cases (55%), tumors had wild type RAS complex status, and of these 39 (88,6%) were left sided primary lesions, while in RAS mutated tumors, 12 (33,3%) had primary origin in right colon, with statistically a significant association between sidedness and RAS complex status (p = 0.017). Among patients with RAS complex wild type tumors, median OS was 33 months (min 3, max 45 months) for patients treated with anti-EGFR in first setting, and was not achieved in those treated with anti-VEGF targeted agents. The choice of first line treatment did not influenced OS in left sided tumors, while all patients with RAS wild type and right sided tumors were treated with anti-EGFR treatment first. Considering the hole population study, OS of patients treated with anti-VEGF was 20 months (min 6, max 67 months). Among patients with RAS wild type tumors, 36,5% were considered to be suitable for curative surgery after systemic treatment, and submitted to metastasectomy while surgery was only performed in 8,3% of RAS mutated patients (p = 0,004). There was no significant difference in proportion of patients submitted to metastasectomy according to first line biological agent used. Regarding features that influenced OS, left sided primary tumor patients were associated with longer median OS (24 months, CI95%[19,1-28.8]) than right sided (19 months, CI95%[11,5-24.4]), with nearly statistical significance p = 0.05. Age (less than 70 years, p = 0,009), RAS complex wild type status (p < 0.001), and accomplishment of metastasectomy (p < 0.001) were associated with improved OS. Stage IV disease (versus initially localized disease), as well as burden of disease (more than 3 metastatic sites) were not associated with worse OS in our population.

Conclusion: This report of prognostic factors of mCRC in our clinical practice is concordant with literature reports. Further studies in the future might integrate this in treatment algorithms, focusing in conversion to radical treatment

P – 279 Effectiveness of TAS-102 in patients with metastatic colorectal cancer in a single comprehensive cancer center

C Sales[1], I Julião[1], A Rosinha[1], D Marques[1], F Carneiro[2], C Faustino[3], M Machado[1], P Ferreira[4], M Fragoso[1], N Sousa[4]

[1]IPO-Porto, Porto, Portugal, [2]Portuguese Institute of Oncology FG Porto, Portugal - Medical Oncology Service, Porto, Portugal, [3]Instituto Português de Oncologia do Porto, Porto, Portugal, [4]Portuguese Institute of Oncology, Porto, Portugal

Introduction: Trifluridine/tipiracil (TAS-102) prolongs progression free survival (PFS) and overall survival (OS) of patients with metastatic colorectal cancer (mCRC) whose disease progressed after at least two standard therapies. TAS-102 is available in Portugal since 2016. The authors evaluate the effectiveness of TAS-102 in patients with mCRC in routine clinical practice.

Methods: Consecutive case series of mCRC patients treated with TAS-102, between November 2016 and March 2018. Clinical and pathologic characteristics are described. Tolerance to treatment is evaluated by cumulative incidence of adverse events and therapeutic efficacy by response rate, PFS and OS. Patient follow-up was complete by March 2018.

Results: Twenty-seven patients were included, with a median age of 61 years (min. 40; max. 72) of which, 20 (74%) were male. Twenty-two patients (81%) had left-sided colon cancer and 17 patients (63%) had metastatic disease in two or more organs (70% with liver metastasis and 67% with lung metastasis). RAS complex mutation was present in 14 patients (52%). Median duration of treatment was 3 months with 21 patients (78%) presenting at least 1 adverse event. Nineteen patients (70%) presented haematological toxicity of any grade (48% neutropenia and 22% anemia). Grade ≥3 haematological toxicity was seen in 7 patients (26%). Sixteen patients (59%) had non-haematological toxicity (41% nausea, 30% anorexia, 22% asthenia, 15% diarrhea and 11% vomiting), all grade 1 or 2. Only one patient discontinued treatment due to an adverse event. Eleven patients (41%) required hospitalization during treatment with TAS-102 (22% due to cancer-related symptoms, 11% due to infectious intercurrences and 7% due to grade 3 haematological toxicity). At the time of data censorship, median follow up for patients alive was 5,8 months with 7 patients (26%) still undergoing treatment. Best response to treatment was stable disease (22%), with no partial or complete responses. Median PFS was 3,5 months (95% CI 2.3-4.7) and median OS was 6,6 months (95% CI 5.8-7.3).

Conclusion: TAS-102 has been adopted to current clinical practice with a toxicity profile that is similar from what was observed on its pivotal trial, and no new treatment adverse reactions were noted. Efficacy of TAS-102 in our center is similar to that which was described in the RECOURSE trial.

P – 280

WITHDRAWN

P – 281 The impact of primary tumor location in patients with resected colorectal liver metastasis

V Pacheco-Barcia[1], O Donnay[1], R Mondéjar Solís[1], R Serrano[2], E Martin[2], L del Campo[2], J Rogado[1], B Vera[2], A Ballesteros[3], R Colomer[1]

[1]Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria La Princesa, Madrid, Spain, [2]Hospital Universitario La Princesa, Madrid, Spain, [3]Hospital Universitario La Princesa., Madrid, Spain

Introduction: Recent prospective studies suggest that the primary tumor site in patients with metastatic colorectal cancer correlates with evolution. However, it is unclear whether there is an association between the side of the primary tumor and survival in patients with resected colorectal liver metastasis. The aim of our study is to evaluate the clinical outcome of patients with resected colorectal liver metastasis according to the side of the primary tumor.

Methods: All patients with resected colorectal liver metastasis between 2008 and 2016 who underwent perioperative chemotherapy and completed hepatectomy were reviewed retrospectively. It is considered right colon (RC) from cecum to transverse colon and left colon (LC) from the splenic flexure to rectum sigma. Differences in clinical characteristics were assessed by the Chi-square test and overall survival (OS) with the log-rank test.

Results: 34 cases were included. 21 (63.6%) were male. Median age was 64 years. 25 patients (74%) had the primary tumor in LC and 9 (26%) had RC. From the total number of patients, the RAS status was: 17 (50%) native, 16 (47%) mutated and 1 (3%) unknown. There were no differences in RAS status between LC and RC. Chemotherapy regimens: 29 (85%) received fluoropyrimidine doublet + oxaliplatin and 5 (15%) doublet with irinotecan. Patients with native RAS status: 14 (82%) received anti-EGFR therapy, 1 (6%) anti-VEGF and 2 patients (12%) did not receive a biological target. Patients in the RAS mutated group: 8 (50%) received anti-VEGF, 5 (30%) had a contraindication to anti-VEGF and the other patients had no indication. Median OS was 36 months. Regarding the median OS according to the primary tumor location, in the LC it was 45 months compared to 16 months on the RC (chi-square 3.925, p = 0.04). The Kaplan-Meier study shows a statistically significant difference in survival according to the location of the primary colon tumor in the first 12 months after resecting colorectal liver metastasis (log Rank 8.253, p = 0.004).

Conclusion: In patients with resected colorectal liver metastasis the primary tumor location showed an impact on survival. Our study suggests that patients with right-sided primary tumor location have a worse prognosis.

P – 282 RAS status in metastatic colorectal cancer: What is the relationship to epidemiological and anatomo-clinical factors?

M Haffadi[1], N Tawfiq[1], M Karkouri[2], Z Bouchbika[1], N Benchakroun[1], H Jouhadi[1], S Sahraoui[1], A Benider[1]

[1]Oncology Centre Mohammed VI for the Treatment of Cancers, University Hospital Center Ibn Rochd, Casablanca, Morocco, [2]Anatomical Pathology Service, University Hospital Center Ibn Rochd, Casablanca, Morocco

Introduction: In Morocco, colorectal cancer (CRC) is the first digestive cancer. The identification of RAS status has modified the management of metastatic colorectal

cancer (mCRC). Very few RAS status studies in the mCRC have been conducted in developing countries, such as Morocco, to identify the profile of its patients. The aim of this study is to evaluate the epidemiological and anatomo-clinical profile of mCRC patients based on the RAS status.

Methods: It is a cross-sectional study, conducted from March 2017 to February 2018 and involving 65 patients with mCRC in the Mohammed VI Center for the treatment of Cancers of Casablanca. The testing RAS status was requested at the time of mCRC diagnostic. The main criteria studied were age, sex, family history of CRC, BMI, tumor location, histological type and metastatic site.

Results: RAS status was wild in 48% of cases and mutated in 52%. The median age in the wild-type RAS group was 55 years and 57 years in the mutated RAS group. There was no difference in sex between the two groups (wild-type and mutated RAS). A familial history of CRC was noted in 26% of cases in the mutated RAS group in 9% in the wild type RAS group. The BMI> 25kg/m2 was observed in 44% and 41% of patients in the mutated RAS group and wild-type respectively. The colon was the most frequent seat in our series with a predominance of the left colon in both groups. The most common histological type in both groups was Lieberkühn adenocarcinoma with good to moderate differentiation. Metastases were synchronous in 80% in both groups. The most predominant metastatic site was the liver in both groups.

Conclusion: According to our series, we note that the patients in the two groups (RAS wild type and RAS mutated) share the majority of epidemiological and anatomo-clinical criteria.

P – 283 Skin disorders and primary tumor location as a prognostic factor of cetuximab plus chemotherapy in the treatment of advanced colorectal cancer

T Shinya[1], S Tamotsu[2], K Fujikawa[2], T Kana[3], F Yuta[3], H Hiroki[3], E Masayuki[3], Y Takahashi[2]

[1]National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan, [2]Department of Gastroenterology, Hokkaido Cancer Center, Sapporo, Japan, [3]Hokkaido Cancer Center, Sapporo, Japan

Introduction: Treatment with cetuximab is known to significantly increase overall and progression-free survival in patients with left-sided colorectal cancer, but not in patients with right-sided colorectal cancer. Skin rash is a major side effect of cetuximab treatment, and the presence of skin disorder caused by cetuximab is associated with prolonged survival. To date, however, no report has compared the incidence of skin disorder according to tumor location. Furthermore, no report has evaluated overall survival according to both tumor location and skin disorder presence. Therefore, we investigated the frequency of rash according to primary tumor location (left vs. right) in metastatic colorectal cancer (mCRC), and additionally evaluated overall survival.

Methods: This study was a retrospective trial conducted in a single hospital. A total of 50 patients with mCRC were enrolled between January 2011 and December 2015. Among them, 41 patients who used prophylactic steroid ointment were analyzed. We evaluated the associations between tumor location, survival parameters, and skin rash in patients with previously untreated mCRC receiving first-line chemotherapy plus cetuximab. Left-sided primary tumors were defined as tumors from the rectum to the splenic flexure, while right-sided primary tumors were defined as tumors from the cecum to the distal part of the transverse colon. Skin disorder was defined as the appearance of skin symptoms when at least one of the following was observed: acneiform rash, paronychia, or dry skin.

Results: Thirty patients had left-sided primary tumors and 11 had right-sided primary tumors. In the left-sided group, 77%, 70%, and 43% of patients had acneiform rash, paronychia, and dry skin, respectively. In the right-sided group, 23%, 36%, and 27% of patients had acneiform rash, paronychia, and dry skin, respectively. We found that rash and tumor location strongly correlated with overall survival. The median survival was 17.6 months in patients with left-sided mCRC and no rash, 56.3 months in patients with left-sided mCRC and rash, and 13.7 months in patients with right-sided mCRC ($P < 0.05$). Multivariable analysis showed that left-sided mCRC with skin disorder was an independent predictor of OS (median 56.3 vs.11.3 months, HR = 0.23, $P < 0.01$).

Conclusion: Our study shows that the two factors (the primary tumor location and the presence or absence of a skin disorder) are important prognostic factors of mCRC that has not been previously treated. The location of the primary tumor on the left side mCRC and the presence or absence of a skin disorder may be potent predictors of OS in cetuximab therapy. The present study evaluated skin disorders and further conclude that both left-sided tumor location & skin disorder can be a prognostic factor.

P – 284 Characteristics of colorectal cancer in the elderly patients about 60 cases

H Aliane[1], S Ghomari-Bezzar[2], A Belhadj[2], N Madani[3], N Charif[2]

[1]Medical Oncology Department, CHU Tlemcen Faculte de Médecine, Laboratoire Toxicomed, Université de Tlemcen, Tlemcen, Algeria, [2]Medical Oncology Department, CHU Tlemcen, Faculte de Medecine, Laboratoire Toxicomed, Universite de Tlemcen, Tlemcen, Algeria, [3]Medical Oncology Department, CHU Tlemcen, Faculte de Medecine, Laboratoire Toxicomed, Universite de Tlemcen, Tlemcen, Algeria

Introduction: Older people constitute a heterogeneous population, according to World Health Organization, the elderly person is defined as any individual with a chronological age equal to or higher than 60 years. In most cases, colorectal carcinoma is a disease of the elderly. Occurs mostly in the elderly people of more than 65 years and it poses public health problem. For several years geriatric evaluation has shown multiple benefits and we are witnessing a significant improvement in the oncological management of these patients.

Methods: This is a retrospective study conducted in the Medical Oncology Department CHU Tlemcen for patients aged 65 years and over with colorectal carcinoma. The objective of this study is the geriatric evaluation before treatment and establish the different epidemiological, clinical, endoscopic, histological and therapeutic profile of colorectal cancer and survival without recurrence in this population.

Results: We collected 60 cases of which 56% were men. The mean age was 71.3 years [65-91], The majority of patients had comorbidities associated with diabetes (20%), hypertension (34%), heart disease (8%) and 38% had others, 18% had a family history of cancers. The mean time to consultation was 9.1 months [1-36], The reason for consultation was rectorrhagia (45%), abdominal pain (25%), constipation (11%), diarrhea (10%) and occlusive syndrome (8%). Endoscopic appearance of the tumor was dominated by the burgeoning ulcerative appearance in the majority of cases, the tumour was colic in 72%. The well differentiated lieberkuhnal adenocarcinoma was the dominant histological type (89%). Tumor resection with node dissection was performed in 80% of cases. The tumor was classified as stage I (14%), II (14%), III (47%) and IV (25%). The metastases were synchronous at diagnosis in 25% of cases and metachronous in 15%, they were liver metastases (42%), peritoneal carcinomatosis (27%), pulmonary (21%) and other (10%). Before treatment evaluating oncogeriatric was done in patients older than 75 years the score G8 was superior than 14 in 69% of cases which 28% were classified as fragile according to BALDUCCI. The toxicity score of HURRIA was low for standard dose monochemotherapy in 46%. 51% of patients had an indication of adjuvant chemotherapy however only 45% received the recommended protocol. The evolution was marked by 15% of recurrences and 36% of deaths.

Conclusion: Elderly patients with colorectal cancer deserve to be treated in the same way as younger subjects. These treatments must be targeted and adapted according to age and associated co-morbidities, only a collaboration of oncologists and geriatricians strengthened in a multidisciplinary consultation that will facilitate the care of these patients.

P – 285 Optimizing the use of EGFR antibodies across the continuum of care in mCRC: Effect of online education on clinician knowledge, competence and confidence

G Fisher[1], W Guerra[1], C Day[1], C Montagut[2]

[1]WebMD Global, New York, New York, USA, [2]Department of Medical Oncology, Hospital Universitari del Mar, Barcelona, Spain

Introduction: Optimal application of EGFR antibodies across the continuum of care in metastatic colorectal cancer (mCRC) is critical to achieve the best patient outcomes. A good understanding of the implications of current evidence on treatment beyond progression and re-challenge is important in informing clinical decision making. This study determined whether online continuing medical education (CME) could increase-knowledge and competence related to applying best practices for RAS screening and monitoring, and selecting the right treatment approach for the individual patient across the continuum of care.

Methods: A 30-minute online video roundtable discussion between 3 experts was launched for countries outside the United States in March 2017, with data collected until June 2017. Educational effect was assessed with a repeated-pairs pre-/post-assessment study design, in which each individual participant served as his/her own control. 3 multiple-choice, knowledge questions and 1 self-efficacy, 5-point Likert scale (confidence) question were analyzed. Chi-squared test assessed pre- to post-assessment change (5% significance level, $P < .05$). Magnitude of change in total number of correct responses overall, and for each question, were determined with Cramer's V (effect size: <0.05 none/minimal; 0.06-0.15 small, 0.16-0.30 medium, >0.30 large).

Results: 141 oncologists completed both pre- and post-assessments. Baseline understanding was modest with 39-64% of participants identifying the correct answer for each question. Overall, a medium education effect was observed ($V = 0.212$, $p < 0.001$). The number of participants answering 3/3 questions correctly increased from 16% to 41% from pre- to post-assessment. Specific improvements included: identification of the advantage of liquid biopsy for assessment of RAS status to inform 2nd and further line treatments (95% improvement, $P < .001$; $V = 0.373$), identification of the need for RAS and other mutation testing post-progression on 1st line EGFR inhibitor combined with chemotherapy to inform treatment decisions (17% improvement, $P = 0.038$; $V = 0.123$), identification of the potential to use cetuximab combined with irinotecan as a treatment option in a patient that had previously progressed on cetuximab + chemotherapy then bevacizumab + chemotherapy in the 1st and 2nd lines, with a confirmed RAS WT tumour (25% improvement, $P = 0.022$, $V = 0.137$). 27% of participants reported increased confidence in using RAS mutational testing to inform treatment decisions for mCRC that is progressing.

Conclusion: This on-demand, online video roundtable discussion resulted in a positive education effect and increased confidence amongst the participants. However, the data indicate that there remains a persistent educational need with less than half of participants answering all 3 questions correctly post-assessment. Online medical education is valuable in supporting the application of best practice, as well as identifying areas of continued educational need.

P – 286 Integrating a paradigm shift in the treatment of metastatic colorectal cancer: Effect of online CME on oncologists' knowledge and competence

T Herrmann[1], D Cameron[1], A Carothers[1], T Bekaii-Saab[2]
[1]Medscape Education, New York, New York, USA, [2]Mayo Clinic, Phoenix, Arizona, USA

Introduction: The objective of this study was to determine the effect of online continuing medical education on the knowledge and competence of oncologists regarding the management of metastatic renal cell cancer (mCRC) among community oncologists.

Methods: The effect of two case-based educational interventions (5000 word interactive text-based and 30-minute video-based) on the treatment of mCRC was analyzed to determine efficacy of online, on-demand, education. The activities launched online in July and December 2017 and data were collected through February 2018. To assess educational effectiveness, participants were asked a set of case-based questions prior to, and again after, exposure to one of the activities. A Chi-square Test of Independence determined statistical significance while Cramer's V was used to estimate the effect of each intervention on oncologists' knowledge and competence.

Results: 185 oncologists, 78% of whom saw 10 or fewer patients with mCRC per month indicating that they work in the community, were assessed. Upon completion of either activity, a pre- to post-activity assessment improvement was observed in oncologists': Identification of the most appropriate evidence-based regimen for a patient with mCRC that has progressed on two prior therapies (53% vs 65%, $P = 0.10$; 58% vs 87%, $P < 0.001$). Implications of tumor characteristics including BRAF mutational status and presence of right-sided disease on the care of patients with mCRC (65% vs 82%, $P < 0.001$). Confidence in selecting the most appropriate option for a patient with mCRC whose disease has progressed on therapy (+10% and +17%). Recognition of, and counseling on, common treatment-related adverse events in a patient with mCRC (72% vs 87%, $P < 0.001$).

Conclusion: Use of online, text and video, case-based CME interventions improved the knowledge and competence of participating oncologists, showing that unique educational methodologies and platforms, which are available on-demand can be effective tools for advancing clinical decision making in the rapidly changing environment of mCRC disease management. Additional studies are needed to assess whether improved aptitude translates to improved performance during clinical practice.

P – 287 Treatment based on tumor sidedness in mCRC: Effect of online education on clinician knowledge, competence and confidence

G Fisher[1], W Guerra[1], C Day[1], M Ducreux[2]
[1]WebMD Global, New York, New York, USA, [2]Gustave Roussy Cancer Campus Grand Paris, Villejuif, France

Introduction: Emergent data on the impact of tumour sidedness on the treatment of metastatic colorectal cancer (mCRC) has important implications to clinical practice. This study determined whether online continuing medical education (CME) could improve oncologists' knowledge of the most current data supporting the use of available therapeutic options in left- vs right-sided tumors, and improve clinician competence in evidence-based selection and optimal use of EGFR antibodies in clinical practice.

Methods: A 30-minute online video roundtable discussion between 3 experts was launched for countries outside the United States in March 2017, with data collected until June 2017. Educational effect was assessed with a repeated-pairs pre-/post-assessment study design, where individual participants served as his/her own control. 3 multiple-choice, knowledge questions and 1 self-efficacy, 5-point Likert scale (confidence) question were analyzed. Chi-squared test assessed pre- to post-assessment change (5% significance level, $P<.05$). Magnitude of change in total number of correct responses overall, and for each question, were determined with Cramer's V (effect size: <0.05 none/minimal; 0.06-0.15 small, 0.16-0.30 medium, >0.30 large).

Results: 142 oncologists completed both pre- and post-assessments. Although these specialists demonstrated a good baseline knowledge for all three questions (70-80% with the correct answer), a significant improvement and small/medium education effect was observed regarding: identification of EGFR antibody as the correct treatment preference for a patient with a left sided tumour (21% improvement, $P = .005$; $V = 0.169$) and recognising that this is based on the superior OS and PFS observed for EGFR antibodies in this patient group compared with those with right-sided tumours (21% improvement, P .001; $V = 0.222$). Interestingly, when asked to identify the correct management approach for a patient presenting with a Grade 2 EGFR-related rash, there was a 15% decrease in the number of participants identifying the correct answer post-assessment (from 80 to 68%). This suggests a lack of certainty on the right approach and a potential need for further education. Approximately 30% of participants reported increased confidence in selecting treatment based on tumour sidedness as a result of participation in this activity.

Conclusion: This on-demand, online video roundtable discussion resulted in a positive education effect. Encouragingly, the participants had a good baseline understanding of the importance of tumour sidedness in informing treatment selection. However, further education appears to be required in the area of management of EGFR-related side effects. Online medical education is valuable in supporting the interpretation and application of new data, as well as identifying areas of continued educational need.

P – 288 Causes of death in a cohort of early stage colorectal cancer patients at a regional centre in Australia

L Lim, W Faisal, M Wuttke, G Chong
Ballarat Regional Integrated Cancer Centre, Ballarat, Australia

Introduction: Australia has amongst the highest incidence of colorectal cancer in the world. The Australian state of Victoria has amongst the best survival rates nationally and internationally. However, inequalities in CRC survival for cancer patients living in rural and regional areas persist. In particular, there is an absolute difference of 10% in 5-year survival rates of patients diagnosed between 2005 – 2009 in Metropolitan Melbourne compared to the Grampians region in regional Victoria. These differences are also apparent in those with early stage colorectal cancer. We conducted an analysis in a regional cohort of early stage patients to explore potential contributing factors for increased mortality.

Methods: A cohort of patients with early stage colorectal cancer diagnosed from 2005 - 2009 at Ballarat Health Services, Victoria, who did not receive adjuvant chemotherapy, were identified via the Victorian Cancer Registry. Demographic, tumour and treatment data were extracted from medical records. Survival data was obtained from the Victorian Cancer Registry, with correlation with hospital records to identify cause of death.

Results: A total of 123 patients were included. The median age was 73 years. 21% of patients (n = 26) were diagnosed after presenting as an emergency. Most tumours were T3 (47%) and 93% were node negative. Patients lived a median distance of 13km from the hospital, with 30% living alone. 5.7% were employed at diagnosis. The median Charlson score at diagnosis was 2, and the median ECOG performance status of 1. 69% of patients were either overweight (BMI 25.0–29.9) or obese (BMI >30). As of December 2016, 63 of the 123 patients had died. The median time from surgery to death was 56 months. Colorectal cancer was identified as the cause of death in 12 of 63 deaths. The majority of deaths (51 out of 63) were not related to cancer, with heart failure (n = 8), chronic obstructive pulmonary disease (n = 6), and stroke (n = 6) as the most common causes. 11 of the 63 deaths occurred within 12 months of surgery. The median Charlson score for these patients was 2, 45% were overweight or obese, and the median ECOG of 2 was poorer than the whole cohort. 7 of the 11 deaths were in patients who had presented as emergencies, but only 2 of these were directly attributable to cancer (perforation and sepsis). The other causes of death were hospital-acquired pneumonia (n = 2), end stage airways disease (n = 2), ischaemic heart disease (n = 2).

Conclusion: The majority of deaths in this cohort of early stage colorectal cancer were non-cancer related. The Charlson index and the median ECOG performance status for the whole cohort were not particularly high. Patients who presented as an emergency accounted for a majority of early deaths, however this was not directly related to malignancy in the majority. Further investigation of causes of death in the first-year post resection may lead to strategies to reduce or prevent such deaths. To further elucidate factors contributing to non-cancer mortality, data from a contemporaneous cohort of early stage patients from a Victorian metropolitan centre will be analysed and compared.

P – 289 Prognostic factors for early recurrences following cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal and appendiceal peritoneal metastases

N Chandran[1], G Tan[2], C Chia[2], M Teo [3]
[1]Duke-NUS Medical School, Singapore, [2]National Cancer Centre Singapore, Singapore, [3]National Cancer Centre Singapore, Singapore

Introduction: The introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has improved the prognosis of selected patients with peritoneal metastases (PM) of colorectal and appendiceal primaries. However, despite careful patient selection and complete macroscopic resection, early recurrences (ER) still occur. This study aims to identify risk factors for ER.

Methods: Patients with appendiceal and colorectal PM treated with CRS and HIPEC between January 2001 and June 2016 at the National Cancer Centre Singapore were analyzed. Comparison between patients who developed ER (< 12 months) and those with late recurrence (>12 months) or no recurrence was performed using univariate and multivariate analyses.

Results: In the appendiceal group, 9 out of 58 patients (16%) developed ER. The median disease-free interval (DFI) of patients with ER was 10 months and in patients with no ER was 26 months. Univariate analysis identified male gender, elevated preoperative CEA levels, preoperative CA 19-9 levels and high PCI score as factors associated with ER. There were no significant factors for ER on multivariate analysis. For the colorectal cohort, 30 out of 83 patients (36%) developed ER. The median DFI of patients with ER was 11.5 months and in patients without ER it was 21 months. Univariate analysis identified that increased age, elevated CA-125 levels, high PCI score, intraoperative complications and longer length of hospital stay after CRS and HIPEC was associated with ER. Multivariate analysis identified elevated preoperative CA-125 levels as significantly associated with ER.

Conclusion: ER is a considerable consequence in patients with peritoneal metastases of appendiceal and colorectal primaries. By identifying factors associated with ER, patients at risk may benefit from an alternative treatment strategy and follow up.

P – 290 Simultaneous versus staged resections of liver metastases in patients with advanced colorectal cancer

O Kolesnik[1], A Lukashenko[1], Y Ostapenko[2], N Chorna[2]

[1]National Cancer Institute, Kiev, Ukraine, [2]National Cancer Institute of Ukraine, Kiev, Ukraine

Introduction: Surgical management of metastatic colorectal cancer remains the best method to use which significantly improves overall 5-year survival. There are two well-known possible approaches of surgical treatment of patients with synchronous colorectal liver metastasis. The former includes synchronous resection of the colorectal primary with the following resection of the liver metastases and the latter is a staged resection approach. However, at present the issue of feasibility and effectiveness of simultaneous operations for metastatic liver lesions in patients with synchronous metastatic colorectal cancer (SMCLC) is negotiated and remains uncertain. This study aimed to compare the surgical outcomes and survival benefit between synchronous and staged resections of the colorectal liver metastases.

Methods: Data of 144 patients with colorectal cancer and synchronous liver metastases was analyzed between 2008-2017. There were two groups of patients. Fifty-eight patients from group A were undergone synchronous liver and colon resection whereas eighty-six patients from group B - staged resection of colon and liver, respectively.

Results: Overall 3-year survival in group A with synchronous resections was 41% and in the group B - 50% ($p>0.001$). There were no significant differences in overall level of post-operative complications in the groups A and B after surgical stages finishing, 30.5%($n=44$) and 36.1%($n=52$), respectively ($p>0.001$). Shorter duration of the operation was observed in the group A – 316.3 (± 10.3) min in comparison with the group B 484.1(± 18.3) min ($p<0.001$). Patients after staged resection stayed longer in clinic - 23.3$\pm$0.8 bed-days, then those who undergone synchronous resections - 10.2$\pm$0.4 bed-days ($p < 0.001$) provided with shorter recovery terms in post-operative period.

Conclusion: Analysis of our research has indicated necessity of the development of differentiated approach in SMCLC surgical treatment. Subsequent research should be directed towards study of prognosis factors and criteria for patients' selection for surgical treatment groups, assessment of economic efficacy and patients' life quality.

P – 291 The DISTINCTIVE study: A biologically enriched phase II study of seconD-line folfiri/aflIbercept in proSpecTIvely stratified, anti-EGFR resistaNt, metastatic coloreCTal cancer patIents with RAS Validated wild typE status - Trial in progress

P Ziranu[1], L Demurtas[1], M Puzzoni[2], F Loupakis[3], B Daniele[4], L Rimassa[5], D Bilancia[6], S Lonardi[3], A Avallone[7], N Pella[8], D Ferrari[9], L Frassineti[10], G Beretta[11], A Zaniboni[12], A Santoro[13], M Zampino[14], M Sarobba[15], V Zagonel[16], S Barni[17], G Palmieri[18], R Labianca[19], S Cascinu[20], M Scartozzi[21]

[1]Departments of Medical Oncology, University of Cagliari, University Hospital 'Duilio Casula', Cagliari, Italy, [2]Departments of Medical Oncology, University of Cagliari, University Hospital 'Duilio Casula', Monserrato, Italy, [3]Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [4]Dipartimento di Oncologia - Ospedale Rummo, Benevento, Italy, [5]Humanitas Research Hospital – IRCCS, Rozzano, Italy, [6]UO Oncologia - Ospedale S. Carlo di Potenza, Potenza, Italy, [7]Abdomen Medical Oncology, Istituto Nazionale Tumori - IRCCS - Fondazione G. Pascale, Naples, Italy, [8]Department of Oncology, Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia, Udine, Italy, [9]A.O. San Paolo, Milan, Italy, [10]Medical Oncology Unit, "Istituto Scientifico Romagnolo", Meldola, Italy, [11]Humanitas Gavazzeni, Bergamo, Italy, [12]Fondazione Poliambulanza, Brescia, Italy, [13]Humanitas Cancer Center, Istituto Clinico Humanitas IRCCS, Rozzano, Italy, [14]European Institute of Oncology, Milan, Italy, [15]Medical Oncology Department, ASL Nuoro, Nuoro, Italy, [16]Oncologia Medica 1, Istituto Oncologico Veneto - IRCCS, Padua, Italy, [17]AO Ospedale Treviglio-Caravaggio, Treviglio, Italy, [18]CNR - Unità di Genetica dei Tumori, Sassari, Sassari, Italy, [19]Medical Oncology Unit ASST Papa Giovanni XXIII, Bergamo, Italy, [20]Azienda Ospedaliera-Università di Modena, Modena, Italy, [21]Medical Oncology, University of Cagliari, University Hospital, Cagliari, Italy

Introduction: The use of chemotherapy in combination with anti-angiogenic treatment represents a standard of care in the second-line setting of metastatic colorectal cancer. In patients pretreated with an oxaliplatin-based chemotherapy either aflibercept or bevacizumab in combination with FOLFIRI are considered equivalent options. However, data regarding second-line anti-angiogenic therapy in RAS wild type patients receiving first-line anti-EGFR treatment are lacking and clinical practice is essentially based on speculations deriving from first-line studies. Moreover, biological data seem to indicate a different clinical outcome according to serum concentrations of angiogenesis-related factors, but prospective validation was not performed. VEGFR2 may play a role as predictive marker of response to antiangiogenic drugs and it should be considered a prognostic marker in patients treated with anti-VEGF therapies, as shown in both preclinical studies and exploratory analysis over randomized trials.

Methods: The DISTINCTIVE study (EudraCT-No.: 2017–002219-33; SC/2017/10687) is a biologically enriched, prospectively stratified phase II trial in RAS wild type metastatic colorectal cancer patients progressing after first-line treatment with oxaliplatin, fluoropyrimidines and an anti-EGFR monoclonal antibody. Eligible patients will be prospectively allocated to two groups according to their VEGFR2 plasma levels (ELISA-based technique, pg/ml) at study entry (VEGFR2 > 4 pg/ml favourable prognosis group, VEGFR2 $\leq$4 pg/ml unfavourable prognosis group). Plasma levels concentrations of other angiogenetic factors (VEGF, PlGF, HGF, VEGFR1, IL8, IL1a, T-cad, VEGFR3, SAP, VDBP, neuropilin1, CRP, endoglin) will be evaluated before the treatment start and before each cycle according to an ELISA-based technique. VEGFR2 and other angiogenic factors assessments will be centralized at the laboratory of Medical Oncology Unit – AOU Cagliari. All patients will undergo a blood test for retrieving circulating tumor DNA (Liquid Biopsy) at selected time-points before and during treatment for determining whether the status of selected tumor biomarkers evolve during tumor progression by comparing different ctDNA samples. Liquid biopsy will be performed by a central laboratory at the Unit of Cancer Genetics, ICB-CNR of Sassari. All patients will receive aflibercept in combination with FOLFIRI as for approved indication. The primary endpoint is overall survival (OS) according to VEGFR2. Secondary endpoints are Overall Survival (OS), Progression Free Survival (PFS), Response Rate, Toxicity Profile, Angiogenetic factors levels concentration before and during treatment. This study was designed to test the efficacy of aflibercept in combination with FOLFIRI (administered as for approved indication) in the second-line treatment of RAS wild type metastatic colorectal cancer patients progressing after first-line treatment with oxaliplatin, fluoropyrimidines in combination with an anti-EGFR monoclonal antibody (either panitumumab or cetuximab) and to evaluate differences in overall survival according to VEGFR2 levels. Furthermore, the DISTINCTIVE study aims to prospectively validate VEGFR2 plasma levels as predictive factor for efficacy of aflibercept in combination with FOLFIRI in the study population. The study was partially supported by Sanofi Genzyme.

P – 292 A phase II study of dose-escalation of regorafenib for patients with previously treated metastatic colorectal cancer – DEREGULATE study - Trial in progress

K Kawaguchi[1], R Nishitai[1], D Manaka[1], T Ota[1], Y Nishikawa[2], R Kudo[1], H An[2], S Hamasu[1], S Konishi[1]

[1]Department of Surgery, Gastrointestinal Center, Kyoto Katsura Hospital, Nishikyo-ku, Japan, [2]Department of Surgery, Gastrointestinal Center, Kyoto Katsura Hospital, Nishikyo-ku, Japan

Introduction: Regorafenib (REG) is a standard salvage line therapy for metastatic colorectal cancer (mCRC) after a pivotal phase III study (CORRECT). However, administration of full dose of REG often leads to severe adverse effects, which makes the clinical use of this drug restricted to the patients(pts) relatively in good conditions. In a phase II ReDOS study (regorafenib dose optimization study NCT02368886), the median overall survival (OS) was improved more favorably in dose escalating regimen, which began at 80mg per day and increased weekly up to 160mg per day, than in standard regimen of 160mg per day. The Japanese subpopulation of CORRECT is reported to have received only 69.3% (110.9 mg/day) of the planned dose of REG, although non-Japanese subpopulation has received 80.4%, which suggests that dose escalating regimen may be more suitable for Japanese pts. The aim of this DEREGULATE study is to test the hypothesis that this dose-escalation regimen might have better sustainability and comparative disease-control compared with the standard dose regimen in Japanese pts.

Methods: DEREGULATE is a multi-center phase II study. Pts are eligible when they have heavily treated mCRC and sufficient organ functions regardless of performance status grades. Patients are initially administered 80 mg/day of REG, and dose-escalation is considered every two weeks during the course of treatment. Primary endpoint is time to treatment failure (TTF). Secondary endpoints are disease control rate, survival and safety. The median TTF of CORRECT was 1.7 months, and that of Japanese post-marketing surveillance was 2 months. Thirty participants will be recruited to prove the hypothesis that the dose-escalation regimen should prolong the TTF by 40% (2.8 months) with the alpha and beta errors of 0.1. Clinical trial identification: UMIN000014661.

P – 293 Comorbidities (CM) and potential impact in outcomes of advanced colorectal cancer patients (ACC) in Argentina: EVIREPRO real life program - Trial in progress

A Schmilovich[1], F Ramello[2], M Malicki[3], N Colombo Berra[4], S Rojo[5], G Davila[6], V Binner[7], H Barrionuevo[8], J Capria[9], M Poggio[7], R Arca[10], D Tabares[11], D Vicente[12], D Santillan[13], J Burre[11], M Vazquez[11]

[1]Grupo Biotoscana, Buenos Aires, Argentina, [2]Private Practice, Gualeguaychu, Argentina, [3]Private Practice, Lanus, Argentina, [4]Private Practice, Rosario, Argentina, [5]Private Practice, La Calera, Argentina, [6]Private Practice, Villa Maria, Argentina, [7]Private Practice, San Nicolas, Argentina, [8]Private Practice, Santa Fe, Argentina, [9]Fundacion Investigar, Pilar, Argentina, [10]Private Practice, Caba, Argentina, [11]Private Practice, La Plata, Argentina, [12]Private Practice, Rosario, Argentina, [13]Private Practice, Lomas de Zamora, Argentina

Introduction: CM may influence systemic treatment decisions in cancer care and it could potentially impact outcomes of patients (pts) who receive it. We sought to determine whether CM impacts systemic treatment and survival in pts with ACC.

Methods: Pts with diagnosis of ACC between 11/2015 through 1/2018 were selected from the EVIREPRO database. The program is planned to include pts since 11/2015 to 11/2020.It is an electronic private database of real life office medical practice in oncology, hematology and other chronic ill conditions where 275 physicians from all over the country and related with the medical care of those disease conditions are participating. EVIREPRO is conducted by the Investigar Foundation and is funded by Grupo Biotoscana. All participants signed a contract before participation and pt anonymity is warranted. Physicians complete surveys and questionnaires at inclusion, follow up and exit of the program. They include diagnostic procedures (laboratory, biologic markers, and image studies), clinical data (tumor stage and sided location, comorbidities, performance status, quality of life, treatment response and tolerability) and previous treatments (surgery, radiotherapy, chemotherapy, target therapy or palliative treatment). CM was categorized as no CM or with CM. Pts in the last subset are stratified according 1, 2 or 3 or more CM. A multivariate Cox proportional model will be used to estimate the association of CM with overall survival. As of 1/31/2018, 81/203 enrolled pts have ACC.

P – 294 Multicenter phase Ib/II study of biweekly TAS-102 with bevacizumab combination for patients with metastatic colorectal cancer refractory to standard therapies (BiTS study) - Trial in progress

T Kato[1], H Satake[2], K Oba[3], Y Kagawa[4], H Yasui[5], M Nakamura[6], T Watanabe[7], T Matsumoto[8], K Hirata[9], K Muro[10], Y Komatsu[11], T Yoshino[12], K Yamazaki[13], H Mishima[14], M Kotaka[15], A Tsuji[16], Y Kakeji[17], E Oki[18], N Nagata[19], J Sakamoto[20]

[1]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [2]Department of Medical Oncology, Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan, [3]Department of Biostatictics, The University of Tokyo, Tokyo, Japan, [4]Department of Gastrointestinal Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [5]Department of Oncology, Kobe City Medical Center General Hospital, Kobe, Japan, [6]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan, [7]Department of Surgery, Japanese Red Cross Society Himeji Hospital, Himeji, Japan, [8]Department of Internal Medicine, Japanese Red Cross Society Himeji Hospital, Himeji, Japan, [9]Deparment of Surgery 1, University of Occupational and Environmental Health, Kitakyushu, Japan, [10]Department of Clinical Oncology and Outpatient Treatment Center, Aichi Cancer Center Hospital, Chikusa-Ku, Nagoya, Japan, [11]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [12]National Cancer Center Hospital East, Kashiwa, Japan, [13]Department of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun, Japan, [14]Division of Cancer Center, Aichi Medical University, Nagakute, Japan, [15]Department of Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan, [16]Department of Medical Oncology, Kagawa University Hospital, Kida-gun, Japan, [17]Division of Gastrointestinal Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan, [18]Department of Surgery, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Japan, [19]Department of Surgery, Kitakyushu General Hospital, Kitakyushu, Japan, [20]Tokai Central Hospital, Kakamigahara, Japan

Introduction: TAS-102 (trifluridine/tipiracil) plus bevacizumab combination therapy has shown a promising activity with manageable safety profile in patients with heavily pretreated metastatic colorectal cancer. In a previously reported study assessed this combination therapy, TAS-102 has been given orally every 4 weeks (35mg/m2 given orally twice daily on day 1-5 and 8-12 in a 28-day cycle) and bevacizumab has been administered every 2 weeks (5mg/kg, administered by intravenous infusion for 30 min every 2 weeks) (C-TASK FORCE, Kuboki et al., Lancet Oncol 2017). The aim of this phase Ib/II study was to assess the activity and safety of biweekly TAS-102 with bevacizumab combination for patients with metastatic colorectal cancer who were refractory or intolerant to standard therapies.

Methods: We conducted an investigator-initiated, open-label, single-arm, multicenter, phase Ib/II study of biweekly TAS-102 with bevacizumab combination. Inclusion criteria were $\geq$ 20 years; histologically confirmed unresectable metastatic colorectal adenocarcinoma; refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy, and anti-EGFR therapy (for tumors with wild-type RAS); Eastern Cooperative Oncology Group performance status 0 or 1; evaluable lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Phase Ib part is designed to evaluate the incidence of dose limiting toxicities during the first cycle and to determine the recommended phase II dose (RP2D) in the dose de-escalation design (3 + 3) with TAS-102 (35mg/m2 given orally twice daily on day 1-5 and bi-weekly bevacizumab. In phase II part, patients received the RP2D in phase Ib part were included in efficacy and safety populations. The primary endpoint in phase II part was an investigator assessed progression-free survival rate at 16 weeks (16w-PFS). Major secondary endpoints included PFS, overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. We set the threshold 16w-PFS rate at 15% and the expected 16w-PFS rate at 38.7% on the basis of the results of C-TASK FORCE study. Given a one-sided α of 0.025 and statistical power of 90%, a minimum of 40 patients were required using an exact single-stage binomial design. With 10% of drop-out, we set 45 patients as a target sample size in this study.

P – 295 A multicenter, multicohort, phase 2 study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing metastatic colorectal cancer - Trial in progress

T Yoshino[1], S Siena[2], R Dalal[3], Y Okuda[4], E Yamamoto[5], A Grothey[6]

[1]National Cancer Center Hospital East, Kashiwa, Japan, [2]Niguarda Cancer Center, Università degli Studi di Milano, Milan, Italy, [3]Daiichi Sankyo, Inc., Basking Ridge, New Jersey, USA, [4]Daiichi Sankyo Co., Ltd, Tokyo, Japan, [5]Daiichi Sankyo Co., Ltd, Chuo-ku, Japan, [6]Mayo Clinic, Rochester, Minnesota, USA

Introduction: Approximately 1% to 5% of metastatic colorectal cancers (mCRC) are HER2-overexpressing. HER2 is considered to be an important target for mCRC, however no HER2-targeted therapies are approved for mCRC. Trastuzumab deruxtecan (DS-8201a) is a novel HER2-targeted antibody-drug conjugate with a humanized HER2 antibody attached to a topoisomerase I inhibitor payload by a cleavable peptide-based linker (deruxtecan), and with a high drug-to-antibody ratio of 7 to 8. In the ongoing phase 1 DS8201-A-J101 trial, DS-8201a provided durable antitumor activity with a manageable safety profile in subjects with HER2-expressing solid tumors, including subjects with mCRC (preliminary objective response rate [ORR] of 20.0% in mCRC) (Tsurutani et al, ESMO 2017).

Methods: This multicenter, open-label, 3-cohort, phase 2 study (ClinicalTrial.gov: NCT03384940) will assess the efficacy and safety of DS-8201a in subjects with HER2-expressing mCRC. Cohort A will include approximately 50 subjects with HER2-positive (IHC 3+ or IHC 2+/ISH+) mCRC. At the start of the study, only cohort A will be active. Depending on the risk/benefit assessment after at least 20 subjects in cohort A complete tumor assessments at week 12, cohort B (IHC 2+/ISH-) and cohort C (IHC 1+) will open to enroll approximately 20 subjects each. All enrolled subjects will receive a 6.4 mg/kg dose of DS-8201a once every 3 weeks; study treatment will be continued until disease progression, unacceptable toxicity, or other treatment discontinuation criteria are met. The anticipated duration of the study is at least 24 months. The primary endpoint is ORR (complete response or partial response), as assessed by an independent central review committee, in cohort A. Secondary efficacy endpoints include progression-free survival, duration of response, disease control rate, and overall survival. Safety assessments include serious and treatment-emergent AEs, physical examination findings, and vital sign measurements. The study will enroll subjects in Japan, the US, and Europe. Recruitment began in December 2017.

P – 296 ABT-165 plus FOLFIRI vs bevacizumab plus FOLFIRI in patients with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine/oxaliplatin and bevacizumab - Trial in progress

Z Wainberg[1], L Wang[2], H Yue[2], M Motwani[3], S Kasichayanula[4], M Blaney[2], L Naumovski[2], J Strickler[5]

[1]Ronald Reagan UCLA Medical Center, Los Angeles, California, USA, [2]Oncology Early Development, AbbVie Inc., Redwood City, California, USA, [3]Oncology Early Development, AbbVie Inc., North Chicago, Illinois, USA, [4]Clinical Pharmacology and Pharmacometrics, AbbVie Inc., Redwood City, California, USA, [5]Duke University Medical Center, Durham, North Carolina, USA

Introduction: The dual variable domain immunoglobulin ABT-165 targets human vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4). Combined VEGF and DLL4 blockade increased inhibition of subcutaneous xenograft growth of human colon cancer-derived cell lines vs blockade of either axis alone. In vivo, ABT-165 plus chemotherapy (CT) induced tumor regression with improved efficacy, vs anti-VEGF monoclonal antibody plus CT. In a phase 1 study, a tolerable recommended phase 2 dose was identified for ABT-165 plus FOLFIRI and showed promising efficacy. This phase 2 trial in progress assesses the efficacy/safety of ABT-165 plus FOLFIRI vs bevacizumab (bev) plus FOLFIRI in patients with second-line mCRC.

Methods: This is an open-label, multicenter, phase 2 randomized (1:1) trial (NCT03368859) in patients ($\geq$18 years; Eastern Cooperative performance status: 0–1) with histologically/cytologically confirmed mCRC who progressed after fluoropyrimidine/oxaliplatin and bev. ABT-165 (2.5 mg/kg) plus FOLFIRI (irinotecan: 180 mg/m2; leucovorin: 400 mg/m2; fluorouracil bolus: 400 mg/m2, infusion: 2400 mg/m2) or bev (5 mg/kg) plus FOLFIRI are given intravenously on day 1 of each 14-day cycle, until disease progression/intolerable toxicity. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS), objective response rate (ORR), and safety. Exploratory endpoints include biomarkers predictive for efficacy/safety, correlation of DLL4 levels with PFS, OS, and ORR, pharmacodynamic effects, and the efficacy/safety-exposure relationships in the ABT-165 arm. The hazard ratios of PFS and OS comparing the 2 groups are estimated using the Cox proportional hazard model. Kaplan-Meier methodology is used to estimate the PFS and OS curves, median

PFS and OS, and their 90% confidence intervals. Safety is assessed by ABT-165 exposure, adverse events (AEs), serious AEs, all deaths, and changes in laboratory data and vital signs. Archival tissue is collected and evaluated for DLL4 expression and angiogenesis signature. Approximately 100 patients are planned to be enrolled, with recruitment initiated in January 2018.

P – 297 CanStem303C trial: A Phase 3 Study of napabucasin (NAPA) in combination with 5-fluorouracil (5-FU), leucovorin, and irinotecan (FOLFIRI) in adult patients (pts) with previously treated metastatic colorectal cancer (mCRC) - Trial in progress

M Shah[1], A Grothey[2], N Tebbutt[3], R Xu[4], T Yoshino[5], A Cervantes[6], J Tabernero[7], J Taieb[8], A Falcone[9], B Xu[10], M Fontaine[11], L Borodyansky[11], E Van Cutsem[12]

[1]Weill Cornell Medical College and New York Presbyterian Hospital, New York, New York, USA, [2]Mayo Clinic, Rochester, Minnesota, USA, [3]Olivia Newton-John Cancer & Wellness Centre, Austin Health, Melbourne, Australia, [4]Sun Yat-Sen University Cancer Center, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China, [5]National Cancer Center Hospital East, Kashiwa, Japan, [6]University Hospital of Valencia, Valencia, Spain, [7]Vall d'Hebron University Hospital, Barcelona, Spain, [8]Sorbonne Paris Cité, Paris Descartes University, Georges Pompidou European Hospital, Paris, France, [9]University of Pisa, Pisa, Italy, [10]The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China, [11]Boston Biomedical, Cambridge, Massachusetts, USA, [12]UZ Leuven-Campus Gasthuisberg, Leuven, Belgium

Introduction: NAPA is an oral investigational agent, which has been hypothesized to inhibit cancer stemness pathways, including STAT3 pathway implicated in cancer stem-cell viability. Preclinical studies suggest that NAPA may sensitize cancer cells to chemotherapeutics, including 5-FU and irinotecan. Encouraging anticancer activity in advanced CRC was observed in a phase 1b/2 study (NCT02024607). In the subset of FOLFIRI-naive patients with an on-study RECIST evaluation, disease control rate (DCR) was 85% (33/39) and objective response rate (ORR) was 21% (8/39).1 On the basis of these data, a phase 3 trial is being conducted in North America, Europe, Australia, and Asia.

Methods: This randomized, multicenter, open-label study (NCT02753127) will assess the efficacy of NAPA + FOLFIRI vs FOLFIRI in pts with mCRC (N = 1250). Addition of bevacizumab (bev) to FOLFIRI backbone is permissible per investigator decision. Pts must have failed 1 prior line of therapy with oxaliplatin and a fluoropyrimidine +/- bev for metastatic disease. Pts are randomized 1:1 to receive NAPA 240 mg PO BID plus FOLFIRI bi-weekly (5-FU at 400 mg/m 2 bolus followed by 1200 mg/m 2 continuous infusion, leucovorin 400 mg/m 2, and irinotecan 180 mg/m 2) , or FOLFIRI biweekly. Patients are stratified by geography (North America/Western Europe/Australia vs. Japan/Korea vs. rest of the world), time to progression on 1st-line therapy (<6 months vs. ≥6 months), RAS mutation status (mutant vs. wild type), bev as part of study treatment (yes vs. no), and primary tumor location (left vs. right colon). Treatment will continue until disease progression or another discontinuation criterion. The primary endpoint is overall survival (OS) in the general study population (HR 0.80 for OS improvement from 12.54 to 15.68 months); secondary endpoints include progression free survival (PFS), ORR and DCR, safety and quality of life. Blood and tumor archival tissue will be assessed for PK and biomarker analyses. An interim analysis for non-binding futility set at HR > 1 will be performed on OS at 50% of events (424). Additionally, early efficacy analysis based on OS will be performed at the time of the interim analysis. Should the trial not stop at time of the interim analysis, study will continue to final analysis at 850 events. Study enrollment is ongoing with >50% of planned patients enrolled to date.

P – 298 A phase II study of avelumab in MSI-H metastatic colorectal cancer patients - Trial in progress

D Proszynski[1], M Winiarek[2], K Marcisz-Grzanka[3], J Krynski[4], J Zwolinski[4], J Pałucki[5], A Cencelewicz-Lesikow[1], K Kokoszynska[1], L Wyrwicz[6]

[1]M Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland, [2]Dept of Gastrointestinal Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [3]Mria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [4]Department of Gastrointestinal Oncology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [5]Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [6]Centrum Onkologii-Instytut im. M. Sklodowskiej Curie, Warsaw, Poland

Introduction: Colorectal cancer is one of the most common malignancies in the Western world. The treatment strategy of metastatic disease (mCRC) includes cytotoxic agents (oxaliplatin, irinotecan and fluoropyrimidines) and targeted agents (anti-VEGF and anti-EGFR). Le et al in their fundamental report presented in 2015, has shown that immunomodulating agents can control the progression and potentially affect overall survival in colorectal cancer patients as well as other gastrointestinal malignancies that harbor mismatch-repair deficiency. This molecular phenomenon is leading to the hypermutated phenotype called microsatellite instability (MSI-H). On the phenotypic level, such tumors harbor hundreds-to-thousands mutations, which can make the tumor immunogenic if immune-reaction is not blocked by PD1-PDL1 axis. Avelumab is anti-PD-L1 antibody which can exhibit the similar efficacy in this rare subtype of mCRC.

Methods: This is a phase II, two-step, single-arm, open-label study in the biomarker preselected population (MS100070-066; MazoviaGI-2). The eligibility criteria includes diagnosis of metastatic colorectal cancer, refractory to standard therapy with confirmed microsatellite instability or loss of expression of mismatch repair genes (MLH1, MSH2, PMS) by local standards. Other inclusion criteria are good performance status (ECOG 0-1), sufficient organ function and no contraindications for immunotherapy (like autoimmune disorders). Two-step protocol will include two subsequent cohorts. Cohort 1: The cohort of 10 subjects with metastatic colorectal cancer refractory to standard therapy preselected by biomarker (microsatellite instability or mismatch repair deficient tumors) will receive avelumab at dose 10 mg/kg (1h IV infusion) Q2W. Subjects will receive Avelumab until confirmed progression, unacceptable toxicity, or any criterion for withdrawal from the trial. Subjects who have experienced a confirmed complete response (CR), partial remission (PR) or stable disease (SD) should be treated with avelumab for a maximum of 24 months and a minimum of 6 months after response confirmation, at the discretion of the investigator. Subjects who experienced a CR and have already stopped treatment before they could receive at least 6 months of treatment can resume treatment with avelumab at the same dose and schedule in order to complete a minimum exposure of 6 months. The patients will be observed for response per RECIST 1.1 criteria. If 2 patients of 10 are reported with CR or PR, the second cohort will be initiated. If 2 patients with objective response are observed before recruitment of all 10 patients, the second cohort will be started without delay. Cohort 2: The additional cohort of 30 subjects with the metastatic colorectal cancer refractory to the standard therapy preselected by biomarker (microsatellite instability or mismatch repair deficient tumors) will receive avelumab at dose 10 mg/kg (1h IV infusion) Q2W. The study procedures in the second cohort will be the same as in the first one. Total up to 40 patients are planned to be recruited.

P – 299 Predictive factors of complete pathological response in operated patients with locally advanced rectal cancer after chemoradiotherapy neoadjuvant treatment in Peru

R Motta, P Ybazeta, O Cordova, S Quiroz, A Figueroa, C Aliaga, R Salas, J Geronimo

Edgardo Rebagliati Hospital, Lima, Peru

Introduction: Surgery after neoadjuvant treatment with chemoradiotherapy is the standard treatment in locally advanced rectal cancer (LARC). One of the objectives of neoadjuvant treatment is to increase the rate of R0 surgeries after tumor downstaging. The 10-30% of patients achieve complete pathological response (CPR) after chemoradiotherapy treatment, which has shown reduced local recurrence and better overall survival in several studies. However, surgery has several genitourinary, sexual and gastrointestinal postoperative complications. Because of this, the recognition of patients who would achieve CPR could allow us to consider a "watch and wait" therapeutic option instead of surgery in selected patients. The objective of this study is to determine predictive factors of CPR in order to try to identify patients in whom surgical treatment may be avoided and preserve organ function.

Methods: Medical records of operated patients with LARC were reviewed. All patients who were operated and received concurrent chemoradiotherapy with capecitabine (dosis 825 mg/m2 bi) and radiotherapy (total dose = 5040 cGy/28 fx) as neoadjuvant treatment during period 2011-2015 at Edgardo Rebagliati Martins Hospital were included. All patients who had incomplete information in their medical records were excluded. The studied factors were: the platelet-lymphocyte ratio (PLR), the neutrophil-lymphocyte ratio (NLR), body mass index (BMI) and CEA. All were determined before neoadjuvant treatment. Comparisons of the CPR rate according to clinical characteristics were performed using the Chi square test. In multivariate analysis, the factors associated with CPR were determined by the logistic regression model. The data were analyzed using the SPSS program, version 24.

Results: A total of 57 patients were finally included. The median age was 63.6 years and the 57.8% were female. All had an ECOG 0-1 and an adenocarcinoma subtype, 81.2% were G2. 50.9% had a CE II and 49.1% had a CE III. The neoplasia was located in lower rectum in 49.2% of patients; meanwhile the 40.36% were located in middle rectum and 10.52% in middle-lower rectum. 10 patients achieved complete clinical response after neoadjuvant treatment. The 49.1% of patients underwent abdominoperineal resection (APR), 19.3% ultra-low anterior resection, 19.3% local resection and 12.3% low anterior resection. 17.5% of patients achieved CPR. In the univariate analysis, the CPR rate shows a significant difference in relation to the PLR ($p = 0.025$) and a statistical tendency in terms of CEA ($p = 0.062$). The rest of the clinical characteristics were not significant. In the multivariate analysis, using the logistic regression model, the only variable associated with CPR was CEA ($p = 0.027$, OR = 11.8). The PLR was not significant ($p = 0.077$).

Conclusion: Patients with LARC with a CEA < 3 before neoadjuvant are more likely to achieve CPR. There is a trend that states that patients with LARC with a PLR < 150 before neoadjuvant are more likely to achieve CPR. Studies with a larger number of patients are needed to analyze these results. Predictive factors of CPR may help to choose between different strategies of treatment.

P – 300 Predictive value of circulating tumor-derived DNA (ctDNA) in patients with locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiotherapy (CT-RT): Preliminary results

P Ravenda[1], G Gregato[1], M Rotundo[1], S Frassoni[2], V Dell'Acqua[1], C Trovato[1], W Petz[1], P Rafaniello Raviele[1], V Bagnardi[2], F Bertolini[1], M Zampino[1]

[1]European Institute of Oncology, Milan, Italy, [2]University of Milan, Bicocca, Milan, Italy

Introduction: In patients with LARC, neoadjuvant CT-RT followed by curative surgery is the standard of care. Risk-adopted treatment is based on MRI-predicting local T and N stage, radial margins and vascular involvement while no molecular predictive markers are available. In the present prospective study, we investigated the predictive role of serum ctDNA in patients with LARC.

Methods: Patients with diagnosis of LARC (T3-T4, N0 or any T, N+, M0) adenocarcinoma receiving neoadjuvant standard CT-RT with capecitabine concomitant to 50,4 Gy followed after 8-10 weeks by surgery, are included. 18 ml of peripheral blood samples were collected for ctDNA analysis extracted by using QIAamp Circulating Nucleic Acid QIAGEN. Baseline tumor biopsies and serum ctDNA collected at different time points (before CT-RT, after CT-RT/before surgery, after surgery and at the end of adjuvant CT, if indicated) were assessed for mutations in KRAS/NRAS exons 2-3-4, BRAF exons 11-15, and PIK3CA exons 9-20. CEA serum level was evaluated at the same time points. This preliminary analysis reports results on first consecutive 28 patients out of the 88 patients planned in the study protocol. The outcome of interest was the pathological complete response (pCR). Area under the receiver operating characteristic curves (AUC) was used to evaluate the ability of pre- and post-treatment value of ctDNA and CEA serum levels in predicting pCR. AUCs were compared using the DeLong, DeLong and Clarke-Pearson non-parametric approach.

Results: The first consecutive 28 patients with detectable mutations, out of 71 screened, completed study calendar of blood draw collection and were included in this preliminary analysis. Main patient characteristics were: 20/8 male/female ratio; median age (range): 62 (37-79); rectum adenocarcinoma site: 2 proximal, 11 middle and 15 distal; clinical T stage: 3 T2, 23 T3, 1 T4, 1 TX; clinical N stage: 1 N0, 16 N1, 11 N2; mutations detected on tumor biopsy/serum ctDNA: 18 KRAS, 1 BRAF(not V006E), 3 NRAS and 7 PIK3CA. Pre-CT-RT, median values of ctDNA and CEA were respectively 0.06 ng/2ml (range 0 - 17.4) and 3.5 ng/ml (range 0.8 - 7); post-CT-RT median values of ctDNA and CEA were respectively 0 ng/2ml (range 0 - 0.60) and 1.9 ng/2ml (range 0.6 - 11). Seven out of the 28 evaluated patients (25%) achieved pCR. All patients achieving pCR were concentrated at the lowest values of pre-treatment ctDNA, while no clear pattern emerged for CEA. The median value of pre-treatment ctDNA was 0.0 in patients achieving pCR, 0.11 in patients with residual tumor ($p = 0.18$). The AUCs were 0.67 (95% CI: 0.47-0.87) for ctDNA and 0.51 (95% CI: 0.24-0.78) for CEA (p-value for difference between the two ROC curves: 0.45). Similar results were observed for post-treatment ctDNA and CEA values.

Conclusion: Preliminary analysis conducted in 28 patients with LARC showed a promising role of low baseline value of ctDNA in predicting pCR. Statistically not significant results could be due to the small sample size considered in this interim analysis; however the study is ongoing and it is adequately powered to detect the suggested effect at final analysis.

P – 301 CRP/albumin ratio can be a predictor of response to neoadjuvant chemoradiotherapy (CRT) in rectal cancer

T Yetisyigit[1], S Seber[1], A Yolcu[2]

[1]Namik Kemal University Hospital, Tekirdag, Turkey, [2]Tekirdag State Hospital, Tekirdag, Turkey

Introduction: C-reactive protein to albumin (CRP/Alb) ratio is a surrogate marker of hosts reaction to systemic inflammation generated by tumor microenvironment. Recent studies have reported its efficacy as a prognostic marker in various cancers. However, its association with tumor response to treatment has not been fully elucidated. We aimed to investigate the effect of pretreatment CRP/Albumin ratio on treatment response in rectum cancer patients receiving CRT.

Methods: 35 consecutive patients diagnosed with rectum cancer who received neoadjuvant CRT with capecitabine between 2015 - 2017 were included in the study. CRP, Albumin, and hemogram values determined before treatment initiation along with data for other clinical and biochemical factors were retrieved from the medical records. Cut off values for CRP/Alb and neutrophil/lymphocyte ratio (NLR) were taken as 0.1 and 2.6, respectively. Both of the values are reported in meta analysis studies elucidating thresholds of CRP/Alb and NLR ratios.

Results: Seven patients (20%) achieved complete response while 26 patients (74%) had ypN0 disease. The distribution of ypT1, ypT2 and yp T3 stage were 13,10,5 patients respectively. Complete responders and patients with ypT1NO disease were grouped as good responders while patients with yp T3 or with post CRT node positive disease were grouped as poor responders. When the correlation between biochemical and clinical parameters with post treatment pathological stage was analyzed in univariate analysis; patients with a low CRP/Alb ratio (OR 1.8, %95 CI 1.00- 3.34, $p = 0.001$) and distance from anal verge < 4cm (OR 0.2,%95 CI 1.24- 4.23, $p = 0.014$) were found to independent predictors for good response.

Conclusion: CRP/Alb ratio along with tumor distance from the anal verge was shown to be predictive factors for tumor response to therapy. Further prospective studies are needed for validation of our findings for identification of clinical subgroups most likely to benefit from neoadjuvant treatment.

P – 302 Pathological complete response after chemoradiotherapy in locally advanced rectal cancer: Capecitabine or 5-fluorouracil? Which is better?

X Hernández-Yagüe[1], E Canals-Subirats[1], G Mateu Esquerda[2], C Auñón Sanz[1], A Maroto Genover[3], D Julià Bergkvist[2], N Gómez Romeu[2], M Osorio Fernández[3], P Planellas Gine[2], B Queralt[4], R Farrés-Coll[5]

[1]Catalan Institute of Oncology Girona, Girona, Spain, [2]Hospital Dr. Josep Trueta de Girona - Institut Català de la Salut, Girona, Spain, [3]Institut Diagnòstic per la Imatge (IDI)-Hospital Dr. Trueta de Girona, Girona, Spain, [4]Institut Català d'Oncologia Girona, Gerona, Spain, [5]Hospital Dr. Josep Trueta de Girona- Institut Català de la Salut, Girona, Spain

Introduction: Infusional 5-fluorouracil (5FU) has been the standard radiation sensitizer in patients undergoing preoperative long-course chemoradiotherapy (CRT) for locally advanced rectal cancer. It has been stablished non-inferior results, in terms of pathological complete response (pCR), of capecitabine compared with 5FU administered in bolus or continuous infusion schedule in two phase III studies1,2. Recently it has been reported a reduced rate of pathological complete response related to capecitabine compared to 5FU in a large retrospective Australian cohort3. It seems the ypT0ypN0 and ypT1ypN0 pathological stage after CRT have a similar good survival.

Methods: Patients of the Catalan Institute of Oncology-Dr. Josep Trueta Hospital in Girona (Spain) who underwent CRT and surgery for biopsy-proven locally advanced rectal adenocarcinoma between January 2014 and July 2017 were included from a retrospective-prospective recruited database. Data from 2014 to 2015 has been collected retrospectively and data from 2016 to 2017 prospectively. The evaluation of the pathological tumor regression grade was made following the indications of the American Joint Committee for Cancer included in the AJCC Cancer Staging Manual 7.0 version. We consider pCR if the pathology report informs ypT0-1 ypN0, Tumor Regression Grade=0. This is an observational academic study and the main objective is to improve the knowledge and outcome of patients affected by locally advanced rectal cancer. No additional procedures or therapeutics has been performed over the patients. We consider there was not necessary informed consent of the patients because of these two last reasons.

Results: To compare the efficacy of capecitabine and 5FU as radiosensitizer in terms of Pathological Complete Response, 153 patients have been included in the final analysis. 105 (68.6%) men and 48 (31.4%) women. 97.4% stage III and 2.8% stage II. 74.5% was staged as cT3N1 or cT3N2 (UICC 7th edition) by Magnetic Resonance Imaging. 130 (85%) and 22 (15%) patients received 5FU and capecitabine respectively as radiosensitizer. Median Dose of pre-operative radiotherapy was 50.44 Gy. Median time from end of CRT to surgery was 10.6 weeks (range 3-61, Typical Deviation 5.612). Median level of Carcinoembryonic Antigen was 18.91 ng/mL (normal range: 0 to 4.3 ng/mL). 43 patients had pCR (41 received 5FU and 2 received capecitabine). Exact Fisher Test found statistical differences between two arms ($p = 0.039$).

Conclusion: 5FU improves the probability to pCR in locally advanced rectal cancer compared to capecitabine in our cohort. This results recommend 5FU concomitant to radiotherapy as standard of treatment in pre-operative setting of locally advanced rectal cancer in our center in the same way as data reported by Jootun N et al in January 2018.

P – 303 Food intake and nutritional status of colorectal cancer patients undergoing radio-chemotherapy in Sardjito hospital

M Purba, H Winarti, R Pangastuti

Nutrition Department, Dr Sardjito Hospital, Jogjakarta, Indonesia

Introduction: Diet has long been thought to have a role in the etiology of colorectal cancer (CRC), particularly when a poor diet is combined with excess calorie intake and weight gain, physical inactivity, and unhealthy practices, such as smoking and consuming a great deal of alcohol. Current knowledge about food consumption patterns indicates that a diet high in vegetables, fruit, and fibre is protective against certain types of cancer, but the evidence that fruit and vegetable consumption is specifically related to a reduced risk of CRC was recently challenged. In an attempt to clarify the relationship between diet and CRC, researchers are examining individual food intake and nutritional status of patients undergoing radio-chemotherapy in Dr Sardjito Hospital.

Methods: The study was observational with cross sectional design. The subject of the study is colorectal cancer patients undergoing chemotherapy in the hospital. Total of 181 colorectal patients, men and women aged 21-79 years participated in the study. A measuring instrument used are a semi quantitative food frequency questionnaire, microtoise and weight scales. Analysis of data use univariate, bivariate and multivariate analysis with significant p value < 0.05.

Results: This study found that 58% of the subjects are male, 73% anemia, 77% low in body mass index (BMI). Moreover, most of the patient had low consumption in energy, protein, Fe, folic acid, and B12 vitamin (71%, 71%, 79%, 52%, 40% respectively). Mean daily intake for energy is 1254 $\pm$270 kcal, protein 46 $\pm$12 g, Fe 8.9 $\pm$10.7 mg, Folic acid 252$\pm$154 mg, B12 vit 8.9$\pm$10.7 mg. Subjects with a higher BMI tend to have a higher nutrient intake

(p<0.005). There was a significant association between food intake and nutritional status (Risk prevalence 2.11 for energy, and 1.93 for protein with p value <0.05), and 0.65 for Fe, 0.91 for folic acid, 0.53 for B12 vit respectively with p value > 0.05.

Conclusion: Most of the patients had a low intake and body mass index. This study found that there was a significant association between food intake and nutritional status.

P – 304 Preoperative chemoradiation in locally advanced rectal cancer: A single center experience

L Oliveira[1], A Rolo[1], C Carvalho[1], I Faustino[1], C Alpoim[2], C Calçada[3], A Costa[3], G Fonseca[3], J Conde[3], A Teixeira[1], C Fardilha[3], P Costa[3], C Coutinho[1]

[1]Department of Oncology, Hospital Senhora da Oliveira, Guimarães, Portugal, [2]Department of General Surgery, Hospital da Senhora da Oliveira, Guimarães, Portugal, [3]Department of Radiation Oncology, Hospital de Braga, Braga, Portugal

Introduction: Preoperative chemoradiation (CRT) is the standard treatment for locally advanced rectal cancer (LARC). The aim of this study was to evaluate the efficacy and tolerability of neoadjuvant CRT in the treatment of LARC in Hospital de Guimarães.

Methods: A retrospective review was conducted between June 2012 and December 2017 for patients with stage II and III rectal cancer treated with neoadjuvant CRT. All patients performed a long course of radiotherapy with concurrent chemotherapy (87% with 5-fluorouracil 225mg/m2 for 24 hours 7 days/week and 13% with capecitabine 825 mg/m2 twice daily 5 days/week). All patients were treated with 3D conformal radiotherapy using multiple fields (>4) and mixed photon energies. The most common treatment schedule (96,8%) was 50-50,4 Gy (2-1,8 Gy/fraction), 5 fractions per week.

Results: There were 92 patients identified, the median age was 61 years (26-83 years) and 64,1% were males. Rectal cancer location was low (up to 5cm) in 30,4%, middle (>5 to 10 cm) in 43,5% and high (>10 to 15 cm) in 26,1% of cases. The main symptom present at diagnosis in 50% of patients was rectal bleeding and improved with neoadjuvant treatment in 89,1% of cases. Treatment was well tolerated, 40,2% of patients experienced acute grade 1 or 2 toxicities [National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03]. Acute grade 3 toxicity (NCI-CTCAE v4.03) was found in 3,2% of patients: tenesmus, diarrhea and mucositis. The median time to surgery after neoadjuvant CRT was 8 weeks. After complete CRT, 95,7% of patients underwent surgical resection: 71,6% anterior resections and 28,4% abdominal-perineal amputation. The remaining 4,3% of patients did not undergo surgical resection due to early metastatic progression or unresectable disease. R0 resection was achieved in 95,4% of cases. Tumour downstage after CRT was observed in most patients (76,1%), with 14,1% cases showing a pathological complete response. Considering tumour location, the rate of downstage was 73,9%, 78,9% and 87,5% for low, middle and high rectum, respectively. Anal sphincter preservation was not possible in 29,5% of patients (22,7% with low and 6,8% with middle rectal cancer). Among the 28 tumours located up to 5 cm from the anal verge, 21,4% were resected with a sphincter preservation. Most of the patients (94,3%) received fluoropyrimidine-based adjuvant chemotherapy. Concerning the patients that totalize surgical resection, 11,3% experienced recurrence in a median time of 14 months following surgery (4 – 32 months): 7,9% with distant disease recurrence and 3,4% developed both local and distant disease recurrence. Most of the patients (84,1%) are free of disease.

Conclusion: CRT for LARC in neoadjuvant setting it's a treatment modality with excellent outcomes concerning tolerability and pathologic response. In this sample, we achieved high pathologic responses rates specially in high rectum tumours (pathologic response rate 87,5%) with a low toxicity profile (acute grade 3 toxicity rate: 3,2%). Our results are similar to the data published in the literature. In addition, CRT allowed sphincter sparing surgery in 21,4% of patients whose tumours were located up to 5 cm from the anal verge.

P – 305 The role of adjuvant chemotherapy according to the status of surgical margin in rectal cancer patients who received preoperative chemoradiation and total mesorectal excision

S Sung[1], J Lee[2], S Kim[2], J Lee[2]

[1]Department of Radiation Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, SuWon, Republic of Korea, [2]St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Republic of Korea

Introduction: Adjuvant chemotherapy has been recommended for patients who have locally advanced rectal cancer. However, the role of adjuvant chemotherapy in patients with positive surgical margin has not been clarified. We investigated the benefit of adjuvant chemotherapy according to the surgical margin in locally advanced rectal cancer patients who received preoperative chemoradiation (CRT) and total mesorectal excision (TME).

Methods: A total of 1801 rectal cancer patients staging cT3-4N0-2M0 were included. The patients were eligible when tumors were pathologically confirmed adenocarcinoma, located within 10cm from anal verge, and staged cT3-4N0-2M0. Before surgery, all patients received radiation therapy at a dose of 50.4 Gy in 28 fractions with concurrent 5-fluorouracil or capecitabine. Curative surgery including TME was performed 4 to 8 weeks after radiotherapy. Adjuvant chemotherapy was performed after 4-6 weeks after surgery.

Results: Adjuvant chemotherapy was given to 1531 patients (85.0%). Patients with positive circumferential resection margin or distal resection margin were 205 (11.4%). With patients with positive surgical margin (n = 205), the 5-year recurrence-free survival (RFS) showed a significant difference between adjuvant chemotherapy group and no adjuvant chemotherapy group (50.3% vs. 30.9%, p = 0.01). The 5-year overall survival rate was 72.6% in adjuvant chemotherapy group and 57.2% in no adjuvant chemotherapy group (p = 0.09). With patients with the negative margin (n = 1596), the 5-year RFS rate did not show any difference between two groups (75.6% vs. 76.8%, p = 0.94). On multivariate analysis, adjuvant chemotherapy was significantly associated with RFS in patients who had the positive surgical margin (Hazard ratio (HR): 0.48, 95% confidence interval (CI): 0.25-0.94, p = 0.032). In contrast, there was no significant association between adjuvant chemotherapy and RFS in those with negative surgical margin (HR: 0.99, 95% CI: 0.72-1.35, p = 0.94).

Conclusion: Patients who received adjuvant chemotherapy showed a significantly improved 5-year RFS rate compared with those who did not receive adjuvant chemotherapy if the patients had positive surgical margin. The benefit of adjuvant chemotherapy was more remarkable in patients with positive surgical margin compared to those with negative surgical margin.

P – 306 The relationship between primary tumor regression grade and lymph nodes status in local advanced rectal cancer after neoadjuvant chemoradiation therapy

H Ju[1], L Liu[2], W Wu[1], Y Cai[1], X Lu[1]

[1]Zhejiang Cancer Hospital, Hangzhou, China, [2]Zhejiang Cancer Hospital, Zhejiang, China

Introduction: Neoadjuvant chemoradiation therapy may affect the lymph node status in local advanced rectal cancer. In this study, we evaluate the relationship between tumor regression grade and lymph nodes status and prognosis value in local advanced rectal cancer after neoadjuvant chemoradiation therapy.

Methods: AJCC-TRG classifications were evaluated on surgical specimens from 201 locally advanced rectal cancer patients receiving CRT. The relationship between tumor regression grade and lymph nodes status were evaluated. The impacts of TRG and lymph node status on survival were estimated using Kaplan–Meier method.

Results: Classifications of TRG 0, 1, 2, and 3 were found in 18.9%, 40.8%, 32.3%, and 8.0% of the resected specimens respectively. TRG have significant relationship with harvest lymph node number, positive lymph node number and lymph node metastasis ratio. TRG were significant predictors of OS, DFS, LRFS and DMFS. Positive lymph node number and lymph node metastasis ratio but not total lymph node number have relationship with survival.

Conclusion: TRG have significant relationship with lymph node status in local advanced rectal cancer after neoadjuvant chemoradiation therapy. TRG, positive lymph node number and lymph node metastasis ratio have significant predictors of survival, but total lymph node number have little impact on prognosis.

P – 307 Preoperative predictors for pathologic response and prognosis of rectal cancer after neoadjuvant chemoradiation

G Yoo[1], J Yu[2], H Park[2], D Choi[2], W Cho[2], Y Park[3], J Park[2], H Lim[4], W Kang[2], H Kim[5], K Song[1]

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Samsung Medical Center, Seoul, Republic of Korea, [3]Division of Hematology and Oncology, Department of Medicine, Samsung Medical Center, Seoul, Republic of Korea, [4] Samsung Medical Center, Seoul, Republic of Korea, [5]Department of General Surgery, Seoul, Republic of Korea

Introduction: A watch-and-wait approach following neoadjuvant chemoradiation (NCRT) could avoid the morbidity of surgery for rectal cancer. To determine which patients would be candidates of watch-and-wait approach, it is important to identify reliable factors predictive for the poor responses after the chemoradiation. In this study, we aimed to identify factors associated with pathologic response and long-term disease control.

Methods: We retrospectively reviewed 353 patients who received NCRT and surgical resection. Patients who did not have magnetic resonance imaging (MRI) before and after NCRT (N = 161) and those who did not undergo total mesorectal excision were excluded (N = 13). Finally, 179 patients were included in the analyses. The dose regimen of NCRT was median 44 Gy (range, 34.4 to 60.0 Gy) in 22 fractions (range, 12 to 30 fractions). Among the total cohort, adjuvant chemotherapy was undergone in 160 patients. We evaluated both tumor regression grade (TRG) in MRI (mrTRG) and pathologic TRG (pTRG).

Results: The median follow-up was 71 months (range, 6 to 101 months). The median age was 56 years (range, 27 to 81 years). Twenty-four patients were with cT1-2 disease, 150 with cT3 and 5 with cT4 disease. Twenty-two patients had cN0 disease. The median value of carcinoembryonic antigen (CEA) before and after NCRT were 2.19 ng/mL (range, 0.50 to 88.00 ng/mL) and 1.53 ng/mL (range, 0.40 to 12.79 ng/mL), respectively. Overall survival (OS), local control (LC), and disease-free survival (DFS) rates at 5 years were 84.8%, 91.2%, and 73.5%, respectively. The mrTRG 1 or 2 were achieved in 41 patients (22.9%). Pathologic complete responses (pCR; pTRG 4) were observed in

43 patients (24.0%). Among the patients with pCR, 37 patients achieved mrTRG 1 or 2. On multivariate analysis, mrTRG (1, 2 vs. 3, 4, 5; P = 0.005), ΔCEA, that is post-NCRT CEA minus pre-NCRT (< 0.33 vs. ≥ 0.33 ng/mL; P = 0.004), and circumferential margin (CRM) on MRI (mrCRM; P = 0.001) were identified as independent factors associated with DFS among the preoperative parameters. The DFS rates were significantly discriminated along the risk groups defined according to the number of the risk factors (mrTRG ≥ 3, ΔCEA ≥ 0.33 ng/mL, mrCRM) with 84.7% in low risk group (0 risk factor), 76.1% in intermediate risk group (1 risk factor), and 44.1% in high risk group (2 or more risk factors; P < 0.001). For OS, mrCRM (P < 0.001) and ΔCEA (P < 0.001) showed significantly association on the multivariate analysis. Among the patients with mrTRG 1, pTRG 3 or 4 was achieved in 70.7% of the patients. However, 60% of the patients who showed mrTRG grade 1 or 2 with post-NCRT CEA ≥ 3 ng/mL showed poor pTRG less than minimal response.

Conclusion: The mrTRG, ΔCEA, and mrCRM were preoperative factors predicting the DFS, significantly. Although good mrTRG seems to be correlated with good pTRG, increased post-NCRT CEA might be associated with poor pTRG, even for patients with good mrTRG.

P – 308 Comparison of incidence and survival outcomes in mucinous and signet-ring cell colorectal cancers with classical adenocarcinoma: A SEER analysis

T Mehmood

Northwest General Hospital and Research Centre, Peshawar, Pakistan

Introduction: Besides classical adenocarcinoma (AC), mucinous adenocarcinoma (MAC) and signet-ring cell carcinoma (SRCC) are less frequent subtypes of colorectal cancer, and their recent epidemiologic data are lacking. The current study was designed to explore the evolving epidemiology and prognosis of patients with colorectal MAC and SRCC, compared with AC.

Methods: The Surveillance, Epidemiology and End Results (SEER) registry database was adopted for patients with pathologically confirmed colorectal neoplasms as their first malignancy. Incidence and survival trends were estimated by age and histologic subtype. 5-year cancer specific survival (CSS) were evaluated for entire cohort, and compared in subgroups by age, grade and stage. Multivariate analysis of CSS was conducted for entire cohort.

Results: MAC incidence (per 100,000) declined slightly from 6.1 in 1975 to 5.6 in 2001, and fell to 2.5 in 2012 with an APC of -7.8% (95%CI=-8.8%–6.8%, P < 0.001), then reached a plateau. SRCC incidence gradually climbed from 0.1 in 1975 to 0.6 in 1999 with an APC of 8.3% (95%CI=7.2%-9.4%, P < 0.001) and went down to 0.4 in 2014 with an APC of -3.0% (95%CI=-5.0%–1.0%, P < 0.001). Among patients younger than age 50 years, MAC incidence decreased at an APC of -2.6% (95%CI: -3.6%–1.6%, P < 0.001), and SRCC remained stable, whereas AC incidence increased greatly at an APC of 1.9% (95%CI: 1.6%-2.2%, P < 0.001). Survival of both MAC and AC increased over time, while the survival of SRCC fluctuated without evident improvement. The 5-year CSS of SRCC was 31.3%, significantly lower than AC (66.6%) and MAC (60.4%). For AC and MAC Survival rate of patients aged below 50 years was superior to those aged 50 years or over through time, while in SRCC, after follow-up of approximately 20 months, the survival rate of younger patients dropped and became lower than older patients. Histologic subtype was an independent factor for CSS of CRC.

Conclusion: The incidence and survival of colorectal MAC and SRCC differs from traditional AC. Despite of the low incidence of SRCC, the survival is significantly worse than AC and MAC, especially for patients aged younger than 50 years. Further studies of the etiologies and treatment for rare subtypes of CRC are needed.

P – 309 Quality improvement in the management of rectal cancer in a large healthcare system in the United States

W Sause

Intermountain Healthcare, Murray, Utah, USA

Introduction: Intermountain Healthcare is a twenty-three hospital care delivery system located in the State of Utah. The system represents large referral hospitals and smaller community facilities. Approximately sixty percent of patients who reside in the State of Utah receive their care at an Intermountain facility. Intermountain Healthcare has a long history of quality improvement. In order to facilitate quality improvement Intermountain has developed clinical programs for a variety of disciplines. Oncology represents a focused area of interest. These clinical programs have dedicated infrastructure and leadership in place to evaluate care and initiate improvement in a variety of disease sites.

Methods: Colorectal cancers represents one of the more common malignancies in the system. System initiatives to eliminate variations in care delivery for colorectal cancer have been continuous for 15 years. Most recently we analyzed care for primary rectal cancer. The analysis substantiated variation in care delivery and variation from standard of care across the system. From 2012 to 2015 224 cases of rectal cancer had primary surgery in the system. Forty patients received care which would be outside the standard of care either by omission of preoperative staging or treatment. Eight of the forty were deemed to be emergent by the provider and received emergent surgical resection. Analysis of outcomes revealed improved local control in those patients deemed appropriate.

Results: Analysis of baseline data suggested variation in care delivery. The goal of our quality improvement initiative is to change behavior and improve care. In order to address these treatment inadequacies we initiated a statewide improvement process. This included a continual timely monitoring process. Individual provider score cards comparing their results to their peers. Infrastructure improvement relating to tumor conference presentation and timely pathology review. The resulting behavioral change and outcomes will be presented.

Conclusion: Same as above.

P – 310 Diagnosis and selection of method of combined treatment of local-distributed cancer of the rectum with invasion into organs of the genitals

S Lukmonov[1], O Usmanov[1], K Madatov[1], U Allazarov[1], U Kurbankulov[1], M Ismailov[2]

[1]Tashkent Medical Academy, Tashkent, Uzbekistan, [2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Introduction: Diagnosis optimization and treatment choice of the locally advanced rectal cancer with invasion in the organs of the genitals.

Methods: We analyzed the results of combined operations for rectal cancer with invasion in the genital organs, for 2013-2017 on the basis of the Department of Oncology and Radiology of the Tashkent Medical Academy. Under our supervision, there were 118 women aged 21 to 68 years. Methods of examination of patients included the following: colonoscopy with biopsy, irrigoscopy, transrectal ultrasonography (TRUS), CT, hysteroscopy. 12 patients underwent hormonal status examination. The tumor in the rectosigmoid section of the rectum was in 12 patients, in the upper ampullar department in 17 patients, in the middle-ampullar department in 32 patients, in the lower ampullar department in 45 patients, in the anal canal in 12 patients. The nature of operations on the rectum with combined surgical interventions was as follows: abdominal perineal extirpation of the rectum with sigmostomy was performed in 57 patients (48.3%), abdominal-anal rectal resection in 22 patients (18.6%), anterior resection of the rectum in 12 patients (10.2%), Hartmann's operation was performed in 27 patients (22.9%).

Results: Vaginal resections were performed most often in 58 patients, nasal amputation of the uterus without appendages in 21, extirpation of the uterus with appendages in 22 patients, removal of the uterine appendages in 31 patients. It should be noted that more than one organ was resected or removed in 14 patients from these patients. It is important to note that the metastatic lesion of regional lymph nodes was established in 28.0% of patients (in 33 of 118), whereas for all radically operated patients this indicator was 29.1%. Postoperative complications of a purulent-inflammatory nature occurred in 21 patients (17.7%). The overall lethality was 3.4%, 4 patients from 118 patients died after combined operations. The incidence of relapse after combined operations for colorectal cancer was 28%. The average duration without a relapse period was 14 months. 5-year survival after combined operations with locally advanced rectal cancer in our observations was 47.1%.

Conclusion: Thus, the data presented indicate that such important indicators as the rate of recurrence (28%), 5-year survival (47.1%), with combined interventions and standard volume operations for colon cancer are approximately the same. Given that the true invasion of a tumor into neighboring structures can often be established only after histological examination of a distant macro preparation and that combined surgical interventions currently do not actually worsen the immediate results of treatment (according to the number of postoperative complications and lethality from them), then the expediency of their implementation in our opinion there is no doubt.

P – 311 Comparison between the toxicity profile of fluorouracil versus capecitabine concomitant with radiotherapy in patients with non-metastatic rectal cancer

A Lotfy[1], M Yassin[2], G Rashwan[3], A Nagy[1]

[1]Ain Shams University, Cairo, Egypt, [2]Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt, [3]Nasser Institute, Cairo, Egypt

Introduction: The incidence of colorectal cancer varies considerably around the world. About 944,717 cases were identified worldwide in the year 2000. High incidences of colon and rectal cancer cases are identified in the developed countries. Concurrent preoperative radiotherapy with chemotherapy (5-Flurouracil based) followed by total mesorectal excision (TME) surgery and further systemic therapy is the recommended standard first-line treatment. Fluorouracil (5-FU) remains the most widely used agent for colorectal cancer. Capecitabine is a rationally designed 5-FU pro-drug developed to mimic the continuous infusion of 5-FU while avoiding complications and inconvenience of intravenous administration.

Methods: This is a retrospective study aiming at evaluating the toxicity profile (Hematological and non-hematological) in rectal cancer patients who received fluorouracil with radiotherapy versus those who received capecitabine with radiotherapy as neoadjuvant treatment in period from 1-1-2012 till 1-1-2015 in Ain shams university Department of Clinical Oncology and Nasser institute in Cairo-Egypt. Data collected

from files of patients included 196 patients (male 101 patients and female 95 patients), the patients were arranged into two groups: group I included 96 patients received 5-FU concomitant with radiotherapy and group II included 103 patients received capecitabine concomitant with radiotherapy. The evaluated side effects were: anemia, neutropenia, thrombocytopenia, hepatotoxicity, renal impairment, cardiotoxicity, neurotoxicity, diarrhea, emesis, mucositis, alterations in taste, xerostomia, gingival bleeding, hypersensitivity reactions, pigmentary changes, alopecia, nail disorders, acral erythema. The collected data was revised, coded, tabulated and introduced to PC using statistical package for social science (SPSS 20.0 for windows; SPSS Inc, Chicago, IL, 2001). Suitable analysis was done according to the type of data obtained for each parameter.

Results: The evaluated toxicities showed that there was a statistical significant difference with increase in number of patients who suffered from hypersensitivity reactions ($p < 0.009$) and alopecia ($p < 0.005$) in the group who received 5-Fu compared to Capecitabine group, while acral erythema was higher in the Capecitabine group ($p < 0.001$). The remaining toxicities were not statistical significantly higher in either groups.

Conclusion: Capecitabine and 5-flurouracil have comparable toxicity profile but capecitabine offers the feasibility of being oral drug.

P – 312 Role of consolidative radiation therapy after surgery in patients with stage IV rectal cancer

T Mehmood

Northwest General Hospital and Research Centre, Peshawar, Pakistan

Introduction: Radiotherapy (RT) and surgery are known to effectively palliate many symptoms of patients with metastatic rectal cancer (mRC). However, whether RT would provide survival benefit to mRC after surgery remains unclear.

Methods: Results Program (SEER) database. Patient demographics between the RT and no-RT groups were compared using Pearson Chi-Square tests. Propensity score (PS) matching and Cox proportional hazards regression analyses were performed to evaluate prognostic power of variables on cause-specific survival (CSS).

Results: A total of 5520 mRC patients who have received surgery were identified in SEER database. Multivariable Cox regression analyses showed that RT was a protective factor of mRC patients after surgery in mRC patients (hazard ratio [HR] = 0.654, 95% confidence interval [CI] = 0.607-0.704, $p < 0.001$). PS matching produced 3887 mRC patients and univariable Cox regression analyses indicated that RT was associated with a significant improvement of CSS in mRC patients after surgery (HR = 0.455, 95%CI=0.422-0.491).

Conclusion: Using SEER database, we have identified that RT was associated with a significant survival advantage in the setting of mRC patients after surgery. This study strongly supports the use of RT after surgery for patients with mRC. In order to accurately define the role of RT in the comprehensive treatment for mRC patients, more prospective studies are clearly needed to be conducted.

P – 313 Nonstandard hypofraction radiotherapy in neoadjuvant chemo-radiation therapy of locally advanced rectal cancer

A Abdujapparov[1], S Tkachev[2], F Djuraev[3], Y Ten[1]

[1]National Cancer Research Center, Tashkent, Uzbekistan, [2]National Cancer Research Center, Moscow, Russian Federation, [3]Tashkent Medical Academy, Tashkent, Uzbekistan

Introduction: Neoadjuvant chemoradiotherapy has become the standard treatment for locally advanced rectal cancer. Neoadjuvant chemoradiotherapy not only can reduce tumor size and recurrence, but also increase the tumor resection rate and anus retention rate with very slight side effect. Comparing with preoperative chemotherapy, preoperative chemoradiotherapy can further reduce the local recurrence rate and downstage.

Methods: In our department of Radiation Oncology were retrospectively analyzed 150 patients with locally advanced rectal cancer from 2008 to 2013. Patients were divided into two groups by randomization. Study of the efficacy of the developed neoadjuvant method of treatment of rectal cancer, with the use of remote nonstandard hypofraction radiotherapy 10 x 4 Gy 3 fraction in week to achieve cumulative dose 40 Gy conducted in patients receiving capecitabine at a dose of 1650 mg/m2 during on the days of radiotherapy in 73 patients (Study group), Control group who receive standard neoadjuvant method of treatment prolonged radiotherapy 26 x 2 Gy cumulative dose 56 Gy conducted in patients receiving capecitabine at a dose of 1650 mg/m2 during on the days of radiotherapy in 78 patients with low and middle rectal cancer. Age of patients is from 56 to 74, with IIIB-C stage (T3-4N0-2M0) (CRM+) of rectal cancer. After a neoadjuvant treatment, all patients underwent surgery within 7-8 weeks.

Results: The results of our study were as follows: pCR in 16.4%, a partial response in 46.57% patients. Postoperative complications were seen in 6.8% cases in study group, pCR 15.4%, partial response 46.15% and postoperative complications 6.4% in control group. The rate of 5-year OS 75.34% ($p > 0.05$), 5 year disease-free survival rate 64.38%, in study group, and in the control group, the results were 5-year OS 74,35% and 5 year disease-free survival rate 65.4%. The rate of local control in both group were identical.

Conclusion: Method of neoadjuvant treatment (10 x 4 Gy + capecitabine at a dose of 1650 mg/) in combined therapy of rectal cancer in patients does not affect intra-and postoperative complications and slightly increases the frequency of the local control and 5-year OS. In the hypofractive course of radiotherapy, the amount of fractions will be reduced by increasing the single dose, which will shorten the duration of the treatment course. Developing and implementation of the hypofraction method of radiotherapy by reducing the number of radiotherapy sessions will shorten the duration of the course of radiotherapy from 38 to 22 days, which will improve the tolerability of CRT and the quality of life of patients, and will decrease the usage of equipment and save the financial resources introduced to maintain it. Based on the results analysis obtained, the hypofraction method of radiation therapy will be introduced with neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer in oncological institutions in Uzbekistan and CIS countries.

P – 314 Prone vs supine position in patients with rectal cancer treated with volumetric arc therapy and concurrent chemotherapy

L Diaz Gomez[1], A Seguro Fernandez[2], P Ramirez Daffos[3], J Tisaire[4], J Jaen Olasolo[1]

[1]HU Jerez, Jerez de la Fra, Spain, [2]H. Jerez, Jerez de la Fra, Spain, [3]HU Puerta del Mar, Cadiz, Spain, [4]Hospital de Jerez, Jerez de la Fra, Spain

Introduction: Patients undergoing radiotherapy often are treated in prone position using a belly board as immobilization system with a full bladder protocol. Doing this, we reduce doses to organ at risk, but the position is difficult to maintain and hardly reproducible. This fact served for previous techniques of radiotherapy, but with the current ones we must suspect that the protection of normal tissues is assured regardless of the position. The objective of our study is to compare both positions and verify the protection of organ at risk, without loss of coverage of the treatment volume, using volumetric arc radiotherapy (VMAT) and concomitant chemotherapy.

Methods: 12 patients were eligible for the study. We did CT scanning for VMAT planning first in prone position and immediately in supine, with full bladder protocol and using the corresponding immobilizers for each case. At the end of the test, we asked the patient's choice. Planning target volume (PTV) was delimited in both CT by the same facultative as the organ at risk (bladder and small bowel) We considered 2 PTVs, pelvis with a total dose of 45Gy, 1,8Gy/fraction and simultaneous integrated boost for tumour to 54Gy, 2.16Gy/fraction, all in 25 fractions. Radiotherapy was planned with double-arc VMAT, 6-MV photons, with a maximum variable dose rate of 600 MU/min. These two arcs were delivered with opposite rotation (clock and counter-clock) and two coplanars arcs of 360° sharing the same isocentre and optimised independently. Chemotherapy was capecitabine 825mg/m2 twice a day or 5-FU continuous infusion through an indwelling central venous catheter with ambulatory pump.

Results: In terms of coverage for treatment volume, both positions were similar, without significant differences in homogeneity or median dose. At high doses, a significant volume of small bowel was irradiated in prone position (median 1,23% supine to 14,4% prone at 40Gy) being not significant for bladder (7,2% supine to 5,7% prone at 40Gy) As the patient's choice, most of them preferred the supine position, moreover the carriers of infusion pumps

Conclusion: As a patient's choice and with better dose-volume histograms for organ at risk, with VMAT radiotherapy we recommend supine position for rectal cancer treatment.

P – 315 The role of palliative re-irradiation in management of rectal cancer

T Janjua[1], M Hingorani[2], R Cooper[3], P Hatfield[3], N Casanova[3], M Williams[1], M Teo[3], D Sebag-Montefiore[4]

[1]St James University Hospitals, Leeds, UK, [2]St James University Teaching Hospitals, Leeds, UK, [3]St James University Hospital, Leeds, UK, [4]University of Leeds, Leeds, UK

Introduction: The role of re-irradiation for management of loco-regional pelvic recurrence in rectal cancer remains poorly defined. Previous studies have employed range of dose-schedules with variable outcomes and the use of higher biological effective dose (BED) regimes has been associated with increased rates of Grade 3-4 toxicity ranging from 20-30 percent. We report on retrospective evaluation of outcomes in rectal cancer following re-irradiation with a palliative fractionated regime of 15 Gy in 5 fractions.

Methods: Twenty rectal cancer patients were identified from the radiotherapy (RT) data registers all of whom received re-irradiation with a dose-schedule of 15 Gy in 5 fractions between 2012-2017. The hospital clinical and RT records of patients were reviewed to evaluate the following study parameters: demographics, stage of disease and treatment at presentation, pattern of relapse, specifics of re-irradiation schedule, symptom control, toxicity, and survival outcomes.

Results: The median age of patients was 71.5 years (males =18, females=2). Nineteen patients had pathologically confirmed diagnosis of adenocarcinoma and in one patient biopsy was inconclusive. Most patients (n = 16) had localised disease at original diagnosis and 15 patients were treated with common neo-adjuvant RT regimes [short-course RT = 8 (25 Gy/5 fractions), chemo-RT=7 (45 Gy/25 fractions with concurrent chemotherapy)]. Twelve patients underwent subsequent surgery (APER=6, anterior resection=4, Hartmann's=2). Five patients were initially treated with palliative RT using 20 Gy in 5 fractions. All patients developed loco-regional pelvic recurrence (local progression=9, sacral=5, rectal stump=2, pelvic side wall=2, anastomotic =2). There were equal proportion of patients with localised (n = 10) and metastatic disease (n = 10) at time of re-irradiation. The common symptoms were bleeding and mucus

discharge (n = 8), pain (n = 10), tenesmus (n = 3), and numbness (n = 1). The median time interval of re-irradiation from original RT was 33 months (inter-quartile range = 13-65 months). There was definite evidence of symptomatic improvement in more than 50% of patients (n = 11) with only 3 patients reporting no improvement in local symptoms. Six patients were discharged following re-irradiation and had limited follow-up to comment on the level of symptomatic improvement. Most importantly, there were no reports of significant toxicity and only one patient reported grade 2 fatigue and nausea. The median survival of patients who had previously received RT for localised disease was 10.25 months (range=7.3-13.1 months) after irradiation.

Conclusion: Palliative re-irradiation with 15 Gy in 5 fractions is well tolerated in patients with rectal cancer and associated with good symptomatic improvement and minimal toxicity. It should be considered as a possible therapeutic option in those with symptomatic loco-regional recurrence after previous radiotherapy. Further studies should be designed to evaluate the dose-response characteristics of reirradiated tissues with the aim of defining an optimum dose-level that may be safely employed to treat such patients.

P – 316 Is there any association of dose received by pelvic bone marrow in preoperative radiotherapy in rectal cancer with hematological toxicity of subsequent oxaliplatin-based chemotherapy?

M Spalek[1], W Michalski[2], K Bujko[3], L Wyrwicz[4]

[1]M Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland, [2]Laboratory of Bioinformatics and Biostatistics, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [3]Dept of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland, [4]Centrum Onkologii-Instytut im. M. Sklodowskiej Curie, Warsaw, Poland

Introduction: Preoperative radio(chemo)therapy in rectal cancer may irreversibly damage pelvic bone marrow (PBM) and impair the tolerance of subsequent chemotherapy. The aim of the study was to assess the association between irradiated volume of PBM and the tolerance of subsequent FOLFOX-4 chemotherapy in rectal cancer.

Methods: The target population was a retrospective cohort of consecutive patients with adenocarcinoma of rectum who received FOLFOX-4 as adjuvant or because of cancer relapse in our institution between 2011-2016. The PBM was automatically contoured and divided into iliac (IM), lumbosacral (LSM), and lower pelvic (LPM) marrow. We assessed mean dose, and percentage of volume receiving 10-90% (V10%-V90%) of the prescribed dose for PBM, IM, LSM, LPM. To evaluate the association between mean dose, V20% and V40% with $\geq$2 (TOX2) and $\geq$ grade 3 (TOX3) hematological toxicity, Chi-2 and T-test were used. Generalized linear model (GLM) was used to test an influence of dose-volumes distribution on TOX2 and TOX3.

Results: 39 patients met eligibility criteria. 26 of them received preoperative 5x5 Gy, 7 of them underwent 5x5 Gy with consolidative 3 cycles of FOLFOX-4, 6 of them received 25x2 Gy with concomitant 5-FU/LV. No dependence of V20% and V40% of PBM and its areas on toxicity was found. We found no influence of dose-volume distribution on TOX2 and TOX3.

Conclusion: No relationship between doses received by pelvic bone marrow in preoperative radio(chemo)therapy in rectal cancer and hematological tolerance of subsequent FOLFOX-4 chemotherapy was found.

P – 317 A single centre experience of in-field recurrence following pre-operative radio(chemo)therapy in patients with rectal cancer

O Coen[1], L Karsera[1], N Tambe[1], R Roy[2]

[1]Hull & East Yorkshire NHS Trust, Cottingham, UK, [2]Queen's Centre of Oncology & Haematology, Hull, UK

Introduction: Preoperative radio(chemo)therapy is commonly used in the management of rectal cancer. It has consistently shown to improve local recurrence rates over surgery alone and improve progression free survival1,2. There is however limited data as to what proportion of patients develop recurrence within the radiotherapy field. This retrospective review reports outcomes for patients treated with pre-operative radio(-chemo) therapy followed by surgery depending on response.

Methods: Data was obtained by retrospective case record review for 55 patients diagnosed with stage I to III resectable rectal cancer, using the TNM7 classification 3, between 2013-2017. All patients received pre-operative radiotherapy, in the form of short course radiotherapy (5X5 Gray) or long course chemoradiotherapy (45Gray in 25 fractions with Concurrent capecitabine), at Castle Hill Hospital, UK. Surgery was undertaken in eligible patients with total mesorectal excision (TME). Data was collected on time to surgery, radiological and pathological response and rate and site of recurrence. Data for recurrence was followed up to December 2017.

Results: Patients had a median age of 66 years (range 36-86) and a male predominance (65% male vs 35% female). The majority of patients had stage III tumours (76%) compared to stage II (22%) and stage I (2%). Overall 75% patients had received long course chemoradiation and 25% short course radiotherapy. For long course chemoradiation, the median time to surgery was 12.3 weeks (8.6 - 32 weeks) and for short course it was 6 days (3-132 days). 96% of patients had completed radiotherapy as planned and of these 89% had proceeded to TME surgery. Reasons for not proceeding to surgery included a complete radiological response (2 patients), patient choice (1 patient), progressive disease (3 patients) and death (2 patients). Following treatment downstaging was observed in 36% of patients, determined either by surgical histology or by radiological response on MRI in those who did not proceed to surgery. A pathological complete response rate of 17% was observed in all patients who received combination treatment [pre operative (chemo)radiotherapy and surgery]. In patients who received long course chemoradiotherapy and surgery the pathological complete response had improved to 22%. The overall rate of recurrence (local and distant) at 3 years was 31%. This include 7 patients who had experienced distant recurrence immediately following radio(-chemo) therapy with 3 of the 7 not proceeding to surgery. Overall distant only recurrence was observed in 24% patients, local out of field recurrence in 2% and local in-field recurrence in 5% of patients at 3 years. Of note, there were involved surgical margins in 2 of the 3 patients who developed local in-field recurrence.

Conclusion: This retrospective review shows that pathological complete response rates are in keeping with previously published results and the rate of in-field recurrence is small in number. Hence, future strategies should concentrate on preventing distant recurrence, which is the main site of treatment failure.

P – 318 Laparoscopic technologies in the treatment of patients with locally advanced rectal cancer: The possibilities and prospects

S Khoshimov

Tashkent Medical Academy, Tashkent, Uzbekistan

Introduction: To improve the results of treatment of patients with locally advanced rectal cancer by using a combined approach in the treatment with the use of minimally invasive technologies.

Methods: The study included 39 patients with locally advanced rectal cancer in the stage of cT3-4 cN0-2 cM0-1 treated at the Department of Oncology and Radiology of the Tashkent Medical Academy from 2014 to 2017. Radiation therapy was performed using the classical fractionation of the dose at the RPM of 2 Gy, 5 days a week, up to a total of 50 Gy. Chemotherapy: oxaliplatin 50 mg/m 2 IV on days 1, 8, 22, 29 and capecitabine at a dose of 825 mg/m 2 2 times a day from 1 to 14 and from 22 to 33 days of radiotherapy. Evaluation of the rectal tumor response to chemoradiotherapy was performed after 8-10 weeks, based on pelvic MRI findings, and according to the mrTRG criteria (Brown G.). The surgical stage was carried out in accordance with modern principles of surgery for rectal cancer: high vasoconstriction, total or partial mesorectomyectomy, nerve-preserving interventions. Adjuvant therapy: was performed by all patients, except patients with stage ypT0N0, in standard regimens.

Results: The study included 39 patients with locally advanced rectal cancer in the stage of cT3-4 cN0-2 cM0-1 treated at the Department of Oncology and Radiology of the Tashkent Medical Academy from 2014 to 2017. Radiation therapy was performed using the classical fractionation of the dose at the RPM of 2 Gy, 5 days a week, up to a total of 50 Gy. Chemotherapy: oxaliplatin 50 mg/m 2 IV on days 1, 8, 22, 29 and capecitabine at a dose of 825 mg/m 2 2 times a day from 1 to 14 and from 22 to 33 days of radiotherapy. The surgical stage was carried out in accordance with modern principles of surgery for rectal cancer: high vasoconstriction, total or partial mesorectomyectomy, nerve-preserving interventions. Adjuvant therapy: was performed by all patients, except patients with stage ypT0N0, in standard regimens.

Conclusion: Disadvantages of laparoscopic interventions: increase in the duration of the operation ($p < 0.05$); difficulty in visualization in the small pelvis due to the size of the tumor; The presence of edema of tissues after chemoradiotherapy; lack of tactile sensitivity in determining the level of rectal resection and the presence of tumor invasion in neighboring structures; cost of consumables. Advantages: low traumatism; early activation of the patient; reduction of postoperative blood pressure ($p < 0.01$); previously started adjuvant or curative chemotherapy; Requirements: thorough preoperative diagnosis of the prevalence of the tumor in order to determine the critical organs in relation to the line the proposed resection; preparation and coordinated work of the operating team, anesthesiologist; availability of energy devices for the quality of surgical intervention. Prospects: increased use of laparoscopy in the treatment of patients with rectum cancer; introduction in practice of multivisceral resections.

P – 319 Long term efficacy results from the phase II CRAB trial: Neoadjuvant bevacizumab, capecitabine and radiotherapy in locally advanced rectal cancer

V Velenik[1], M Omejc[2], J Ocvirk[1], I Edhemović[1], F Anderluh[1], I Oblak[1], J But-Hadzic[1]

[1]Institute of Oncology, Ljubljana, Slovenia, [2]University Medical Centre, Ljubljana, Slovenia

Introduction: Neoadjuvant capecitabine based chemoradiotherapy and radical surgery are considered to be optimal treatment approach to locally-advanced rectal cancer This prospective, nonrandomised, open -label phase II study investigated the efficacy and safety of bevacizumab (Bev) in combination with capecitabine and concurrent radiotherapy (CRT) for the treatment of locally advanced resectable rectal cancer (LARC). The pathological complete response (pCR) was assessed as primary endpoint and local control and survival parameters as secondary endpoints.

Methods: Enrolled patients (pts) with MRI-confirmed stage II/III rectal cancer were treated with an infusion of Bev (5 mg/kg) 2 weeks prior to neoadjuvant CRT, followed by Bev 5mg/m2 on week 3, 5, 7 and capecitabine 825 mg/m2 bid including weekends

during RT. RT was administered at 50.4 Gy (25 × 1.8 Gy with boost 3 × 1.8 Gy, 3D conformal technique), starting on week 3. Total mesorectal excision was scheduled 6-8 weeks after completion of CRT. Four to six cycles of adjuvant capecitabine chemotherapy were recommended.

Results: Sixty-one patients were treated according to protocol: median age was 60 years (range 31-80), 64% of pts were male. Twelve pts (19.7%) presented with stage II and all other with stage III of disease. In 28 patients (45.9%) the tumour invaded the mesorectal fascia. Radical resection was achieved in 57 pts (95%). Sixty patients were eligible for efficacy analysis. TRG 4 (pCR) was recorded in 8 pts (13.3%) and TRG 3 in 9 pts (15%). Fifty-one pts (83.6%) received capecitabine postoperatively. In median follow-up of 60 months (7-60) we recorded four local relapses. The 5-y overall survival, recurrence-free survival, disease-free survival and local control rates were 72.2%, 75.6%, 70% and 92.4%, respectively.

Conclusion: In LARC preoperative treatment intensification with bevacizumab concurrently with capecitabine based radiotherapy is well tolerated, with a high compliance rate and acceptable toxicity, as previously reported. Although the investigated treatment does not improve the local effect (pCR), updated long term efficacy results indicate that it achieves high LC rate, DFS, RFS and OS.

P – 320 Pilot trial of YIV-906 with neoadjuvant chemoradiotherapy (CRT) in patients with locally advanced rectal cancer

K Johung[1], B Kann[1], J Lacy[2], S Stein[3], J Kortmansky[1], W Zaheer[1], Y Cheng[1], W Lam[1], S Liu[1], R Decker[1], H Hochster[4], S Higgins[1]

[1]Yale University School of Medicine, New Haven, Connecticut, USA, [2]Yale Cancer Center, New Haven, Connecticut, USA, [3]Yale University Cancer Center, New Haven, Connecticut, USA, [4]Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA

Introduction: Neoadjuvant CRT is the standard of care for clinical stage T3-4 or node positive rectal adenocarcinoma, but it is associated with a 12% rate of acute grade 3-4 diarrhea and 9% rate of longterm gastrointestinal (GI) toxicities1. Furthermore, the rate of complete pathologic responses to neoadjuvant therapy is low in historic studies (8%)1. Reducing GI toxicity is important because these side effects can lead to delayed or incomplete treatment, which may compromise patient outcomes. Novel agents which may improve pathologic response are of interest, as pCR is associated with improved local control and survival. YIV-906 is derived from Huang-Qin-Tang, a traditional Chinese medicine used to treat GI ailments. YIV-906 is a standardized pharmaceutical subjected to quality-control measures including chemical fingerprinting, individual target bioassays, and genomic bioresponse profiling. Phase I/II clinical trials demonstrated the safety of YIV-906 in combination with irinotecan- and capecitabine-based chemotherapy and a reduction in GI side effects. In addition, these studies suggest that YIV-906 may enhance the tumor response to chemotherapy by altering the expression of pro-inflammatory cytokines. In a preclinical study, YIV-906 selectively decreased intestinal injury from abdominal radiation (RT) without compromising tumor control. Therefore, a pilot phase I trial was launched to evaluate the novel combination of YIV-906 with neoadjuvant CRT for rectal cancer.

Methods: A total of 22 patients with clinical stage T3-T4 and N0-N2 rectal adenocarcinoma have enrolled out of a goal accrual of 24 patients. To date, 19 patients have completed the treatment protocol which consists of 3D-conformal pelvic RT to 50.4 Gy in 1.8 Gy fractions with capecitabine (825mg twice daily on days 1-5 of RT each week) and YIV-906 (800mg PO twice daily on days 1-4 of RT each week). The primary endpoint is grade 3-4 GI toxicity by CTCAE v4.0 assessed weekly during RT, and until at least 30 days after RT, with a goal of $\leq$ 10% grade 3-4 acute GI toxicity. The secondary endpoint is pathologic response.

Results: Of the 19 patients who have completed the protocol, 1 patient (5.3%) developed grade 3 diarrhea. There were no other grade 3-4 GI toxicities, and no toxicities attributed to YIV-906. Rates of grade 1-2 GI toxicities were as follows: 84% anorectal pain, 68% diarrhea, 58% nausea, 42% constipation, 21% emesis, and 5% dyspepsia. Three patients (15.8%) had a complete pathologic response at the time of surgery, while 1 had a near complete response, 13 had a moderate response, 1 had a minimal response, and 1 had no definite response. At a median follow up of 18.3 months, 1 patient developed a local recurrence, and 3 patients developed metastatic disease.

Conclusion: This is the first clinical trial to evaluate YIV-906 in combination with RT. Preliminary results demonstrate the safety of YIV-906 with chemoradiation for locally advanced rectal cancer. The rate of GI toxicities and pathologic response are favorable compared to historical controls. Thus YIV-906 is a promising adjunct to pelvic chemoradiation that warrants further evaluation. 1Sauer R, Becker H, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731-40.

P – 321 Profile of neurotoxicity of oxaliplatin in young versus elderly patients treated for colorectal carcinoma

H Aliane[1], S Ghomari-Bezzar[2]

[1]Medical Oncology Department, CHU Tlemcen Faculte de Médecine, Laboratoire Toxicomed, Université de Tlemcen, Tlemcen, Algeria, [2]Medical Oncology Department, CHU Tlemcen, Faculte de Medecine, Laboratoire Toxicomed, Universite de Tlemcen, Tlemcen, Algeria

Introduction: Peripheral neuropathy secondary to oxaliplatin is very frequent, these neuropathies are characterized by the symmetry of the neurological disorders and their distal predominance. In most patients, this neuropathy is only partially reversible and can persist long after the stop of chemotherapy. This is one of the major dose-limiting side effects of chemotherapy that may lead not only to the loss of function physical activity associated with a decrease in the quality of life and difficulties in daily activities, especially if it is an elderly person but which can also result in the reduction and or delay of the administration dose or even in the worst Of the cases the stop of the treatment.

Methods: This is a prospective descriptive, analytical and comparative study that includes elderly and young patients with colorectal cancer treated with oxaliplatin-based chemotherapy whose main objective is to compare the characteristics of neurotoxicity and its impact on the quality of life between the elderly and the young.

Results: We collected 30 patients. 16 versus 14 were elderly. 75 versus 28% were female in the elderly patients. The mean age was 47 [26-59] versus 65 years [61-68]. 68 versus 78% in elderly patients were treated for localised colorectal carcinoma. A total of oxaliplatin-based cures 103 versus108 in the elderly (XELOX: 81 versus 85% in the elderly patients)at the total dose or 130 mg/m2(50 versus 59% in the elderly patients) were administered with an average of 3 cures per patient [3-12]. Peripheral neuropathy was reported in 77/103 versus 81/108 cycles in the elderly patients, after the 1st cure (62 versus 44% in the elderly patients) after the 2nd and 3rd cures (31 versus 56%). Peripheral neuropathy occurs on the first day after the cycle (45/77) versus (52/81) cycles in the elderly patients, with swarming (66/77) versus (72/81) de grade I (47/77) versus (56/81) (92/109), spontaneous (55/77) versus (60/81) located at the hands, feet and the perioral region (57/77) versus (60/81), symmetrical in 100% of the case with persistence of the symptomatology at least one week (47/77) versus (54/81) in the elderly patients. Clinical examination revealed motor function and osteo-tendinous reflexes conserved. We noted an episode of laryngeal spasm in a young patient. Clinical examination revealed motor function and osteo-tendinous reflexes conserved. Our conduct was to prolong the duration of the oxaliplatin infusion at 4 hours and a vitamin supplement medication or pregabalin in 30 versus 21% in the elderly and we definitely stopped treatment in 01 versus 02 elderly patients. Despite all its measures 18 versus 14% of elderly patients had an impact on the quality of life namely a limitation of daily activities. Neurotoxicity persisted even after the end of treatment.

Conclusion: Neurotoxicity induced by the oxaliplatin is the limiting factor in treatment in patients with colorectal carcinoma. Its severity in its character persistent and evolutionary even after the stop of the treatment, its early detection is capital and can modify the subsequent therapeutic management in order to limit or to regress the induced disorders.

P – 322 First study in North Africa: Screening colorectal cancer

C Mazouzi[1], K Bouzid[2]

[1]CHU Bejaia, Bejaia, Algeria, [2]CPMC Algiers Algeria, Algiers, Algeria

Introduction: In Algeria in 2015 colorectal cancer represents the 2nd cause of cancer mortality after lung cancer in men and after breast cancer in women. The increasing CRC incidence and mortality can be reduced by screening and treating adenomas and early cancers. A pilot CRC screening programme using immunochemical faecal occult blood testing (iFOBT) and colonoscopy for test-positives were implemented in Béjaia a northeast district of Algeria. This study aims to evaluate the acceptability, feasibility, validity of screening tests, and scaling-up of screening in Algeria. This report describes the implementation, coverage and performance indicators of this pilot project.

Methods: This is a pilot study for colorectal cancer screening with an immunological test of an average risk population aged [50-74] over a 20-month period. A target population aged 50–74 years was informed about and invited to undergo CRC screening by community –clinics. faecal sample collection kits were provided through local primary care units for home sample collection. iFOBT-positive persons were referred for colonoscopy at the Béjaia University hospital, and endoscopic polypectomy/biopsies were performed according to the colonoscopies findings. Those with confirmed CRC received appropriate treatment.

Results: Of the 10,000-target population, 2562 (26%) were screened using iFOBT between January 2016 and November 2017. The main issue in the program was accessing people living in study areas due to lack of valid registry system. Of those screened, 156 (6.11%) were found positive; positivity was equitably between men and woman, a rate of 39.4% polyps among the pathological colonoscopies, 6 cancers are found which corresponding 3.7% of positive tests and a colorectal cancer detection rate of 2.35%. The high false positive rate in our study would be investigated during the next stage through assessment of several kits in Algeria to compare their validity.

Conclusion: The successful implementation of the pilot CRC screening with satisfactory process measures indicate the feasibility of scaling-up organized CRC screening through existing health services In Algeria. More work is needed in assessment of kits to be used in the national program. Also, the process of identification of the population based on their residential access will be evaluated further. An economic evaluation for the program to be conducted before the end of 2018.

P – 323 Perioperative treatment of gastric cancer: FLOT or not

F Djuraev[1], A Abdujapparov[2], N Atakhanova[1]
[1]Department of Oncology Tashkent Medical Academy[2]National Cancer Centre

Introduction: Gastric cancer is one of the most common cases among oncological diseases especially in developing countries of Asia. The same picture nowadays can be observed in Uzbekistan. Despite of breakthrough developments in chemotherapy, gastric cancer is still one of the most leading causes of cancer deaths. Up to day accepted standard of perioperative treatment of patients with operable gastric cancer includes ECF, however survival is still very poor. The aim of this study was to compare docetaxel based triplet FLOT with anthracycline based triplet ECF.

Methods: The study enrolled 294 patients with gastric cancer treated in department of Oncology of Tashkent Medical Academy between 2011-2013yy. Eligibility criteria consisted of : stage ≥cT2 and/or cN+ M0, no distant metastatic lesion, absence of severe comorbidities (renal failure, liver failure etc.), no previous chemotherapy. Patients were randomized into 2 arms: 1st arm - 197 patients who received 3 cycles of preoperative and 3 cycles of ECF after radical gastrectomy D2 (cycles repeated every 3 weeks). 2nd arm - 97 patients received 4 preoperative cycles and after surgery 4 postoperative cycles of FLOT regimen (cycle every 2 weeks). Baseline characteristics across 2 arms were similar with respect to age – median age constituted 61; cT3/T4 - 86%, cN+ 83%, disease stage and histological type of cancer.

Results: Planned pre- and postoperative cycles in 1st group of ECF were completed in 85,7% and 30,9% correspondingly. However the same indexes in 2nd arm constituted: preoperative 4 cycles were completed in 88,6% and postoperative in 46,3% of cases. Median follow up was 44 months.156 patients died, of them 113 (57,3%) patients form ECF arm, and 43 (44,3%) from FLOT arm. FLOT also improved OS rate 32 months with ECF and 48 months with FLOT (HR 0,72 [CI 0,57-0,89]; p=0.010). 3 year overall survival rate was 43% with ECF and 56% with FLOT. In addition to that FLOT also improved PFS: median PFS made up with ECF 16 months versus 28 months with FLOT, HR 0.72 [0.59 - 0.88]; p = 0.004). However complications rate was slightly higher in group of patients who received FLOT especially diarrhea 2-3 grade, nevertheless these complications were did not impact on the course of chemotherapy and were immediately eliminated.

Conclusion: Nevertheless of breakthroughs in targeted and immune therapy, the issue of preoperative and postoperative chemotherapy of gastric cancer is still very important in developing countries, as the choices of immune therapy are very limited due to high financial toxicity in these states. FLOT showed improved outcomes in patients with resectable tumors of stomach in comparison with ECF. The promising results of FLOT let us step forward in fighting gastric cancer.

P – 324 Phenformin-induced mitochondrial dysfunction sensitizes hepatocellular carcinoma for dual inhibition of mTOR

S Veiga[1], X Ge[1], C Mercer[2], M Hernández-Álvarez[3], H Thomas[2], J Hernandez-Losa[4], SR Y Cajal[4], A Zorzano[3,5,6], G Thomas[1,2,7], S Kozma[1,2]
[1]Laboratory of Cancer Metabolism, ONCOBELL Program, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain, [2]Division of Hematology/Oncology, Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio, USA, [3]Complex Metabolic Diseases and Mitochondria Group, Institute for Research in Biomedicine (IRB), Barcelona, Spain, [4]Department of Anatomy/Pathology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain, [5]Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona, Barcelona, Spain, [6]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain, [7]Physiological Sciences Department, Faculty of Medicine and Health Science, University of Barcelona, Barcelona, Spain

Introduction: Hepatocellular carcinoma (HCC) ranks second in cancer mortality and has limited therapeutic options. We recently described the synergistic effect of allosteric and ATP-site competitive inhibitors against the mammalian target of rapamycin (mTOR) for the treatment of HCC. However, such inhibitors induce glycemia and increase mitochondrial efficiency. Here we determined whether the mitochondrial complex I inhibitor Phenformin could reverse both side effects, impose an energetic-stress on cancer cells and suppress HCC growth.

Methods: Human HCC cell lines were used in vitro to access the signaling and energetic impact of mTOR inhibitors and Phenformin, either alone or in combination. Next, the therapeutic utility of these drugs alone or in combination was investigated pre-clinically in human orthotopic tumors implanted in mice, by analyzing their impact on the tumor burden and overall survival.

Results: We found Phenformin caused mitochondrial dysfunction and fragmentation, inducing a compensatory shift to glycolysis. In contrast, dual inhibition of mTOR impaired cell growth and glycolysis, while increasing mitochondrial fusion and efficiency. In a mouse model of human HCC, dual inhibition of mTOR, together with Phenformin, was highly efficacious in controlling tumor burden. However, more striking, pretreatment with Phenformin sensitized tumors to dual inhibition of mTOR, leading to a dramatic improvement in survival.

Conclusion: Treatment of HCC cells in vitro with the biguanide Phenformin causes a metabolic shift to glycolysis, mitochondrial dysfunction and fragmentation, and dramatically sensitizes orthotopic liver tumors to dual inhibition of mTOR. We therefore propose this therapeutic approach should be tested clinically in HCC.

P – 325 Gut microbial community diversity is associated with systemic vascular endothelial growth factor A levels among colorectal cancer patients

A Holowatyj[1], W Stephens[2], C Warby[1], K Buhrke[2], B Gigic[3], T Lin[1], J Boehm[1], N Habermann[4], E Herpel[5], J Ose[1], M Schneider[3], P Schrotz-King[6], P Schirmacher[6], A Ulrich[3], A Toriola[7], J Round[2], C Ulrich
[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA, [2]University of Utah, Salt Lake City, Utah, USA, [3]University Hospital of Heidelberg, Heidelberg, Germany, [4]European Molecular Biology Laboratory (EMBL), Heidelberg, Germany, [5]University Hospital of Heidelberg, National Center for Tumor Diseases, Heidelberg, Germany, [6]National Center for Tumor Diseases, German Cancer Research Center, Heidelberg, Germany, [7]Washington University School of Medicine, Siteman Cancer Center, St. Louis, Missouri, USA

Introduction: Dysbiosis in the gut microbiota and activation of the angiogenic switch in the tumor microenvironment contribute to colorectal carcinogenesis.

Methods: Analyses of baseline fecal samples via 16S rRNA gene sequencing, and evaluation of angiogenic stimulators, vascular endothelial growth factor (VEGF) A and D, in patient sera among n=125 patients diagnosed with colorectal cancer in the ColoCare Study were used to explore the link between the gut microbiome and systemic biomarkers of angiogenesis.

Results: Baseline clinicopathologic and demographic characteristics were evaluated. Relative contributions of taxonomic groups identified through 16S sequencing were examined. Diverse microbial taxa, including previously cancer-associated microbes, were detected in fecal biospecimens. A significant association of gut microbial community diversity was observed by circulating VEGFA (Bray-Curtis metric: R2=0.94; false discovery rate [FDR] q-value=0.007; weighted Unifrac: R2=0.95, FDR q-value=0.026) but not by VEGFD (Bray-Curtis metric: R2=0.81, FDR q-value=0.77; weighted Unifrac: R2=0.80, FDR q-value=0.8) levels. Differences in systemic VEGFA or VEGFD levels were not directly correlated with individual taxa.

Conclusion: These findings suggest that microbial community level function is important for driving the association between gut microbial community diversity and circulating VEGFA biomarker levels. Together, profiling of the microbial taxa and systemic angiogenesis biomarkers among colorectal cancer patients demonstrates that circulating levels of angiogenic stimulator VEGFA may reflect changes in the microbial ecosystem of the human gut that influence colorectal carcinogenesis.

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Annals of Oncology 29 (Supplement 5): v92–v99, 2018
doi:10.1093/annonc/mdy150

POSTER DISCUSSIONS

PD – 001 Endoscopic prediction of tumor invasion depth in early gastric signet ring cell carcinoma

H Moon[1], S Kang[2], J Sung[2], H Jeong[3]

[1]Department of Internal Medicine, Chungnam National University College of Medicine, Daejeon, Republic of Korea, [2]Departments of Internal Medicine, Chungnam National University College of Medicine, Daejeon, Republic of Korea, [3]Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, Republic of Korea

Introduction: Endoscopic resection of early gastric cancer (EGC) is now widely accepted in many countries, especially in Korea and Japan. Endoscopic resection is often preferred over surgical resection due to better quality of life. signet ring cell carcinoma (SRC) is categorized as undifferentiated or a diffuse type, endoscopic treatment was originally not considered in early gastric SRC. However, recent studies have proven excellent prognosis of early gastric signet ring cell carcinoma with fewer lymph node (LN) metastasis. Thus, some now regard early gastric SRC as a condition for endoscopic treatment. However, many of them still do not accept endoscopic treatment of SRC due to several reasons. Depth prediction scoring systems have been developed based on the endoscopic features of all histologic types including differentiated and undifferentiated cancer. However, the same endoscopic criteria may not be applied to SRC due to different biological characteristics. We, therefore, evaluated the endoscopic features of M and SM cancers in early gastric SRCs.

Methods: Medical records of early gastric SRC patients who underwent surgery or endoscopic resection, from January 2011 to December 2016 in 7 tertiary hospitals (Daejeon and Chungcheong province, South Korea), were reviewed to examine endoscopic findings and clinical data. Endoscopic features of the derivation group were analyzed, namely: tumor location, tumor size (mm), macroscopic morphology, fold convergence, and color change of lesions. From the results of the derivation group, we developed a depth prediction scoring system to distinguish M cancer from SM cancer. Statistical analysis was performed using the SPSS software (version 18.0, Chicago, IL, USA). A univariate analysis was performed using a chi square test, while the Fisher's exact test was used to evaluate the causal relationship between the risk of SM invasion and endoscopic features. A multivariate analysis was performed using a logistic regression analysis to calculate odds ratios (ORs) of SM invasion. To evaluate cut-off value for our depth prediction scoring system, ROC curve was used. The relative weightage of each factor in our depth prediction score system was based on their odds ratio. The accepted level of statistical significance was $p < 0.05$.

Results: In total, 331 patients (129 patients, derivation group; 202 patients, validation group) were enrolled in this study. In the derivation group, the risk factors for SM invasion, namely fold convergence, nodular mucosal change, and deep depression were risk factors of SM invasion determined by logistic regression analysis (OR = 3.4, 5.9, 6.0, $p < 0.05$). A depth-prediction score was created by assigning 1 point for fold convergence and 2 points for other factors. When validation lesions of 0.5 points or more were diagnosed as SM invasion, the sensitivity and the specificity were 76.8%-78.6% and, 61.6%-74.7%, respectively.

Conclusion: Fold convergence, nodular mucosal change, and deep depression are the risk factors for SM invasion cancer in early gastric SRCs. Our depth prediction scoring system may be useful for differentiating SM cancers.

PD – 002 A phase I/II trial of hafnium oxide nanoparticles activated by radiotherapy in hepatocellular carcinoma and liver metastasis

E Chajon[1], M Pracht[1], T De Baere[2], F Nguyen[2], J Bronowicki[3], V Vendrely[4], A Baumann[5], V Croisé-Laurent[6], E Rio[7], Y Rolland[8], S Le Sourd[8], P Gustin[2], C Perret[7], F Mornex[9], D Peiffert[10], P Merle[11], E Deutsch[2]

[1]Centre Eugène Marquis, Rennes, France, [2]Institut Gustave Roussy, Villejuif, France, [3]INSERM 954, CHU de Nancy, Université de Lorraine, Nancy, France, [4]Groupe Hospitalier Sud - Hôpital Haut-Lévêque, Pessac, France, [5]Institut de Cancérologie de Lorraine, Vandoeuvre-lès-Nancy, France, [6]Institut de Cancérologie de Lorraine, Vandœuvre-lès-Nancy, France, [7]ICO - Site René Gauducheau, Saint Herblain, France, [8]Centre Eugène-Marquis, Rennes, France, [9]Centre Hospitalier de la Croix Rousse, Lyon, France, [10]Institut de Cancérologie de Lorraine, Vandoeuvre les Nancy, France, [11]Hepatology Unit, Groupement Hospitalier Lyon Nord, Lyon, France

Introduction: Management of hepatocellular carcinoma (HCC) and liver metastasis (mets) requires complementary expertise of multiple specialties. Treatment decisions are increasingly complex and physicians must face a wide range of underlying liver dysfunctions and concomitant malignancies. Among available treatments, stereotactic body radiation therapy (SBRT) is well-tolerated. Yet, like with all radiation therapy (RT) techniques, the energy dose deposit needs to be maximized in tumor cells without affecting the surrounding healthy tissues. For such purpose, nanoparticles of hafnium oxide, NBTXR3, were designed to effectively absorb ionizing radiation and augment the dose deposited within the tumor cells only when activated by RT. NBTXR3 is characterized by one single administration before the first RT session and it fits into existing standard of care with no change in patient treatment schedule protocol or equipment occupancy. It is currently evaluated in a phase I/II clinical trial bringing together multiple medical fields to introduce the use of NBTXR3 with SBRT in patients with HCC or liver mets [NCT02721056].

Methods: The trial follows a 3 + 3 dose escalation design at dose levels of NBTXR3 corresponding to 10%, 15%, 22%, 33% and 45% of the baseline tumor volume. Treatment is performed as a single intralesional or intraarterial injection followed by SBRT (45Gy / 3 fractions / 5 to 7 days) on patients with HCC with/without Portal Vein Tumor Thrombosis or liver mets. As SBRT is not supported by all French hospitals, the coordination of two institutions was needed in managing the patients course. This study aims primarily at identifying the Recommended Dose and of early Dose Limiting Toxicities (DLTs). Secondary endpoints include target lesions investigator assessment by mRECIST via MRI.

Results: The first two dose levels at 10% and 15% are completed with 6 and 4 patients respectively. Two patients are currently included at the third dose level at 22%. All currently recruited patients were treated by intralesional injection. No early DLTs nor adverse events (AE) related to NBTXR3 were observed. One grade 2 malaise and two grade 3 abdominal pain AEs were reported to be related to the injection procedure. No serious adverse events related to NBTXR3 nor to the injection procedure were observed. Dispersion and permanence assessments by CT scan confirmed NBTXR3 to stay within the tumor without negatively impacting liver functions nor the reliability of the image-guided radiation therapy. Investigator assessment on target lesions by mRECIST via MRI resulted with the following best observed responses of target lesions to date in 7 evaluable patients: 3 complete responses, 3 partial responses and 1 stable disease.

Conclusion: Overall, NBTXR3 is well tolerated with a positive safety profile. Indeed, NBTXR3 could constitute an encouraging perspective for patients vulnerable to liver complications. The success of the cooperation between different medical disciplines and several sites paves the way to an innovative mean of managing multidisciplinary affections. In parallel, NBTXR3 is also evaluated in 5 other clinical trials, including a phase II/III in soft tissue sarcoma [NCT02379845] and phases I/II for head and neck [NCT01946867; NCT02901483], prostate [NCT02805894] and rectum cancers [NCT02465593].

PD – 003 Comparison of prognosis after hepatic resection of hepatocellular carcinoma between intermediate stage tumor and early stage tumor

J Arita, T Kokudo, N Akamatsu, J Kaneko, T Ishizawa, K Hasegawa

University of Tokyo, Bunkyo-ku, Japan

Introduction: Despite that patients with intermediate stage hepatocellular carcinoma (HCC), i.e., "4 or more tumors" or "2-3 tumors more than 3 cm in size" without vascular tumor thrombus or extrahepatic metastasis, are candidate for sorafenib according to the BCLC staging system, most of such patients undergo hepatic resection, transcatheter chemoembolization, or radiofrequency ablation. This mono-centric retrospective study assesses the long-term results after hepatic resection for the intermediate stage HCC comparing with that for patients with early or very early stage HCC.

Methods: Patients without extrahepatic metastasis or macroscopic vascular invasion undergoing radical hepatic resection between October 1994 and December 2015 were classified into the following 4 categories. A: early or very early stage, i.e., Single tumor within 5 cm and 2-3 tumors within 3 cm, B1: Single tumor over 5 cm, B2: 2-3 tumors over 3 cm, B3: 4 or more tumors. Overall survival were compared among the 4 groups and prognostic factors were analyzed.

Results: A total of 1030 patients were included. The patient number and the median ICG-R15 value were 606 Pts and 14.1% in Group A, 198 Pts and 11.1% in Group B1, 158 Pts and 14.6% in Group B2, and 68 Pts and 12.3% in Group B3. In Group A, 296 Pts had single tumor, 51 Pts had 2 tumors, and 18 Pts had 3 tumors. The median tumor size was 7.2 cm in Group B1. The median tumor size was 5.2 cm in Group B2, and 119 Pts had 2 tumors and 39 Pts had 3 tumors. The median tumor size was 3.9 cm (1-17 cm) in Group B3, and 31, 11, 7, and 19 patients had 4, 5, 6, 7 or more tumors, respectively. The 5-year OS rate of all 1030 patients was 65.1%, and those of Group A, B1, B2, B3 were 71.7%, 63.7%, 52.4%, and 36.8%, respectively. The OS of Group A was better than that of Group B1-3 (5y-OS rate: 55.2%). However, that of Group A was not significantly better than that of Group B1. On the other hand, significant difference of OS was seen between Group B1 and B2, and between Group B2 and B3. Among the patients in Group B3, who had the poorest prognosis, serum AFP value > 50 ng/mL was found

as the only independent prognostic factor after multivariate analysis of OS using Cox proportional hazard model (HR = 1.93, 95%CI 1.04-3.56), and the 5-year OS rate of the patients with serum AFP value < = 50 in Group B3 was 47.3% and comparable with Group B2.

Conclusion: Among patients with intermediate stage HCC, patients with single tumor over 5 cm show similarly fair prognosis. Patients with 2-3 tumors over 3 cm also show acceptable prognosis. Patients with 4 or more tumors may be candidate for hepatic resection if serum AFP value is 50 or less.

PD – 004 Baseline characteristics and second-line treatment for metastatic pancreatic adenocarcinoma (mPAC) patients receiving first-line FOLFIRINOX, gemcitabine+nab-paclitaxel or gemcitabine-monotherapy in routine clinical practice across Europe

G Prager[1], T Macarulla Mercadé[2], àMellbring[3], J Taieb[4], A Carrato[5], D Melisi[6], B Westphalen[7], N D'Esquermes[8], A Ferreras[9], F de Jong[10]

[1]Clinical Division of Medical Oncology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria, [2]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [3]Shire Sweden AB, Kista, Sweden, [4]Sorbonne Paris Cité, Paris Descartes University, Hôpital Europeen Georges Pompidou, Paris, France, [5]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain, [6]Medical Oncology, University of Verona, Verona, Italy, [7]Comprehensive Cancer Center München, Klinikum der Universität München, Munich, Germany, [8]Genactis, Chateauneuf, France, [9]Genactis, Antibes, France, [10]Shire International GmbH, Glattpark-Opfikon, Switzerland

Introduction: Both FOLFIRINOX and gemcitabine+nab-paclitaxel have shown superior overall survival over gemcitabine-monotherapy in fitter and younger first-line mPAC patients, but with increased toxicity. No randomized phase III data comparing FOLFIRINOX and gemcitabine+nab-paclitaxel are available to help clinical decision making. Furthermore, data on systemic treatment choices in first-line mPAC and outcomes outside clinical trials are scarce. The goal of this large pan-European project was to generate data on diagnosis, treatment patterns and outcomes from the records of patients who completed first-line mPAC treatment across Europe.

Methods: In this observational chart review, physicians completed retrospective electronic records from initial diagnosis onwards for patients with the following minimal inclusion criteria: completed first-line mPAC treatment between 07/2014-01/2016 and ≥18 years. In each country, respondents were recruited across different regions and settings (university and general hospitals, cancer and reference centers, office-based specialists) to ensure a balanced selection. Physicians were encouraged to enter as many second-line metastatic patients as possible. We report here on baseline characteristics and subsequent second-line treatment of patients receiving (m)FOLFIRINOX/gemcitabine+nab-paclitaxel/gemcitabine-monotherapy as first-line mPAC treatment, including variations across countries. All data are descriptive.

Results: A total of 2,565 online patient records were completed by 225 physicians (9 countries; n = 500-504 for France/Germany/Italy/Spain/UK). At start of first-line treatment, median age was 64 years, 57.7% was male and median CA19-9/albumin/bilirubin levels were 457U×ml-1/32.0g×L-1/1.30mg×dL-1. WHO performance status was grade 0/1/2/3/4 in 14.3%/55.5%/26.9%/2.6%/0.2%. Although substantial variations was noted in countries, (m)FOLFIRINOX/gemcitabine+nab-paclitaxel/gemcitabine-monotherapy were most frequently used first-line treatments and accounted for 35.6%/25.7%/20.5% of patients across Europe. Patients treated with (m)FOLFIRINOX versus gemcitabine+nab-paclitaxel versus other gemcitabine-combinations versus gemcitabine-monotherapy had a better performance status, were more often ≤65 years of age, were more often male, had lower median CA19-9 and bilirubin levels and higher median albumin levels. WHO performance status grade 0/1/2/3/4 for patients receiving (m)FOLFIRINOX/gemcitabine+nab-paclitaxel/gemcitabine-monotherapy was 22.5%/64.7%/11.1%/1.0%/0.1%, 13.6%/62.9%/21.8%/1.7%/0.0%, and 4.2%/35.0%/55.3%/4.6%/0.4%, respectively. 70.1%/50.6%/26.8% of patients were 65 years or younger, and 63.7%/56.8%/51.3% of patients were male. Median CA19-9/albumin/bilirubin levels were 456/480/593U×mL-1, 34.0/33.0/31.0g×L-1, and 1.18/1.30/1.42mg×dL-1, respectively. Similar trends were seen in individual countries, although percentages and values differed and differences were sometimes less outspoken. Overall, no substantial differences between FOLFIRINOX full and modified dose at start were noted. Of the patients who had received (m)FOLFIRINOX/gemcitabine+nab-paclitaxel/gemcitabine-monotherapy, 12.2%/9.8%/78.1%, 23.2%/9.4%/67.4%, and 54.8%/4.8%/40.5% patients were not scheduled for further treatment/were waiting to receive further treatment/had started second-line treatment, respectively. For patients who had received (m)FOLFIRINOX as first-line treatment, most frequent second-line treatments were gemcitabine-monotherapy/gemcitabine+nab-paclitaxel/other gemcitabine-combinations with 45.9%/33.1%/10.5%. For gemcitabine+nab-paclitaxel, most frequent second-line treatments were 5FU+oxaliplatin/5FU-monotherapy/5FU+irinotecan/FOLFIRINOX/gemcitabine-monotherapy/other gemcitabine-combinations in 39.1%/23.4%/10.8%/9.0%/7.6%/7.4%. For gemcitabine-monotherapy, most frequent second-line treatments were 5FU-monotherapy/5FU+oxaliplatin/5FU+irinotecan/gemcitabine+nab-paclitaxel in 42.7%/28.2%/8.0%/8.0%. Substantial variation across countries was noted.

Conclusion: Overall, mPAC first-line treatment application across Europe is in line with ESMO recommendations. (m)FOLFIRINOX/gemcitabine+nab-paclitaxel/gemcitabine-monotherapy were applied most often and choice appears to be strongly related to the patient's overall condition: performance status/age/CA19-9/bilirubin/albumin and gender. Second-line treatment choice was dependent on first-line as well and varied to some degree between countries. Insights into use and efficacy of treatments in real-world may help developing treatment plans and improve outcomes of mPAC patients.

PD – 005 Post-operative venous thromboembolism increased mortality in patients with either adenocarcinoma or non-adenocarcinoma pancreatic cancer

K Majmudar[1], L Diaz Quintero[1], H Fuentes[2], S Stocker[1], A Tafur[1], M Talamonti[1]

[1]NorthShore University HealthSystem, Evanston, Illinois, USA, [2]John H. Stroger Jr. Hospital of Cook County, Chicago, Illinois, USA

Introduction: Pancreatic Cancer is strongly associated with thrombosis and early thrombosis in adenocarcinoma patients has an independent impact on mortality. It is not known whether timing of post-operative thrombosis in pancreatic cancer surgery is an independent predictor of mortality in adenocarcinoma (ACPC) or non-adenocarcinoma pancreatic cancer (NACPC) patients. We investigated post-operative VTE mortality among patients with ACPC compared to NACPC.

Methods: We analyzed a prospectively collected database of patients who underwent pancreatic cancer-related surgery with either palliative or curative purposes from 2007 to 2016. Diagnosis of pancreatic malignancy was confirmed by histology. The surgical procedures performed include standard Whipple, pyloric-preserving modified Whipple, exploratory laparotomy, open or laparoscopic distal pancreatectomy with or without splenectomy and total pancreatectomy. Patients were guideline compliant with post-operative prophylaxis. All VTE events were confirmed by imaging. We selected patients with NACPC and a random sample of patients with ACPC. Post-operative VTE (PVTE) was defined as VTE occurring within 3 months of surgical intervention. Mortality was determined by patient follow-up and combined with review of the Social Security Death Index. Statistical analysis for the main outcome was performed using Cox Proportional Hazards Regression using IBM SPSS.

Results: 441 pancreatic cancer surgery patients were included. 331 had ACPC and 110 had NACPC, including 46 (41.8%) IPMN and 17 (15.4%) neuroendocrine tumors. Median follow up was 449 days during which 90 (20.4%) patients developed VTE. PVTE occurred in 53 (12.0%) patients, including 41 (12.4%) ACPC patients and 12 (10.9%) NACPC patients. Those with PVTE had 60% higher mortality rate. A multivariable analysis including cancer type, patient age >75 years old, Whipple technique, surgical time, gender and presence of metastatic disease found that PVTE is an independent predictor of increased mortality [HR Adj 1.6 (1.1 - 2.2), p;0.01)]. The mortality impact was not consistent between the ACPC [HR 3.2 (1.3; 7.9)] and NACPC groups [HR 1.3 (0.9; 1.8), p= NA].

Conclusion: Post-operative venous thromboembolism is an independent predictor of increased mortality in pancreatic cancer including those with non-adenocarcinoma pancreatic cancer.

PD – 006 Characterizations of DNA copy number variations and spatio-temporal intra tumor heterogeneity in liver metastasis from colorectal cancer patients

M Marques[1], K Gambaro[2], M Couetoux du Tertre[2], M Witcher[3], B Samson[4], B Lesperance[5], Y Ko[6], R Dalfen[7], E St-Hilaire[8], L Sideris[9], F Couture[10], S Tejpar[11], R Burkes[12], M Harb[13], T Alcindor[14], E Camlioglu[15], A Gologan[15], V Pelsser[15], S McNamara[2], P Kavan[16], C Kleinman[3], G Batist[17]

[1]The Lady Davis Institute of the Jewish General Hospital, Departments of Oncology and Experimental Medicine, McGill University, Montréal, Quebec, Canada, [2]Exactis Innovation, Montréal, Quebec, Canada, [3]Segal Cancer Centre-Jewish General Hospital, Montréal, Quebec, Canada, [4]Centre de Santé et de Services Sociaux Champlain Charles-Lemoyne, Greenfield Park, Quebec, Canada, [5]Hospital Sacre-Coeur de Montreal, Montréal, Quebec, Canada, [6]Sunnybrook Research Institute (SRI), Toronto, Ontario, Canada, [7]St. Mary's Hospital, Montréal, Quebec, Canada, [8]Georges Dumont Hospital, Moncton, New Brunswick, Canada, [9]Hôpital Maisonneuve Rosemont, Montréal, Quebec, Canada, [10]CHAU Lévis, Levis, Quebec, Canada, [11]University of Leuven, Leuven, Belgium, [12]Mount Sinai Hospital, Toronto, Ontario, Canada, [13]Moncton Hospital, Moncton, New Brunswick, Canada, [14]McGill University Health Centre , Montréal, Quebec, Canada, [15]Jewish General Hospital, Montréal, Quebec, Canada, [16]McGill University, Montréal, Quebec, Canada, [17]Department of Oncology, McGill University and the Segal Cancer Center, Sir Mortimer B. Davis, Jewish General Hospital, Montréal, Quebec, Canada

Introduction: Metastatic colorectal cancers (mCRC) are highly heterogeneous, representing a challenge in treatment management. Studies have largely investigated the genomic landscape of primary tumors at diagnosis. As metastasis is responsible for 90% of cancer patient deaths, this highlights the need to characterize the genomic landscape of metastasis over time of treatment to decipher their evolution and role in therapeutic resistance.

Methods: Metastatic liver tissue samples were collected at baseline (pre-biopsies) and at relapse (post-biopsies) in responder and non-responder mCRC patients undergoing the same treatment. Paired pre/post biopsies were collected from 14 patients (4 of them had multiple post-biopsies) to assess intra-patient, inter-tumour and intra-tumour

heterogeneity following treatment exposure. Biopsies were profiled using RNA and whole exome sequencing (WES) as well as high-density Single-Nucleotide Polymorphism (SNP) array.

Results: Profiling of 45 samples with both high-density SNP array and WES revealed 97.4% similarity between both technologies in the identification of genes targeted by copy number (CN) changes. The metastatic and primary tumor had similar somatic copy number aberration (SCNA) profiles. Using chemo-naïve biopsies, we identified 120 CN gains and 47 CN losses that were significantly associated with patient progression free survival. Integrative analysis with transcriptomic data from the same samples revealed that only 10% of the CN gains and 17% of the CN loss regions showed concordance between SCNA and expression levels. Similarly, at the gene level, higher concordance between SCNAs and expression change was observed in CN deletions compared to CN amplifications (11% vs 4.2%), suggesting other regulatory mechanisms involved. Interestingly, some of the genes showing high correlation between SCNA and gene expression were previously known for their involvement in cancer such as MYC and CD44. For each paired sample pre/post or post/post from the same patient, we computed a heterogeneity score (HS) based on SCNA calling using as two parameters, identical type of event called and 70% reciprocal overlap. We found high temporal intra-tumor heterogeneity in our cohort with a mean value of HS = 0.84 (range: 0.47-0.98). As expected, we observed more heterogeneity when comparing intra-patient inter-tumors heterogeneity (mean = 0.89, range: 0.77-0.95). Interestingly, the intrinsically resistant lesion had a lower score, and pre/post samples from the same or different lesion having the same response to treatment were less heterogeneous. This implies that acquisition of resistance correlates with an increase in genomic changes.

Conclusion: Overall, we showed that liver metastasis and primary tumors from mCRC patients have similar SCNA profiles. From a technical perspective, we concluded that the use of WES data to identify genes located in SCNAs (gain and loss) is comparable to high-density SNP array. From a clinical point of view, we showed that approximately 10% of the genes affected by SCNA showed concordant changes in expression and therefore the use of CN results may not be suitable for making therapeutic decision. Furthermore, the high intra-tumor heterogeneity observed following treatment exposure highlights the importance of post-treatment biopsies to identify and understand mechanisms of mCRC resistance.

PD – 007

WITHDRAWN

PD – 008 Molecular characterization of immune microenvironment in colorectal cancers with microsatellite instability by digital RNA counting

M Giordano[1], R Moretto[2], R Giannini[3], G Zucchelli[2], F Pietrantonio[4], C Antoniotti[2], C Ugolini[5], F Morano[6], F Marmorino[2], E Sensi[1], A Belfiore[7], D Rossini[2], C Lupi[1], G Masi[2], B Borelli[2], E Ongaro[8], A Boccaccino[2], A Falcone[3], C Cremolini[2], G Fontanini[9]

[1]Divisione di Anatomia Patologica, Dipartimento di Chirurgia, Università di Pisa, Pisa, Italy, [2]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [3]University of Pisa, Pisa, Italy, [4]Department of Medical Oncology, IRCCS Fondazione Istituto Nazionale dei Tumori, Milan, Italy, [5]Department of Laboratory Medicine, Section of Pathology, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [6]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [7]Istituto Nazionale dei Tumori Foundation, Milan, Italy, [8]Department of Oncology, Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia, Udine, Italy, [9]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy

Introduction: Alterations in the mismatch repair (MMR) mechanism in colorectal cancers (CRCs) lead to high levels of microsatellite instability (MSI-h) causing considerable endogenous immune anti-tumor response, counterbalanced by immune inhibitory signals. We evaluated the mRNA immune-profile of a series of MSI-h CRCs to identify new potential targets for future CRC immunotherapy trials by combining an extensive gene expression analysis and the clinicopathological characteristics such as presence of metastases, staging, genotype and primary tumor sidedness.

Methods: Fifty primary MSI-h CRCs were analysed. Among these, 24 were non-metastatic, 13 had metachronous metastases and 13 had synchronous metastases. According to tumor staging 26 were stage I – II, 10 stage III and 14 stage IV at the time of diagnosis. Mutational status was as follows: 12 samples were RAS mutated, 22 BRAF mutated and 16 RAS and BRAF wild type. Finally, 36 tumors were right-sided and 14 left-sided. NanoString nCounter® PanCancer Immune Profiling Panel (Seattle, WA, USA), covering 730 immune-related genes, was employed to measure gene expression. A linear regression analysis was performed to investigate the differential gene expression related to above mentioned clinicopathological characteristics. The Benjamini-Yekutieli false discovery rate (FDR) was used for adjusting p-values. In this study we set a FDR<0.05 to select differentially expressed genes.

Results: Several immune-related genes resulted differentially expressed according to primary tumor sidedness. Most of the deregulated genes showed higher expression in right-sided compared to left-sided MSI-h CRCs and belong to the following "immune response categories": chemokines (STAT1, CXCL10, CXCL13), innate immune response (ATG5, MAP2K1), T-cell functions (IDO1, LAG3, PTPRC), antigen processing (HLA-DPA1, HLA-DPB1, PSMB7), cytotoxicity (GNLY, GZMA), adhesion (ITGAE), NK cell functions (KLRC2) and cell cycle check point (CASP3). No significant differences based on presence of metastases, tumor stage or mutational status were observed.

Conclusion: Immune-related genes investigated in this study are heterogeneously expressed in MSI-h CRCs. Interestingly, genes mainly implicated in the inhibition of the immune system are more expressed among right- than left-sided CRCs, thus suggesting a potential different responsiveness to checkpoint inhibitors. According to their putative role in the clinical practice, these preliminary results deserve further validation.

PD – 009 Emergence of KRAS mutation may play a major role in the secondary resistance to EGFR blockade

T Yamada[1], G Takahashi[1], T Iwai[1], K Takeda[1], H Furuki[2], M Koizumi[1], S Shinji[1], A Matsuda[3], Y Yokoyama[1], M Hotta[1], K Hara[1], H Yoshida[1]

[1]Nippon Medical School Department of Digestive Surgery, Bunkyo-ku, Japan, [2]Nippon Medical School, Bunkyo-ku, Japan, [3]Nippon Medical School, Inzai, Japan

Introduction: Oncogenic KRAS mutations are negative biomarkers of response to epidermal growth factor receptor (EGFR) blockade. KRAS mutation is usually detected in biopsies of primary colorectal tumors. However, the genomic profiles of primary tumors and metastases are not always concordant, and chemotherapeutic agents and targeted drugs can alter the tumor molecular landscape. Circulating tumor DNA (ctDNA) is a novel tool to detect molecular heterogeneity. In this study, we tried to

clarify the mechanism of primary or secondary resistance to EGFR blockade as first-line treatment of metastatic colorectal cancer.

Methods: We enrolled 33 chemotherapy-naïve patients with metastatic CRC and no RAS mutations in their primary tumors. Patients with BRAF mutation in a primary tumor or ctDNA were excluded. Patients were treated with first-line systemic chemotherapy that included EGFR blockade. We obtained ctDNA from each patient before they started chemotherapy, and every 2–3 months during chemotherapy until disease progression. We detected KRAS (codons 12, 13, 61, and 146), BRAF (V600E) and EGFR (S492R) mutations using digital polymerase chain reaction.

Results: KRAS mutations were detected in the ctDNA of 5 of the 33 patients (15%) before chemotherapy. Twenty-seven of the 28 patients (96%) without ctDNA KRAS mutations achieved early tumor shrinkage (ETS). Two patients achieved a complete response (CR), 24 achieved a partial response (PR), and two patients experienced stable disease (SD). The five patients with ctDNA KRAS mutations did not achieve ETS. One patient had SD and four experienced disease progression (PD). Of the 26 initial responders, 17 (65%) acquired resistance. Emerging KRAS mutations were detected in the ctDNA of 16 of these 17 patients (94%); ten of these patients had multiple mutations. BRAF mutations were also detected in seven patients (39%). Eight patients (44%) had S492R mutations; none of the patients had solo S492R mutations. One patient, who had no KRAS mutation, had S492R mutations.

Conclusion: KRAS mutation was detected in 5 of 7 patients who had no response by EGFR blockade. Emerging KRAS mutations were detected in most of the patients (94%) who acquired resistance. This indicates that emergence of KRAS mutation may play a major role in the primary and secondary resistance to EGFR blockade.

PD – 010 REVERCE: Randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan: Quality of life analysis

T Yoshino[1], T Yamanaka[2], T Denda[3], Y Tsuji[4], K Shinozaki[5], Y Komatsu[6], Y Kobayashi[7], J Furuse[8], H Okuda[9], M Asayama[10], K Akiyoshi[11], Y Kagawa[12], T Kato[13], E Oki[14], T Ando[15], Y Hagiwara[16], Y Ohashi[17], K Shitara[18]

[1]National Cancer Center Hospital East, Kashiwa, Japan, [2]Yokohama City University School of Medicine, Yokohama, Japan, [3]Chiba Cancer Center, Chiba, Japan, [4]Department of Medical Oncology, Tonan Hospital, Sapporo, Japan, [5]Hiroshima Prefectural Hospital, Hiroshima, Japan, [6]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [7]Department of Medical Oncology, Kushiro Rosai Hospital, Kushiro, Japan, [8]Kyorin University Hospital, Tokyo, Japan, [9]Department of Medical Oncology, Keiyukai Sapporo Hospital, Sapporo, Japan, [10]Saitama Cancer Center, Saitama, Japan, [11]Osaka City General Hospital, Osaka, Japan, [12]Department of Gastrointestinal Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [13]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [14]Department of Surgery, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Japan, [15]University of Tsukuba, Tsukuba-shi, Japan, [16]University of Tokyo, Bunkyo-ku, Japan, [17]Chuo University, Tokyo, Japan, [18]National Cancer Center Hospital East, Kashiwa-city, Japan

Introduction: REVERCE demonstrated longer overall survival (OS) with the therapeutic sequence of regorafenib (R) followed by cetuximab (C) ± irinotecan (R-C arm) compared with that of C ± irinotecan followed by R (C-R arm) for patients (pts) with pretreated metastatic colorectal cancer (mCRC; median OS 17.4 vs. 11.6 months, HR 0.61; Shitara K, et al. GI Symposium 2018). Here we report quality of life (QOL) analysis.

Methods: Pts with KRAS exon 2 wild-type mCRC after failure of fluoropyrimidine, oxaliplatin, and irinotecan were randomized to receive sequential treatment with R as treatment 1, followed by C ± irinotecan as treatment 2 (R-C arm), or the reverse sequence (C ± irinotecan followed by R; C-R arm). The primary endpoint was overall survival (OS). Key secondary endpoints included progression-free survival with initial treatment (PFS1), PFS with second treatment (PFS2), safety, and quality of life (QOL). Patients were assessed with the EQ-5D questionnaire at baseline, 4, and 8 weeks after the beginning of each treatment.

Results: Between November 2013 and September 2016, 101 pts (51 in the R-C arm and 50 in the C-R arm) were randomized. Hypertension, hand-foot syndrome and elevated lipase were more frequent with R treatment than C treatment (>10%), whereas acneiform rash and hypomagnesemia was more frequent with C than R. The average EQ-5D index during sequential treatment were not significantly different between the two arms ($p = 0.65$), although R treatment was associated with a lower score than C in both treatments 1 and 2. Scores in mobility and pain/discomfort were lower during R than that of C at 4 weeks in both treatments 1 and 2. Self-care and usual activities were also lower for R treatment, in the C-R arm, at 4 weeks in treatment 2.

Conclusion: The safety profiles of R and C in REVERCE study were consistent with those previously observed. QOL score was comparable in the two arms but lower during R treatment.

PD – 011 SAPPHIRE: A randomized phase II study of oxaliplatin discontinuation after 6 cycles of mFOLFOX6 + panitumumab therapy in patients with colorectal cancer: Final analysis of efficacy and safety results

M Takahashi[1], Y Munemoto[2], M Nakamura[3], M Kotaka[4], H Kuroda[5], T Kato[6], N Minagawa[7], S Noura[8], M Fukunaga[9], H Kuramochi[10], T Touyama[11], T Takahashi[12], Y Akagi[13], H Satake[14], S Kurosawa[15], T Miura[15], H Mishima[16], J Sakamoto[17], K Oba[18], N Nagata[19]

[1]Yokohama Municipal Citizen's Hospital, Yokohama, Japan, [2]Fukui-ken Saiseikai Hospital, Fukui, Japan, [3]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan, [4]Department of Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan, [5]Kitakyushu General Hospital, Kitakyushu, Japan, [6]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [7]Department of Surgery 1, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan, [8]Osaka Rosai Hospital, Sakai, Japan, [9]Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan, [10]Tokyo Woman's Medical University Yachiyo Medical Center, Yachiyo, Japan, [11]Nakagami Hospital, Okinawa, Japan, [12]Gifu University Hospital, Gifu, Japan, [13]Kurume University Hospital, Kurume, Japan, [14]Kobe City Medical Center General Hospital, Kansai Medical University Hospital, Kobe, Japan, [15]Takeda Pharmaceutical Company Limited, Chuo-ku, Japan, [16]Division of Cancer Center, Aichi Medical University, Nagakute, Japan, [17]Tokai Central Hospital, Kakamigahara, Japan, [18]Department of Biostatictics, The University of Tokyo, Tokyo, Japan, [19]Department of Surgery, Kitakyushu General Hospital, Kitakyushu, Japan

Introduction: mFOLFOX6 is a common first-line chemotherapy regimen for patients with unresectable, advanced or recurrent colorectal cancer (CRC). However, the long-term administration of oxaliplatin is associated with peripheral neuropathy (PN). Recently, we reported that 5-fluorouracil (5-FU)/leucovorin (LV) + panitumumab therapy after 6 fixed cycles of mFOLFOX6 + panitumumab therapy maintained efficacy with reduced incidence of PN, compared with continued treatment with mFOLFOX6 + panitumumab. Here, we report results from the final analysis of efficacy and safety endpoints (data cut-off: 31 Aug 2017), and from subgroup analyses according to tumor location and early tumor shrinkage (ETS).

Methods: Chemotherapy-naïve patients, aged ≥20 years with RAS wild-type advanced or recurrent CRC were enrolled to receive 6 cycles of panitumumab + mFOLFOX6 once every 2 weeks. Patients who completed 6 cycles of panitumumab + mFOLFOX6 and confirmed no progressive disease were randomized 1:1 to continue receiving mFOLFOX6 + panitumumab (Group A) or 5-FU/LV + panitumumab (Group B). Allocation factors included study site, age, number of liver metastases at enrolment, and response at randomization. Efficacy endpoints included progression-free survival (PFS), depth of response (DpR) and overall survival (OS) after randomization. Primary tumor was classified as right-sided if located in the cecum, ascending and proximal two-thirds of transverse colons; and otherwise as left-sided. ETS was defined as > 20% decrease of tumor load within 8 weeks from enrolment.

Results: 164 patients were enrolled to receive initial mFOLFOX6 + panitumumab treatment, of which 56 were randomized to Group A and 57 to Group B. Median follow-up was 20 months. Median PFS and DpR were: Group A, 9.1 months (95% confidence interval [CI]: 8.6–11.1) and –65.4%, respectively; Group B, 9.3 months (95% CI: 6.0–13.0) and –64.3%, respectively. Median OS was not reached in either group. In patients with right-sided tumors, median PFS and DpR were: Group A ($n = 9$), 3.8 months (95% CI: 0.8–10.5) and –46.2%, respectively; and Group B ($n = 14$), 8.0 months (95% CI: 4.3–13.0) and –68.1%, respectively. In patients with left-sided tumors, median PFS and DpR were comparable between Group A ($n = 47$) (10.5 months and –69.9%, respectively) and Group B ($n = 42$) (11.5 months and –63.1%, respectively). Median PFS in patients who achieved ETS was 10.5 months in Group A and 11.5 months in Group B. In patients who did not achieve ETS, median PFS was 6.8 months in Group A and 7.8 months in Group B. Grade ≥2 PN occurred in 13.5% and 1.9%, and serious adverse events in 14 (25.0%) and 11 (20.4%) of patients in Groups A and B, respectively.

Conclusion: Results from this final analysis support the use of 5-FU/LV + panitumumab after 6 fixed-cycles of mFOLFOX6 + panitumumab as a suitable treatment option for patients with RAS wild-type, chemotherapy-naïve, advanced or recurrent CRC. PFS was numerically lower in patients with right-sided tumors compared to those with left-sided tumors. Tumor location was not only a prognostic factor, but might be a predictive factor for these regimens. Primary tumor location may need to be considered as a stratification factor in future trials. Clinical trial identification: NCT02337946

PD – 012 Early tumour shrinkage (ETS) and its impact on tumour-related symptoms in patients with previously untreated RAS wild-type metastatic colorectal cancer (mCRC): A retrospective analysis of three panitumumab studies

J Taieb[1], M Geissler[2], F Rivera[3], M Karthaus[4], R Wilson[5], F Loupakis[6], T Price[7], M Tracy[8], P Burdon[9], M Peeters[10]

[1]Sorbonne Paris Cité, Paris Descartes University, Georges Pompidou European Hospital, Paris, France, [2]Klinikum Esslingen, Cancer Center Esslingen, Esslingen, Germany, [3]Hospital Universitario Marqués de Valdecilla, Santander, Spain, [4]Department of Hematology and Oncology, Städtisches Klinikum München, Klinikum Neuperlach, Munich, Germany, [5]Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK, [6]Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [7]Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia, [8]Amgen Ltd., Milton, UK, [9]European Medical, Amgen (Europe) GmbH, Zug, Switzerland, [10]Department of Oncology, Antwerp University Hospital, Edegem, Belgium

Introduction: Systemic therapy with epidermal growth factor receptor (EGFR) inhibitors ± chemotherapy can result in tumour shrinkage in patients with wild-type (WT) RAS mCRC, potentially facilitating curative surgery. Treatment decisions should be guided in part by patients' disease symptoms, yet there is no standardised assessment of symptomatic events. This retrospective analysis aimed to investigate whether ETS is related to the time to occurrence of new tumour-related symptoms during first-line treatment of mCRC.

Methods: Three studies of patients with previously untreated mCRC were retrospectively analysed: PRIME (NCT00364013; phase III; FOLFOX4 ± panitumumab 6mg/kg Q2W); PEAK (NCT00819780; phase II; mFOLFOX6 ± either panitumumab 6mg/kg Q2W or bevacizumab 5mg/kg Q2W); and '314 (NCT00508404; phase II; panitumumab 6mg/kg Q2W + FOLFIRI). The current analyses included WT RAS mCRC patients only. The proportion of patients who developed the following symptoms during study treatment was calculated: Eastern Cooperative Oncology Group (ECOG) performance decline; new opiate use; first weight-loss event; new anaemia-type event; and new asthenia-type event. Due to their low clinical relevance, grade 1 events were excluded from the analysis. ETS was defined as a reduction of $\geq$ 30% in the sum-of-the-longest-diameters of measurable target lesions at 8 weeks after initiation of study treatment. Time to occurrence of new symptomatic events pooled across all 3 studies was analysed by ETS status using the Kaplan-Meier method. A composite symptomatic endpoint was also analysed; this included any symptom listed above except ECOG (as any symptom can impact on ECOG performance status). KM medians and adjusted HRs (calculated by Cox proportional hazard model) are presented with 95% confidence intervals (CI) and HR pvalues.

Results: 659 patients were included in the analyses and categorised by ETS<30% (n = 330 [PRIME: n = 227; PEAK: n = 70; '314: n = 33]) and ETS$\geq$30% (n = 329; 49.9% [PRIME: n = 213; PEAK: n = 84; '314: n = 32]). In pooled analysis, median time (95% CI) to ECOG decline was numerically longer for patients with ETS$\geq$30% (13.9 [8.6–non-estimable (NE)] vs. 7.9 months [6.3–14.3] for ETS<30%, HR [95% CI]: 0.87 [0.69–1.08], p = 0.204). ETS$\geq$30% was significantly associated with delayed time-to-onset of new opiate use (HR: 0.71 [0.55–0.92], p = 0.009), first weight-loss event (HR: 0.64 [0.48–0.85], p = 0.002), new anaemia-type event (HR: 0.60 [0.41–0.88], p = 0.008) and new asthenia-type event (HR: 0.77 [0.60–1.00], p = 0.049); median time to all these symptoms was not reached except for time to new opiate use in patients with ETS<30% (27.4 [10.8–NE] months). For the composite endpoint, ETS$\geq$30% was associated with delayed median time to onset of any of the assessed symptoms (5.0 [3.9–7.0] vs. 3.4 [2.8–4.6] months for ETS<30%, HR: 0.80 [0.66–0.97], p = 0.021). More patients with ETS$\geq$30% than ETS<30% had not experienced any new symptom at both 6 (46.1% vs. 39.6%) and 12 months (35.0% vs. 28.6%).

Conclusion: The onset of new tumour-related symptoms was delayed in patients with RAS WT mCRC who achieved ETS $\geq$30% relative to those who did not. These data are consistent with an early response to treatment and tumour shrinkage leading to better symptomatic control and improved quality of life. Regimens with high cytoreductive potential may delay the onset of symptoms.

PD – 013 Usefulness of colonic tattooing using ICG in patients with colorectal tumors

J Park[1], H Moon[2], I Kwon[3], J Kim[4], S Kang[5], E Lee[2], S Kim[2], J Sung[5], B Lee[2], H Jeong[5]

[1]Division of Gastroenterology, Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University School of Medicine, Daejeon, Republic of Korea, [2]Department of Internal Medicine, Chungnam National University College of Medicine, Daejeon, Republic of Korea, [3]Clinical Trials Center, Chungnam National University Hospital, Daejeon, Republic of Korea, [4]Departments of Internal Medicine, Chungnam National University School of Medicine, Daejeon, Republic of Korea, [5]Departments of Internal Medicine, Chungnam National University College of Medicine, Daejeon, Republic of Korea

Introduction: Preoperative endoscopic tattooing assists in finding small-sized lesions on the movable part of the colon, especially in limited operative fields of vision. The aim of this study is to prove that tattooing using indocyanine green (ICG) dye is beneficial in the reduction of operation time, postoperative management, and to prove its usefulness according to stage and type of laparoscopic surgery.

Methods: From Jan 2012 to Dec 2016, all patients underwent laparoscopic colonic surgery at Chungnam National University Hospital were retrospectively screened, and 1010 patients with colorectal neoplasms were included in the study. Their lesions were tattooed with ICG the day before operation. The tattooed group (TG) included 114 patients, and the non-tattooed group (NTG) were selected by propensity score matching of subjects based on age, sex, tumor staging, and operation method (n = 228). In total, 342 patients were enrolled. Between the groups, the change in (Δ, preoperative − postoperative) hemoglobin and albumin levels, operation time, hospital stay, oral ingestion period, transfusion, and perioperative complications were compared. To compensate for the difference in the operation time due to lymph node dissection in the advanced stage, Non-lymph node invasion group were classified as early stage and lymph node invasion group as advanced stage. The TG and NTG were compared in early stage and advanced stage.TG and NTG were compared according to surgical method to determine the efficacy of tattooing for different colonic surgical procedures. Data were obtained from surgical and anesthesia records, pathologic reports, and medical charts.

Results: Preoperative TG had a shorter operation time (174.76 ± 51.6 vs. 192.63 ± 59.9, p = 0.007), hospital stay (9.55 ± 3.36 vs. 11.42 ± 8.23, p = 0.003), and post-operative oral ingestion period (1.58 ± 0.96 vs. 2.81 ± 1.90, p < 0.001). Δ Hemoglobin (0.78 ± 0.76 vs. 2.2 ± 1.18, p < 0.001) and Δ albumin (0.415 ± 0.44 vs. 1.08 ± 0.39, p < 0.001) showed less blood loss intraoperatively in the TG. On comparison of patients with early and advanced tumor stages, early-stage colon cancer patients had better results for operation time, hospital stay, oral ingestion period, Δ hemoglobin, and Δ albumin than did advanced stage patients. Operation methods affected the results, and laparoscopic anterior resection (LAR) showed similar results. However, for left and right hemicolectomy, both groups showed no difference in operation time or hospital stay.

Conclusion: Therefore, preoperative tattooing with ICG is useful for laparoscopic colectomy, especially for non-lymph node invasive colon cancer and LAR.

PD – 014 Survival following curative indented treatment of brain metastases from colorectal cancer: A Danish population-based cohort study

A Boysen[1], A Ording[2], A Astradsson[3], M Høyer[4], K Spindler[5]

[1]Aarhus University Hospital, Dep. of Oncology, Aarhus, Denmark, [2]Aarhus University Hospital, Dep. of Clinical Epidemiology , Aarhus, Denmark, [3]Aarhus University Hospital, Dep. of Neurosurgery , Aarhus, Denmark, [4]Danish Center for Particle Therapy , Aarhus, Denmark, [5]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Introduction: Brain metastases (BM) are an uncommon presentation of metastatic colorectal cancer (mCRC) with reported incidence of about 2-4%. Previously, the focus has been on a palliative treatment course with whole brain radiation, corticosteroids and supportive care, resulting in an expected survival of a few months. Today, there is an increased awareness towards a localized curative intended treatment approach with either surgical resection, stereotactic body radiotherapy (SBRT) or both. We examined the survival for patients treated with a localized modality for BM from CRC in a nationwide population-based study.

Methods: We retrieved data from the Danish Cancer Registry and the Danish National Patient Registry (DNPR) on all patients who underwent surgery for primary CRC during 2000-2013. The study was restricted to patients undergoing surgical resection of an intracranial metastases or those receiving cranial SBRT. For patients with a surgical specimen, the adenocarcinoma histology of BM was validated by the Danish Pathology Register. Patients with other malignant disorders were excluded. Overall survival was calculated from the date of BM treatment until death from any cause. We used the Kaplan-Meier method for survival analysis and for comparison of frequencies the chi2 test.

Results: A total of 38131 patients had surgery for a primary CRC and 235 patients underwent a curative intended treatment for BM, comprising resection alone (n = 158), SBRT alone (n = 51) and combined resection and SBRT (n = 26). The median age was 64.8 years (interquartile range 57.3-71.1 years) and a male/female ratio of 49.8%/50.2%. In the cohort of all patients with a resected CRC (n = 38131) rectal cancer comprised 36% compared to 49% in the cohort of BM treated patients (p < 0.001). Furthermore, 3% of patients from the full CRC cohort were registered with a surgical resection of lung metastases, compared to 12% in the group of patients treated for BM (p < 0.001), indicating a higher risk of BM in patients with rectal cancer and lung metastasis. The median survival was 0.8 years (95% CI 0.6-0.9), in the cohort of patients treated for BM (n = 235), and the 1-and 5-year overall survival were 41.7% (95% CI 35.4-47.9%) and 12.7% (95% CI 8-17.8%), respectively.

Conclusion: In this national population based study, we report a median overall survival of 0.8 years for patients receiving localized treatment for BM from CRC. Rectal tumors and lung metastasis seem associated to development of BM, and a subset of highly selected patients are long term survivors with a 5-year survival of 12.7%.

PD – 015 Optimizing the use of first-line chemotherapy in metastatic colorectal cancer patients with mucinous histology. A multicenter, retrospective, combined analysis on 897 patients

V Catalano[1], F Bergamo[2], C Cremolini[3], B Vincenzi[4], F Negri[5], P Giordani[1], D Santini[4], D Sarti[1], U Torresi[6], R Bisonni[7], R Silva[8], M Rocchi[9], S Lonardi[10], A Falcone[11], R Mattioli[12], F Graziano[1]

[1]A.O. Ospedali Riuniti Marche Nord, Pesaro, Italy, [2]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [3]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [4]Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy, [5]Medical Oncology, University Hospital, Parma, Italy, [6]Ospedale di Macerata, Macerata, Italy, [7]UOC Oncologia Medica - Ospedale Murri, Fermo, Italy, [8]UO Oncologia Medica - Ospedale Profili, Fabriano, Italy, [9]University of Urbino Carlo Bo, Urbino, Italy, [10]Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [11]University of Pisa, Pisa, Italy, [12]A.O.Ospedali Riuniti Marche Nord, Pesaro, Italy

Introduction: In metastatic colorectal cancer (MCRC), mucinous histology has been associated with poor response rate and prognosis. We have confirmed that mucinous colorectal cancer (MC) have an unfavourable prognosis to oxaliplatin/irinotecan-based first-line combination chemotherapy compared with nonmucinous (NMC) colorectal cancer patients (pts) (Catalano et al, BJC 2009, 100:881-887). Subgroup analysis showed a possible poor outcome of MCRC pts with mucinous histology treated with oxaliplatin-based regimens (Catalano et al, Ann Oncol 2017, 28 Supplement 6:A1). Therefore, we addressed this study to evaluate whether oxaliplatin-based chemotherapy regimens may affect survival of MCRC pts with mucinous histology.

Methods: We analyzed the population from two consecutive studies, consisting of 897 MCRC pts who were treated with first-line chemotherapy. Chemotherapy regimens consisted of OXA-based (FOLFOX, capecitabine and oxaliplatin, raltitrexed and oxaliplatin); IRI-based (FOLFIRI, capecitabine and irinotecan), FOLFOXIRI, or the same regimens plus bevacizumab (B). Pts were classified according to the histology in MC and NMC. The possible prognostic interaction between histology and different chemotherapy regimens was assessed by multivariate Cox proportional hazards analyses.

Results: One hundred thirty-nine (15.4%) pts had MC, male/female 528/369, median age 65 years (range, 25-89). More pts in the MC group had right-sided tumours (MC 47.5% vs NMC 30.9%, $p = 0.0002$) and peritoneal disease (MC 31.7% vs NMC 16.5%, $p < 0.0001$), whereas pts in the NMC group had more frequently liver metastasis (NMC 74.7% vs MC 58.3%, $p = 0.0001$). All other variables were comparable among the two groups. Pts received the following treatments: B+IRI-based, MC/NMC=43/263; B+OXA-based, MC/NMC=18/159; B+FOLFOXIRI, MC/NMC=29/130; IRI-based, MC/NMC 9/56; OXA-based, MC/NMC 34/135; FOLFOXIRI, MC/NMC 6/15. The overall response rates for MC and NMC were 33.8% (95% CI, 25.9-41.7) and 58.2% (95% CI, 54.7-61.7), respectively (chi-test, $p < 0.0001$). After a median follow-up of 50 months, median overall survival for the mucinous MCRC patients was 25.2 months compared with 26.4 months in the control group (univariate analysis, HR = 0.89; 95% C.I., 0.71-1.12; $p = 0.333$).The analysis of interaction between chemotherapy regimens and histology has given a highly significant result ($p < 0.0001$). In particular, in mucinous MCRC, by assuming as reference treatment OXA-based regimens, pts having a better outcome were those who were treated with IRI-based (HR = 0.47; 95% C.I., 0.29-0.75; $p = 0.002$) or FOLFOXIRI (HR = 0.40; 95% C.I., 0.23-0.70; $p = 0.001$). As expected, patients with non-mucinous histology treated with IRI-based ($p = 0.0001$), OXA-based ($p = 0.005$) and FOLFOXIRI ($p = 0.001$) achieved better survival than MC treated with OXA-based chemotherapy.

Conclusion: Pts with mucinous histology have poor survival and responsiveness to chemotherapy as compared with non-mucinous MCRC. However, OXA-based regimens may not represent the optimal chemotherapy treatment options in MCRC with mucinous histology. In this subgroup of pts, regimens containing irinotecan should be considered.

PD – 016 Safety of self-expandable metal stents (SEMS) or emergency surgery for acute colonic obstruction in metastatic colon cancer patients treated with bevacizumab

V Pacheco-Barcia[1], R Mondéjar Solís[1], O Martínez Saez[2], F Longo Muñoz[3], E Bermejo[4], J Moreno Monteagudo[5], C Marin[4], A Correa[4], R Maqueda[6], J Rogado[1], A Garcia de Paredes[7], E Rodriguez de Santiago[8], V Pachón Olmos[9], R Ferreiro Monteagudo[9], M Rodriguez Garrote[9], A Carrato[10], O Donnay[1], E Martin[4], C Santander[4], R Colomer[1]

[1]Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria La Princesa, Madrid, Spain, [2]Ramón y Cajal Univsersity Hospital, Madrid, Spain, [3]Hospital Universitario Ramón y Cajal, Madrid, Spain, [4]Hospital Universitario La Princesa, Madrid, Spain, [5]Hospital La Princesa, Madrid, Spain, [6]Hospital Universitario La Princesa, Madrid , Spain, [7]Hospital Universitario Ramon y Cajal , Madrid, Spain, [8]Hospital Universitario Ramon y Cajal, Madrid, Spain, [9]Ramón y Cajal University Hospital, Madrid, Spain, [10]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain

Introduction: Colorectal cancer presents with malignant bowel obstruction in about 10% of cases. SEMS can be an alternative for immediate surgery although long-term data is limited regarding clinical outcomes and safety of Bevacizumab (BV) in this subset of patients. The aim of this study was to evaluate procedure-related morbidity in relation to the type of previous or subsequent medical treatment used, including BV.

Methods: We performed a retrospective review of 2850 cases of metastatic colon cancer diagnosed from January 2012 to October 2017, and identified those patients with malignant bowel obstruction that were initially treated with either SEMS or emergency surgery. Differences in procedure-related morbidity were assessed by the Chi-square test, overall survival (OS) with the log-rank test and a multivariate analysis with Cox proportional-hazards model was performed.

Results: We selected 119 cases, 79 of which were treated with SEMS and 40 with surgery. Median age was 76. Median follow-up time was 11 months. No differences in sidedness or RAS status between cohorts. SEMS had a similar rate of complications compared to surgery (32.5% vs 35.5%, $p = 0.45$) and showed longer time to complications (18m vs 1m, $p = 0.004$). In patients treated with BV, complications were similar in SEMS and surgery groups (40% vs 31%, RR 1.28, $p = 0.45$), the incidence of perforation was similar in patients with SEMS compared to surgery (16% vs 7%, RR 1.09, $p = 0.16$) and when BV regimen is compared to chemotherapy alone (16% vs 6%, RR 1.11, $p = 0.16$). SEMS and surgery showed similar OS (14m vs 15m, $p = 0.5$). Treatment with BV increased OS in both the SEMS group (18 months vs 7 months, $p = 0.001$) and the surgery group (20 months vs 4 months, $p = 0.001$) compared to patients without subsequent medical treatment. Also, BV treatment showed a trend for longer OS when compared to chemotherapy alone in the SEMS group (18 months versus 15 months, $p = 0.13$) and in the surgery group (20 months versus 17 months, $p = 0.13$). In the multivariate analysis, patients treated with subsequent medical treatment showed a statistically significant longer OS [Hazard Ratio (HR) 0.43, Confidence Interval (CI) 95% 0.19-0.94, $p = 0.02$], patients with left-sided colon cancer showed a trend for longer OS (HR 0.5, CI95% 0.22-1.13, $p = 0.09$) and, in those patients who had complications, we observed shorter OS (HR 2.45, CI95% 1.17-5.12, $p = 0.01$).

Conclusion: SEMS was associated with a similar outcome than emergency surgery and, furthermore, using BV was not associated with a higher risk of complication. In patients with metastatic colorectal cancer with acute malignant colon obstruction, SEMS is a safe option, including patients that received BV.

PD – 017 Clinical and molecular determinants of extrahepatic disease progression (ePD) in initially unresectable, liver-limited metastatic colorectal cancer (mCRC)

E Ongaro[1], D Rossini[2], F Pietrantonio[3], F Morano[4], F de Braud[4], V Mazzaferro[5], F Corti[4], G Randon[4], A Raimondi[4], L Battaglia[6], L Morelli[7], L Urbani[8], G Masi[2], R Moretto[2], C Antoniotti[2], F Marmorino[2], B Borelli[2], G Zucchelli[2], A Boccaccino[2], C Cremolini[2], A Falcone[9]

[1]Department of Oncology, Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia, Udine, Italy, [2]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [3]Department of Medical Oncology, IRCCS Fondazione Istituto Nazionale dei Tumori, Milan, Italy, [4]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [5]Gastrointestinal and Hepatobilio-Pancreatic Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [6]Peritoneal Surface Malignancies Unit, Colon and Rectal Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [7]Department of Translational Research and New Technologies in Medicine and Surgery, General Surgery Unit, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy, [8]General Surgery Unit, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy, [9]University of Pisa, Pisa, Italy

Introduction: In the last years, the availability of active upfront systemic regimens, the development of surgical techniques and the diffusion of other locoregional treatments increased the therapeutic options for mCRC patients with liver-limited disease. Estimating the likelihood to develop extra-hepatic metastases may affect clinicians' attitudes towards locoregional procedures. No tools to predict the probability of ePD of initially liver limited mCRC are currently available.

Methods: We retrospectively analysed a cohort of 225 patients with initially unresectable liver-limited disease, treated from January 2004 to December 2017 with first-line doublets or triplet plus a biologic agent at two Italian Institutions. Information about baseline clinical, pathological and molecular features, treatments received and metastatic sites from the diagnosis of mCRC to death or last follow up were collected. The impact of baseline characteristics and treatments received on extra-hepatic progression-free survival (ePFS) was assessed in uni- and multi-variable models.

Results: Overall, 52 (23%) patients were ePD-free and 173 (77%) experienced ePD which occurred within 1, 2 or 3 years from the diagnosis of mCRC in 20%, 63%, and 86% of patients, respectively. Globally, 164 (73%) patients underwent a secondary liver resection at some point of their disease history, and 66 (40%) of them underwent a subsequent locoregional treatment. Among 164 resected patients, 118 (72%) experienced ePD, occurring within 1, 2 or 3 years from resection in the 43%, 71%, and 91% of cases, respectively. Age < 70 years, ECOG performance status (PS) 0, < 4 liver metastases, longest diameter of liver lesions < 30 mm, the involvement of < 6 liver segments and secondary resection were significantly associated with prolonged ePFS. In the multivariable model, ECOG PS ($p = 0.022$), number ($p = 0.011$) and diameter (p 0.005) of liver metastases and secondary liver resection ($p = 0.006$) were still associated with ePFS. In the subgroup of analysed patients (N = 35), microsatellite instability was

associated with shorter ePFS (p = 0.029). In the subgroup of patients who did not undergo metastases' resection in their disease history (N = 61), ECOG PS 0 (p = 0.024), longest diameter of liver lesions < 30 mm (p = 0.011) and left-sidedness (p = 0.081) were independently associated with longer ePFS.

Conclusion: In this contemporary cohort, the vast majority of mCRC patients with initially unresectable liver-limited disease underwent surgical procedures (73%) and further locoregional interventions (40%) in their disease history. ECOG PS, number and diameter of liver metastases, and sidedness independently predict ePFS. These factors could help physicians in personalizing the intensity and aggressiveness of liver directed treatments in mCRC patients with initially unresectable liver-limited disease.

PD – 018 Comparing survival in left-sided and right-sided colorectal carcinoma: A Belgian population-based study

K Janssens[1], N Boeckx[2], G Van Camp[3], K Op De Beeck[4], E Fransen[5], F Calay[6], N Van Damme[6], M Peeters[7]

[1]University of Antwerp, Antwerp, Belgium, [2]Center of Oncological Research (CORE), University of Antwerp, Wilrijk, Belgium, [3] Center of Medical Genetics, University of Antwerp and Antwerp University Hospital , Edegem, Belgium, [4]a Center of Oncological Research (CORE), University of Antwerp, Wilrijk, Belgium, [5]StatUa Center for Statistics, University of Antwerp, Antwerp, Belgium, [6]Belgian Cancer Registry, Sint-Joost-ten-Node, Belgium, [7]Department of Oncology, Antwerp University Hospital, Edegem, Belgium

Introduction: In recent years, the difference in survival between right-sided and left-sided colorectal cancer (CRC) has been extensively studied. Various studies have convincingly shown that patients with tumors originating on the left side of the colon have a significantly better prognosis than those with tumors originating on the right side of the colon. However, these conclusions are mostly based on data of clinical trials and therefore selected patients. These findings need to be confirmed in population-based studies. Therefore, the aim of this study is to compare survival rates in left-sided and right-sided CRC in the (non-selected) Belgian population.

Methods: In Belgium, data on patient and tumor characteristics of all new diagnosed cancers is collected in a national and population based cancer registry, the Belgian Cancer Registry (BCR). Patients diagnosed with CRC between 2004 and 2015 were included in our analysis. We obtained information on age, sex, stage, location of the primary tumor and survival. Furthermore, we collected biomarker data (MSI status and BRAF, KRAS and NRAS mutational status) in a random sample of 1.000 metastatic CRC patients diagnosed in 2014. Cancers were classified as right-sided cancer if they were located in the caecum, ascending colon, hepatic flexure and transverse colon. Left-sided colon cancer was defined as cancer of the splenic flexure, descending colon, sigmoid and rectosigmoid colon. We constructed a logistic regression model, using location, age, gender and biomarkers as independent variables and fraction of deceased patients as dependent variable.

Results: The study included 93,011 patients: 27,863 (30%) with right-sided CRC, 35,815 (38.5%) with left-sided CRC, 27,359 (29.4%) with rectal cancer and 1,974 (2.1%) with an overlapping lesion of the colon or unknown localization. In all stages combined, the 5-year relative survival rate for patients with right-sided colon cancer was 65.6% (95% CI: 64.7% to 66.4%) compared with 68.4% (95% CI: 67.7% to 69.1%) for patients with left-sided colon cancer and 66.1% (95% CI: 65.4% to 66.9%) for patients with rectal cancer. In stage IV CRC, the 5-year relative survival rate was 13.4% (95% CI: 12.2% to 14.5%) in right-sided colon cancer compared with 19.6% (95% CI: 18.4% to 20.7%) for patients with left-sided colon cancer and 20.2% (95% CI: 18.8% to 21.6%) for patients with rectal cancer. Overall, left-sided CRC had a statistical significant better prognosis than right-sided CRC. However, right-sided CRC had a significant better survival in certain subgroups: stage I > 80-year-old males, stage II > 70-year-old males and females, stage III >80 year old females and stage IV > 80 year old males.

Conclusion: We present the survival data of all colorectal cancer patients diagnosed between 2004 and 2015 in Belgium according to tumor location, age, sex and stage. We conclude that the prognostic value of tumor location is age and stage dependent in the Belgian population. When combining all stages, left-sided CRC has a statistical significant better prognosis than right-sided CRC. These findings correspond with previous research.

PD – 019 RMB (RENCA Macrobead) therapy in advanced mCRC: Phase IIb preliminary multi-site survival findings; correlation & combination with Phase I and IIa data including imaging and lab profiles [U.S.FDA BB-IND 10091]

A Nazarian[1], Z Andrada[2], J Thomas[2], S Sureshbabu[2], N Berman[2], D Wolf[3], L Gazda[4], T Fahey[5], A Ocean[6], B Smith[2]

[1]The Rogosin Institute, New York, New York, USA, [2]The Rogosin Institute / Weill Cornell Medical Center, New York, New York, USA, [3]Weill Cornel Medical Center, New York, New York, USA, [4]The Rogosin Institute, Xenia, Ohio, USA, [5]Weill Cornell Medical Center, New York, New York, USA, [6]Weill Cornell Medical College, New York, New York, USA

Introduction: Because cancer can be considered as a complex, biological-systems disease, we have explored a cell-based systems therapeutic approach based on this concept. We report ongoing human experience using mouse renal adenocarcinoma cells (RENCA) entrapped in agarose macrobeads (RMB) for late-stage mCRC therapy (Chin J Cancer Res 2018;30(1):72-83). Such cells undergo genomic changes that release multiple anti-neoplastic factors (> ten). One or more achieve 40% of their tumor-cell inhibitory effect via MEF-2 regulation. (Cancer Res. 2011;71(3): 716–724;725–735). Other pathways are currently under study with Lund University. Phase I and IIa RMB trials provided evidence of survival and quality of life benefit in treatment-resistant, late-stage mCRC patients (Cancer Growth Metastasis.2016;9:9–20). Here, we report the combined findings of the P I/IIa, along with new preliminary survival and other-benefit findings from a PIIb multi-site trial.

Methods: Eighty-nine mCRC patients who failed all available cancer treatments underwent laparoscopic intraperitoneal implantation of RMBs up to 4 times in these open-label PI/IIa/IIb trials. The PIIb multi-site trial (40 patients), closed for enrollment, currently includes four in LTFU and one patient undergoing a fourth implantation. OS was the primary endpoint, with serial physical examinations, lab profiles and PET-CT imaging performed pre- and three months post-implantation to further evaluate safety/efficacy in all three trials. Survival was measured from time of study entry until death. The P I/IIA trials differed from IIb in that none of their patients had been treated with regorafenib or trifluridine/tipiracil.

Results: Mean survival for 84/89 patients (all three trials) was 41 weeks [median survival=33 weeks; SD +/-37.5 wks]. For all patients in Phase IIb only (n = 36/41), preliminary analysis indicates mean survival of 34 weeks [median, 29.5 wks; SD +/-24 wks]. For patients who received regorafenib and/or trifluridine/tipiracil prior to RMBs in this trial (n = 12/13), mean survival was 26.5 weeks [median survival=21wks; SD+/-23 wks]. For the patients not receiving either (n = 23/36), mean survival was 37wks [median survival=35wks; SD+/-25 wks]. In all three trials, the ancillary testing described in Methods indicated that there were responders (R), as well as non-responders (NR) to the RMB. For the combined PI/IIa data, two groups of patients: R (n = 25) and NR (n = 9) were defined by their LDH values at days 30 and 60 after first implantation (D30, mean R value 305.92+/-284.76 vs. NR, 649.33+/- 363.60; p < 0.0070), D60 (R, 333.88+/-445.89 vs. NR, 1278.50+/- 761.9; p < 0.0001). These correlated with CEA and/or CA19-9 decreases (≥20%), and with the PET-CT SUVmax findings. Eighty-four FDG-positive mCRC lesions were detected in 26/34 patients at D90. Of the 25 LDH responders, 14 showed stable or decreased SUVmax values; seven an increase (4 non-evaluable) (doi:10.3252/pso.eu.19wcgic.2017). Parallel data from PIIb will be presented at WCGIC 2018.

Conclusion: Taken together, the PI/IIa/IIb trial data are encouraging in indicating improved survival of late-stage mCRC patients with RMB treatment. The laboratory data (LDH levels, CEA and CA19-9) decreases, as well as PET-CT imaging (decreased SUVmax) support this. The data to date merit development of a Phase III randomized trial of RMB vs. standard therapy to further assess the effectiveness of the RMB in late-stage mCRC.

PD – 020 Age and RAS status to select patients with metastatic colorectal cancer (mCRC) for initial sequential versus combination therapy including fluoropyrimidines (FP), irinotecan (Iri) and bevacizumab (Bev): XELAVIRI- study

D Modest[1], L Fischer von Weikersthal[2], T Decker[3], U Vehling-Kaiser[4], J Uhlig[5], M Schenk[6], J Freiberg-Richter[7], B Peuser[8], C Denzlinger[9], C Peveling genannt Reddemann[10], U Graeven[11], G Schuch[12], I Schwaner[13], A Stahler[14], A Jung[15], T Kirchner[15], S Held[16], S Stintzing[17], C Giessen-Jung[18], V Heinemann[19], on behalf of AIO KRK0110 investigators

[1]Department of Medical Oncology & Comprehensive Cancer Center, University Hospital Grosshadern, Munich, Germany, Munich, Germany, [2]Department of Oncology, Gesundheitszentrum St. Marien GmbH, Amberg, Amberg , Germany, [3]Onkologie Ravensburg, Germany, Ravensburg, Germany, [4]Onkologische Praxis, Landshut, Germany, Landshut, Germany, [5]Onkologie Muldental, Naunhof, Germany, [6]Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany, [7]Gemeinschaftspraxis Freiberg-Richter, Jacobasch, Illmer, Wolf, Dresden, Germany, [8]Onkologische Praxis am Diakonissinnenhaus, Leipzig, Germany, [9]Marienhospital Stuttgart, Stuttgart, Germany, [10]Onkologische Praxis, Leverkusen, Germany, [11]German Rectal Cancer Study Group; Kliniken Maria Hilf, Mönchengladbach, Germany, [12]Hlpa Hamburg, Hamburg, Germany, [13]ONkologie Kurfürstendamm, Berlin, Germany, [14]LMU Großhadern, Munich, Germany, [15]Department of Pathology, Ludwig-Maximilians University of Munich, Munich, Germany, [16]Clinassess, Leverkusen, Germany, [17]Department of Oncology, Klinikum Grosshadern and Comprehensive Cancer Center, LMU, Munich, Germany, [18]Department of Medical Oncology, Klinikum Grosshadern, University of Munich, Munich, Germany, [19]Comprehensive Cancer Center, Krebszentrum München, Munich, Germany

Introduction: The XELAVIRI (AIO KRK0110) study compared upfront application of FP+BEV plus sequential escalation to IRI+ FP+ BEV (arm A) vs. initial combination therapy with FP+ IRI+ BEV (arm B) in patients (pts) with mCRC, trial identification: NCT01249638. In the full analysis set of the study, non-inferiority of time to failure of strategy (TFS, primary endpoint) was not shown;

Methods: Patients were stratified for age (<65, > =65<75, > =75 yrs) and molecular subgroups (RAS status). TFS as well as overall survival (OS) and 60-day mortality were evaluated in age categories by Kaplan-Meier method, log rank test and Cox regression.

Results: Of the full analysis set (FAS) of 421 pts, 128 pts were <65yrs, 177 pts > =65<75 yrs and 116 pts > =75 yrs. In the FAS, age did not seem to influence TFS, but an association of (increasing) age with less OS benefit from initial combination chemotherapy was evident. This finding was pronounced in pts with RAS mutant (MT) as compared to pts with RAS wildtype (WT) mCRC. In pts with RAS WT mCRC, benefit from initial combination chemotherapy was seen in all age categories. 60-day mortality was 1.6% in pts <65yrs, 2.8% in pts > =65<75 yrs and 5.2% in pts > =75 yrs.

Conclusion: This exploratory analysis suggests that age and RAS status influence benefit from combination therapy. The trend of increasing 60-day mortality in higher age-categories underlines the necessity for careful patient selection and surveillance during initiation of therapy.

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Annals of Oncology 29 (Supplement 5): v100–v110, 2018
doi:10.1093/annonc/mdy149

ORALS

O – 001 Efficacy of TAS-120, an irreversible fibroblast growth factor receptor (FGFR) inhibitor, in cholangiocarcinoma patients with FGFR pathway alterations who were previously treated with chemotherapy and other FGFR inhibitors

F Meric-Bernstam[1], H Arkenau[2], B Tran[3], R Bahleda[4], R Kelley[5], C Hierro[6], D Ahn[7], A Zhu[8], M Javle[9], R Winkler[10], H He[10], J Huang[10], L Goyal[8]

[1]University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [2]Sarah Cannon Research Institute, HCA Healthcare, London, UK, [3]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia, [4]Gustave Roussy Cancer Center, Villejuif, France, [5]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California, USA, [6]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [7]Mayo Clinic, Scottsdale, Arizona, USA, [8]Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA, [9]University of Texas, Anderson Cancer Center, Houston, Texas, USA, [10]Taiho Oncology, Inc., Princeton, New Jersey, USA

Introduction: TAS-120, an oral and highly selective, irreversible FGFR1-4 tyrosine kinase inhibitor, has demonstrated inhibition of cancer cell growth in human xenografts of tumors bearing FGFR aberrations. TAS-120 inhibited mutant and wild-type FGFR2 with similar IC50 (wild-type FGFR2, 0.9 nM; V5651, 1-3 nM; N550H, 3.6 nM; E566G, 2.4 nM) and has shown efficacy in cell lines with acquired resistance to FGFR inhibitors. In this Phase I study in patients with advanced solid tumors, TAS-120 was evaluated at 8-24 mg once daily (QD). 20 mg QD was determined as the maximum tolerated dose/recommended Phase II dose, while 24 mg QD had dose-limiting toxicity. Here we report results from cholangiocarcinoma (CCA) patients enrolled in this Phase I study.

Methods: Adult patients (≥18 years) with CCA who were treated at 16, 20, and 24 mg QD continuously during the Phase I dose-escalation and expansion phases were included. FGF/FGFR status was evaluated by local institutions or at a commercial laboratory. Patients were treated with TAS-120 until disease progression or unacceptable toxicity. Safety was assessed using CTCAE version 4.03. Tumor response was evaluated by local radiologists using RECIST version 1.1.

Results: Forty-five patients with CCA (intra-hepatic n = 41) harboring FGF/FGFR aberrations were treated at 16 mg (n = 24), 20 mg (n = 14), and 24 mg (n = 7) QD. Median age was 53 years (range 29-73), 76% were female, 58% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1, and 42% had an ECOG PS of 0. Twenty-eight patients (62%) had FGFR2 gene fusions and 17 (38%) had other FGF/FGFR aberrations, e.g. mutations, amplifications, and re-arrangements. All patients had received prior systemic therapies and 13 had received at least one prior reversible FGFR inhibitor. Of 28 patients with FGFR2 gene fusions, 20 (71%) experienced tumor shrinkage and seven achieved confirmed partial response (cPR). The objective response rate was 25%. Of the seven responders, six remain on treatment, including one patient with an ongoing cPR of > 1 year. Of 28 patients, 15 patients (54%) experienced stable disease as their best response, with seven still on treatment. The overall disease control rate was 79%. Of 17 patients with other FGF/FGFR aberrations, three had cPR (two with FGFR2 re-arrangement and one with co-expression of FGFR2 re-arrangement and amplification). Median time on treatment was 7.4 months and ongoing. Of the 13 patients who had received prior FGFR inhibitors, four (three with FGFR2 gene fusions and one with FGFR2 amplification) had cPR on TAS-120. The most common treatment-related adverse events (AEs) of all grades in 45 CCA patients were hyperphosphatemia (78%), increased aspartate aminotransferase (29%), dry skin (29%), diarrhea (27%), and dry mouth (27%). Grade ≥3 treatment-related AEs were reported in 23 out of 45 patients (51%); the most common was hyperphosphatemia in 10 patients (22%).

Conclusion: TAS-120 demonstrated compelling clinical activity and a manageable AE profile in CCA patients with FGFR2 gene fusions and showed efficacy in patients who progressed on prior FGFR inhibitors. A Phase II study of TAS-120 in CCA patients with FGFR2 gene fusions has been initiated.

O – 002 Geographic variation in systemic treatment of metastatic pancreatic adenocarcinoma (mPAC) patients in real world across Europe

J Taieb[1], A Carrato[2], àMellbring[3], G Prager[4], D Melisi[5], B Westphalen[6], T Macarulla Mercadé[7], N D'Esquermes[8], A Ferreras[9], F De Jong[10]

[1]Sorbonne Paris Cité, Paris Descartes University, Hôpital Europeen Georges Pompidou, Paris, France, [2]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain, [3]Shire Sweden AB, Kista, Sweden, [4]Clinical Division of Medical Oncology, Department of Medicine I, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria, [5]Medical Oncology, University of Verona, Verona, Italy, [6]Comprehensive Cancer Center München, Klinikum der Universität München, Munich, Germany, [7]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [8]Genactis, Chateauneuf, France, [9]Genactis, Antibes, France, [10]Shire International GmbH, Glattpark-Opfikon, Switzerland

Introduction: mPAC remains associated with poor outcomes. While new compounds/combinations continue to be explored, treatment options are still limited. Data on systemic treatment choices in mPAC and outcomes outside clinical trials are scarce. The goal of this pan-European project was to generate data on diagnosis, treatment patterns and outcomes from the records of patients who completed first-line mPAC treatment across Europe.

Methods: In this observational chart review, physicians completed retrospective electronic records from initial diagnosis onwards for patients with the following minimal inclusion criteria: completed first-line mPAC treatment between 07/2014-01/2016 and ≥18 years. In each country, respondents were recruited across different regions and settings (university and general hospitals, cancer and reference centers, office-based specialists) to ensure a balanced selection. Physicians were encouraged to enter as many second-line metastatic patients as possible. We report here on first-line and second-line mPAC treatment choices, including variation across countries. Data are descriptive.

Results: A total of 2,565 online patient records were completed by 225 physicians (9 countries; n = 500-504 for France/Germany/Italy/Spain/UK). All patients had completed first-line mPAC treatment and 1,666 had started/completed second-line. At metastatic diagnosis, median age was 64 years and 57.7% was male. At first-line and second-line initiation, median CA19-9/albumin/bilirubin levels were 457U×mL-1/32.0g×L-1/1.30mg×dL-1 and 560U×ml-1/30.0g×L-1/1.30mg×dL-1, respectively. WHO performance status was 0/1/2/3/4/unknown in 14.3%/55.5%/26.9%/2.6%/0.2%/0.5% at first-line initiation and 5.7%/45.9%/41.3%/6.0%/0.8%/0.2%, at second-line initiation. (m)FOLFIRINOX/gemcitabine+nab-paclitaxel/gemcitabine-monotherapy were most frequently used first-line treatments and accounted for 35.6%/25.7%/20.5% of patients. France/UK reported higher (m)FOLFIRINOX and gemcitabine-monotherapy and lower gemcitabine+nab-paclitaxel application [(m)FOLFIRINOX in France/Germany/Italy/Spain/UK: 47.4%/33.5%/27.2%/29.0%/40.1% ; gemcitabine+nab-paclitaxel: 10.9%/31.0%/36.4%/32.7%/17.9%; gemcitabine-monotherapy: 26.8%/15.9%/19.8%/17.9%/23.4%]. Other gemcitabine-combinations were applied in 9.6% (France/Germany/Italy/Spain/UK: 7.1%/10.5%/6.2%/10.3%/12.9%): in France/Italy typically combined with oxaliplatin, in Germany with erlotinib, and in UK with capecitabine. FOLFIRINOX was modified upfront (22.2%) relatively more often in UK/Italy versus France/Germany (France/Germany/Italy/Spain/UK: 15.4%/12.5%/32.4%%/22.7%/31.2%). Other 5FU-based regimens were applied in 5.4-9.5%, typically 5FU+oxaliplatin. Second-line 5FU-based (45.0%) and gemcitabine-based (53.3%) treatment choices varied substantially among countries. 5FU-based treatment was lower in France/Germany versus Italy/Spain/UK (France/Germany/Italy/Spain/UK: 31.6%/37.2%/58.1%/52.6%/47.9%). Use of 5FU+oxaliplatin/5FU+irinotecan (17.6%/7.0%) was comparable, except for France (5FU+oxaliplatin: 10.9%) and UK (5FU+irinotecan: 1.6%). 5FU monotherapy (16.7%; mainly capecitabine) was more often prescribed in Italy/Spain/UK (France/Germany/Italy/Spain/UK 9.5%/9.0%/24.4%/23.9%/18.3%). Gemcitabine-based second-line treatment was lower in Italy/Spain versus Germany/France (France/Germany/Italy/Spain/UK: 67.3%/61.6%/38.7%/44.9%/51.1%). Gemcitabine+nab-paclitaxel was applied more often than gemcitabine-monotherapy in Germany/Spain, while in France/UK/Italy gemcitabine-monotherapy was used more. Overall, 17.8% of patients received gemcitabine+nab-paclitaxel (highest in Germany; France/Germany/Italy/Spain/UK: 12.8%/34.8%/11.1%/22.4%/4.5%) and 27.1% gemcitabine-monotherapy (highest in France/UK; France/Germany/Italy/Spain/UK: 50.0%/16.2%/22.6%/12.5%/34.1%). Other gemcitabine-based combinations were used in 8.4% (France/Germany/Italy/Spain/UK: 4.5%/10.5%/5.0%/9.9%/12.5%): in France typically combined with oxaliplatin, in Germany with erlotinib, and in UK with capecitabine.

Conclusion: In this large European study, mPAC treatment choices seem overall in line with ESMO recommendations. However, substantial geographical variation was reported between countries. Apart from WHO performance status and comorbidities, first-line treatment choices followed local reimbursement status of individual compounds and showed country-specific preferences. Second-line treatment was also guided by first-line treatment. At the time this research was conducted, no second-line

mPAC treatment was approved and over 20 treatments/combinations were reported. A more standardized approach may help improving mPAC treatment outcomes.

O – 003 Gemcitabine with nab-paclitaxel in patients with locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC): A quality of life randomized cross-over study (QOLINPAC)

G Chiritescu[1], K Dumon[1], C Verslype[2], H Prenen[3], G Houbiers[4], M Peeters[5], J Janssens[6], D Van Daele[7], S Laurent[8], J Arts[9], K Hendrickx[10], I Borbath[11], M Ferrante[12], F Bastin[13], J Goeminne[14], J Van Laethem[15], E Vanderstraeten[16], J Decaestecker[17], W Van Vaerenbergh[18], B Delhougne[19], E Van Cutsem[20]

[1]University Hospitals Leuven, Leuven, Belgium, [2]Division of Digestive Oncology, University Hospitals Leuven and Department of Oncology, Leuven, Belgium, [3]University Hospital Gasthuisberg, Leuven, Belgium, [4]Clin Saint Joseph Liège Belgium, Liege, Belgium, [5]Department of Oncology, Antwerp University Hospital, Edegem, Belgium, [6]AZ Turnhout, Turnhout, Belgium, [7]CHU Sart-Tilman Liege, Liege, Belgium, [8]University Hospital Ghent, Gent, Belgium, [9]A.Z. Sint Lucas Brugge, Brugge, Belgium, [10]OLV Aalst, Aalst, Belgium, [11]Cliniques Universitaires Saint-Luc, Brussels, Belgium, [12]A.Z. Sint Maarten Mechelen, Mechelen, Belgium, [13]CHU Charleroi Belgium, Montigny-le-Tilleul, Belgium, [14]Clinique Sainte Elisabeth Namur, Namur, Belgium, [15]Hôpital Universitaire Erasme, Brussels, Belgium, [16]A.Z. Maria Middelares Gent, Gent, Belgium, [17]AZ Delta Roeselare, Roeselare, Belgium, [18]Heilig Hartziekenhuis Lier Belgium, Lier, Belgium, [19]CHR Citadelle Belgium, Liege, Belgium, [20]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

Introduction: Nab-paclitaxel added to standard gemcitabine significantly improves overall survival, progression-free survival and response rates when compared to gemcitabine alone in metastatic PDAC. Baseline quality of life (QOL) indicators such as global health status (GHS) may be predictive for survival in this disease setting, together with clinical variables and tumour markers.

Methods: In an academic multicentric phase II study, patients with locally advanced or metastatic PDAC were randomized to receive gemcitabine 1000mg/m2 alone or with nab-paclitaxel 125mg/m2 in standard schedules. Patients progressing on monotherapy could cross-over to combination. The EORTC QLQ-C30 v. 3.0 questionnaire was applied monthly. Deterioration-free rate of GHS at three months was the primary endpoint. Clinically significant deterioration was considered at first 10-point score decrease from baseline without further improvement. Safety, response rates, progression free and overall survival, exploratory biomarker and hypoxia studies on blood samples were secondary endpoints.

Results: One hundred forty-six consenting patients (21 locally advanced and 125 metastatic) with median age 65 were included in 17 hospitals of the BGDO network between May-2014 and Nov-2015 and randomized to combination (72) versus monotherapy (74). Thirty-seven patients crossed-over. Total cumulative drug exposure to nab-paclitaxel was 73% from planned dose in the combination group and 67% in cross-overs. Median duration on treatment was 5 months (range 0-28), 10 patients being on treatment > 18 months. One hundred and eighty-three serious adverse events were reported in 98 unique patients (67%), 51% occurring in the combination group vs 37% in monotherapy and 12% after cross-over. Six had fatal outcome, one was possibly related to gemcitabine (sepsis). Most frequent toxicities were gastrointestinal or infections. Five gemcitabine-related cases of hemolytic uremic syndrome occurred. Overall, 1465 QOL questionnaires were completed, 85% of patients responded to at least three. Unweighted analysis of GHS showed a deterioration-free rate at three months of 83% (60/72) in the combination group, 60% (28/47) in patients on monotherapy at the time of definitive deterioration and 96% (26/27) in cross-overs. Median times to definitive deterioration were 12.8, 8.9 and 12.3 months in combination, monotherapy and cross-overs respectively. Baseline GHS scores correlated at 0.05 significance level with survival times in the combination group. Other QOL indicators showed equivalent patterns. Tumour response (locally assessed) was observed in 43% of patients (95%CI_31-55) in combination, 19% (95%CI_6-32) in monotherapy and 24% (95%CI_10-39) in cross-over, the difference being statistically significant (p = 0.006). Two patients had complete response. Disease control was observed in 116 patients (79%) for a median duration of 6.8 (0.7-28.1) months. Median progression free survival was 6.8 months (95%CI_5.5-8.1) with 7.4, 7.2 and 5.4 in the three groups. Overall survival was 11.9 months (95%CI_10-14) with 10.7, 8.8 and 13 months respectively.

Conclusion: Median survival was long and response rates significantly higher in combination groups. Patients receiving the combination nab-paclitaxel/gemcitabine seem to report better quality of life scores for longer duration compared to patients on gemcitabine monotherapy. Further QOL analyses and translational studies are ongoing.
Conducted with financial support and study medication from Celgene. Clinical trial registration: EudraCT 2013-004101-75; NCT02106884.

O – 004 Selected subgroup analyses of liposomal irinotecan (nal-IRI) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) in the global NAPOLI-1 phase III trial

T Macarulla Mercadé[1], K Lee[2], G Lakatos[3], A Wang-Gillam[4], L Chen[5], B Mirakhur[6], F De Jong[7]

[1]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [2]Seoul National University Hospital, Seoul, Republic of Korea, [3]Department of Oncology, St. István and St. László Hospital, Budapest, Hungary, [4]Washington University in St.Louis, St Louis, Missouri, USA, [5]National Institute of Cancer Research, National Health Research Institutes, Miaoli, Republic of Taiwan, [6]Ipsen Biopharmaceuticals, Inc., Basking Ridge, New Jersey, USA, [7]Shire International GmbH, Glattpark-Opfikon, Switzerland

Introduction: NAPOLI1 (NCT01494506; Wang-Gillam et al., Lancet 2016;387:545-57) was a global phase 3 study of patients with mPDAC who progressed following gemcitabine-based therapy. In patients receiving nalIRI+5FU/LV, median overall survival (mOS) was significantly higher (6.1 months) compared with 5FU/LV (4.2 months; unstratified HR = 0.67; P = 0.012). Here, we summarise four separate NAPOLI-1 subgroup analyses investigating the effect of selected baseline parameters.

Methods: These post-hoc analyses explored outcomes in patients with or without metabolism and nutrition disorders (including hypercholesterolemia and decreased appetite, comprising anorexia, poor appetite, lack of appetite and loss of appetite; abstract_#327), by primary tumour location (pancreatic head only, body only, tail only, and multiple locations including or excluding the head; abstract_#335), with or without a biliary stent (abstract_#338), and by best response to prior therapy (complete response/partial response [CR/PR] vs not-CR/PR, and CR/PR/stable disease [CR/PR/SD] vs not-CR/PR/SD; abstract_#339).

Results: For ITT patients in the metabolism and nutrition disorders analysis (abstract_#327), survival was significantly reduced in those patients (n = 77) with baseline decreased appetite compared with patients (n = 340) without decreased appetite (mOS: 3.6 vs 5.3 months; HR = 1.65; P < 0.001). A trend for lower survival was observed in patients with hypercholesterolemia.

In the analysis investigating the effect of primary tumour location on outcomes (abstract_#335), survival was comparable across primary tumour location subgroups (HRs=0.87–1.06). However, patients receiving nal-IRI+5-FU/LV showed an increased survival across primary tumour location subgroups compared with 5-FU/LV (HRs=0.39–0.88 for groups n > 10 per arm).

In ITT patients with a biliary stent at baseline (n = 37), survival was comparable to those without a stent (mOS: 5.3 vs 4.8 months; HR = 0.97) (abstract_#338). In patients with a stent and receiving nal-IRI+5-FU/LV (n = 15), we observed a trend for increased survival compared with patients receiving 5-FU/LV (mOS: 6.2 vs 5.2 months; HR = 0.44; n = 8). In patients without a stent, a similar survival benefit was seen for nal-IRI+5-FU/LV (n = 102) versus 5-FU/LV (n = 111) (mOS: 6.1 vs 4.2 months; HR = 0.68).

For subgroups stratified by response to prior therapy (abstract_#339), there was a trend for increased survival in patients with CR/PR compared with not-CR/PR (mOS: 5.6 vs 4.8 months; HR = 0.73). In patients with CR/PR/SD survival was similar compared with not-CR/PR/SD (mOS both 4.9 months, HR = 0.95). A trend for increased survival was also shown in patients receiving nal-IRI+5-FU/LV with CR/PR (n = 11) compared with not-CR/PR (n = 106) (mOS: 9.3 vs 6.1 months; HR = 0.64). Survival was comparable in patients with CR/PR/SD (n = 58) vs not-CR/PR/SD (n = 59) (mOS: 6.2 vs 6.1 months; HR = 1.04).

Drug related AEs and dose modifications/discontinuations in the different subgroups were generally comparable to the NAPOLI-1 study.

Conclusion: In the NAPOLI-1 study, decreased appetite at baseline was shown to be prognostic for survival in patients with mPDAC who progressed after gemcitabine-based therapy. These results indicate that appropriate management is essential in patients with decreased appetite. We did not identify a significant prognostic effect of primary tumour location, biliary stent, or best response to prior therapy in either the NAPOLI-1 ITT population or the nal-IRI+5-FU/LV treatment arm on survival after trial inclusion. Nonetheless, a consistent treatment benefit was observed in patients treated with nal-IRI+5-FU/LV vs 5-FU/LV alone across subgroups.

O – 005 A multicentre, prospective clinical evaluation study for analyzing RAS mutational status utilizing plasma circulating tumor DNA in patients with metastatic colorectal cancer

Y Kagawa[1], T Kato[2], H Bando[3], K Akagi[4], T Denda[5], T Nishina[6], Y Komatsu[7], E Oki[8], T Kudo[9], T Yamanaka[10], T Yoshino[11]

[1]Department of Gastrointestinal Surgery, Kansai Rosai Hospital, Amagasaki, Japan, [2]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [3]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [4]Saitama Cancer Center, Kitaadachi-Gun, Japan, [5]Chiba Cancer Center, Chiba, Japan, [6]Shikoku Cancer Center, Matsuyama, Japan, [7]Digestive Internal Medicine, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, [8]Department of Surgery, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Japan, [9]Osaka University Graduate School of Medicine, Suita, Japan, [10]Yokohama City University School of Medicine, Yokohama, Japan, [11]National Cancer Center Hospital East, Kashiwa, Japan

Introduction: Liquid biopsy has emerged as an excellent molecular diagnostic tool for assessing predominant spatial and temporal intratumoral heterogeneity with minimal

invasiveness. The OncoBEAM RAS kit is a circulating tumor DNA (ctDNA) test intended for detecting plasma RAS mutational status in metastatic colorectal cancer (mCRC). We conducted multicentre, prospective clinical evaluation study investigating the concordance of RAS mutational status between plasma ctDNA and tumor tissue DNA in patients with mCRC.

Methods: mCRC patients who have an adequate archived FFPE tumor tissue specimen obtained within 5 years and who have no prior treatment with anti-EGFR antibodies and regorafenib were enrolled. Plasma- and tissue-based RAS mutational status were determined by the OncoBEAM RAS kit and by the Tissue OncoBEAM RAS assay; the concordance of RAS mutational status was compared as the primary analysis. Plasma samples in discordant cases were transferred to RAS test using the plasma-NGS technology of Oncomine Colon cfDNA assay to cross-validate the accuracy of the OncoBEAM RAS kit.

Results: A total of 280 mCRC out of 350 enrolled patients were eligible from eight hospitals in Japan. The overall agreement between plasma- and tissue-based analyses was 86.4% (242/280), with positive percent agreement of 82.1% (110/134) and negative percent agreement of 90.4% (132/146). Plasma RAS mutational status determined by OncoBEAM RAS showed 96% concordance with plasma-NGS, indicating the assay performance (accuracy) of plasma result of OncoBEAM RAS kit is highly reliable. Of 38 discordant cases, plasma-positive and tissue-negative results were observed in 14 cases, 6 out of which were determined as RAS-positive by plasma-NGS; the discordance was deemed due to tumor heterogeneity and a longer interval in sample collection from archived tissue to plasma. In contrast, plasma-negative and tissue-positive results were observed in 24 cases, 15 out of which were confirmed as negative by plasma-NGS, indicating ctDNA release into the blood stream was relatively low. Interestingly, 10 out of the 24 plasma-negative and tissue- positive cases (42%) had lung metastasis alone. The overall agreement between plasma- and tissue-based analyses in patients with lung metastasis alone (n = 31) was only 64.5%, while that in patients excluding lung metastasis alone (n = 249) was 89.2%.

Conclusion: The accuracy of plasma RAS mutational status determined by OncoBEAM RAS kit was confirmed for Japanese mCRC patients. The concordance rate between plasma- and tissue-based analyses was 86.4% in overall, rising to 89.2% in patients excluding lung metastasis alone, with 13.6% of discordant cases being potentially attributed to variables of tissue heterogeneity, a longer interval in sample collection from archived tissue to plasma and a lower amount of ctDNA shed into plasma. Careful attention should be paid for mCRC patients with lung metastases alone when considering use of plasma ctDNA test instead of tissue-based test.

O – 006 Ultra-selection of metastatic colorectal cancer patients using next generation sequencing platform to improve clinical efficacy of anti-EGFR therapy

J Vidal[1], A Dalmeses[2], C Santos Vivas[3], R Garcia-Carbonero[4], P García-Alfonso[5], A Carrato[6], E Elez[7], M Ortiz[8], F Losa[9], B Massutí[10], M Valladares-Ayerbes[11], J Manzano[12], J Vieitez de Prado[13], J Gallego[14], C Grávalos[15], M Varela[16], D Azuara[17], J Tabernero[18], R Salazar[19], E Aranda[20], B Bellosillo[21], C Montagut[22]

[1]Hospital del Mar, Barcelona, Spain, [2]Molecular Biology Laboratory Hospital del Mar, Barcelona, Spain, [3]Translational Research Laboratory and Department of Medical Oncology, Institut Català d'Oncologia-IDIBELL, LHospitalet de Llobregat, Spain, [4]Hospital Universitario Virgen del Rocio, Seville, Spain, [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [6]IRYCIS, CIBERONC, Alcalá University, Hospital Universitario Ramón y Cajal, Madrid, Spain, [7]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [8] IMIBIC, Reina Sofía Hospital, University of Córdoba, CIBERONC, Instituto de Salud Carlos III, Córdoba, Spain, [9]Hospital Sant Joan Despí - Moisés Broggi, Hospitalet de Llobregat, Spain, [10]H. General Universitario de Alicante, Alicante, Spain, [11]Complejo Hospitalario Universitario La Coruña, La Coruña, Spain, [12]H. Germans Trias i Pujol, Badalona, Spain, [13]Asturias Central University Hospital, Oviedo, Spain, [14]Hospital General Universitario de Elche, Elche, Spain, [15]Hospital Universitario 12 de Octubre, Madrid, Spain, [16]Pathological Anatomy Laboratory, Institut Català d'Oncologia, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain, [17]Translational Research Laboratory, Institut Catala d'Oncologia-IDIBELL, L'Hospitalet de Llobregat, Spain, [18]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain, [19]Medical Oncology Department and IDIBELL, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Spain, [20]IMIBIC, Reina Sofía Hospital, University of Córdoba, CIBERONC, Instituto de Salud Carlos III, Córdoba, Spain, [21]Department of Pathology, Hospital Universitari del Mar, Barcelona, Spain, [22]Department of Medical Oncology, Hospital Universitari del Mar, Barcelona, Spain

Introduction: Extended RAS and BRAF analysis is mandatory in metastatic colorectal cancer (mCRC) patients to establish the best therapeutic strategy. Recent studies aimed to determine the optimal threshold of RAS mutated subclones to identify patients most likely to benefit from anti-EGFR treatment (Laurent-Puig, CCR 2015; Santos C. Molec Can Ther 2017). Our aim is to assess the clinical relevance of highly sensitive Next Generation Sequencing (NGS) technology to detect point mutations in KRAS, NRAS, BRAF, and EGFR S492R in tissue tumor samples and its correlation with clinical outcome in terms of progression-free survival (PFS), overall response rate (ORR) and overall survival (OS) in mCRC patients treated with chemotherapy plus anti-EGFR or anti-VEGF therapy.

Methods: 580 mCRC pre-treatment tumor tissue samples from retrospective series and clinical trials from TTD/RTICC Spanish network were collected. Mutational analysis was performed by pyrosequencing using NGS 454 GS Junior platform (Roche Applied Science, Mannheim, Germany), which reaches sensitivity below 1%. We defined two cutoff of mutant allele fraction (MAF) detection, 5% and 1%.

Results: After quality assessment, 442 samples have been sequenced by Junior 454, and we have obtained enough coverage to evaluate the results from 380 samples. Using a 5% cutoff of sensitivity we detected RAS/BRAF mutations in 191 patients (49.77%) with a range MAF between 71.55% and 5.13%; 151 KRAS mutations (39.74%), 25 NRAS mutations (6.58%) and 13 BRAF mutations (3.42%). Using a 1% cutoff of sensitivity we detected 197 KRAS mutations (51.84%), 73 NRAS mutations (19.21%) and 24 BRAF mutations (6.32%). The lowest MAF detected was 1.02%. Patients all RAS/BRAF wt varied from 50.26% with a MAF cutoff of 5% to 22.63% with cutoff at 1%. As expected, the majority of tumors harbored mutations in KRAS exon 2 independently of cutoff used (83.44% and 83.25% in 5% and 1% respectively). No EGFR S492R mutations were detected in both cutoff thresholds. Patients follow-up is ongoing, correlation between mutational profile and clinical outcome will be presented.

Conclusion: This study analyses the impact of using a NGS platform for molecular diagnosis of mCRC patients. Increasing the sensitivity of MAF cutoff from 5% to 1% we identified mutations in RAS/BRAF hotspots in 27.63% more patients. Confirming results from our previous reports, no mutations in EGFR ECD have been detected in untreated samples.

O – 007 Liquid biopsy allows predicting benefit from rechallenge with cetuximab(cet)+irinotecan(iri) in RAS/BRAF wild-type mCRC patients(pts) with resistance to 1st-line cet+iri: Final results and translational analyses of the CRICKET study by GONO

D Rossini[1], C Cremolini[1], E Conca[2], M Del Re[3], A Busico[2], F Pietrantonio[4], F Bergamo[5], R Danesi[3], G Cardellino[6], E Tamburini[7], E Dell'Aquila[8], A Strippoli[9], G Masi[1], G Tonini[8], F Negri[10], D Corsi[11], N Pella[6], R Intini[12], A Falcone[13], D Santini[8]

[1]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [2]Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [3]Clinical Pharmacology and Pharmacogenetics Unit, Department of Clinical and Experimental Medicine, Pisa, Italy, [4]Department of Medical Oncology, IRCCS Fondazione Istituto Nazionale dei Tumori, Milan, Italy, [5]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [6]Department of Oncology, Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia, Udine, Italy, [7]Department of Medical Oncology, Infermi Hospital, Rimini, Italy, [8]Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy, [9]Unit of Clinical Oncology, Università Cattolica del Sacro Cuore, Rome, Italy, [10]Medical Oncology, University Hospital, Parma, Italy, [11]Medical Oncology Unit, Fatebenefratelli-Isola Tiberina Hospital, Rome, Italy, [12]Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [13]University of Pisa, Pisa, Italy

Introduction: CRICKET (NCT02296203) was designed to investigate the activity of the rechallenge with cet and iri as 3 rd -line treatment in RAS/BRAF wild-type mCRC pts with acquired resistance to 1st-line cet- and iri-based therapy. The role of liquid biopsies as a tool to identify pts more likely to benefit from this strategy was investigated.

Methods: Eligibility criteria included RAS/BRAF wild-type status on tissue samples; prior 1 st -line iri-based, cet-containing regimen with at least RECIST partial response (PR), 1 st -line PFS ≥6 months, and progression within 4 weeks after the last cet; prior 2 nd -line oxaliplatin- and bevacizumab-based treatment. Pts received 3rd-line cet + iri until PD. The primary endpoint was response rate (RR) according to RECIST v1.1. With p0 = 5%, and p1 = 20%, 1-sided-α and β errors of 0.05 and 0.20, 27 pts were required. The null hypothesis can be rejected if responses are observed in ≥ 4 pts. Liquid biopsies were collected at the rechallenge baseline. ctDNA was analyzed with ddPCR for specific RAS/BRAF mutations (mut), and then by ultra-deep NGS with Ion Torrent S5 XL.

Results: Between Jan 2015 and Jun 2017, 28 pts were enrolled in 9 centres. The primary endpoint was met. Six PRs (two unconfirmed) and 9 disease stabilizations (RR: 21%, 95%CI: 10-40%, disease control rate: 54%, 95%CI: 36-70%) were reported. RAS mut were found in liquid biopsies collected at the rechallenge baseline in 12 (48%) out of 25 evaluable pts (6 KRAS G12D, 5 KRAS G12V with 1 harboring also Q61H and 1 NRAS Q61L). No RAS mut were detected in samples from pts who achieved a confirmed PR. Pts with RAS wt ctDNA had significantly longer PFS than those with RAS mut ctDNA (mPFS: 3.9 vs 1.9 mos; HR: 0.48 [95%CI 0.20-0.98], p = 0.048). No BRAF or PIK3CA mut were found.

Conclusion: This is the first prospective demonstration of the activity of rechallenge with cet + iri in some mCRC pts initially sensitive and then resistant to first-line iri- and cet-based therapy, with no RAS/BRAF mut in pre-treatment liquid biopsies.

Partially funded by Merck Serono SpA.

O – 008 The prognostic role of microsatellite status, tumor mutational burden and protein expression in CRC

J Lam[1], Y Kim[2], F Cecchi[3], S Woo[3], A Chambers[2], I Tan[1], C Chua Wei Ling[1], K Si-Lin[4], L Wei Qiang[1], T Lim Kiat Hon[1], S Anders Martin Jacobsen[1], T Hembrough[5]

[1]National Cancer Centre Singapore, Singapore, [2]NantOmics, Rockville, Maryland, USA, [3]Nantomics, Rockville, Maryland, USA, [4]National Cancer Centre Singapore, Singapore, [5]NantOmics , Rockville, Maryland, USA

Introduction: Comprehensive molecular profiling of CRC can inform treatment decisions by identifying patient subgroups at varying risks of death. Microsatellite instability (MSI) is prognostic in CRC and is used to select patients for immunotherapy. High tumor mutational burden (TMB) is associated with genomic instability and is prognostic in melanoma. Expression of p16 protein is prognostic in many tumor types. We used proteomic and genomic profiling to measure MSI, TMB and p16 in CRC tumors and to assess associations with patient survival. The global proteome data was also used to identify potentially prognostic protein biomarkers.

Methods: In archived clinical samples of CRC, 76 proteins were quantitated with mass spectrometry-based proteomics. MSI was measured by whole genome sequencing; unstable loci were quantified in tumor and normal samples. Cutoffs were derived via ROC analysis: high TMB was defined as > 4.5 somatic mutations per megabase; p16 as > 108 amol/ug. Patients were grouped by microsatellite status (MSI vs. microsatellite stable [MSS]), TMB (high vs. low), and p16 protein expression level. Survival curves were compared with the Mantel-Cox log-rank test.

Results: Of 145 samples, 39 (27%) had high TMB and 29 (20%) had MSI. Patients with MSI tumors had longer OS than patients with MSS tumors (HR: 0.096; $p = 0.003$). Similarly, patients with high TMB had longer OS than those with low TMB (HR: 0.076; $p < 0.001$). High p16 expression was prognostic of poor survival (HR: 2.874; $p = 0.019$). Among patients with MSS tumors or low TMB, those with low p16 levels had longer OS than patients with high p16 (HR: 0.257; $p = 0.002$ and HR: 0.249; $p = 0.002$, for MSS and low TMB, respectively). A combination of MSS, low TMB, and low p16 also differentiated between long and short survivors (HR: 0.249; $p = 0.002$). These associations remained after adjustment for tumor sidedness. Analysis of proteome expression profiles of individual CRC biopsies ($n = 80$) detected 5021 quantifiable proteins. Among these, we identified a list of proteins that separated CRC patients by CMS subtypes. Further analyses of clinical correlates will be presented

Conclusion: A combination of MSS, low TMB and low p16 expression characterized a subset of patients with longer survival. This is important because patients with MSS tumors have limited treatment options but may respond to CDK4/6 inhibitors due to low p16 expression. Molecular profiling of CRC may identify patient subgroups with a relatively poor prognosis who could benefit from personalized therapy.

O – 009 A Phase II multi institutional study of nivolumab in patients with advanced refractory biliary tract cancers (BTC)

R Kim[1], D Kim[2], O Alese[3], D Li[4], B El-Rayes[5], N Shah[1], M Schell[1], J Zhou[1], V Chung[4]

[1]Moffitt Cancer Center, Tampa, Florida, USA, [2]Moffitt Cancer Center, Tampa, Florida, USA, [3]Emory University, Atlanta, Georgia, USA, [4]City of Hope, Duarte, California, USA, [5]Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia, USA

Introduction: Biliary tract cancers (BTC) typically include intra and extrahepatic cholangiocarcinoma and cancers of the gallbladder. There is no established second line option for patients with advanced BTC who have failed one prior systemic therapy. There are pre-clinical and small series of clinical data which supports the usage of immune modulatory agents in BTC. Therefore we propose to evaluate the anti-PD1 agent nivolumab in advanced, refractory BTC.

Methods: Pts with histologically proven BTC who progressed on at least one line of systemic therapy received nivolumab 240mg IV q2weeks for 16 weeks and then 480 mg IV every 4 weeks until disease progression or unacceptable toxicity The Simon two staged design was used to assess objective response rate (ORR) by RECIST 1.1 every 8 weeks as a primary endpoint. In the first stage, 18 patients were accrued and if one response was seen, the plan was to accrue additional 14 patients for total of 32 patients. Secondary endpoints were PFS, OS and safety profile.

Results: Median age was 64.5 (range: 28-86) years and the primary sites of tumor were intrahepatic cholangiocarcinoma 64.7%, extrahepatic 2.9%, and gallbladder 32.4%. 17 (50.0%) of the patients were female. Twenty pts (59%) failed 1 line of therapy and 14 pts (41%) failed more than one line of therapy. Thirty-four pts received at least 1 dose of nivolumab of whom 29 pts (1 pt withdrew consent and 4 pts came off the study due to clinical progression) were evaluable for response rate. Out of 29 pts, 5 pts (17%) achieved PR and 11 pts (38%) achieved SD. DCR was 55%. Four patients who responded were all microsatellite stable and still remain on treatment (2 pts have durations of response > 12 months). For all 34 pts with median follow up of 8 months, median PFS was 3.5 months (95% CI: 2.1-7.6) and the median OS has not been reached. 6-month OS was 76.3%. Most common treatment related AEs(TRAE) were fatigue (23.5%) and elevated AST and ALT (15% and 11%). Grade III TRAEs were seen in 7pts (21%); most common were elevated bilirubin (3%) and elevated alkaline phosphatase (6%). There were no grade IV or V toxicities reported. Tissue samples were collected in all pts with planned correlative studies underway.

Conclusion: The primary endpoint of ORR was met. Nivolumab was well tolerated and has shown promising efficacy in refractory BTC including durable responses lasting over 1 year. Further randomized trial is warranted in refractory BTC.

O – 010 Cisplatin/5-fluorouracil +/- panitumumab for patients with non-resectable, advanced or metastatic esophageal squamous cell cancer: A randomized phase III AIO/EORTC trial with an extensive biomarker program

M Moehler[1], A Maderer[2], P Thuss-Patience[3], B Brenner[4], J Hecker[5], F Longo Muñoz[6], J Meiler[7], T Ettrich[8], R Hofheinz[9], S Al-Batran[10], A Vogel[11], L Mueller[12], M Lutz[13], K Borchert[14], R Greil[15], M Alsina[16], A Karatas[17], E Van Cutsem[18], R Keller[17], J Larcher-Senn[19], S Lorenzen[5]

[1]Johannes-Gutenberg University Mainz, Mainz, Germany, [2]University Medical Center Mainz, Berlin, Germany, [3]Medizinische Klinik Hämatologie, Onkologie und Tumorimmunologie, Berlin, Germany, [4]Rabin Medical Center – Tel Aviv University, Petah Tiqva, Israel, [5]Klinikum rechts der Isar der TU München, Munich, Germany, [6]Hospital Universitario Ramón y Cajal, Madrid, Spain, [7]Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany, [8]Department of Internal Medicine I, University of Ulm, Ulm, Germany, [9]University Hospital Mannheim, Mannheim, Germany, [10]Krankenhaus Nordwest, Frankfurt, Germany, [11]Hannover Medical School, Hannover, Germany, [12]Oncological Practice, Leer, Germany, [13]EORTC, Saarbrücken, Germany, [14]University Hospital Rostock, Rostock, Germany, [15]III Medizinische Universitätsklinik Salzburg, Salzburg, Austria, [16]Vall d'Hebron Institute of Oncology, Barcelona, Spain, [17]AIO-Studien-gGmbH, Berlin, Germany, [18]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium, [19]Assign Data Management and Biostatistics GmbH, Innsbruck, Austria

Introduction: Most esophageal squamous cell cancer (ESCC) patients (pts) have advanced disease at time of diagnosis. Chemotherapy (CTX) improved overall survival (OS), but still with limited impact. Prior studies suggested increased efficacy of EGFR antibodies (AB) combined with cisplatin (C) / 5-fluorouracil (F).

Methods: This open-label, randomized (1:1), multinational phase III trial included ECOG 0-1 pts with non-resectable, advanced or metastatic ESCC (RECIST1.1), not eligible for radiochemotherapy (RCTX). Previous CTX in metastatic setting, concurrent RCTX and previous exposure to EGFR-AB were excluded. To test for overall survival (OS) superiority of CFP vs CTX alone, pts received CF (C 100 mg/m^2 d1 + F 1000 mg/m^2/d, d1-4) + panitumumab (P) (9 mg/kg d1) or CF alone (each q3 weeks) until disease progression. To define prognostic and predictive markers, EGFR and MET expression status were determined by immunohistochemistry. Serum samples were collected before first CTX cycle for enzyme-linked immunosorbent assay (ELISA) analyses.

Results: Between 6.2012-5.2015, the ITT population consisted of randomized 146 patients with 73 in each treatment arm, 71 of each group received at least one dose of study medication. The per-protocol set (PPS) contained 101 patients. Due to more Gr3-4 SAEs in the first 60 pts with CFP, C was reduced to 80mg/m^{2}d1. Recruitment and trial was terminated prematurely after a scheduled safety interim analysis and an unscheduled efficacy interim analysis. Median progression-free survival was similar in both groups: 5.8 months with CF vs. 5.3 months in CFP (HR 1.21, 95% CI 0.85–1.73, $p = 0.29$). Median OS in CF (10.3 months) was similar to CFP (9.6 months, HR 1.17, 95% CI 0.79–1.75, $p = 0.43$). After C was reduced in 85 pts, OS favored CFP vs CF, with 9.8 vs. 8.3 mo (HR 0.84, 95%CI 0.49-1.43; $P = 0.51$). Safety: 60 (83%) of CFP and 55 (79%) of CF pts had any AE, mostly diarrhoea, hypokalaemia, hypomagnesaemia, rash, or hand-foot syndrome. Main Gr ≥ 3 AEs were balanced with low neutrophils (21/24%) and anaemia (13/16%) for CFP vs CF, respectively. Gr 3-4 skin reactions and rash were higher in CFP (10%) vs CF (0%). Overall, 51/72 (71%) of CFP and 36/70 (51%) of CF had an SAE. Main SAEs were dysphagia, acute kidney injury, diarrhoea, fevers and febrile neutropenia. EGFR and MET expression showed no correlation to any clinical or pathological parameters. Low sEGFR serum levels were linked to better PFS ($p = 0.014$) in all patients, especially in the CF arm ($p = 0.039$). Moreover, sEGFR levels increased during CF-P therapy but not with CF.

Conclusion: To our knowledge, this has been the largest European first-line palliative phase III trial of chemotherapy +/- EGFR targeting agent in ESCC patients only. Addition of Panitumumab to CF provided no benefit to first-line CTX alone. A low sEGFR level was associated with better PFS and increased under CF+ Panitumumab. Further results of second line therapies and further biomarker analysis will be presented at the meeting.

O – 011 Assessment of tumor response, AFP response, and time to progression in the phase 3 CELESTIAL trial of cabozantinib versus placebo in advanced hepatocellular carcinoma (HCC)

P Merle[1], L Rimassa[2], B Ryoo[3], I Cicin[4], W Harris[5], E Banu[6], D Sarker[7], B Tan[8], H Van Vlierberghe[9], S Sen[10], C Love[10], A Cheng[11], T Meyer[12], R Kelley[13], G Abou-Alfa[14]

[1]Hepatology Unit, Groupement Hospitalier Lyon Nord, Lyon, France, [2]Humanitas Research Hospital – IRCCS, Rozzano, Italy, [3]Asan Medical Center, Ulsan University College of Medicine, Seoul, Republic of Korea, [4]Trakya University, Erdirne, Turkey, [5]Department of Medicine, University of Washington, Seattle, Washington, DC, USA, [6]Medical Oncology Department, Teo Health SA, St. Constantin Hospital, Brasov, Romania, [7]Department of Oncology, King's College Hospital, London, UK, [8]Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA, [9]Department of Gastroenterology and Hepatology, Ghent University Hospital, Gent, Belgium, [10]Exelixis, Inc., San Francisco, California, USA, [11]Department of Oncology and Internal Medicine, National Taiwan University Hospital, Taipei, Republic of Taiwan, [12]Royal Free Hospital, University College London, London, UK, [13]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California, USA, [14]Memorial Sloan Kettering Cancer Center, New York, New York, USA

Introduction: Cabozantinib inhibits tyrosine kinases including MET, vascular endothelial growth factor receptors, and AXL. In the CELESTIAL trial (NCT01908426), cabozantinib improved overall survival and progression-free survival compared with placebo in patients with previously treated advanced HCC. The study met the primary end point, with a median overall survival of 10.2 months with cabozantinib versus 8.0 months with placebo (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63–0.92; P = 0.0049). Median progression-free survival was 5.2 months with cabozantinib versus 1.9 months with placebo (HR, 0.44; 95% CI, 0.36–0.52; P < 0.0001), and the objective response rate was 4% with cabozantinib versus 0.4% with placebo (P = 0.0086) per Response Evaluation Criteria in Solid Tumors v1.1. Here, we report a secondary analysis of tumor response including the best percentage change at any timepoint in tumor target lesion size, the best percentage change at any timepoint in serum alpha-fetoprotein (AFP) levels, and time to progression (TTP).

Methods: A total of 707 patients, stratified by disease etiology, geographic region, and extent of disease, were randomized 2:1 to receive cabozantinib 60 mg once daily (n = 470) or placebo (n = 237). Eligible patients had a pathologic diagnosis of HCC, Child-Pugh score A, and an Eastern Cooperative Oncology Group performance status ≤1. Patients must have received prior sorafenib and were allowed up to 2 lines of prior systemic therapy for HCC. Change in the sum of target lesion diameters (SOD) from baseline was determined every 8 weeks by the investigator. Best percentage change in SOD was defined as the maximum reduction in SOD at any postbaseline timepoint. Serum AFP levels were measured centrally at baseline and every 8 weeks on the same schedule as tumor assessments. TTP was defined as the time from randomization to radiological progression or clinical deterioration and was determined retrospectively.

Results: Based on the intention-to-treat population, 222 of 470 patients (47%) in the cabozantinib arm and 27 of 237 patients (11%) in the placebo arm had any postbaseline reduction in SOD as a best response. Thirty-nine of 470 patients (8%) in the cabozantinib arm and 3 of 237 patients (1%) in the placebo arm had at least 1 postbaseline tumor assessment with a ≥ 30% reduction in SOD. The percentages of patients in the cabozantinib arm with a ≥ 30% reduction in postbaseline SOD were 9% (n = 26/278) and 7% (n = 13/192) among those with a baseline AFP level <400 ng/mL versus ≥400 ng/mL, respectively. Overall, 109 of 470 patients (23%) in the cabozantinib arm and 13 of 237 (5%) in the placebo arm had a ≥ 50% postbaseline decrease in serum AFP levels. Median TTP was 5.4 months with cabozantinib versus 1.9 months with placebo (HR, 0.41; 95% CI, 0.34–0.49).

Conclusion: Cabozantinib is associated with improved TTP, higher rates of target lesion regression, and AFP response compared with placebo in patients with previously treated advanced HCC.

O – 012 Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer (mCRC) in routine clinical practice: Final analysis from the prospective, observational CORRELATE study

M Ducreux[1], L Petersen[2], L Öhler[3], F Bergamo[4], J Metges[5], J de Groot[6], J Wang[7], B García Paredes[8], N Kumar[9], S Fiala-Buskies[10], A Cervantes[11], J O'Connor[12], A Falcone[13], on behalf of the CORRELATE Investigators

[1]Gustave Roussy Cancer Campus Grand Paris, Villejuif, France, [2]Rigshospitalet, Copenhagen, Denmark, [3]St. Josef Krankenhaus, Vienna, Austria, [4]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [5]CHU de Brest – Hôpital Morvan, Brest, France, [6]Isala, Zwolle, Netherlands, [7]Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung City, Republic of Taiwan, [8]Hospital Clínico San Carlos, Madrid, Spain, [9]Bayer HealthCare Pharmaceuticals, Whippany, New Jersey, USA, [10]Bayer AG, Wuppertal, Germany, [11]University Hospital of Valencia, Valencia, Spain, [12]Institute Alexander Fleming, Buenos Aires, Argentina, [13]University of Pisa, Pisa, Italy

Introduction: In the randomized, phase 3 CORRECT and CONCUR trials, regorafenib significantly improved overall survival (OS) versus placebo in patients with mCRC who progressed on standard therapies. The approved dose of regorafenib is 160 mg daily administered 3 weeks on/1 week off. The aims of CORRELATE (NCT02042144) were to characterize the safety and effectiveness of regorafenib for the treatment of mCRC in real-world clinical practice. Here we present the results of the final analysis.

Methods: This prospective, observational study was conducted in 13 countries across Europe, Latin America, and Asia and recruited patients with mCRC who were previously treated with approved therapies, and for whom the decision to treat with regorafenib was made by the treating physician prior to enrollment, according to the local health authority approved label. Dose interruptions and reductions were permitted for the management of adverse events (AEs). The primary endpoint was the incidence of treatment-emergent AEs (TEAEs; NCI-CTCAE v4.03). Secondary endpoints included OS, progression-free survival (PFS), and disease control rate (DCR).

Results: A total of 1037 patients (61% male, 39% female) received treatment. At study entry, the median age was 65 years (range: 24–93), most patients were ECOG PS 0–1 (87%) versus PS 2–4 (6%), 56% had KRAS mutations and 37% did not, and the most common metastatic sites were the liver (72%) and the lung (57%). The median treatment duration was 2.5 months (range: 0.03–29.5). The initial daily regorafenib dose was 160 mg in 57% of patients, 120 mg in 30%, and 80 mg in 12%. Overall, 40% of patients had dose reductions; 48% had an interruption/delay, and 35% had no dose modifications. TEAEs of any grade occurred in 95% of patients, and were considered regorafenib related in 80% of patients. Grade ≥3 TEAEs occurred in 62% of patients, and in 36% of patients they were attributed to regorafenib. The most common grade ≥3 TEAEs were fatigue (10%), hypertension (8%), and hand–foot skin reaction (HFSR; 7%), with most being regorafenib related (fatigue 9%; HFSR 7%; hypertension 6%). Grade 5 TEAEs occurred in 17% of patients, and were considered regorafenib related in 1% of patients. Median OS was 7.6 months (95% confidence interval [CI]: 7.1–8.2) and median PFS was 2.8 months (95% CI: 2.6–2.8). DCR was 21.0% by radiologic assessment, with a partial response in 3.1% of patients as best response.

Conclusion: In this real-world, observational study, AEs were generally consistent with the known safety profile of regorafenib in mCRC, although reported incidence rates of some AEs were lower than in clinical trials. The starting dose for almost half of patients was less than 160 mg/day. Median OS and PFS were in the range observed in phase 3 trials in this setting.

O – 013 Safety and efficacy of trifluridine/tipiracil in previously treated metastatic colorectal cancer (mCRC): Preliminary results from the phase IIIb, international, open-label, early-access PRECONNECT study

A Falcone[1], T André[2], J Edeline[3], E François[4], J Taieb[5], J Phelip[6], F Portales[7], T Price[8], M Becquart[9], S Moreno Vera[9], N Mounedji[9], E Van Cutsem[10], J Seitz[11]

[1]Unit of Medical Oncology 2, Azienda Ospedaliera-Universitaria Pisana, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy, [2]Hôpital Saint Antoine, AP-HP, Paris, France, [3]Centre Eugène Marquis, Rennes, France, [4]Centre Antoine Lacassagne, Nice, France, [5]Sorbonne Paris Cité, Paris Descartes University, Hôpital Europeen Georges Pompidou, Paris, France, [6]CHU de St Etienne, St Etienne, France, [7]Institut régional du Cancer, Montpellier, France, [8]Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia, [9]Global Medical Affairs, Servier, Suresnes, Suresnes, France, [10]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium, [11]Aix-Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France

Introduction: Trifluridine/tipiracil (FTD/TPI) was approved following the results of the RECOURSE study (Mayer et al. N Engl J Med 2015;372:1909-19), which demonstrated that FTD/TPI significantly improved overall survival (OS) and progression-free survival (PFS) versus placebo. FTD/TPI is approved for treatment of previously treated mCRC patients, in the same setting as regorafenib. In October 2016, a phase IIIb PRECONNECT study was set up in mCRC patients to assess safety and efficacy of FTD/TPI in daily practice (NCT03306394).

Methods: PRECONNECT is enrolling patients who have histologically confirmed mCRC previously treated with, or who are not considered candidates for, available therapies, with an ECOG PS of 0 or 1. Patients receive FTD/TPI (35 mg/m2 twice daily) orally on days 1–5 and 8–12 of each 28-day cycle. Patients were followed-up up to end of study treatment. Withdrawal criteria include disease progression, unacceptable toxicity and commercial availability of FTD/TPI. Primary endpoint is safety and PFS as key secondary endpoint.

Results: A study cohort of 462 patients from 10 countries had received at least one dose of treatment at cutoff (1 November 2017). Median age was 64 years (range 28–87); 63.6% were male; 46.5% were ≥65 years old. Of the 450 patients evaluable for PS, 46% and 54% had ECOG PS 0 and 1, respectively at baseline. 52.2% had known RAS mutation. Primary site of disease was left-sided for 62.8%, right-sided for 24.5%, and not specified for 12.8%. Prior to study start, more than 94% received fluoropyrimidine and/or oxaliplatin and/or irinotecan, while 83%, 41% received anti-VEGF, anti-EGFR respectively and only 35% patients received regorafenib. Emergent adverse events (AEs) were reported in 92.4%. Drug-related AEs were reported in 74.5%; most common were neutropenia, nausea and diarrhea, which occurred in 49.5%, 27.7%, and 20.6% of patients, respectively. Drug-related grade ≥3 AEs were reported in 48.6%; most common hematological were neutropenia (38%), anemia (7.1%), febrile neutropenia (1.7%), and thrombocytopenia (1.3%) while most common non-hematological were diarrhoea (3.5%) and fatigue (2.2%). At cutoff time, 29 patients remained on treatment (6.2%). Of the 435 patients withdrawn from the study, 77.4% withdrew for

progressive disease, 6.7% for AE and 6.4% for commercial availability of FTD/TPI that remained on treatment at withdrawal. Median FTD/TPI treatment duration and number of cycles were 12.9 weeks (range 2–48) and 3 (range 1–12), respectively. Median relative dose intensity was 89%. Dose of FTD/TPI was reduced due to AE in 8% of patients mainly due to neutropenia (2.8%). FTD/TPI was associated with a median PFS of 3.2 months (95% CI 2.8–3.4) and disease control rate of 41.1% (95% CI 36.3–46.0) in the 414 patients who received FTD/TPI and had one post-baseline tumor evaluation. Median time to ECOG PS $\geq$ 2 was 8.7 months. At cutoff time, 91.3% were still alive; therefore median OS was not yet reached.

Conclusion: These are first data on the widespread clinical use of FTD/TPI outside US and Japan. Preliminary encouraging safety and efficacy data obtained make FTD/TPI a favorable treatment option for mCRC patients.

O – 014 Regorafenib Dose Optimization Study (ReDOS): Randomized phase II trial to evaluate escalating dosing strategy and pre-emptive topical steroids for regorafenib in refractory metastatic colorectal cancer (mCRC) – An ACCRU Network study

T Bekaii-Saab[1], F Ou[2], D Anderson[3], D Ahn[4], P Boland[5], K Ciombor[6], N Jacobs[7], R Desnoyers[8], J Cleary[9], J Meyers[2], E Chiorean[10], K Pedersen[11], A Barzi[12], J Sloan[13], J McCune[14], M Lacouture[15], H Lenz[16], A Grothey[11]

[1]Mayo Clinic Cancer Center, Scottsdale, Arizona, USA, [2]Mayo Clinic, Rochester, Minnesota, USA, [3]Healthpartners Clinic, St Paul, Minnesota, USA, [4]Mayo Clinic, Scottsdale, Arizona, USA, [5]Roswell Park Cancer Institute, Buffalo, New York, USA, [6]Vanderbilt University, Nashville, Tennessee, USA, [7]Coon Rapids Clinic, Coon Rapids, Minnesota, USA, [8]Wake Forrest, Winston-Salem, North Carolina, USA, [9]Dana Farber Cancer Institute, Boston, Massachusetts, USA, [10]University of Washington, Seattle, Washington, DC, USA, [11]Mayo Clinic, Rochester, Minnesota, USA, [12]University of Southern California, Los Angeles, California, USA, [13]Mayo Clinic, Rochester, Minnesota, USA, [14]City of Hope, Duarte, California, USA, [15]Memorial Sloan Kettering, New York, New York, USA, [16]USC Norris Comprehensive Cancer Center, Los Angeles, California, USA

Introduction: Regorafenib (Rego) confers a survival benefit in refractory mCRC patients (pts). Toxicities such as palmar-plantar erythrodysesthesia syndrome (PPES) have limited its use. Despite absence of supportive data, various dosing variations are used in clinical practice.

Methods: Patients with mCRC were randomized to Arm A: 80 mg/day (d), weekly escalation if no significant drug-related toxicity, up to 160 mg/d vs. Arm B: 160 mg/d for 21 ds of a 28-d cycle. Randomization was 1:1:1:1 to arms A1 and B1 (Arm 1 Pre-emptive topical Clobetasol [CL] for 12 weeks); A2 and B2 (Arm 2 Reactive CL for PPES). Primary endpoint was the proportion of pts who initiate a 3rd cycle in Arm A (A1 + A2) vs. Arm B (B1 + B2). Superiority for Arm A is declared if one-sided p-value with Fisher's exact method was less than 0.2. Quality of Life (QoL) was collected using Linear Analogue Self-Assessment over 8 weeks. Plasma pharmacokinetic (PK) analysis of Regorafenib and its M2 and M5 metabolites were performed prior to dosing (Cmin, trough levels) on cycle 1 days 7,14, 21 and cycle 2 days 1 and 21.

Results: A total of 123 pts were randomized with 116 (A = 54, B = 62) evaluable for the primary endpoint. Median age of 61 years and ECOG PS 0/1 (37/63%). The study met its primary endpoint with 43% of pts in Arm A initiating the 3rd cycle vs. only 25% of pts in Arm B [one-sided p-value 0.028]. Most common reason for not initiating cycle 3 was progressive disease (35% in A vs. 47% in B). Median overall survival was improved in Arm A vs. Arm B (9.0 mos vs. 5.9 mos; p = 0.094). Median progression free survival was 2.5 mos vs 2.0 mos for Arm A vs. Arm B (p = 0.55). In cycle 1, rates of common dose modifying toxicities such as PPES (grade [G] 2-3) and fatigue or hypertension (G3) were more favorable in Arm A vs. Arm B. Pts on Arm 1 vs. Arm 2 experienced less G2-3 PPES in the first 2 cycles (28% vs. 35% in cycle 1 and 13% vs. 34% in cycle 2, in Arm 1 vs. Arm 2 respectively). Multiple QoL parameters were favorable in A vs. B primarily at week 2 of cycle 1.

Conclusion: A strategy with weekly dose escalation of Rego from 80 to 160 mg/d was found to be superior to a starting dose of 160 mg/day. These results conceivably establish a new standard for optimizing Rego dosing through dose escalation. A preemptive strategy with CL may decrease the risk of PPES warranting further investigation. PK analysis and correlation with clinical parameters of interest will be reported at the meeting.

O – 015 A two arm phase II study of FOLFIRI in combination with standard or escalating dose of cetuximab as first line treatment for metastatic colorectal cancer: Everest 2 final results

G Chiritescu[1], K Dumon[1], T Macarulla Mercadé[2], I Lang[3], C Santos Vivas[4], Z Papai[5], J Janssens[6], K Hendrickx[7], M Pracht[8], M Van den Eynde[9], J Taïeb[10], V Moons[11], K Geboes[12], J Van Laethem[13], R Greil[14], A Cervantes[15], P Vergauwe[16], M Ferrante[17], E Vanderstraeten[18], M Fridrik[19], E Wöll[20], M Limón[21], F Rivera[22], X Sagaert[1], S Tejpar[1], E Van Cutsem[25]

[1]University Hospitals Leuven, Leuven, Belgium, [2]Vall d'Hebron University Hospital (HUVH) and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [3]National Institute of Oncology, Budapest, Hungary, [4]Translational Research Laboratory and Department of Medical Oncology, Institut Català d'Oncologia-IDIBELL, LHospitalet de Llobregat, Barcelona, Spain, [5]State Health Center, Budapest, Hungary, [6]AZ Turnhout, Turnhout, Belgium, [7]OLV Aalst, Aalst, Belgium, [8]Centre Eugène Marquis, Rennes, France, [9]Clin. Univ. St-Luc Bruxelles, Brussels, Belgium, [10]Georges Pompidou European Hospital, Paris, France, [11]Imelda Ziekenhuis Bonheiden, Bonheiden, Belgium, [12]UZ Gent, Gent, Belgium, [13]Hôpital Universitaire Erasme, Brussels, Belgium, [14]III Medizinische Universitätsklinik Salzburg, Salzburg, Austria, [15]University Hospital of Valencia, Valencia, Spain, [16]A.Z. Groeninge Kortrijk, Kortrijk, Belgium, [17]A.Z. Sint Maarten Mechelen, Mechelen, Belgium, [18]A.Z. Maria Middelares Gent, Gent, Belgium, [19]Kepler Univ Hospital Linz, Linz, Austria, [20]Krankenhaus St. Vinzenz, Innere Medizin, Zams, Austria, [21]H.U.V. del Rocío, Seville, Spain, [22]Universitario Marqués de Valdecilla, Santander, Cantabria, Spain, [25]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

Introduction: Adding cetuximab to first-line FOLFIRI improves clinical and surgical outcomes in RAS wild-type metastatic colorectal (mCRC) patients. Skin-toxicity secondary to cetuximab has been reported to be related to the activity of the cetuximab-based regimens.

Methods: In an academic multinational phase II study, chemo-naïve patients with unresectable mCRC received standard FOLFIRI (irinotecan 180mg/m2, leucovorin 400mg/m2, 5-FU 400mg/m2 bolus, 5-FU 2400mg/m2 infusion every 2 weeks) with cetuximab (250mg/m2 weekly after loading with 400mg/m2). If no cetuximab-related skin toxicity occurred by day (D)22 or 36 respectively, cetuximab was escalated to 350, then to 500mg/m2. Patients were tested K-Ras (codons 12, 13) wild-type to participate. Progression-free survival (PFS) rate at 9 months in the dose escalation group was the primary endpoint. Overall survival (OS), response rates (RR) and safety were secondary endpoints. Molecular exploratory analyses on tumour tissues and blood from consenting patients and pharmacokinetic evaluations were foreseen per protocol. The study was terminated early for low accrual in the escalation group.

Results: One hundred eight patients with median age 60 were included in five countries between Jan-2011 and Mar-2014; 90 (83%) had left-sided mCRC. Seven patients were discontinued before arm allocation. Eight were assigned to dose escalation on D22, and three escalated further on D36 based on the "no skin toxicity" criterion. Average dose exposure was 94% of the planned doses for cetuximab and 85-90% for all other drugs. Overall RR was 67% (95% CI_57-75) with 14 (13%) patients in complete response. Following tumour shrinkage, surgery with curative intent was performed in 19 (18%) patients with median disease-free interval of 9 months (range 1-57). PFS rates at 9 months and median PFS times will be reported at the meeting. Median OS of all patients was 30 months (95%CI_25-36) with 77% and 57% alive at one and two years. Standard and dose escalation schedules were generally well tolerated. Most serious adverse events (SAE) were due to mCRC, 12/76 were deemed related to study treatment (diarrhea, infection or hematological modifications). Six deaths unrelated to treatment were recorded during study treatment. Skin reactions during the first three weeks of treatment occurred at much higher rates than foreseen (over 90% instead of 30% estimated historically) leading to very low assignment to the escalation arm. Post study analyses showed K-Ras mutated tumours in 9 patients for other codons than initially tested, NRAS mutations in 3 patients and BRAF mutations in 4; 4 other patients presented ERBB2 amplification.

Conclusion: The Everest 2 study could not demonstrate that dose escalation of cetuximab in patients without early skin toxicity is a feasible strategy because most patients had skin reactions in the first three weeks. FOLFIRI in combination with cetuximab had an acceptable safety profile with good RR influenced by RAS mutation status. Secondary resections could be performed in a relatively high number of patients with initially unresectable disease. Patient selection by tumour molecular characteristics is needed for maximal benefit. Translational studies are ongoing. Conducted with financial support and medication from Merck BV, Belgium, affiliate of Merck KGaA, Darmstadt, Germany. Trial registration: EudraCT 2009-009992-36; NCT01251536.

O – 016 First-line FOLFOX plus panitumumab followed by 5-FU/LV plus panitumumab or single-agent panitumumab as maintenance therapy in patients with RAS wild-type metastatic colorectal cancer (mCRC): The VALENTINO study

F Pietrantonio[1], F Morano[2], S Corallo[3], A Raimondi[2], F Loupakis[4], C Cremolini[5], V Smiroldo[6], R Berenato[7], A Sartore Bianchi[8], M Tampellini[9], S Bustreo[10], M Clavarezza[11], R Murialdo[12], A Zaniboni[13], G Tomasello[14], G Peverelli[3], C Antoniotti[5], L Procaccio[15], S Cinieri[16], L Antonuzzo[17], M Di Bartolomeo[18], F de Braud[2]

[1]Department of Medical Oncology, IRCCS Fondazione Istituto Nazionale dei Tumori, Milan, Italy, [2]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [3]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [4]Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [5]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [6]Istituto Clinico Humanitas, Rozzano, Italy, [7]Department of Oncology, Fondazione I.R.C.C.S. Istituto Nazionale Tumori, Milan, Italy, [8]Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, and Università degli Studi di Milano, Milan, Italy, [9]AOU San Luigi Gonzaga, Orbassano, Italy, [10]Città della Salute e della Scienza di Torino, Turin, Italy, [11]Ospedale Galliera, Genoa, Italy, [12]Department of Oncology, Istituto di Ricerca a Carattere Clinico e Scientifico (IRCCS), Azienda Ospedaliera Universitaria San Martino - IST, Genoa, Italy, [13]Fondazione Poliambulanza, Brescia, Italy, [14]Department of Medical Oncology, Azienda Istituti Ospitalieri di Cremona, Cremona, Italy, [15]Istituto Oncologico Veneto, Padua, Italy, [16]Medical Oncology Unit,P.O. "A. Perrino" Hospital, Brindisi, Italy, [17]Medical Oncology, Careggi University Hospital, Florence, Italy, [18]Department of Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Introduction: Since mCRC registration first-line trials scheduled the continuation of doublets plus anti-EGFRs until progressive disease (PD), there is still no evidence if de-escalating treatment intensity after an anti-EGFR-based induction phase might be not inferior in terms of disease control, while reducing toxicity burden and improving quality of life. The MACRO-2 trial suggested that maintenance with cetuximab alone after mFOLFOX + cetuximab achieved a progression-free survival (PFS)% not inferior than mFOLFOX + cetuximab until PD in KRAS exon 2 wild-type patients.

Methods: 229 RAS wild-type unresectable mCRC patients were enrolled and received FOLFOX + panitumumab induction (8 cycles) followed, in absence of PD, by 1:1 randomly-assigned maintenance with panitumumab (arm B) or panitumumab + 5-FU/LV (arm A) until PD/unacceptable toxicity/death. The primary endpoint was to demonstrate the non-inferiority of 10-month (10-m) PFS% of arm B vs A. An overall sample size of 224 subjects (112 in the control group and 112 in the study group) achieved 90% power to detect a 50% 10-m PFS in arm A and a maximum 15% difference in arm B, with a significance level of 0.1 and a 15% drop-out rate. Secondary endpoints were safety, PROs, response rate, duration of response, time to treatment failure and overall survival.

Results: Will be provided after primary analysis with central RAS and BRAF molecular analyses.

Conclusion: NA

O – 017 FOLFOXIRI plus bevacizumab (bev) followed by maintenance with bev alone or bev plus metronomic chemotherapy (metroCT) in mCRC: Final results of the phase II randomized MOMA trial by GONO

F Marmorino[1], C Cremolini[1], F Bergamo[2], N Pella[3], C Antoniotti[1], D Rossini[1], E Dell'Aquila[4], G Masi[1], L Salvatore[1], F Loupakis[5], L Marcucci[6], D Gemma[7], G Cardellino[3], B Borelli[1], V Ricci[8], S Delfanti[9], E Mori[10], G Tonini[4], S Lonardi[5], G Fontanini[11], L Boni[12], A Falcone[13]

[1]Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [2]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [3]Department of Oncology, Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia, Udine, Italy, [4]Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy, [5]Medical Oncology Unit 1, Clinical and Experimental Oncology Department, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [6]U.O. Oncologia Medica, Azienda USL-5 Istituto Toscano Tumori, Pontedera, Italy, [7]Department of Medical Oncology, Hospital of Frosinone, Frosinone, Italy, [8]Medical Oncology, Oncology Department, S. Croce & Carle Teaching Hospital Cuneo, Cuneo, Italy, [9]Medical Oncology, Foundation IRCCS Policlinico San Matteo, Pavia, Italy, [10]SOC Oncologia Medica- Nuovo Ospedale di Prato "Santo Stefano" Az.USL Toscana Centro, Prato, Italy, [11]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy, [12]Clinical Trials Coordinating Center, Istituto Toscano Tumori, University Hospital Careggi, Florence, Italy, [13]University of Pisa, Pisa, Italy

Introduction: The MOMA study investigated whether the addition of metroCT to bev as maintenance treatment following 4 months of upfront therapy with FOLFOXIRI plus bev could improve PFS of mCRC patients. From May 2012 to March 2015, 232 patients, mostly RAS (65%) or BRAF (9%) mutant, were randomized in 16 Italian centers. The primary endpoint was not met. Here we provide final clinical results of the study including OS findings, subgroup analyses and treatments after progression.

Methods: Patients with unresectable mCRC were randomized 1:1 to receive up to 8 cycles of FOLFOXIRI plus bev, followed by bev (arm A), or the same induction followed by bev plus metroCT (capecitabine 500 mg/tid and cyclophosphamide 50 mg/die per os, arm B) until disease progression (PD). According to the comparative Rubinstein and Korn's design, estimating a first-line PFS of 11 months, to detect a HR of 0.75 favoring arm B, with 1 sided-alpha and beta errors of 15% and 80%, 173 events were required. In the case of PD during maintenance, the re-introduction of FOLFOXIRI plus bev or of a modified FOLFOXIRI plus bev regimen (i.e. FOLFOXIRI/FOLFOX or FOLFIRI plus bev) was recommended up to 4 cycles, followed by maintenance, according to randomization arm.

Results: At a median follow up of 43.9 months, 210 and 164 progression and death events were registered. No significant differences between arms were reported in terms of PFS (median PFS arm A/B: 9.4 / 10.3 months; HR: 0.94 [70%CI: 0.82-1.09], p = 0.680) and OS (median OS arm A/B: 28 / 22.5 months; HR: 1.16 [70%CI: 0.99-1.37], p = 0.336). Response rate with FOLFOXIRI plus bev was 63% (arm A/B: 68%/57%). No interaction effect between treatment arm and RAS/BRAF status or tumour sidedness was reported in PFS or OS. In the overall study population median PFS among RAS/BRAF wt (N = 36), RAS mutant (N = 150) and BRAF mutant (N = 20) patients were 10.2, 10.1 and 9.4 months (log-rank test, p = 0.759) and median OS were 31.3, 24.9 and 19.2 months, respectively (log-rank test, p = 0.457). 152 (72%) out of 210 patients with progression event received a treatment after PD. In 87 (57%) and 44 (29%) cases FOLFOXIRI plus bev or modified FOLFOXIRI plus bev were re-introduced, respectively. Main grade 3/4 adverse events occurring during the reintroduction of FOLFOXIRI plus bev were neutropenia (20%), diarrhea (9%), stomatitis (3%), vomiting (2%), hypertension (1%), and venous thrombosis (1%).

Conclusion: The addition of metroCT to maintenance with bev does not significantly improve PFS or OS of mCRC patients irrespective of their RAS/BRAF mutational status and tumour sidedness. Activity results of FOLFOXIRI plus bev are confirmed with a shorter treatment duration (4-months). Outcome results in the BRAF mutant subgroup are consistent with previous findings with the triplet plus bev. Re-introduction of FOLFOXIRI plus bev was feasible and associated with a favourable safety profile.

O – 018 Plasma miRNAs signature validation for early detection of colorectal cancer

M Herreros-Villanueva[1], S Durán-Sanchón[2], A Martín[1], R Pérez-Palacios[1], E Vila-Navarro[2], M Marcuello[2], M Díaz-Centeno[3], J Cubiella[4], M Diez[5], L Bujanda[6], A Lanas[7], R Jover[8], V Hernández[9], E Quintero[10], J Lozano[2], I Martínez[11], A Castells[12], M Gironella[2], R Arroyo[1]

[1]Amadix, Valladolid, Spain, [2]CIBERehd, Barcelona, Spain, [3]Hospital Clínic de Barcelona, Barcelona, Spain, [4]Complexo Hospitalario Universitario de Ourense, Ourense, Spain, [5]Hospital Universitario de Burgos, Burgos, Spain, [6]Hospital Donostia, San Sebastián, Spain, [7]Hospital Lozano Blesa, Zaragoza, Spain, [8]Hospital General Universitario de Alicante, Alicante, Spain, [9]Complejo Hospitalario Universitario de Vigo, Vigo, Spain, [10]Hospital Universitario de Canarias, La Laguna, Santa Cruz de Tenerife, Spain, [11]Owl Metabolomics, Derio, Spain, [12]Hospital Clinic, Barcelona, Spain

Introduction: Specific miRNA signatures in biological fluids can facilitate earlier detection of the tumors being then minimally invasive diagnostic biomarkers. Circulating miRNAs have also emerged as promising diagnostic biomarkers for CRC screening. In this study we investigated the performance of a specific signature of miRNA in plasma samples in order to design a robust predictive model able to distinguish healthy individuals from those with Colorectal cancer and Advanced Adenomas.

Methods: Case control study of 300 patients from eight Spanish hospitals including 100 healthy individuals, 101 diagnosed with advanced adenomas and 96 colorectal cancer cases. Real time quantitative reverse-transcriptase PCR was used to quantify a signature of miRNA (miR19a, miR19b, miR15b, miR29a, miR335, miR18a) in plasma samples. Binary classifiers (SVM linear, SVM radial, SVM polynomial) were built for the best predictive model.

Results: A receiving operating characteristic curve (AUC ROC) of 0.9159 was obtained retrieving a model with a sensitivity of 0.9375 and specificity of 0.7403, positive predictive valued (PPV) of 0.8710 and negative predictive value (NPV) of 0.8836 when controls were compared to patients with advanced neoplasm (colon cancer and advanced adenomas).

Conclusion: We identified and validated a signature of 6 miRNAs (miR19a, miR19b, miR15b, miR29a, miR335, miR18a) as predictors able to differentiate significantly patients with colon cancer and advanced adenomas from those who are healthy. This signature could be used for CRC screening purposes.

O – 019 PETACC-6: Preop chemoradiation and postop chemotherapy (capecitabine +/- oxaliplatin) in locally advanced rectal cancer: Overall survival after long term follow-up

H Schmoll[1], K Haustermans[2], T Price[3], B Nordlinger[4], R Hofheinz[5], J Daisne[6], J Janssens[7], B Brenner[8], P Schmidt[9], H Reinel[10], S Hollerbach[11], K Caca[12], F Fauth[13], C Hannig[14], J Zalcberg[15], N Tebbutt[16], M Mauer[17], S Marreaud[18], M Lutz[19], E Van Cutsem[20]

[1]Martin Luther University Halle-Wittenberg, Halle, Germany, [2]University Hospitals Leuven, Leuven, Belgium, [3]Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia, [4]Centre Hospitalier Universitaire Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt, France, [5]University Hospital Mannheim, Mannheim, Germany, [6]Université Catholique de Louvain, Namur, Belgium, [7]AZ Turnhout, Turnhout, Belgium, [8]Rabin Medical Center – Tel Aviv University, Petah Tiqva, Israel, [9]Staedt. Klinikum Neunkirchen, Neunkirchen, Germany, [10]Leopoldina-Krankenhaus der Stadt Schweinfurt GGMBH, Schweinfurt, Germany, [11]Allgemeines Krankenhaus Celle, Celle, Germany, [12]Klinikum Ludwigsburg, Ludwigsburg, Germany, [13]Onkologische Schwerpunktpraxis, Hanau, Germany, [14]Gemeinschaftspraxis Haematologie und Onkologie, Bottrop, Germany, [15]Peter MacCallum Cancer Centre, Melbourne, Australia, [16]Austin Hospital, Melbourne, Australia, [17]EORTC Headquarters, Brussels, Belgium, [18]na, na, Belgium, [19]Caritasklinik St. Theresa, Saarbruecken, Germany, [20]UZ Leuven-Campus Gasthuisberg, Leuven, Belgium

Introduction: The PETACC-6 trial investigated the role of oxaliplatin in combination with preoperative capecitabine-based chemoradiation (CRT) and postoperative capecitabine (CT) to improve disease-free and overall survival (DFS, OS) in locally advanced rectal cancer.

Methods: 1090 patients with locally advanced rectal cancer (within 12 cm from the anal verge, T3/4 and/or node-positive, no metastatic disease, potentially resectable) have been randomized between 11/2008 and 09/2011 in Europe and Australia. The primary analysis was intent-to-treat adjusted for stratification factors (clinical T category, nodal status, distance from the tumor to the anal verge, method of locoregional staging).

Results: 1069 patients are evaluable. DFS has been reported (Schmoll H et al, Proc ASCO 2014) after a medium follow-up of 31 months, without difference: HR: 1.036 (CI 0.806 – 1.331, p 0.78); 3yrs DFS 74.5% vs 73.9%. However, there was a striking difference in outcome with significant improvement of DFS by oxaliplatin for the subgroup of non-German (N = 353) vs. the German patients (N = 728), with a reciprocal effect with borderline significant superior DFS for the control group.

Conclusion: The overall survival analysis was planned, as specified in the protocol, after a minimum follow-up of 5 years from the last "patient in". The survival data are now available after a minimum follow-up of 5 years and a maximum of 10 years (data lock 02/18). Evaluation of all data including DFS and OS for all subgroups and multivariate analysis for prognostic factors, with particular reference to the German and non-German group is ongoing. The final outcome data of the trial will be presented at the meeting.

O – 020 Activity of larotrectinib in patients with TRK fusion GI malignancies

M Nathenson[1], G Demetri[2], U Lassen[3], D Hong[4], V Boni[5], J Deeken[6], A Dowlati[7], M Cox[8], N Ku[8], S Cruickshank[8], H Qamoos[8], A Drilon[9]

[1]Dana-Farber Cancer Institute, Boston, Massachusetts, USA, [2]Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA, [3]Rigshospitalet - Copenhagen University Hospital, Copenhagen, Denmark, [4]UT MD Anderson Cancer Center, Houston, Texas, USA, [5]START Madrid-CIOCC, Madrid, Spain, [6]Inova Translational Medicine Institute, Falls Church, Virginia, USA, [7]University Hospitals of Cleveland Medical Center, Cleveland, Ohio, USA, [8]Loxo Oncology, South San Francisco, California, USA, [9] Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, New York, USA

Introduction: TRK fusions arise from aberrant rearrangements of neurotrophic receptor kinase genes NTRK1-3 with a variety of gene partners; these are constitutively active ligand-independent oncogenic drivers in a broad range of solid tumors. The highly selective TRK inhibitor larotrectinib achieved objective responses of 75% by independent review (80% by investigator assessment) in patients with a wide variety of TRK fusion cancers (Drilon et al., NEJM, 378:731-739, 2018). We report here on the activity and safety of larotrectinib in the treatment of GI malignancies from three separate studies (NCT02122913, NCT02637687, and NCT02576431).

Methods: Patients with locally advanced or metastatic solid tumors who had received prior standard therapy or had no treatment alternatives were eligible. Evidence of a NTRK gene fusion as detected by CLIA or equivalently certified laboratory was required. Larotrectinib (100 mg or 150 mg po bid) was administered until disease progression, withdrawal, or unacceptable toxicity. Disease status was assessed by investigators and by independent radiologic review using RECIST version 1.1.

Results: As of 17th July 2017, a total of 55 patients across 17 cancer types were enrolled in the overall study and constitute the safety population. A sub-group of 12 patients (age range 32-74 years) had a GI malignancy, including 4 with colorectal cancer, 3 with GIST, 2 with cholangiocarcinoma, and one each with adenocarcinoma of the appendix, pancreas and a peri-rectal soft tissue sarcoma. Nine of those patients had fusions involving NTRK1; all 3 GIST patients had ETV6-NTRK3 gene fusions. Objective responses were documented in 8 of 12 patients (75%; per investigator), including colon cancer, pancreatic carcinoma, cholangiocarcinoma and GIST, with one complete response (GIST) and 7 partial responses. Stable disease noted as best response in 3 patients including a patient with appendiceal cancer, and one patient with cholangiocarcinoma exhibited primary progressive disease. Responses were rapid with maximum time to first response < 2 months. Duration of response ranged from 3.5 months (pancreas) to 22.9 months (GIST; ongoing). Adverse events across all study patients were principally grade 1 or 2. The most common grade 3 events were anemia (11%), increased ALT or AST (7%), increased body weight (7%), or decreased neutrophil count (7%). No patient discontinued larotrectinib due to a drug-related adverse event.

Conclusion: TRK inhibition with larotrectinib in patients with TRK fusion GI malignancies was well tolerated and resulted in rapid induction of durable responses

O – 021 Safety and antitumor activity of pembrolizumab in patients with advanced microsatellite instability–high (MSI-H) colorectal cancer: KEYNOTE-164

D Le[1], P Kavan[2], T Kim[3], M Burge[4], E Van Cutsem[5], H Hara[6], P Boland[7], J Van Laethem[8], R Geva[9], H Taniguchi[10], T Crocenzi[11], M Sharma[12], C Atreya[13], L Diaz[14], L Liang[15], P Marinello[15], T Dai[15], B O'Neill[16]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland, USA, [2]McGill University Health Center, Montreal, Quebec, Canada, [3]Asan Medical Center, Seoul, Republic of Korea, [4]Royal Brisbane and Women's Hospital, Herston, Australia, [5]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium, [6]Saitama Cancer Center, Kitaadachi, Japan, [7]Roswell Park Cancer Institute, Buffalo, New York, USA, [8]Hôpital Universitaire Erasme, Brussels, Belgium, [9]Sourasky Medical Center, Tel Aviv-Yafo, Israel, [10]Aichi Cancer Center Hospital, Nagoya, Japan, [11]Providence Cancer Center, Portland, Oregon, USA, [12]The University of Chicago Medicine, Chicago, Illinois, USA, [13]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California, USA, [14]Memorial Sloan Kettering Cancer Center, New York, New York, USA, [15]Merck & Co., Inc., Kenilworth, New Jersey, USA, [16]IU Health University Hospital, Indianapolis, Indiana, USA

Introduction: Approval of pembrolizumab as treatment for adult and pediatric patients with unresectable or metastatic previously treated MSI-H or mismatch repair–deficient cancer, regardless of tumor type or site, was partly based on data from cohort A of the phase 2 KEYNOTE-164 (NCT02460198) study of patients with MSI-H colorectal cancer (CRC) after ≥2 prior lines of standard therapy. Data are presented herein from cohort B of KEYNOTE-164, which was conducted to evaluate pembrolizumab in patients with metastatic MSI-H CRC previously treated with ≥1 line of therapy.

Methods: Cohort B of the KEYNOTE-164 study enrolled patients with metastatic CRC who had locally confirmed MSI-H status per immunohistochemistry or polymerase chain reaction and had received ≥1 prior line of therapy (irinotecan, oxaliplatin, fluoropyrimidine, or anti-vascular endothelial growth factor/endothelial growth factor receptor). Patients received pembrolizumab 200 mg every 3 weeks (Q3W) for 2 years or until progression, unacceptable toxicity, or withdrawal of consent. Tumor response was assessed per RECIST v1.1 by independent review Q9W. End points included objective response rate (ORR) (primary) and duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety (secondary).

Results: Sixty-three patients were enrolled; median age was 59 years (range: 23-83); 52% were male. Most patients (94%) had ≥1 prior therapy for advanced disease; median number of prior therapies was 2. As of September 12, 2017, median follow-up was 12.6 months (range: 0.1-15.4). ORR was 32% (95% CI, 21-45), with 2 complete responses and 18 partial responses. Median DOR was not reached (NR); 95% of responses were ongoing; and DOR for 75% of responders was ≥6 months. Median PFS was 4.1 months (95% CI, 2.1-NR) and median OS was NR. The 12-month PFS rate was 41% and the 12-month OS rate was 76%. Forty (64%) patients experienced treatment-related adverse events (AEs) of any grade, most commonly (≥10%) fatigue (18%), hypothyroidism (16%), and hyperthyroidism (11%). Seven (11%) patients had grade ≥3 treatment-related AEs of anemia, thrombocytopenia, diarrhea, pneumatosis intestinalis, pneumonitis, syncope, arthritis, and vasculitis (n = 1 each). There were no treatment-related deaths. Twenty (32%) patients had immune-mediated AEs of any grade. Two (3%) patients had grade ≥3 immune-mediated AEs of pneumonitis and colitis (n = 1 each).

Conclusion: Pembrolizumab demonstrated durable antitumor activity with a safety profile that was manageable in cohort B of KEYNOTE-164, which was conducted to evaluate patients with MSI-H CRC whose disease progressed after ≥1 line of prior therapy.

O – 022 Phase II study evaluating trifluridine/tipiracil + bevacizumab and capecitabine + bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): Results of the primary analysis

K Lesniewski-Kmak[1], V Moiseenko[2], M Saunders[3], H Wasan[4], G Argiles[5], C Borg[6], G Creemers[7], M Fedyanin[8], R Glynne-Jones[9], P Pfeiffer[10], C Punt[11], D Stroyakovskiy[12], A Ten Tije[13], A Van de Wouw[14], A Kanehisa[15], R Fougeray[15], N Lopez Busto[15], N Amellal[16], E Van Cutsem[17]

[1]Szpitale Wojewodzkie w Gdyni/Gdansk Medical University, Gdynia, Poland, [2]Saint-Petersburg Scientific Practical Center for Specialized Medical Care (oncological), St.Petersburg, Russian Federation, [3]Christie Hospital NHS Foundation Trust, Manchester, UK, [4]Hammersmith Hospital, Department of Cancer Medicine, London, UK, [5]Department of Medical Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain, [6]University Hospital Besançon, Besançon, France, [7]Catharina Hospital, Eindhoven, Netherlands, [8]N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation, [9]Mount Vernon Centre for Cancer Treatment, London, UK, [10]Department of Oncology, Odense University Hospital, Odense, Denmark, [11]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [12]Moscow City Oncology Hospital N62, Moscow, Russian Federation, [13]Amphia Hospital Breda, Breda, Netherlands, [14]VieCuri Medisch Centrum Noord-Limburg, Venlo, Netherlands, [15]Institut de Recherches Internationales Servier, Suresnes, France, [16]Servier Oncology, Suresnes, France, [17]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

Introduction: Trifluridine/tipiracil, also known as TAS-102, is a novel chemotherapy approved in patients with mCRC refractory to, or not candidates for standard therapies. A phase I/II study evaluated the combination of trifluridine/tipiracil and bevacizumab in mCRC patients who were refractory to standard therapies and showed encouraging antitumor activity with manageable toxicity (C-TASK FORCE) (Kuboki Y et al. Lancet Oncology, 2017). These promising results led to the initiation of a global non-comparative phase 2 study, TASCO1, to evaluate the efficacy and safety of trifluridine/tipiracil + bevacizumab (TT-B) and capecitabine + bevacizumab (C-B) in first-line unresectable mCRC patients who are non-eligible for standard first-line therapy.

Methods: First-line mCRC-patients not candidate for intensive oxaliplatin- or irinotecan-based chemotherapy and without chance for curative resection according to the investigator's judgment were randomized (in a 1:1 ratio; stratified by RAS status, ECOG performance status and country) to receive trifluridine/tipiracil (35 mg/m^2 given orally bid on days 1–5 and 8–12 in a 28-day cycle) plus bevacizumab (5 mg/kg on days 1 and 15 of a 28-day treatment cycle) or capecitabine (1250 or 1000 mg/m^2/dose bid on days 1-14 in a 21-day) plus bevacizumab (7.5 mg/kg on day 1 in a 21-day treatment cycle). The primary endpoint was progression-free survival, the secondary endpoints included overall survival, safety and quality of life assessed by EORTC QLQ-C30 and QLQ-CR29 questionnaires.

O – 023 FOLFOX/bevacizumab +/- irinotecan in advanced colorectal cancer (CHARTA): Long term outcome

H Schmoll[1], B Garlipp[2], C Junghanß[3], A Vogel[4], U Kaiser[5], A Florschütz[6], S Kanzler[7], C Hannig[8], F Meinert[1], F Cygon[1], A Stein[9]

[1]Martin Luther University Halle-Wittenberg, Halle, Germany, [2]Uniklinik Magdeburg, Magdeburg, Germany, [3]Universität Rostock, Rostock, Germany, [4]Hannover Medical School, Hannover, Germany, [5]Bernward Krankenhaus, Hildesheim, Germany, [6]Städtisches Klinikum Dessau, Onkologie, Dessau, Germany, [7]Leopoldina-Krankenhaus Schweinfurt, Med. Klinik II, Schweinfurt, Germany, [8]Gemeinschaftspraxis Haematologie und Onkologie, Bottrop, Germany, [9]University Medical Center Hamburg, Hamburg, Germany

Introduction: FOLFOXIRI/bevacizumab (Bev) was superior to FOLFIRI/Bev in the TRIBE trial. However the comparison with FOLFOX/Bev as the alternative standard was not proven. The CHARTA trial was developed in parallel to TRIBE, but with FOLFOX/Bev as control arm; for comparison reasons TRIBE and CHARTA used the same dose and schedule.

Methods: From 7/11 to 12/14 250 patients were randomized, including ECOG 0-2, $\geq$ 1 measurable lesion > 1cm, stratified by ESMO-Group 1,2,3. Induction: 6 months, maintenance capecitabine+Bev until progression or max. 12 months, at P reinduction by investigators decision. 25% dose reduction was allowed in cycle 1 + 2 on the investigator's discretion. Primary EP: significant improvement of PFS-rate @ 9 months ($p < 0.1$, 2-sided Fisher's-exact test); secondary EP: RR, PFS, OS, toxicity.

Results: 241 pts (1 not elig., 8 prot. violation) are evaluable and have been previously presented after a follow up of 31.4 (0.1-51) months (Schmoll et al, World GI 2017). The Primary Endpoint was met: PFS @ 9 months 56% vs. 68%, $p = 0.086$. PFS was improved: 9.8 vs. 12.0 months, HR 0.7 (ns.), identical to TRIBE with 9.7 vs. 12.1 months. Response rate (A/B): CR: 5%/5%, CR/PR 60%/70%, SD 25%/21%, PD 14%/9%. OS was not significant different (24 vs 28). Toxicity was low to moderate without major differences except grade ¾ diarrhea (12%/16%) and neutrophils (14%/20%). Clinical/molecular prognostic or predictive factors are equally distributed (stratified by ESMO groups). PFS was significantly improved ($p = 0.027$) in the subgroup of pts. with synchronous metastases (91% of pts); the strongest improvement by the 4-drug combination was shown in those pts. with synchronous mets., who never had resection of the primary (52% of the pts.): 17 vs. 26.5 mos. ($p < 0.01$). In the subgroup of "liver/lung only" there was no difference, however with a long OS in both arms (45.3 / 44.2 mos.). In univariate analysis there are major, but mostly not significant differences in RR/ PFS in most subgroups (borderline significant: risk score high HR 0.66; ESMO group 3 HR 0.62; BRAF HR 0.72; right location HR 0.73), however, not strong enough to safely identify patients with high potential to benefit from the 4-drug combination.

Conclusion: After 12 further months of follow-up with a median of 38 with a maximum of 7 years. All data for PFS and OS are mature and ready for final evaluation, including clinical and molecular subgroup and multivariate analyses as well data on reinduction and salvage treatments. Translational research is ongoing. The final clinical data will be available at the meeting.

O – 024 mFOLFOXIRI + Panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild- type metastatic colorectal cancer m(CRC): a randomized phase II VOLFI trial of the AIO (AIO-KRK0109)

M Geissler[1], T Klingler[2], J Riera-Knorrenschield[3], A Tannapfel[4], T Seufferlein[5], S Held[6], A Florschütz[7], S Kanzler[8], V Heinemann[9], A Reinacher-Schick[10], U Martens[11]

[1]Klinikum Esslingen, Cancer Center Esslingen, Esslingen, Germany, [2]Klinikum Esslingen, Hämatologie/Onkologie, Esslingen, Germany, [3]Philips-Universität Marburg, Onkologie, Marburg, Germany, [4]Department of Pathology, Ruhr-University Bochum, Bochum, Germany, [5]Department of Internal Medicine I, University of Ulm, Ulm, Germany, [6]Clinassess, Leverkusen, Germany, [7]Städtisches Klinikum Dessau, Onkologie, Dessau, Germany, [8]Leopoldina-Krankenhaus Schweinfurt, Med. Klinik II, Schweinfurt, Germany, [9]Comprehensive Cancer Center, Krebszentrum München, Munich, Germany, [10]Ruhr University, Bochum, Germany, [11]Dept. of Hematology/Oncology, Cancer Center Heilbronn-Franken, Heilbronn, Germany

Introduction: Triple chemotherapy with an anti-EGFR reported promising activity with some safety concerns in single arm phase II trials. This trial evaluated activity and safety of mFOLFOXIRI + panitumumab vs FOLFOXIRI in ECOG 0-1, primarily non-resectable mCRC patients.

Methods: Prospective 2:1 randomized, multi-center, phase II trial comparing mFOLFOXIRI (Ox 85 mg/m2, Iri 150 mg/m2, 5-FU 3000mg/m2 cont. 48h, LV 200 mg/m2) + panitumumab 6 mg/KG (arm A) with FOLFOXIRI (Ox 85 mg/m2, Iri 165 mg/m2, 5-FU 3200mg/m2 cont. 48h, LV 200 mg/m2; arm B), both arms q2w. Cohort 1: irresectable mCRC; cohort 2: chance of secondary resection of metastatic lesions. Primary endpoint was ORR, secondary endpoints were secondary resection rate (cohort 2), DCR, PFS, OS, toxicity, quality of life (QLQ-C30). Financially supported by an unrestricted grant from Amgen.

Results: A total of 96 patients were randomized (63 arm A, 33 arm B). ORR was 85.7% in arm A and 54.5% in arm B ($p = 0.0013$, OR 5.000; 95%-CI 1.870-13.370). DCR was 96.8% in arm A and 78.8% in arm B ($p = 0.0071$, OR 8.212). ORR in Arm A was 90.6% versus 60.0% ($p = 0.0288$, OR 6.400) and in Arm B 60.0% versus 50% (p = n.s.) for left and right located CRC, respectively. ORR between arms A and B comparing left and right sided CRC was 90.6% versus 60.0% ($p = 0.0039$, OR 6.400; 95%-CI 1.889-21.679) and 60.0% versus 50.0% (p = n.s.), respectively. Secondary resections in cohort 2 were 60% ($n = 12$) and 36.4% ($n = 4$) in arms A and B, respectively. Treatment related serious adverse advents grade 3-5 occurred in 32.8% and 12.1% in arms A and B, respectively ($p = 0.0297$). Nevertheless, no differences in global health status, functional scales, and symptom scales were reported.

Conclusion: mFOLFOXIRI plus panitumumab results in significantly higher response rates compared to FOLFOXIRI in RAS wild-type mCRC. Strong effectivity was observed also in right sided and BRAF mutated CRC. High secondary resection rates could be achieved. Although toxicity (treatment related SAEs) was increased, QL reporting was similar in both arms. Final PFS, AEs, and dosing data will be presented at the meeting.

O – 025 Association between tumor mutation burden (TMB) and MLH1, PMS2, MSH2, and MSH6 alterations in 395 microsatellite instability-high (MSI-High) gastrointestinal (GI) tumors

M Salem[1], A Grothey[2], R Goldberg[3], J Xiu[4], W Korn[4], A Shields[5], J Hwang[1], P Philip[6], H Lenz[7], J Marshall[1]

[1]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, District of Columbia, USA, [2]Mayo Clinic, Rochester, Minnesota, USA, [3]Comprehensive Cancer Center at The Ohio State University, Columbus, Ohio, USA, [4]Caris Life Sciences, Phoenix, Arizona, USA, [5]Karmanos Cancer Center, Detroit, Michigan, USA, [6]Karmanos Cancer Center, Detroit, Michigan, USA, [7]USC Norris Comprehensive Cancer Center, Los Angeles, California, USA

Introduction: Correlation between TMB and objective response to checkpoint inhibitors has been shown. MSI-High tumors usually exhibit high TMB. Relationship between the level of TMB and alterations in the four-mismatch repair deficiency (MMR) genes in gastrointestinal tumors has not been comprehensively studied.

Methods: MSI-High status was determined by examining altered microsatellite (MS) loci using NextGen sequencing (cutoff: > =46) on a 592-gene panel. TMB was calculated by enumerating somatic missense mutations. MMR protein expression was evaluated by IHC. ANOVA and chi-square tests were used for comparisons.

Results: In total, 395 MSI-High gastrointestinal tumors were examined. High TMB ($\geq$ 17 mutations/megabase [mt/MB]) was seen in 89% of the MSI-High tumors. Overall, MSI-High CRC exhibited the highest TMB compared to "all other MSI-High gastrointestinal cancers" (39 vs. 27 mt/MB, respectively, $p < 0.0001$). Left-sided MSI-High tumors had a higher TMB compared to right-sided tumors (51 vs. 35 mt/MB, $p = 0.01$). No significant differences were observed in TMB between BRAF V600 mutant and wild type MSI-High CRC (38.7 vs. 39 mt/MB). Significant association between the microsatellite loci and TMB (Rho=0.60, $p < 0.0001$) was observed. The mean TMB among MSI-High gastrointestinal tumors were as follow: 39 (mt/MB) CRC, 33 (mt/MB) gastric adenocarcinomas, 31 (mt/MB) small bowel adenocarcinomas, and 29 (mt/MB) in esophageal, GEJ, and pancreatic cancers, and cholangiocarcinoma. The most frequently altered (IHC loss or mutation) MMR genes in the MSI-High gastrointestinal tumors were MLH1 and PMS2. In CRC, MSH2 was more frequently altered in left-sided than right-sided tumors (45% vs. 12%), as was MSH6 (67% vs. 40%), $p = 0.01$. In fact MLH1, PMS2, MSH2 and MSH6 gene alterations varied significantly across MSI-H gastrointestinal tumors: CRC 72%, 83%, 21% and 49%; left-sided CRC, 47%, 55%, 45%, 67%; right-sided CRC, 80%, 91%, 12%, 40%; gastric adenocarcinomas, 80%, 86%, 13% and 35%; esophageal and GEJ adenocarcinomas, 100%, 100%, 0% and 13%; small bowel adenocarcinomas, 79%, 75%, 29% and 43%; pancreatic adenocarcinomas, 50%, 60%, 50%, 42%; cholangiocarcinoma, 83%, 80%, 33% and 60%; respectively. Generally, MSH2 or MSH6 alterations were associated with higher TMB (49 and 44 mt/MB, respectively) than MLH1 or PMS2 (33 mt/MB for both), $P < 0.0001$. Furthermore, tumors with a MSH2/MSH6 co-alteration had a significantly higher TMB compared to those with a MLH1/PMS2 co-alteration (51 mt/MB vs. 31, $p < 0.0001$). However, no significant difference was observed in the level of TMB among MSI-High tumors that exhibited a MSH2/MSH6 co-alteration (52 mt/MB), a MSH2 alteration (51 mt/MB), or a MSH6 (48 mt/MB), $p = 0.95$.

Conclusion: Among MSI-High gastrointestinal cancers, CRC exhibited the highest TMB level, and left-sided tumors exhibited higher TMB than right-sided tumors. MSH2 and/or MSH6 alterations were associated with a significantly higher TMB than MLH1/PMS2 alterations across all gastrointestinal cancer types. Additional analysis to assess the correlation between specific MMR gene alterations and response to checkpoint inhibitors is underway.

O – 026 Total circulating cell-free DNA (cfDNA) as a prognostic biomarker in metastatic colorectal cancer prior to first-line oxaliplatin-based chemotherapy

J Hamfjord[1], T Guren[1], O Dajani[1], B Glimelius[2], H Sorbye[3], P Pfeiffer[4], T Christoffersen[5], O Lingjærde[5], K Tveit[1], E Kure[1], N Pallisgaard[6], K Spindler[7]

[1]Oslo University Hospital, Oslo, Norway, [2]Uppsala University, Uppsala, Sweden, [3]Haukeland University Hospital, University of Bergen, Bergen, Norway, [4]Department of Oncology, Odense University Hospital, Odense, Denmark, [5]University of Oslo, Oslo, Norway, [6]Zealand Hospital, Roskilde, Roskilde, Denmark, [7]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Introduction: Small fragments of circulating cell-free DNA (cfDNA) can be detected in blood from cancer patients. Previous studies have shown a prognostic value mainly prior to second and subsequent lines of metastatic colorectal cancer (mCRC). We aimed to analyze the prognostic value of total plasma cfDNA in a patient population prior to first-line oxaliplatin-based chemotherapy for non-resectable mCRC in the NORDIC-VII study.

Methods: A total of 547 patients had blood samples available for pre-treatment quantification of total cfDNA. Plasma samples were used for DNA purification and quantification of total cfDNA by droplet digital polymerase chain reaction (measuring beta-2-microglobulin DNA concentration) with controls for contamination from normal lymphocytes. Clinical endpoint was overall survival (OS).

Results: Total cfDNA levels were successfully quantified in plasma from 499 patients, 48 samples were excluded mainly due to lymphocyte contamination. The median level was 7,833 alleles per mL plasma (range 1,050 – 1,645,000). High total cfDNA levels were associated with poor performance status, intact primary tumor and presence of liver metastases. There was no significant difference in cfDNA levels according to treatment arms. When dividing patients into groups of cfDNA quartiles, worse survival was seen with increasing pre-treatment levels of total cfDNA ($p < 0.001$). Patients with total cfDNA above median levels (n = 250) had an OS of 16.1 months (95% CI 14.4 – 17.8) compared to patients with below median levels (n = 249) with an OS of 25.1 months (95% CI 22.4 –27.8, $p < 0.001$). In a Cox regression multivariate analysis (n = 496), total cfDNA level remained an independent prognostic marker ($p = 0.001$) after adjusting for performance status, carcinoembryonic antigen (CEA) and alkaline phosphatase (ALP) levels.

Conclusion: The level of total cfDNA in plasma has prognostic value in patients with mCRC prior to first-line oxaliplatin-based chemotherapy.

O – 027 BEACON CRC study safety lead-in: Assessment of the BRAF inhibitor encorafenib + MEK inhibitor binimetinib + anti–epidermal growth factor receptor antibody cetuximab for BRAFV600E metastatic colorectal cancer

E Van Cutsem[1], P Cuyle[2], S Huijberts[3], J Schellens[4], E Elez[5], R Yaeger[6], M Fakih[7], C Montagut[8], M Peeters[9], J Desai[10], T Yoshino[11], F Ciardiello[12], H Wasan[13], K Maharry[14], J Christy-Bittel[14], A Gollerkeri[14], S Kopetz[15], A Grothey[16], J Tabernero[17]

[1]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium, [2]Imelda Ziekenhuis, Bonheiden, Belgium, [3]Netherlands Cancer Institute, Amsterdam, Netherlands, [4]The Netherlands Cancer Institute, Amsterdam, Netherlands, [5]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain, [6]Memorial Sloan-Kettering Cancer Center, New York, New York, USA, [7]City of Hope, Duarte, California, USA, [8]Department of Medical Oncology, Hospital Universitari del Mar, Barcelona, Spain, [9]Department of Oncology, Antwerp University Hospital, Edegem, Belgium, [10]Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Walter and Eliza Hall Institute, Parkville, Australia, [11]National Cancer Center Hospital East, Kashiwa, Japan, [12]University of Campania, Naples, Italy, [13]Hammersmith Hospital, Department of Cancer Medicine, London, UK, [14]Array BioPharma Inc., Boulder, Colorado, USA, [15]UT MD Anderson Cancer Center, Houston, Texas, USA, [16]Mayo Clinic, Rochester, Minnesota, USA, [17]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain

Introduction: The BRAFV600E mutation, which occurs in 10%–15% of patients with metastatic colorectal cancer (mCRC), confers a poor prognosis. After failure of first-line approaches, standard therapies in such patients provide limited benefits, with objective response rates (ORRs) <10%, progression-free survival (PFS) of ~2 months, and overall survival (OS) of 4–6 months. BEACON CRC (NCT02928224) is an ongoing phase 3 trial with a primary endpoint of OS for the BRAF inhibitor encorafenib (ENCO) + MEK inhibitor binimetinib (BINI) + anti–epidermal growth factor receptor (EGFR) antibody cetuximab (CETUX) vs control arm (irinotecan/CETUX or FOLFIRI/CETUX) in patients with BRAFV600E mCRC with disease progression after 1–2 previous regimens. To assess the safety and efficacy of the ENCO + BINI + CETUX triplet, a safety lead-in (SLI) was conducted in the BEACON CRC trial.

Methods: Patients received ENCO 300 mg QD + BINI 45 mg BID+ CETUX 400 mg/m2 (initial dose) then 250 mg/m2 QW. Assessments included efficacy (ORR, duration of response, time to response, PFS, ORR, and OS), safety, tolerability, and changes in tumor markers CEA and CA19-9 (evaluated by central laboratory based on blood samples collected on cycle 1 day 1 and day 1 of subsequent cycles, and at end of treatment). Current data reflect patient study drug exposure of up to 11.9 (median: 7.8) months. Updated safety and efficacy from the SLI, including the first analysis of OS, will be presented at the meeting.

Results: Of 30 patients receiving the triplet combination, BRAFV600E mutation was detected in 29. Among these, confirmed ORR (complete response [CR] + partial response) occurred in 14/29 (48%) patients, including CR in 3/29 patients. Responses were ongoing in 6/14 responding patients (43%) at the time of data cutoff; the remaining 15 patients achieved a best response of stable disease (SD; 9 patients [60%] had prolonged SD $\geq$ 6 months). Preliminary estimated median PFS was 8.0 months (95% CI, 5.6–8.5) and similar in patients who had 1 vs 2 previous regimens (7.6 vs 8.1 months, respectively). Among the 30 treated patients, grade 3/4 AEs (in $\geq$ 10%) were fatigue (13%), urinary tract infection (10%), increased aspartate aminotransferase (AST; 10%), and increased blood creatine phosphokinase (10%); of these, all were grade 3 except for grade 4 AST in 1 patient. Grade 3/4 skin-related AE (grade 3 rash) occurred in 1 patient (3%).

Conclusion: The ENCO + BINI + CETUX triplet combination was well tolerated, with AEs consistent with known toxicities of BRAF, MEK, and EGFR inhibitors. Efficacy outcomes showed substantial improvements over historical data in patients with BRAFV600E mCRC, with PFS exceeding OS achieved with current standards of care. The phase 3 portion of the BEACON CRC trial has been initiated, with enrollment ongoing.

O – 028 Long-term effect of peripheral sensory neuropathy (PSN) of 3 or 6 months oxaliplatin-based adjuvant chemotherapy for stage III colon cancer: ACHIEVE as part of the IDEA collaboration

S Takeuchi[1], T Yoshino[2], T Yamanaka[3], M Kotaka[4], D Manaka[5], T Eto[6], J Hasegawa[7], A Takagane[8], M Nakamura[9], T Kato[10], Y Munemoto[11], H Bando[12], H Taniguchi[13], M Gamoh[14], M Shiozawa[15], S Saji[16], Y Maehara[17], T Mizushima[18], A Ohtsu[2], M Mori[19]

[1]Teine-Keijinkai Hospital, Sapporo, Japan, [2]National Cancer Center Hospital East, Kashiwa, Japan, [3]Yokohama City University School of Medicine, Yokohama, Japan, [4]Department of Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan, [5]Department of Surgery, Gastrointestinal Center, Kyoto Katsura Hospital, Nishikyo-ku, Japan, [6]Department of Gastroenterology, Tsuchiura Kodo General Hospital, Tsuchiura, Japan, [7]Department of Surgery, Osaka Rosai Hospital, Sakai, Japan, [8]Hakodate Goryoukaku Hospital, Hakodate, Japan, [9]Aizawa Comprehensive Cancer Center, Aizawa Hospital, Matsumoto, Japan, [10]Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan, [11]Fukui-ken Saiseikai Hospital, Fukui, Japan, [12]Ishikawa Prefectural Central Hospital, Kanazawa, Japan, [13]Department of Surgery, Kyoto Second Red Cross Hospital, Kamigyo-ku, Japan, [14]Department of Medical Oncology, Osaki Citizen Hospital, Osaki-shi, Japan, [15]Kanagawa Cancer Center, Gastrointestinal Surgery, Asahi-ku, Japan, [16]Japanese Foundation for Multidisciplinary Treatment of Cancer, Koto-ku, Japan, [17]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [18]Osaka University Graduate School of Medicine, Suita, Japan, [19] Osaka University Graduate School of Medicine, Suita, Japan

Introduction: ACHIEVE, a part of the IDEA collaboration, was a multicenter study randomizing patients with stage III resected colon cancer to either 3 or 6 months of mFOLFOX6/CAPOX. Previous our report showed that the frequency of PSN during the treatment was markedly lower in the 3 months arm. As many patients undergoing adjuvant chemotherapy are cured and will survive long-term, irreversible PSN is a significant issue. The present study thus aimed to evaluate the frequency of long-lasting PSN in the 3 months arm as compared to the 6 months arm.

Methods: ACHIEVE enrolled 1313 patients in Japan from August 2012 through June 2014 and, of those, 1291 pts received the study treatment (modified ITT population). The hazard ratio of disease-free survival between 3 versus 6 months arm was previously reported to be 0.95 (95%CI, 0.76—1.20), implying an equivalent efficacy between the two arms. The frequency of PSN was evaluated every 3 months after the study treatment up to three years. The grade of PSN was assessed using CTCAE ver 4.0.

Results: During the study treatment, PSN of grade 2/3 was observed more frequently in the 6 months arm (30%/6%) than in the 3 months arm (13%/1%). At two years after the treatment, PSN of grade 1/2/3 lasted in 31.6%/2.6%/0.5% of pts in the 6 months arm whereas 13.7%/0.2%/0.0% of patients in the 3 months arm. At three years after the treatment, PSN of grade 1/2/3 lasted in 21.5%/2.5%/0.3% of patients in the 6 months arm whereas 9.7%/0.0%/0.0% of patients in the 3 months arm. The peak neurotoxicity in the 6-month arm occurs at 6 months, and in the 3-month arm occurs at 3 months.

Conclusion: In the 3-month arm, grade 2 or greater PSN was not observed at 3 years after the treatment. The frequency of grade 1 PSN lasting for three years was decreased to about a half (21.5% -> 9.7%) in the 3rd month as compared to the 6-month arm. The 3 months oxaliplatin-based adjuvant chemotherapy can bring a substantial reduction in long-term neuropathy and potential improvement in quality of life to patients without undermining the efficacy.

O – 029 The impact of combining Selective Internal Radiation Therapy (SIRT) with sorafenib on overall survival in patients with advanced hepatocellular carcinoma: The SORAMIC trial palliative cohort

J Ricke[1,2], B Sangro[3], H Amthauer[4], I Bargellini[5], P Bartenstein[6], E De Toni[6], A Gasbarrini[7], HJ Klumpen[8], M Peck[9], P Popovic[10], O Rosmorduc[11], E Schott[12], C Verslype[13], P Malfertheiner[1,2]

[1]Ludwig-Maximilians University Munich, Munich, Germany, [2]University Hospital Magdeburg, Magdeburg, Germany, [3]Clinica Universidad de Navarra, Pamplona, Spain, [4]Charite University Hospital Berlin, Berlin, Germany, [5]University of Pisa, Pisa, Italy, [6]Ludwig-Maximilians University Munich, Munich, Germany, [7]Catholic University of Rome, Rome, Italy, [8]Academic Medical Center, Amsterdam, Netherlands, [9]Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria, [10]Ljubljana University Medical Centre, Ljubljana, Slovenia, [11]University Hospital St. Antoine, Paris, France, [12]Charite University Hospital, Berlin, Germany, [13]University Hospital Gasthuisberg, Leuven, Belgium

Introduction: SORAMIC is an RCT comprising diagnostic, local ablation and palliative studies. Based on the result of the diagnostic study patients were assigned to either the local ablation or palliative cohort. The palliative cohort (reported here) was designed to determine the efficacy and safety of combining SIRT (Selective Internal Radiation Therapy) with sorafenib in patients with advanced HCC.

Methods: In the palliative treatment cohort, patients not eligible for TACE were randomised 11:10 to either SIRT with Y-90 resin microspheres plus sorafenib (target dose 400 mg bid) or sorafenib alone. The primary endpoint was overall survival (OS; Kaplan-Meier analysis) in the intention-to-treat population.

Results: In the ITT palliative treatment cohort, 216 patients were randomised to SIRT + sorafenib and 208 to sorafenib alone. Median OS was 12.1 months (95% confidence interval [CI], 10.6–14.6) in the SIRT + sorafenib arm, and 11.5 months (95% CI, 9.8–13.9) in the sorafenib arm (hazard ratio [HR], 1.067; 95% CI, 0.82–1.25; p = 0.951). In the per protocol group, median OS was 14.1 months (95% CI, 10.95–16.40) in the SIRT + sorafenib arm (n = 114), and 11.1 months (95% CI, 9.7–13.9) in the sorafenib arm (n = 174; HR, 0.86; 95% CI, 0.67–1.11; p = 0.25). Subgroup analyses of the per-protocol population suggested a survival benefit for patients receiving SIRT + sorafenib ≤65y (HR, 0.65; 95% CI 0.43, 1.00, p = 0.05); non-cirrhotics (HR, 0.46; 95% CI 0.25, 0.86, p = 0.02); and non-alcoholic etiology (HR, 0.63; 95% CI 0.45, 0.89, p = 0.012). Adverse events (AEs) of Common Terminology Criteria for AE Grade ≥3 were reported in 115/159 (72.3%) patients in the SIRT + sorafenib arm and 135/197 (68.5%) patients in the sorafenib arm, respectively.

Conclusion: The addition of SIRT to sorafenib did not result in a significant improvement in overall survival compared to sorafenib alone. Subgroup analyses led to hypothesis generating results for patient groups with potential clinical benefit.

O – 030 Randomized trial of irinotecan and cetuximab (IC) versus irinotecan, cetuximab and ramucirumab (ICR) as 2nd line therapy of advanced colorectal cancer (CRC) following oxaliplatin and bevacizumb based therapy: Result of E7208

H Hochster[1], Paul J. Catalano[2], Peter J. O'Dwyer[3], Edith P. Mitchell[4], Deirdre Jill Cohen[5], Bryan Andrew Faller[6], Jeremy S. Kortmansky[7], Sheetal Mehta Kircher[8], Jill Lacy[9], Heinz-Josef Lenz[10], Udit N. Verma[11], Al Bowen Benson III[12], ECOG-ACRIN

[1]Rutgers-Cancer Institute, New Brunswick, NJ, USA, [2]Dana-Farber Cancer Institute, Boston, MA, USA, [3]University of Pennsylvania Abramson Cancer Center, Philadelphia, PA, USA, [4]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA, [5]NYU Perlmutter Cancer Center, and ECOG-ACRIN, New York, NY, USA, [6]Midwest Hem and Onc Assoc, Clayton, MO, USA, [7]Medical Oncology and Hematology, Hamden, CT, USA, [8]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA, [9]Smilow Cancer Hospital, Yale University, New Haven, CT, USA, [10]University of Southern California, Los Angeles, CA, USA, [11]University of Texas Southwestern Medical Center, Dallas, TX, USA, [12]Northwestern Medicine, Chicago, IL, USA

Introduction: While both anti-VEGF(R) and EGFR antibodies have activity in metastatic RAS wild type CRC, the combination of the two appeared to be detrimental when combined with chemotherapy in unselected CRC patients. We undertook this study to determine whether the anti-VEGFR antibody, ramucirumab, improved activity of Irinotecan and Cetuximab as 2nd line therapy in KRASwt CRC patients, who previously received FOLFOX or CAPOX with bevacizumab (bev) first line therapy, and were now progressing.

Methods: Patients with advanced and measurable (RECIST 1.1) CRC who had previously been treated with a fluoropyrimidine and oxaliplatin (ox) with bev, and recently showed progression on CT scan were randomized to IC (180 mg/m^2 and 500 mg/m^2 respectively) or ICR (R = 8 mg/kg) every 2 weeks. After 35 pt were randomized, planned interim analysis showed excess gr 3-5 toxicity for ICR; modified mICR (150 mg/m^2, 400 mg/m^2 and 6 mg/kg) arm was instituted after study hold. Patients were stratified by PS (0 vs 1), progression on ox (Y vs N), and progression within 6 months of last treatment (or longer). 100 patients were then accrued to IC vs mICR, with 85% power to detect improvement in median PFS from 4.5 to 7.65 months (with 15% type I error of p < 0.15) by stratified log-rank test.

Results: 97 patients were randomized and evaluable from June, 2014 - July, 2017. Patients were 65% male, 9% black and 8% Hispanic with med age 60 years, PS 0 = 52%, with 24% progressing while on ox and 15% progressing more than 6 months off rx. Gr 3-4 overall toxicity for IC vs mICR was 47% vs 54% with diarrhea = 10 v 15%; rash = 13 vs 8%; neutropenia = 9 vs 10%. Reasons off study were: 60% progression, 18% adverse events and 10% patient choice. At interim analysis the stratified log rank analysis showed a HR = 0.65 for PFS of mICR vs IC (overall med 5.8 months; one-sided p = 0.068), meeting the primary endpoint of p < 0.15. Survival was equal in both arms with med = 20.5 months (HR 1.07). An updated analysis 4/15/18 showed continued PFS effect for the primary endpoint with HR 0.51 and p= 0.063 for PFS.

Conclusion: In KRAS selected, wildtype CRC, 2nd line therapy (following ox and bev based treatment), an anti-VEGFR antibody, combined with anti-EGFR and irinotecan, prolongs PFS. This effect is similar to the reported improvement in PFS in other 2nd line anti-VEGF trials and supports the fact that antibodies against these two targets can be combined for additional benefit in the appropriate patient population. This study was coordinated by ECOG-ACRIN & supported by NCI awards: CA180820, CA180794, CA180826, CA180830, CA180888, CA180870, CA189830.

Annals of Oncology 29 (Supplement 5): v111–v121, 2018
doi:10.1093/annonc/mdy163

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