ASCO Daily News®

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HIGHLIGHTS

Ibrutinib/Rituximab Improves PFS in Waldenström's Macroglobulinemia

The combination of ibrutinib and rituximab significantly improved progression-free survival (PFS) and response rates compared to placebo plus rituximab in patients with Waldenström's macroglobulinemia (WM), according to a prospective randomized trial (Abstract 8003) presented during an Oral Abstract Session on June 1.


Dr. Meletios A. Dimopoulos

"Waldenström's macroglobulinemia is an unusual disease," said Meletios A. Dimopoulos, MD, of the National and Kapodistrian University of Athens, Greece. It is characterized by serum monoclonal immunoglobulin M (IgM) levels and by infiltration of bone marrow and of organs by IgM-producing lymphoplasmacytic cells. Rituximab, which has shown activity in patients with treatment-naive and relapsed or refractory disease, is commonly used to treat WM. Dr. Dimopoulos presented results from a planned interim analysis of the iNNOVATE trial that added the Bruton's tyrosine kinase inhibitor ibrutinib to rituximab.

The study included 150 patients with confirmed symptomatic WM. They were randomly assigned to receive either daily ibrutinib (420 mg; 75 patients) or placebo (75 patients), both in combination with rituximab infusions of 375 mg/m^2/week at weeks 1 to 4 and 17 to 20. In both groups, 45% of patients were treatment naive. Patients who had received a prior rituximab-based therapy were required to have had a response to that treatment.

See PFS in WM, Page 3A

LOXO-292 Phase I Results Show Promise in the Treatment of *RET*-Altered Cancers

Rearranged during transfection (*RET*) is an oncogene activated by *RET* fusions or *RET* mutations. *RET* fusions are associated with 2% of non–small cell lung cancers (NSCLCs), 10%-20% of papillary and other thyroid cancers, and smaller proportions of other cancers. In addition, *RET* mutations are commonly found in medullary thyroid cancers (MTCs).


Dr. Alexander Drilon

LOXO-292 is a highly selective RET inhibitor that has shown efficacy in preclinical models. Alexander Drilon, MD, of Memorial Sloan Kettering Cancer Center, presented data from the phase I open-label study of the RET inhibitor LOXO-292 (LIBRETTO001; Abstract 102). Eligible patients were age 12 or older with advanced or metastatic solid tumors refractory to or intolerant of standard treatment. LOXO-292 was administered in 28-day cycles, with the dose escalation following a 3 + 3 design. Dose escalation among patients and additional enrollment at doses considered safe were allowed. The primary endpoint of the study was the determination of the maximum tolerated dose (MTD). Secondary endpoints included safety, pharmacokinetics, overall response rate (ORR; RECIST 1.1), and duration of response.

As of April 2, 82 patients (40 women, 42 men) had been treated. Forty-nine patients (59%) had *RET* fusion–positive tumors (38 NSCLC, nine thyroid, two pancreatic), 29 (35%) had *RET*-mutant MTC, and four patients (5%) had other types of cancer. Twelve patients (15%) had brain metastases. "This was a heavily pretreated population, with two-thirds of patients having previously received a multikinase inhibitor, many of whom were treated with more than one agent," Dr. Drilon noted.

Patients received LOXO-292 at doses ranging from 20 mg once daily to 240 mg twice a day; the MTD has not been reached. LOXO-292 was well tolerated. The most frequently reported (≥ 10% overall) treatment-emergent adverse events (AEs) were fatigue (20%), diarrhea (16%), constipation (15%), dry mouth (12%), nausea (12%), and dyspnea (11%). Most AEs were grade 1. Two grade 3 treatment-related AEs occurred: tumor lysis syndrome (the only dose-limiting toxicity) and increased alanine aminotransferase.

The ORR was 77% (95% CI

See LOXO-292 Phase I, Page 8A

Immunotherapy Now Standard for Some Patients With CRC

With recent approvals of pembrolizumab and nivolumab for the treatment of refractory deficient mismatch repair (dMMR) metastatic colorectal cancer (CRC), immunotherapy has made its way into the field of gastrointestinal oncology. Many questions remain, however, including optimal approaches to dMMR cancers and reasons for a lack of efficacy seen in proficient MMR (pMMR) CRC. Experts discussed these issues and the management of immunotherapy toxicities during the Education Session, "Where We Stand With Immunotherapy in Colorectal Cancer," held June 2.

"dMMR tumors have much better outcomes than pMMR tumor types," said Michael J. Overman, MD, of The University of Texas MD Anderson Cancer Center, who chaired the session and spoke about optimal approaches to dMMR CRC. The exception to this is in stage IV CRC, where the situation is reversed and dMMR tumors have poorer outcomes than pMMR tumors. Approximately 15% of all CRCs have dMMR, but this decreases as stage increases.[1] Only about 4% of stage IV CRCs demonstrate dMMR.

MMR is a mechanism used by cells to repair damaged DNA, particularly during DNA replication. Deficiency in this system leads to an accumulation of

See Immunotherapy and CRC, Page 18A

Tip of the Day

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BCMA-Directed CAR T Cells Yield Deep, Durable Responses in Relapsed/Refractory Multiple Myeloma

The bb2121 chimeric antigen receptor (CAR) T-cell therapy engineered to target B-cell maturation antigen (BCMA) holds great promise for the treatment of multiple myeloma (MM). In 22 evaluable patients who received 150-450 × 10^6 bb2121 CAR T cells in a phase I study, the objective response rate reached 95.5%, and 50.0% of individuals achieved complete response (Abstract 8007).

As Noopur S. Raje, MD, of Massachusetts General Hospital Cancer Center, underscored during her presentation of these data, the findings are particularly impressive considering that this was an extremely heavily pretreated population. The 22 individuals noted above had received a median of eight prior regimens (range, 3-23) for MM, and 32% were refractory to bortezomib, lenalidomide, carfilzomib, pomalidomide, and daratumumab.


Dr. Noopur S. Raje

bb2121 is the most mature CAR T-cell approach undergoing development in MM. The therapy leverages a lentiviral vector system to modify autologous T cells to home in on BCMA, a member of the TNF superfamily and the latest promising target in MM. bb2121 includes the 4-1BB costimulatory domain that triggers T-cell activation after antigen binding, which is associated with less acute toxicity and more durable CAR T-cell persistence than the CD28 costimulatory domain used in other CAR T-cell therapies, as well as a CD3 zeta T-cell activation domain.

CRB-401 represents the phase I dose-escalation and dose-expansion study evaluating the preliminary efficacy and safety of bb2121 in patients with relapsed/refractory MM. As of March 29, 2018, 43 patients had received bb2121 (dose, 50-800 × 10^6 CAR T cells) after undergoing lymphodepletion with fludarabine and cyclophosphamide.

Prior assessment of the dose-escalation portion of CRB-401 garnered bb2121 a breakthrough therapy designation from the U.S. Food and Drug Administration in November 2017. With the dose-expansion data now available, the findings show that patients need a minimum bb2121 dose of 150 × 10^6 CAR T cells to achieve optimal outcomes. The objective response rate steadily increased from 33.3% with 50 × 10^6 CAR T cells, to 57.1% with 150 × 10^6 CAR T cells, to 95.5% with more than 150 × 10^6 CAR T cells. Similarly, median progression-free survival extended to 11.8 months for patients who received at least 150 × 10^6 CAR T cells, as compared to 2.7 months for patients who received lower doses.

Dr. Raje highlighted the impressive depth of response to bb2121. Of 16 patients with morphologic complete remission who were evaluated for the presence of minimal residual disease (MRD), all of them—100%—showed no trace of MM in the bone marrow at one or more time points. Median progression-free survival for these individuals was 17.7 months.

The safety profile of bb2121 appears relatively well-tolerated up to doses as high as 800 × 10^6 CAR T cells. The most common treatment-emergent adverse events overall included neutropenia (81%), cytokine release syndrome (CRS; 63%), thrombocytopenia (61%), infection (61%), and anemia (56%). Neutropenia (79%), thrombocytopenia (51%), and anemia (44%) predominated as the most common treatment-emergent adverse events of grade 3 or higher and were largely associated with the conditioning chemotherapy, according to Dr. Raje.

CRS, now recognized as one of the most prevalent and dangerous adverse effects following infusion of CAR T-cell therapy, has proven manageable in CRB-401. No grade 4 or grade 5 CRS events occurred, and the two cases of grade 3 CRS resolved within 24 hours.

Dr. Raje indicated that the CRB-401 findings have prompted a global pivotal phase II trial of bb2121 called KarMMa that is currently open for enrollment in North America and Europe. Moreover, additional trials in earlier lines of myeloma are planned.


Dr. Parameswaran Hari

Discussant Parameswaran Hari, MD, of the Medical College of Wisconsin, lauded the rapidity and depth of response observed with bb2121 in MM. However, he could not help but be disappointed by the median PFS of 17.7 months among patients with MRD-negative disease, which reflects eventual relapse. "Unfortunately, this is not yet a cure," Dr. Hari commented.

Dr. Hari suggested, as did Dr. Raje, that applying bb2121 in an earlier line of therapy might prove more effective for conferring long-lasting MM remission. ●

–Kara Nyberg, PhD

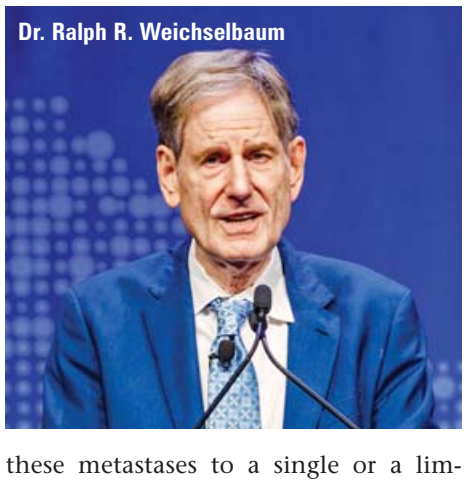
ASCO Honors Radiation Oncologist Dr. Ralph Weichselbaum With David A. Karnofsky Memorial Award

Ralph R. Weichselbaum, MD, accepted the 2018 David A. Karnofsky Memorial Award and Lecture June 2 for his contributions to the field of radiation oncology. Dr. Weichselbaum was honored for his work defining the state of oligometastases and for developing new areas for innovation in translational research.

Daniel F. Hayes, MD, FACP, FASCO, Immediate Past President of ASCO, presented the award that is bestowed on those whose clinical research has "changed the way we practice oncology." In accepting the award, Dr. Weichselbaum said he was "extremely honored," particularly given the "academic and clinical accomplishments of [the] previous recipients."

Dr. Weichselbaum is the Daniel K. Ludwig Distinguished Service Professor of Radiation and Cellular Oncology at the University of Chicago Medicine and co-director of the Ludwig Center at the University of Chicago. In his award lecture, "Oligometastasis From Conception to Treatment," he outlined the framework of the significant hypotheses and subsequent findings that have driven his research interests over the course of his career.

One important area of Dr. Weichselbaum's research was defining, along with his colleague Samuel Hellman, MD, FASCO, the clinical state of oligometastasis, which they hypothesized refers to a distinct clinical entity. For certain tumors, they said, "the anatomy and physiology may limit or concentrate


Dr. Ralph R. Weichselbaum

these metastases to a single or a limited number of organs.…An attractive consequence of the presence of a clinically significant oligometastatic state is

See Karnofsky Memorial Award, Page 22A

PFS in WM

Continued from page 1A

After a median follow-up of 26.5 months, the ibrutinib/rituximab combination resulted in a significantly prolonged PFS. In that group, the median PFS was not yet reached compared with 20.3 months with placebo (HR 0.20, 95% CI [0.11, 0.38]; p < 0.0001). At 30 months, the PFS rate was 82% with ibrutinib and 28% with placebo. Investigator-assessed PFS was similar to the IRC assessment.

This advantage was seen across all relevant subgroups. These included patients with treatment-naive disease (HR 0.34, 95% CI [0.12, 0.95]) as well as patients who relapsed. In patients who relapsed, the 30-month PFS rate was 80% with ibrutinib and 22% with placebo.

Data on $MYD88^{L265P}$ and $CXCR4^{WHIM}$ mutations were available in 136 patients. The PFS advantage with ibrutinib was seen in patients who had $MYD88^{L265P}$ but wild-type CXCR4 (HR 0.165, 95% CI [0.06, 0.49]); those who had both $MYD88^{L265P}$ and $CXCR4^{WHIM}$ mutations (HR 0.237, 95% CI [0.09, 0.66]); and in those with both wild-type variants, although this did not reach statistical significance (HR 0.214, 95% CI [0.04, 1.1]).

The overall response rate was 92% with ibrutinib plus rituximab compared to 47% with placebo and rituximab (p < 0.0001); the major response rates for the two groups were 72% and 32%, respectively (p < 0.0001). There was a more rapid decline in IgM levels with ibrutinib, and 73% of all patients treated with ibrutinib saw an improvement in hemoglobin compared with 41% of patients receiving a placebo (p < 0.0001). Dr. Dimopoulos noted that this is an important outcome with regard to patient quality of life.

The median time to next treatment was not reached in the ibrutinib group compared with 18 months in the placebo plus rituximab group (HR 0.096; p < 0.0001). Overall survival data were not yet mature.

Grade 3 or higher treatment-emergent adverse events occurred in 60% of patients treated with ibrutinib/rituximab and in 61% of those treated with placebo/rituximab. Serious adverse events occurred in 43% and 33% of patients, respectively; there were three fatal adverse events with placebo/rituximab and none with ibrutinib/rituximab. IgM flare of any grade occurred in 8% of the ibrutinib group and in 47% of the placebo group.

"This is a combination with remarkable activity as far as PFS is concerned," Dr. Dimopoulos said. "[It is] well-tolerated, becoming a new standard of care for this disease."

Craig C. Hofmeister, MD, MPH, of The Ohio State University, was the discussant for the abstract. He said that the high response rate in patients with the $MYD88^{L265P}$ mutation make it particularly appealing in that setting. He also pointed out that atrial fibrillation and infections should be closely monitored when using this combination. ●

–Dave Levitan

Patient-Reported Outcomes, Mobile Technology, and Response Burden

The value of patient-reported outcomes (PROs) on increasing physician awareness of patients' functioning and well-being can be useful, but it can have drawbacks depending on the methods used to assess the PROs, according to several presentations at the "Health Services Research, Clinical Informatics, and Quality of Care" Oral Abstract Session, held June 1.

Web-Based Monitoring

In the first of three presentations on PROs (Abstract 6500), Fabrice Denis, MD, PhD, of the Jean Bernard Cancer Institute, France, said using a web-based monitoring system to follow patients with lung cancer resulted in an overall survival (OS) that was significantly higher than that with routine follow-up by CT scans alone.

An overwhelming majority of lung cancer relapses are symptomatic—somewhere between 75% and 90%, he said, but patients may have symptoms weeks before a follow-up visit with their treating physician. Moovcare is an algorithm based on the chaos theory model that reports on 12 symptoms every week, with notifications sent to nurses and/or oncologists.

"In a nonrandomized study, we assessed the survival of 98 patients after their treatment for a stage III/IV lung cancer with our algorithm," Dr. Denis said. "Those first results suggested a 1-year survival that was 27% greater in patients with our web-mediated follow-up than in patients with a standard follow-up."


Dr. Fabrice Denis

The confirmatory phase III, randomized, multicenter study enrolled 133 patients with lung cancer (either small cell [SCLC] or non–small cell) who had internet access (12 were deemed ineligible after randomization); of the remaining 121 patients, median age was 65, 41% were receiving maintenance or tyrosine kinase inhibitors, and 17% had SCLC. At 9 months, OS improvement was observed and patients in the standard follow-up arm were eligible to cross over to the web-based arm.

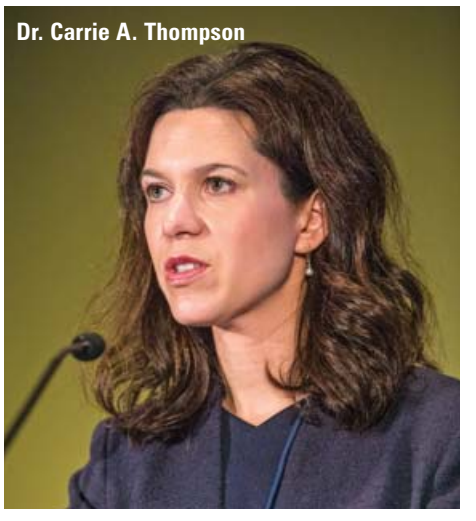
After 2 years of follow-up, 70 deaths occurred and the median OS was 22.5 months in the web-based follow-up arm (60 patients) and 14.9 months in the standard follow-up arm (61 patients), without adjustment for cross-over from the control arm (HR 0.594, 95% CI [0.368, 0.959]; p = 0.03). Censoring cross-over resulted in a hazard ratio of 0.496 (95% CI [0.305, 0.806]; p = 0.004).

Other studies have evaluated intensive follow-up, Dr. Denis said, "but our randomized study is the first assessing the survival rates as a primary outcome." Future plans include initiating large (more than 1,000 patients), multicenter, international studies in other cancers; a similar program will be available soon for cancer screening among patients who smoke.

Emojis and the Apple Watch

In a second study (Abstract 6501), Carrie A. Thompson, MD, of the Mayo Clinic, reported on the ability of an emoji available on the Apple Watch to assess patient-reported quality of life (QOL). The aims of the study were 3-fold: to develop technology to measure physical activity and PROs using the Apple Watch and iPhone, determine feasibility and patient acceptability of collecting PROs using wearable technology, and explore the ability of the emoji to assess PROs.

Recruited adult patients had a range of different cancers with a life expectancy of at least 6 months. All patients had an iPhone version 5.0 or higher and received an Apple Watch. Dr. Thompson and colleagues created the study app by using


Dr. Carrie A. Thompson

Apple's ResearchKit, which is an open-source framework for building medical research, that the patients downloaded to their iPhones and watches.

"All patients were asked to wear the Apple Watch for a minimum of 8 hours per day for 12 weeks, from which we collected physical activity data," Dr.

See Patient-Reported Outcomes, Page 20A

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References: 1. Prescribing Information for LYNPARZA. AstraZeneca Pharmaceuticals LP, Wilmington, DE. **2.** Data on File, US-19893. AstraZeneca Pharmaceuticals LP.

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Seeking a 'Better Mousetrap' for HER2-Positive Tumors

Therapies that target the protein HER2 have changed the landscape of cancer treatment, improving survival in advanced HER2-positive breast and gastric cancers. But researchers at multiple centers are striving to further improve outcomes in these HER2-expressing cancers. During the "Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics" Oral Abstract Session on June 1, speakers discussed novel strategies for addressing HER2-driven tumors, including two new, promising agents and additional indications for a recently approved agent.

Bob T. Li, MD, MPH, of Memorial Sloan Kettering Cancer Center, discussed results with the recently approved agent—ado-trastuzumab emtansine—in a multi-histology basket trial including patients with *HER2*-amplified or *HER2*-mutated cancers (Abstract 2502).


Dr. Bob T. Li

This single-center phase II trial found that "ado-trastuzumab emtansine showed clinical efficacy against *HER2*-amplified lung, endometrial, salivary gland, and other cancers," Dr. Li said. The trial met its primary endpoint, he added, "and further development is warranted in these *HER2*-amplified cancers."

The trial enrolled patients with advanced solid tumors with *HER2* amplification as identified by next-generation sequencing (NGS) and patients with *HER2*-mutated lung cancer. Patients were divided into four cohorts: *HER2*-mutant lung cancers, *HER2*-amplified lung cancers, bladder and urinary tract cancers, and other solid tumors (endometrial, salivary gland, and colorectal). Initially, seven patients were enrolled in each cohort, and an interim response analysis was performed for each cohort. If no response was seen in a cohort, it was closed to accrual. If response was seen in at least one patient in a cohort, 11 more patients were enrolled in that cohort, for a total of 18 patients.

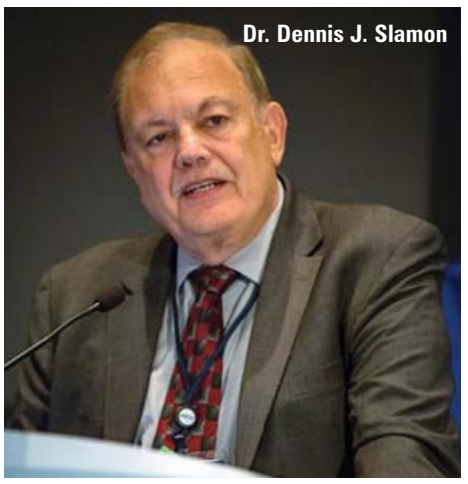
Patients received ado-trastuzumab emtansine at 3.6 mg/kg every 3 weeks until progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR), a combination of complete response (CR) and partial response (PR) as measured by RECIST v1.1. Secondary endpoints included progression-free survival (PFS), duration of response (DOR), and adverse events (AEs).

In total, 62 patients were treated, with a median age of 63 (range, 34-90). The median number of lines of previous systemic therapy was two (range, 1-7), and the ORR was 28% (16/57; 95% CI [17, 42]). Median PFS was 3 months (95% CI [4, 7]), and median DOR was 8 months (range, 2 - >25).

The researchers also looked at results for individual *HER2*-amplified cohorts. For lung cancers, the ORR was 43% (3/7; 95% CI [10, 82]), median PFS was 7 months (95% CI [3, 13]), and median DOR was 5 months (range, 5-17+). For endometrial cancers, ORR was 25% (5/20; 95% CI [9, 49]), median PFS was 3 months (95% CI [2, 9]), and median DOR was not reached (range, 2 - >25). For salivary gland cancers, ORR was 100% (6/6; 95% CI [54, 100]), median PFS was 9 months (95% CI [4, 12]), and median DOR was not reached (range, 2 - >10).

Overall, the researchers found that the degree of *HER2* amplification correlated with response, but not all *HER2*-amplified cancers responded, Dr. Li noted. The ORRs for *HER2*-amplified colorectal cancers and for bladder and urinary tract cancers were both 0%, and these cohorts were not expanded.

Regarding safety, most AEs in the study were grades 1 or 2, with one grade 3 febrile neutropenia and one grade 3 thrombocytopenia. There were no treatment-related deaths.


Dr. Dennis J. Slamon

Discussant Dennis J. Slamon, MD, PhD, of the David Geffen School of Medicine at the University of California, Los Angeles, congratulated the authors for demonstrating that "molecular alteration trumps histology" and that multiple tumor types with *HER2* amplification respond to ado-trastuzumab emtansine.

Results with two new agents targeting HER2 were also presented at the session. Funda Meric-Bernstam, MD, of The University of Texas MD Anderson Cancer Center, presented an interim analysis of single-agent activity of ZW25, a HER2-targeted bispecific antibody, in patients with heavily pretreated HER2-expressing cancers (Abstract 2500). She explained that ZW25 is biparatopic, which simultaneously binds to two HER2 epitopes, resulting in novel mechanisms of action, including increased tumor cell binding and improved receptor internalization and downregulation relative to trastuzumab.

In this two-part phase I study, ZW25 was well tolerated at all dose levels investigated and showed promising antitumor activity in multiple cancers, Dr. Meric-Bernstam said. Part 1, a dose-escalation study, evaluated 5, 10, and 15 mg/kg of ZW25 weekly and 20 mg/kg biweekly to identify a recommended dose for further study.

Part 2 of the study is ongoing, evaluating safety and efficacy in separate expansion cohorts, including HER2-high breast, HER2-high and -intermediate gastroesophageal (GE), and other HER2-high cancers. High HER2 expression was defined as immunohistochemistry 3+ or 2+/fluorescent in situ hybridization positive. Patients enrolled had progressive disease after standard of care, including HER2-targeted agents.

At the time of this interim analysis, 42 patients had been treated in parts 1 and 2, with a median age of 63 (range, 27-79) and a median number of previous systemic regimens of five (range, 0-17). Cancer diagnoses included breast (20 patients; 48%), GE (13 patients; 31%), colorectal (5 patients; 12%), and other tumors (4 patients; 9%).

No dose-limiting toxicities were observed at any of the dose levels evaluated. Treatment-related AEs were all grade 1 or 2, except for reversible grade 3 hypophosphatemia, arthralgia, and fatigue in one patient receiving the 10 mg/kg weekly dose. There were no treatment-related serious AEs or discontinuations, no left ventricular ejection fraction decreases of 10% or greater during treatment, and no new detectable anti-drug antibodies.


Dr. Funda Meric-Bernstam

Decreases in target lesions were seen in most patients with measurable disease. Of 18 patients with breast cancer, six (33%) had a PR and three (17%) had stable disease (SD). In nine patients with GE cancer, four (44%) had a PR and one (12%) had SD. In six patients with other cancers, two (33%) had a PR and two (33%) had SD.

Dr. Meric-Bernstam said the single-

See HER2-Positive Tumors, Page 8A

NCI Director Highlights Progress, Challenges in Cancer Research

Last week, the National Cancer Institute (NCI) of the National Institutes of Health (NIH) released its 2018 Annual Report to the Nation on the Status of Cancer. During the June 2 Opening Session, NCI Director Norman E. Sharpless, MD, was on hand to highlight for Annual Meeting attendees the top-line good news from the report: Overall cancer death rates continue to decrease for men, women, and children in all major racial and ethnic groups.

But Dr. Sharpless brought other good news as well: "the strong and bipartisan support we've been receiving from Congress for cancer research," with budget increases for the NCI and the NIH for the fourth year in a row. The omnibus budget passed by Congress this year provided a $275 million increase for the NCI budget, as well as full continued funding for the Cancer Moonshot, he said.

With improving survival, successful treatment approaches, and continued support for research, there is good reason for the oncology community to be optimistic. "The potential for breakthroughs has never, I believe, been greater than it is now," he said.

At the same time, significant challenges remain, including certain cancer types, such as glioblastoma, that remain resistant to treatment efforts, and the toxicities that accompany some treatments—including, he noted, financial toxicity, a complication of treatment that many are just starting to appreciate, but that "clearly can be devastating for cancer survivors."


Dr. Norman E. Sharpless

Dr. Sharpless identified four areas he wants the NCI to focus on during his term: continued support of basic science; development of a modern, diverse workforce; effective harnessing of big data; and innovation and progress in clinical trial design.

Regarding the first of those foci, support for basic science, Dr. Sharpless announced that this year he has earmarked an additional $127 million for research project grants for investigator-initiated science. This announcement received a robust round of applause. ●

–Tim Donald, ELS

Once-Weekly Dosing With Carfilzomib Promising for Relapsed/Refractory Multiple Myeloma

Patients with relapsed or refractory multiple myeloma treated with once-weekly carfilzomib had a higher response rate than patients treated with the twice-weekly regimen in the ARROW study, introducing the potential for more convenient dosing for patients.

María-Victoria Mateos, MD, PhD, of the University Hospital of Salamanca, Spain, presented results of the phase III trial during the "Hematologic Malignancies—Plasma Cell Dyscrasia" Oral Abstract Session on June 1 (Abstract 8000). According to the trial results, the once-weekly regimen significantly improved progression-free survival by 3.6 months, reducing the risk of progression or death by 30.7% compared with the twice-weekly treatment regimen.

"In comparison with the twice-weekly schedule, once-weekly carfilzomib showed a favorable benefit-risk profile with a more convenient dosing regimen," Dr. Mateos said during the session.

The phase I/II CHAMPION-1 study[1] had earlier assessed once-weekly carfilzomib plus dexamethasone in an effort to find a more convenient treatment regimen for patients, Dr. Mateos said. The study established the maximum tolerated dose of carfilzomib at 70 mg/m^2. Based on the promising results of CHAMPION-1, researchers initiated the ARROW study to compare the once-weekly regimen of 70 mg/m^2 of carfilzomib with dexamethasone to a twice-weekly regimen of 27 mg/m^2 of carfilzomib with dexamethasone for patients with relapsed or refractory multiple myeloma.

Dr. María-Victoria Mateos

The two-arm ARROW study, an international trial conducted at about 100 sites, included 478 patients who had received two to three prior therapies and had prior exposure to a proteasome inhibitor and an immunomodulatory drug. Patients were randomly assigned 1:1 to receive either once- or twice-weekly carfilzomib plus dexamethasone in 28-day cycles until disease progression or unacceptable toxicity.

The once-weekly group received carfilzomib (30-minute infusion) on days 1, 8, and 15 of all cycles, with a 20 mg/m^2 dose on day 1 of the first cycle and 70 mg/m^2 for each subsequent treatment. Patients in the twice-weekly arm were treated with carfilzomib (10-minute infusion) on days 1, 2, 8, 9, 15, and 16, with 20 mg/m^2 on days 1 and 2 during the first cycle and then 27 mg/m^2 for each subsequent treatment. All patients received 40 mg dexamethasone on days 1, 8, and 15 of all cycles; they all also received 40 mg of dexamethasone on day 22 for cycles one through nine only.

Median progression-free survival, the primary endpoint, was 11.2 months in the once-weekly arm vs. 7.6 months in the twice-weekly arm (HR 0.693, 95% CI [0.544, 0.883], p = 0.0029). The overall response rate, a secondary endpoint, was 62.9% in the once-weekly group vs. 40.8% in the twice-weekly group (p < 0.0001). Complete response or better was 7.1% in the once-weekly group vs. 1.7% in the twice-weekly group. Among patients treated with the once-weekly regimen, 27.1% had a very good partial response vs. 11.8% of patients treated twice weekly.

Median duration of treatment in the once-weekly group was 38 weeks with carfilzomib and 37.1 weeks with dexamethasone; in the twice-weekly group, the median duration of treatment was 29.1 weeks with both carfilzomib and dexamethasone.

Dr. Mateos said that the safety findings "were consistent with the known safety profile of carfilzomib" and that "no new risks were identified." The percentage of grade 3 or higher adverse events was 67.6% in the once-weekly group vs. 61.7% in the twice-weekly arm; the percentage of treatment-related grade 5 adverse events was 2.1% in the once-weekly group vs. 0.9% in the twice-weekly group.

Discussant Noopur S. Raje, MD, of Massachusetts General Hospital, said the ARROW trial results present important considerations for future study, including whether there is a more convenient way of administering carfilzomib and whether carfilzomib has a dose response. She pondered, "Will this be the new standard of giving carfilzomib going forward?"

–Kathy Holliman, MEd

Reference:

1. Berenson JR, et al. *Blood*. 2016;127:3360-8.

Expanding the Uses of Cell-Free DNA Assays: From Guiding Treatment Decisions to Applications in Early Disease Detection

Analyzing cell-free DNA (cfDNA) circulating in plasma or serum can help oncologists determine the genotype of tumors noninvasively to guide treatment decisions and may eventually allow them to monitor treatment response, predict recurrence, and screen for cancer. cfDNA is released into the blood following the death of normal and cancer cells, and in patients with cancer the circulating tumor DNA (ctDNA) has been shown to bear the same tumor-related mutations and other genetic alterations found in tissue from tumor biopsies.

The Education Session "Liquid Biopsies: Current Uses and Future Directions," held June 2, covered cfDNA advantages and limitations compared with analyzing tumor tissue and new technologies in development.

"One of the exciting things in this field is that you can imagine using these assays anywhere along a patient's care trajectory," from localized disease to metastasis and recurrence, said Maximilian Diehn, MD, PhD, of the Stanford Cancer Institute, who opened the session. Currently, cfDNA assays are being used in the clinic for genotyping patients with advanced cancer who cannot have or refuse to have biopsies to monitor treatment response and detect resistance variants.

However, cfDNA assays have technical limitations; it can be difficult to detect ctDNA. The polymerase chain reaction (PCR)–based assays, which detect a single mutation or panel of mutations and are typically used clinically to guide treatment decisions, have a sensitivity of 0.05% to 0.1% in a 10-mL blood draw. Yet these assays can fail to pick up potentially clinically important alterations.

Next-generation methods such as whole-genome or whole-exome sequencing, which have the advantage of being able to look broadly, currently have a sensitivity of only about 1.0% because the cost of the technology is still prohibitively expensive, which prevents adequately high sequence coverage for better detection, Dr. Diehn explained.

Emerging Clinical Applications

Many of the emerging applications for cfDNA assays focus on treating patients with early-stage cancer, including detecting disease, monitoring local treatment response such as radiotherapy, detecting minimal residual disease (MRD), and surveillance, explained Dr. Diehn. Assays for detecting MRD could have particular clinical utility for monitoring adjuvant therapy and determining whether to avoid or escalate adjuvant therapy, he said. There are currently no MRD assays for solid tumors.

To that end, Dr. Diehn and colleagues developed an assay called CAPP-Seq (Cancer Personalized Profiling by Deep Sequencing)—a next-generation sequencing capture-based assay that looks at approximately 300 common cancer genes and detects all the major classes of mutations. CAPP-Seq can be performed as either a naive detection method or a tumor-informed detection method, in which a tumor biopsy has already been performed and the same mutations that were found in the tumor tissue can be probed in the cfDNA sample.

In one study, Dr. Diehn and colleagues collected plasma prospectively from patients with stage I-III localized lung cancer prior to curative treatment and following the first treatment. They found that the patients who had detectable ctDNA following treatment went on to have disease recurrence, whereas among patients with no detected ctDNA, only one patient had recurrence, and the presence of ctDNA correlated with disease-specific survival. The levels of ctDNA in this cohort were very low, between


Dr. Maximilian Diehn

See Cell-Free DNA Assays, Page 21A

LOXO-292 Phase I

Continued from page 1A

[61, 89]) in 39 evaluable patients with *RET* fusion–positive cancers, 77% (95% CI [58, 90]) in 30 evaluable patients with NSCLC, and 78% (95% CI [40, 97]) in patients with other *RET* fusion–positive cancers. Importantly, responses in *RET* fusion–positive cancers occurred regardless of tumor type, *RET* fusion partner, starting dose, or prior therapy. Confirmed intracranial responses were observed in the three patients with intracranial disease (Fig. 1). In the 22 evaluable patients with *RET*-mutant MTC, the ORR was 45% (95% CI [24, 68]). Disease regression occurred in most patients, independent of starting dose or *RET* mutation. No responses were seen in the three evaluable patients without a known activating *RET* alteration.


Dr. Christine Marie Lovly

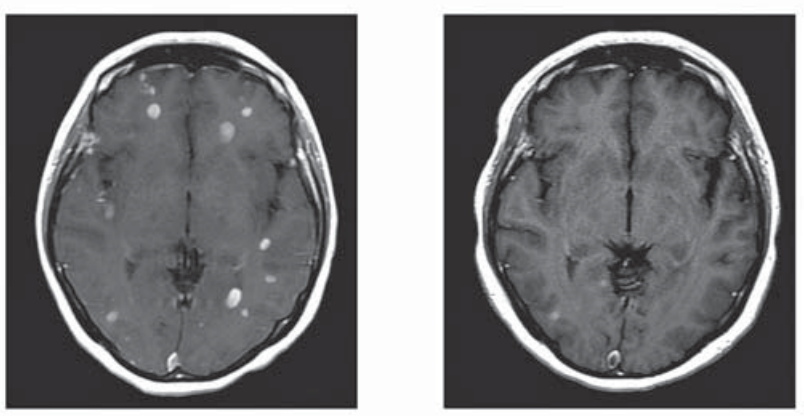
"The activity of LOXO-292 was durable, with over 90% of patients still on treatment as of the data cutoff, including all responding patients," Dr. Drilon said. The study expansion cohorts are currently enrolling additional patients with *RET* fusion–positive solid tumors, MTC, and other cancers with *RET* activation.

Discussant Christine Marie Lovly, MD, PhD, of Vanderbilt University, congratulated the investigators on the findings of the trial. As multikinase inhibitors are not specific to RET, they can come with off-target effects when treating patients with *RET* rearrangements. "Multikinase inhibitors have modest activity, with a response rate of about 30%, and came with the cost of significant toxicity," Dr. Lovly said.

She found the LOXO-292 AE profile encouraging, with RET selectivity leading to better tolerability. Determining the optimal sequence of treatment, the durability of the central nervous system response, effects across different *RET* mutations, and mechanisms of acquired resistance are areas for further study. ●

–Muriel Cunningham

Fig. 1. MRI Images of Intracranial Response to LOXO-292 Therapy in a Patient With *CLIP1-RET* Fusion-Positive NSCLC.



Abbreviation: NSCLC, non–small cell lung cancer
[1]Initiated treatment at 120 mg BID; dose escalated at C5D1 to 160 mg BID; on study in month 4.
Brain metastases only observed in *RET* fusion-positive cancers; April 2, 2018, data cut-off date.

HER2-Positive Tumors

Continued from page 6A

agent evaluation of ZW25 is ongoing, and investigators are also evaluating combinations with other agents in earlier lines of therapy, as well as expanding their dataset with cancers expressing lower levels of HER2.

Hiroji Iwata, MD, of Aichi Cancer Center, Japan, presented long-term efficacy and safety data from a phase I study of trastuzumab deruxtecan (DS-8201a), a HER2-targeted antibody-drug conjugate (ADC), in patients with HER2-expressing solid tumors (Abstract 2501).

Dr. Iwata explained that in preclinical studies, DS-8201a, which targets HER2 cell surface receptors, demonstrated activity across a broad range of tumors with varying degrees of HER2 cell surface expression. Investigators hypothesize that this ADC has a "bystander effect"—the ability to kill neighboring tumor cells regardless of their receptor expression.

In this ongoing trial, DS-8201a has shown promising antitumor activity in patients with heavily pretreated HER2-positive breast and gastric cancers, Dr. Iwata said. Antitumor activity was also observed in nonarchetypical HER2-expressing tumor types other than breast and gastric cancers.

At the time of this interim analysis, the phase I study included 111 patients with HER2-positive breast cancer, a separate cohort of 34 patients with HER2-low breast cancer, 44 patients with HER2-positive gastric cancer, and 51 patients with other cancers. Consistent tumor shrinkage was seen across all tumor types, whether patients were treated with 5.4 or 6.4 mg/kg every 3 weeks. Overall, 86.3% of patients experienced tumor shrinkage, and 91.5% of these patients showed shrinkage at the time of first imaging assessment at 6 weeks. The confirmed ORR in the overall population was 49.3%.


Dr. Hiroji Iwata

Looking at individual cohorts, in HER2-positive breast cancer, the confirmed ORR was 54.5% (54 of 99 patients), and in HER2-low breast cancer it was 50.0% (17 of 34 patients). The median DOR was not reached in HER2-positive breast cancer and was 11.0 months in HER2-low breast cancer. Median PFS was also not reached in HER2-positive breast cancer and was 12.9 months in HER2-low breast cancer.

In HER2-positive gastric cancer, confirmed ORR was 43.2% (19 of 44 patients). Median DOR was 7.0 months, and median PFS was 5.6 months. In other cancers, confirmed ORR was 38.7% (12 of 31 patients), median DOR was 12.9 months, and median PFS was 12.1 months.

The drug's safety profile was generally manageable, Dr. Iwata said, although interstitial lung disease (ILD) and pneumonitis were important identified risks. Almost all patients (98.8%) experienced treatment-emergent AEs (TEAEs), and half of patients (50.2%) experienced grade 3 or greater TEAEs. Any-grade drug-related TEAEs occurred in 97.5% of patients, while those grade 3 or greater occurred in 41.9%.

AEs were generally low grade, with the most frequent being gastrointestinal or hematologic. As noted, ILD/pneumonitis events were observed, including five fatal cases. There were a total of 10 (4.1%) TEAEs leading to death.

In his discussion, Dr. Slamon asked two questions: "Do we need a better mousetrap for HER2-positive cancers?" and if so, can we build one? He said that, if the answer to the first question is yes, the drug(s) should enhance efficacy signals and maintain or improve safety profiles. In conclusion, he proposed that not only can we build a "better mousetrap," but ongoing research is under way to do just that. ●

–Tim Donald, ELS

INBRIEFS

Systemic Therapy Costs and Use in Patients With mCC

Abstract LBA3579

Use and cost of systemic therapy for metastatic colorectal cancer is significantly higher for patients in western Washington state in the United States compared to those in British Columbia, Canada, with no significant differences in overall survival.

Researchers analyzed data from 1,622 patients in British Columbia and 575 in Washington. Patients in British Columbia were more likely to be older (median age, 60 vs. 66) and male (57% vs. 48%, $p \leq 0.01$) than those in Washington. The most common first-line regimen in British Columbia was FOLFIRI plus bevacizumab (32%), whereas FOLFOX was the most common first-line regimen in Washington (39%).

The mean monthly cost of first-line therapy per patient was $12,345 in the United States vs. $6,195 in Canada ($p \leq 0.01$) for all regimens assessed. Mean lifetime monthly costs were also significantly higher in Washington ($7,883 vs. $4,830, $p \leq 0.01$). Overall median survival of patients receiving therapy was similar (21.4 months in Washington vs. 22.1 months in British Columbia), with similar overall median survival among those who did not receive therapy (5.4 months in Washington vs. 6.3 months in British Columbia).

Sex May Affect Toxicity of Adjuvant Chemotherapy in Patients With Colorectal Cancer

Abstract 3603

Researchers compared major adverse events (nausea, vomiting, stomatitis, diarrhea, leucopenia, neutropenia, anemia, thrombocytopenia, and neuropathy) among 28,636 patients (54% men) in the ACCENT database treated with adjuvant chemotherapy after curative resection of colorectal cancer. Their results show that women had a significantly higher risk of several grade 3/4 toxicities in three of the chemotherapy regimens evaluated: single-agent fluoropyrimidine (5-fluorouracil [5-FU]), FOLFIRI, and FOLFOX.

The greatest differences between the sexes were seen in those treated with 5-FU, in which nearly twice as many women as men experienced nausea/vomiting (8.1% vs. 4.3%). A greater percentage of women also experienced stomatitis (7.2% vs. 4.4%); diarrhea (20.0% vs. 16.0%); leucopenia (5.6% vs. 3.1%); and neutropenia (16.0% vs. 11.0%). Under the FOLFOX regimen, women were nearly twice as likely to experience nausea and vomiting (13.0% vs. 6.8%), diarrhea (21.0% vs. 15.0%), and neutropenia (27.0% vs. 18.0%). Significant differences in the FOLFIRI regimen included nausea/vomiting (13.0% vs. 9.6%), diarrhea (21.0% vs. 16.0%), leucopenia (11.0% vs. 7.4%), and neutropenia (40.0% vs. 26.0%).

Although differences in perception could account for the differences in gastrointestinal effects, the researchers noted that they do not explain the significant differences in neutropenia. They recommended additional investigation and suggested that clinicians may need to consider sex-specific strategies for drug dosing and supportive care. ●

–Debra Gordon

New Guidelines Provide Additional Options for Reducing Breast Cancer Recurrence

The use of adjuvant chemotherapy to reduce the recurrence of breast cancer has been linked to significant improvements in mortality and morbidity, including disease-free survival (DFS) and overall survival (OS), in women with early-stage disease. However, the optimal regimen must be personalized, as clinicians weigh the potential life-extending benefits of adjuvant treatment against adverse sequelae like neuropathy, cardiotoxicity, and diminished quality of life.

In 2016, ASCO published a clinical practice guideline on the selection of optimal adjuvant chemotherapy regimens for early-stage breast cancer and adjuvant targeted therapy for HER2-positive breast cancer, which were adapted from Cancer Care Ontario. But with the recent completion of several large-scale phase III clinical trials, an Expert Panel was convened to review and update the 2016 guidelines according to the latest data. Consequently, ASCO has now published a revised set of guidelines, "Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update."

A Trio of Findings

The updated guidelines include a series of potentially practice-changing recommendations designed to improve outcomes in women with early-stage breast malignancies. Three recent phase III randomized controlled trials (i.e., CREATE-X, APHINITY, and ExteNET) on the adjuvant use of capecitabine, pertuzumab, and neratinib, respectively, helped form the basis of the revisions. Changes were implemented following a systematic literature review and discussion by a subset of the original multidisciplinary Expert Panel involved in the development of the 2016 guidelines.

"The revisions were made because these three pivotal trials showed important benefits for a subpopulation of patients with breast cancer," Neelima Denduluri, MD, of The US Oncology Network, Virginia Cancer Specialists, and Expert Panel co-chair, said. "For example, pertuzumab may now be discussed as an additional therapeutic agent for those with high-risk HER2-positive disease. Similarly, neratinib can be considered after the completion of trastuzumab. And for the first time, we have something in the guidelines for women with residual disease after standard chemotherapy, allowing us to incorporate an agent that may improve outcomes after surgery."

Dr. Neelima Denduluri

The first new recommendation concerns the inclusion of up to six to eight cycles of adjuvant capecitabine after completion of standard preoperative anthracycline and taxane-based combination chemotherapy in patients with stage I-III HER2-negative breast cancer with invasive residual disease at surgery. This decision was made based on findings from CREATE-X, which showed that the addition of capecitabine resulted in significant improvements in DFS and OS.

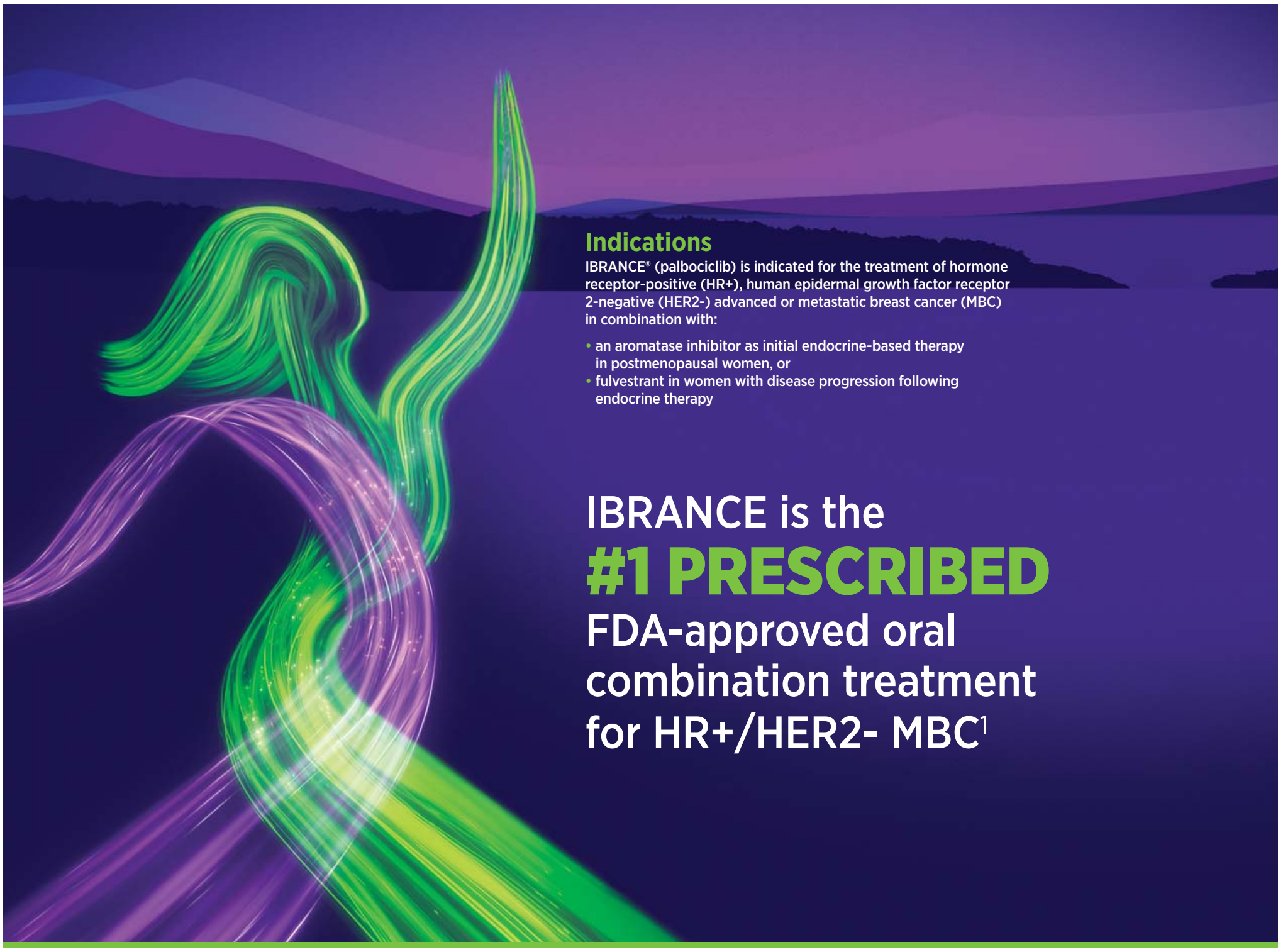
"Even though [CREATE-X] was conducted in Asia and used a higher dose than we typically use in the United States, there was a fairly substantial benefit for a high-risk group. So, we felt this was an important option for doctors to discuss with patients," Sharon H. Giordano, MD, MPH, FASCO, of The University of Texas MD Anderson Cancer Center and Expert Panel co-chair, said.

The second new recommendation pertains to the use of adjuvant pertuzumab in addition to trastuzumab-based combination chemotherapy in patients with high-risk, early-stage, HER2-positive breast cancer. Based on the literature review and results from the APHINITY trial, the Expert Panel decided that oncologists can safely add 1 year of adjuvant pertuzumab to this treatment regimen, as it appears to extend invasive DFS.

Dr. Sharon H. Giordano

Lastly, the Expert Panel considered whether neratinib should be used as extended therapy for patients with early-stage, HER2-positive breast cancer following combination chemotherapy and

See New Guidelines, Page 16A



Indications

IBRANCE® (palbociclib) is indicated for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (MBC) in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women, or
- fulvestrant in women with disease progression following endocrine therapy

IBRANCE is the #1 PRESCRIBED FDA-approved oral combination treatment for HR+/HER2- MBC[1]

Important Safety Information

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Inform patients to promptly report any fever.

Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Based on the mechanism of action, IBRANCE can cause **fetal harm**. Advise females of reproductive potential to use effective contraception during IBRANCE treatment and for at least 3 weeks after the last dose. IBRANCE may **impair fertility in males** and has the potential to cause genotoxicity. Advise male patients with female partners of reproductive potential to use effective contraception during IBRANCE treatment and for 3 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise women **not to breastfeed** during IBRANCE treatment and for 3 weeks after the last dose because of the potential for serious adverse reactions in nursing infants.

The **most common adverse reactions (≥10%)** of any grade reported in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

The **most frequently reported Grade ≥3 adverse reactions (≥5%)** in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (66% vs 2%), leukopenia (25% vs 0%), infections (7% vs 3%), and anemia (5% vs 2%).

Lab abnormalities of any grade occurring in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were decreased WBC (97% vs 25%), decreased neutrophils (95% vs 20%), anemia (78% vs 42%), decreased platelets (63% vs 14%), increased aspartate aminotransferase (52% vs 34%), and increased alanine aminotransferase (43% vs 30%).

IBRANCE is backed by guidelines and unmatched experience in its class

Based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that both palbociclib (IBRANCE) combination regimens are appropriate interventions.[2]

NCCN CATEGORY 1		
	Palbociclib (IBRANCE) + aromatase inhibitor may be considered as a treatment option for first-line therapy for postmenopausal women with HR+/HER2- MBC[2]*	**Palbociclib (IBRANCE) + fulvestrant** for postmenopausal women or premenopausal women receiving ovarian suppression with an LHRH agonist with HR+/HER2- MBC that has progressed on or after prior adjuvant or metastatic endocrine therapy[2]*

CDK4/6=cyclin-dependent kinases 4 and 6; LHRH=luteinizing hormone-releasing hormone.
*If there is disease progression while on CDK4/6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4/6-containing regimen.[2]

3+ years
since initial FDA approval

11,500+ prescribers
have chosen IBRANCE[1†]

75,000+ patients
prescribed IBRANCE[1†]

[†]Data projected as of January 2018.[1]

Visit IBRANCEhcp.com to learn more.

The **most common adverse reactions (≥10%)** of any grade reported in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (83% vs 4%), leukopenia (53% vs 5%), infections (47% vs 31%), fatigue (41% vs 29%), nausea (34% vs 28%), anemia (30% vs 13%), stomatitis (28% vs 13%), diarrhea (24% vs 19%), thrombocytopenia (23% vs 0%), vomiting (19% vs 15%), alopecia (18% vs 6%), rash (17% vs 6%), decreased appetite (16% vs 8%), and pyrexia (13% vs 5%).

The **most frequently reported Grade ≥3 adverse reactions (≥5%)** in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (66% vs 1%) and leukopenia (31% vs 2%).

Lab abnormalities of any grade occurring in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were decreased WBC (99% vs 26%), decreased neutrophils (96% vs 14%), anemia (78% vs 40%), decreased platelets (62% vs 10%), increased aspartate aminotransferase (43% vs 48%), and increased alanine aminotransferase (36% vs 34%).

Avoid concurrent use of **strong CYP3A inhibitors**. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of **strong CYP3A inducers**. The dose of **sensitive CYP3A substrates** with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

For patients with **severe hepatic impairment** (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg. The pharmacokinetics of IBRANCE **have not been studied** in patients **requiring hemodialysis**.

Please see Brief Summary on the following pages.

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2017. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed February 8, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

IBRANCE™
palbociclib | 125 mg capsules
FIRST IN CLASS

Brief Summary of Prescribing Information

IBRANCE® (palbociclib) capsules, for oral use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

IBRANCE is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or
- fulvestrant in women with disease progression following endocrine therapy.

DOSAGE AND ADMINISTRATION

Recommended Dose and Schedule. The recommended dose of IBRANCE is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. IBRANCE should be taken with food.

Administer the recommended dose of an aromatase inhibitor when given with IBRANCE. Please refer to the Full Prescribing Information for the aromatase inhibitor being used.

When given with IBRANCE, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the Full Prescribing Information of fulvestrant.

Patients should be encouraged to take their dose of IBRANCE at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

Pre/perimenopausal women treated with the combination IBRANCE plus fulvestrant therapy should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards.

Dose Modification. If dose reduction is required, the first recommended dose reduction is to 100 mg/day and the second dose reduction is to 75 mg/day. If further dose reduction below 75 mg/day is required, discontinue the treatment.

Dose Modification and Management – Hematologic Toxicities[a]

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated.

For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of cycle: Withhold IBRANCE, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the *same dose*. Day 15 of first 2 cycles: If Grade 3 on Day 15, continue IBRANCE at current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 neutropenia[b] with fever ≥38.5 ºC and/or infection	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.
Grade 4	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.
[a] Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
[b] Absolute neutrophil count (ANC): Grade 1: ANC < LLN - 1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3; Grade 3: ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3.

Dose Modification and Management – Non-Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-hematologic toxicity (if persisting despite optimal medical treatment)	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the *next lower dose*.

Grading according to CTCAE 4.0.

Refer to the Full Prescribing Information for coadministered endocrine therapy dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

Dose Modifications for Use With Strong CYP3A Inhibitors. Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be coadministered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg once daily. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3 to 5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

Dose Modifications for Hepatic Impairment: No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

DOSING FORMS AND STRENGTHS

125 mg capsules: opaque hard gelatin capsules, size 0, with caramel cap and body, printed with white ink “Pfizer” on the cap, “PBC 125” on the body.

100 mg capsules: opaque hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink “Pfizer” on the cap, “PBC 100” on the body.

75 mg capsules: opaque hard gelatin capsules, size 2, with light orange cap and body, printed with white ink “Pfizer” on the cap, “PBC 75” on the body.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Neutropenia. Neutropenia was the most frequently reported adverse reaction in Study 1 (PALOMA-2) with an incidence of 80% and Study 2 (PALOMA-3) with an incidence of 83%. A Grade ≥3 decrease in neutrophil counts was reported in 66% of patients receiving IBRANCE plus letrozole in Study 1 and 66% of patients receiving IBRANCE plus fulvestrant in Study 2. In Study 1 and 2, the median time to first episode of any grade neutropenia was 15 days and the median duration of Grade ≥3 neutropenia was 7 days.

Monitor complete blood counts prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across Studies 1 and 2. One death due to neutropenic sepsis was observed in Study 2. Physicians should inform patients to promptly report any episodes of fever.

Embryo-Fetal Toxicity. Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose.

ADVERSE REACTIONS

Clinical Studies Experience. Because clinical trials are conducted under varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

Study 1: IBRANCE plus Letrozole. Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole in Study 1.

Permanent discontinuation associated with an adverse reaction occurred in 43 of 444 (9.7%) patients receiving IBRANCE plus letrozole and in 13 of 222 (5.9%) patients receiving placebo plus letrozole. Adverse reactions leading to permanent discontinuation for patients receiving IBRANCE plus letrozole included neutropenia (1.1%) and alanine aminotransferase increase (0.7%).

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia.

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leukopenia, infections, and anemia.

Adverse Reactions (≥10%) in Study 1

Adverse Reaction	IBRANCE + Letrozole (N=444)			Placebo + Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[a]	60[b]	6	1	42	3	0
Blood and lymphatic system disorders						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Gastrointestinal disorders						
Stomatitis[c]	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
Skin and subcutaneous tissue disorders						
Alopecia	33[d]	N/A	N/A	16[e]	N/A	N/A
Rash[f]	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

Grading according to CTCAE 3.0.
N=number of patients; N/A=not applicable
[a] Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.
[b] Most common infections (>1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.
[c] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.
[d] Grade 1 events – 30%; Grade 2 events – 3%.
[e] Grade 1 events – 15%; Grade 2 events – 1%.
[f] Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving Ibrance plus letrozole in Study 1 included alanine aminotransferase increased (9.9%), aspartate aminotransferase increased (9.7%), epistaxis (9.2%), lacrimation increased (5.6%), dry eye (4.1%), vision blurred (3.6%), and febrile neutropenia (2.5%).

Laboratory Abnormalities in Study 1

Laboratory Abnormality	IBRANCE + Letrozole (N=444)			Placebo plus Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	97	35	1	25	1	0
Neutrophils decreased	95	56	12	20	1	1
Anemia	78	6	0	42	2	0
Platelets decreased	63	1	1	14	0	0
Aspartate aminotransferase increased	52	3	0	34	1	0
Alanine aminotransferase increased	43	2	<1	30	0	0

N=number of patients; WBC=white blood cells.

Study 2: IBRANCE plus Fulvestrant. Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus fulvestrant. No dose reduction was allowed for fulvestrant in Study 2.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving IBRANCE plus fulvestrant, and in 6 of 172 (3%) patients receiving placebo plus fulvestrant. Adverse reactions leading to discontinuation for those patients receiving IBRANCE plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus fulvestrant arm by descending frequency were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, diarrhea, thrombocytopenia, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus fulvestrant in descending frequency were neutropenia and leukopenia.

Adverse Reactions (≥10%) in Study 2

Adverse Reaction	IBRANCE + Fulvestrant (N=345)			Placebo + Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[a]	47[b]	3	1	31	3	0
Blood and lymphatic system disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	3	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis[c]	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18[d]	N/A	N/A	6[e]	N/A	N/A
Rash[f]	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

Grading according to CTCAE 4.0.
[a] Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.
[b] Most common infections (>1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, rhinitis, influenza, conjunctivitis, sinusitis, pneumonia, cystitis, oral herpes, respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, and paronychia.
[c] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.
[d] Grade 1 events – 17%; Grade 2 events – 1%.
[e] Grade 1 events – 6%.
[f] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving IBRANCE plus fulvestrant in Study 2 included asthenia (7.5%), aspartate aminotransferase increased (7.5%), dysgeusia (6.7%), epistaxis (6.7%), lacrimation increased (6.4%), dry skin (6.1%), alanine aminotransferase increased (5.8%), vision blurred (5.8%), dry eye (3.8%), and febrile neutropenia (0.9%).

Laboratory Abnormalities in Study 2

Laboratory Abnormality	IBRANCE + Fulvestrant (N=345)			Placebo + Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

DRUG INTERACTIONS

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A.

Effect of CYP3A Inhibitors. Coadministration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. Avoid concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole). Avoid grapefruit or grapefruit juice during IBRANCE treatment. If coadministration of IBRANCE with a strong CYP3A inhibitor cannot be avoided, reduce the dose of IBRANCE.

Effect of CYP3A Inducers. Coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85%. Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine, enzalutamide, and St John's Wort).

Drugs That May Have Their Plasma Concentrations Altered by Palbociclib. Coadministration of midazolam with multiple doses of IBRANCE increased the midazolam plasma exposure by 61%, in healthy subjects, compared with administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced as IBRANCE may increase their exposure.

USE IN SPECIFIC POPULATIONS

Pregnancy. Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryofetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on AUC. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

In a fertility and early embryonic development study in female rats, palbociclib was administered orally for 15 days before mating through to Day 7 of pregnancy, which did not cause embryo toxicity at doses up to 300 mg/kg/day with maternal systemic exposures approximately 4 times the human exposure (AUC) at the recommended dose.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses up to 300 mg/kg/day and 20 mg/kg/day palbociclib, respectively, during the period of organogenesis. The maternally toxic dose of 300 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights. At doses ≥100 mg/kg/day in rats, there was an increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra). At the maternally toxic dose of 20 mg/kg/day in rabbits, there was an increased incidence of skeletal variations, including small phalanges in the forelimb. At 300 mg/kg/day in rats and 20 mg/kg/day in rabbits, the maternal systemic exposures were approximately 4 and 9 times the human exposure (AUC) at the recommended dose, respectively.

CDK4/6 double knockout mice have been reported to die in late stages of fetal development (gestation Day 14.5 until birth) due to severe anemia. However, knockout mouse data may not be predictive of effects in humans due to differences in degree of target inhibition.

Lactation. There is no information regarding the presence of palbociclib in human milk, nor its effects on milk production or the breastfed infant. Because of the potential for serious adverse reactions in breastfed infants from IBRANCE, advise a lactating woman not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

Females and Males of Reproductive Potential. Based on animal studies, IBRANCE can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a pregnancy test prior to starting treatment with IBRANCE. IBRANCE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose. Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for 3 months after the last dose. Based on animal studies, IBRANCE may impair fertility in males of reproductive potential.

Pediatric Use. The safety and efficacy of IBRANCE in pediatric patients have not been studied.

Altered glucose metabolism (glycosuria, hyperglycemia, decreased insulin) associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), kidney (tubule vacuolation, chronic progressive nephropathy) and adipose tissue (atrophy) were identified in a 27 week repeat-dose toxicology study in rats that were immature at the beginning of the studies and were most prevalent in males at oral palbociclib doses ≥30 mg/kg/day (approximately 11 times the adult human exposure [AUC] at the recommended dose). Some of these findings (glycosuria/hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present with lower incidence and severity in a 15 week repeat-dose toxicology study in immature rats. Altered glucose metabolism or associated changes in the pancreas, eye, kidney and adipose tissue were not identified in a 27-week repeat-dose toxicology study in rats that were mature at the beginning of the study and in dogs in repeat-dose toxicology studies up to 39 weeks duration.

Toxicities in teeth independent of altered glucose metabolism were observed in rats. Administration of 100 mg/kg palbociclib for 27 weeks (approximately 15 times the adult human exposure [AUC] at the recommended dose) resulted in abnormalities in growing incisor teeth (discolored, ameloblast degeneration/necrosis, mononuclear cell infiltrate). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Geriatric Use. Of 444 patients who received IBRANCE in Study 1, 181 patients (41%) were ≥65 years of age and 48 patients (11%) were ≥75 years of age. Of 347 patients who received IBRANCE in Study 2, 86 patients (25%) were ≥65 years of age and 27 patients (8%) were ≥75 years of age. No overall differences in safety or effectiveness of IBRANCE were observed between these patients and younger patients.

Hepatic Impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Based on a pharmacokinetic trial in subjects with varying degrees of hepatic function, the palbociclib unbound exposure (unbound AUC_{INF}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function.

Review the Full Prescribing Information for the aromatase inhibitor or fulvestrant for dose modifications related to hepatic impairment.

Renal Impairment. No dose adjustment is required in patients with mild, moderate, or severe renal impairment (CrCl >15 mL/min). Based on a pharmacokinetic trial in subjects with varying degrees of renal function, the total palbociclib exposure (AUC_{INF}) increased by 39%, 42%, and 31% with mild (60 mL/min ≤ CrCl <90 mL/min), moderate (30 mL/min ≤ CrCl <60 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (C_{max}) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

OVERDOSAGE

There is no known antidote for IBRANCE. The treatment of overdose of IBRANCE should consist of general supportive measures.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression/Infection
- Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness or any increased tendency to bleed and/or to bruise.

Drug Interactions
- Grapefruit may interact with IBRANCE. Patients should not consume grapefruit products while on treatment with IBRANCE.
- Inform patients to avoid strong CYP3A inhibitors and strong CYP3A inducers.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products.

Dosing and Administration
- Advise patients to take IBRANCE with food.
- If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.

Pregnancy, Lactation, and Fertility

Embryo-Fetal Toxicity
- Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with IBRANCE therapy and for at least 3 weeks after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 months after the last dose.

Lactation
- Advise women not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

Rx only

This brief summary is based on IBRANCE® (palbociclib) Prescribing Information LAB-0723-4.0, Rev. 02/2018.

Patients With Moderate to Severe Anxiety or Depression Symptoms: Recognizing, Assessing, Referring, and Monitoring

EXPERT EDITORIAL

Barbara L. Andersen, PhD, and
Marlena M. Ryba, PhD

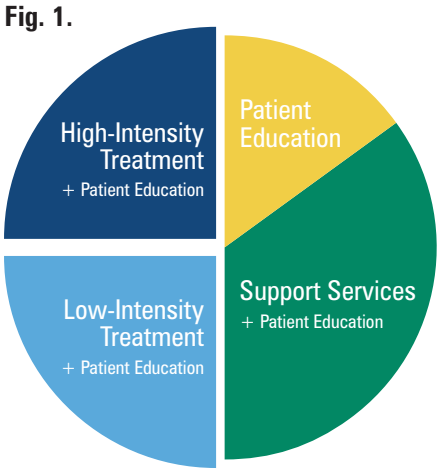
Stress from a cancer diagnosis and anticipation of treatment is ubiquitous among patients. However, for roughly 50% of patients it is overwhelming, promoting a cascade of negative sequelae—psychological, behavioral, and biological. High stress can even generate anxiety or depressive disorders. In fact, psychiatric disorders are more prevalent among patients with cancer than among those with any other chronic illness. Although studies vary, prevalence estimates are near 40% for any mood disorder, 10% for anxiety disorders, and 20% for any adjustment disorder.[1,2] By comparison, the World Health Organization (WHO) World Mental Health reports 12-month prevalence estimates for the United States as 9.7% for mood disorders and 19.0% for anxiety disorders.[3] In this editorial, we focus on the individuals in greatest need—patients with cancer who have moderate to severe symptoms of anxiety and/or depression.

Identification: Who They Are Not

Many patients (50% ± 10%) have no to few symptoms of anxiety or mood disorders. These individuals have naturally available resources that facilitate positive emotional coping (e.g., acceptance, learning to live with cancer), cognitively (e.g., thinking of a plan of action), and behaviorally (e.g., seeking support from others, concentrating on helpful actions). They often have multiple resources that reduce the likelihood of added cancer stress, such as adequate income, food and housing security, adequate employment and/or retirement benefits, health insurance, education beyond high school, a partner or close confidant, and U.S. citizenship.

Still, individuals reporting none to few anxiety and/depressive symptoms benefit from modest psychological or behavioral resources (Fig. 1). Patients need accessibility to information on topics such as cancer as an illness (preferably disease specific); easy to understand descriptions of diagnostic and treatment processes/procedures with sensations/symptom descriptions; medical team contact information; and information regarding supportive care persons or programs in the hospital/clinic and the community for which professional referral is not needed. For example, the Cancer Support Community (CancerSupportCommunity.org) provides free psychosocial services in 44 affiliates in the United States and many more abroad.

Fig. 1.



This is a representation of the prevalence and severity of symptoms of anxiety and depressive symptoms in adults with cancer and the corresponding need for services. All patients need educational information to reduce stress and enhance positive coping. General supportive services are needed for 15% to 20% of patients with low- to low-moderate symptom severity. In contrast, 50% (+/- 10%) of patients have anxiety and/or depressive symptoms in the moderate to severe or severe range. For the latter groups, empirically supported treatments of low or high intensity are needed.

Identification: Who They Are

Patients with anxiety disorders

Anxiety disorders have several variants, but the most common is generalized anxiety disorder (GAD; Box 1). The pathognomonic GAD symptom (i.e., multiple excessive worries) may be evidenced by a patient mentioning multiple concerns or fears rather than worry, per se. Whereas cancer worries are common, GAD worry or fear is disproportionate to actual risk (e.g., excessive fear of recurrence when the probability is low). The patient with GAD also has worries about a range of other, noncancer topics with the focus changing over time, be it probable or improbable, emergent or distant, low intensity or high.

Patients with mood disorders

A major barrier to identifying mood disorders in patients is lack of familiarity with diagnostic criteria for major depressive disorder (Box 2). Even when depression is suspected, there may be inaccurate clinical judgments of severity ("He has lung cancer, of course he is depressed.") or not in need of treatment because of other concurrent problems ("She has a drinking problem."). Regardless, depression is not an acceptable symptom of living with cancer.

That said, distinguishing depression can be difficult. The vegetative symptoms (e.g., poor appetite, sleep problems, and weight loss/gain) may overlap with cancer symptoms or treatment side effects. Instead, a focus on psychological and behavioral indicators may be more informative. Low moods can come and go, but it is persistent depressed or irritable moods coupled with decreased interest or pleasure with most activities on most days (anhedonia) that signals major depressive disorder. Some patients may not view themselves as depressed but report fatigue with energy or activity levels so low that they stop engaging in activities or maintaining relationships previously enjoyed. Feelings of guilt, worthlessness, hopelessness, or negative feelings about oneself are red flags, as they are not in the normal range of patients' responses to cancer. If depression is suspected, having the patient complete the Physicians Health Questionnaire-9 (PHQ-9) is the quickest 5- to 10-minute step to aid in confirming or disconfirming one's clinical hypothesis. Many patients with moderate to severe symptoms will have major depressive disorder as a preexisting chronic illness, and the stresses of cancer can trigger another episode.[4]

Comorbidity of Anxiety and Depression

Life stressors and neurobiological processes and psychological vulnerabilities contribute to both anxious and depressive emotions and behaviors. The disorders share symptoms including avoidance of people and activities, difficulties concentrating, psychomotor restlessness, fatigue, and sleep problems. More than half of patients diagnosed with major depressive disorder (MDD) are found to have an anxiety disorder, usually GAD and/or panic. Conversely, patients with an anxiety disorder have high rates of MDD. Patients with comorbidity have greater symptom severity and a lower response to treatment than those with either disorder alone.[5,6]

When Patients Are Not Diagnosed

The consequences of anxiety or mood disorder diagnosis "misses" are considerable. The disorders produce general life impairment and may interfere with a person's decision-making, undermine the emotional and physical strength required to undergo cancer treatment, yield more symptoms (e.g., pain), and lower treatment tolerance or adherence. They pose a substantial financial burden on the economy and personal finances. Without treatment, symptoms increase

See Severe Anxiety or Depression, Page 16A

ARTICLE HIGHLIGHTS

- Anxiety is the most common mental health problem for cancer survivors, and many patients go undiagnosed.
- The consequences of anxiety or mood disorder diagnosis "misses" are considerable. The disorders produce significant life impairment and lead to lower treatment tolerance and adherence.
- Proper referral to empirically supported treatments is necessary, and continued monitoring will increase the likelihood that patients will receive services and be more successful in meeting cancer's challenges.

Diagnostic Criteria for Generalized Anxiety Disorder* 1

A. Excessive anxiety and worry (apprehensive expectation), occurring more days for at least 6 months, about a number of events or activities (e.g., work, school).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
   1. Restlessness, feeling keyed up or on edge;
   2. Being easily fatigued;
   3. Difficulty concentrating or mind going blank;
   4. Irritability;
   5. Muscle tension; and
   6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important functioning.

**Abbreviated*

Diagnostic Criteria for Major Depressive Disorder 2

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either #1 or #2. Symptoms must occur at a high frequency, i.e., most of the day(s), nearly every day. The symptoms cause clinically significant distress or impairment in social, occupational, or other important functioning.

- Depressed mood reported most of the day, nearly every day (e.g., feels sad, empty, hopeless) or observed by others (e.g., appears tearful);
- Markedly diminished interest or pleasure in all, or almost all, activities;
- Significant weight loss when not dieting or weight gain (e.g., > 5% of body weight in a month), or decrease or increase in appetite;
- Insomnia or hypersomnia;
- Psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down);
- Fatigue or loss of energy;
- Feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick);
- Diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others); and,
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

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Loxo Oncology is currently exploring oncogenic mechanisms involving the following signaling pathways:

- Tropomyosin receptor kinase (TRK)
- Rearranged during transfection (RET) kinase
- Bruton's tyrosine kinase (BTK)
- Fibroblast growth factor receptor (FGFR)

Severe Anxiety or Depression

Continued from page 14A

in severity, recovery becomes difficult, and remission intervals become shorter. These patients have more frequent physician visits, spend more time with physicians, have more hospitalizations, and have higher health care costs. Generally, individuals with depression have higher mortality, with both stress and depression predictive of cancer progression and premature death.[7]

Identifying Patients in Need

The Commission on Cancer (CoC) mandate for distress screening has presented oncology with multiple challenges of implementation (e.g., Which screening measure is to be used? How does referral come about?). ASCO recommends that every person be evaluated for anxiety and depressive symptoms when diagnosed and regularly thereafter.[8] ASCO screening measures were chosen for their psychometric validity, reliability, specificity for anxiety and depression, and successful use in primary care. Distress tools were excluded, as the term "distress" is nonspecific and the tools are neither suited to discovery of criterion symptoms nor determination of the severity.

As GAD is the most common anxiety disorder, the GAD-7 assessment was recommended (Box 2, page 14A). The PHQ-9 includes the items for MDD symptoms, including one for suicide ideation. Survey data suggest approximately 14% of Americans report suicide ideation as having occurred at some point during their lifetime.[9] As might be expected, suicidal thoughts are more frequent for the individual with a chronic illness.[10] If ideation is endorsed, a second step evaluation would include assessment of the presence or absence of characteristics shown empirically and temporally related to the acute onset of suicidal behavior, with the most prominent being threats to kill or hurt oneself, looking for ways to kill oneself, and talking or writing about death, dying, or suicide.[11]

In addition to the GAD-7/PHQ-9, simple questions asked of the patient and recorded in the medical record would inform screening and referral. The following characteristics portend that symptoms may be of longer duration, pose difficulty to treatment, or limit treatment response:

- History: Any prior psychiatric diagnoses, with or without treatment, or history of/or current substance use or abuse;
- Additional chronic illnesses, such as diabetes or severe arthritis;
- Marital status: Single, not married, separated, or divorced;
- Employment status: Unemployed or underemployed;
- Education level: High school or technical school graduate or lower; and
- Financial resources: Low income, no/insufficient insurance coverage, or ongoing financial obligations.

Of these, prior history of psychiatric diagnosis is the most influential. For older patients, further assessment of those scoring in the low-moderate symptom range (PHQ-9 scores of 8-14, GAD-7 scores of 10-14) could be considered when additional risk factors (e.g., social isolation, bereavement, and financial difficulty) are present.[12]

After Patients Are Identified: Next Steps

Committing effort to follow screening with patient discussion

It is estimated that 7.6 million cancer survivors in the United States have not discussed their psychosocial functioning with health care providers.[13] Even though they are aware of their emotional problems, they want their medical team to ask and offer help, and they have generally positive views of psychosocial services.[14] Patients are not surprised when learning a screening measure suggests they are having significant difficulty with anxiety, depression, or both.

Identifying and evaluating referral resources

Persons and/or programs within the clinic/facility and the community who can aid in diagnosis, problem identification, and provide empirically supported treatment need to be identified. In so doing, evaluate the mental health provider/service candidates, including education and licensure, training in the diagnosis and treatment of psychopathology, and cost structure for services provided, with experience in treating patients with cancer and familiarity with ASCO guidelines desirable. Ask the provider which empirically supported psychological and/or behavioral interventions are offered, and have him/her specify the content, mode of treatment (group, individual, phone-based), and typical treatment duration, as ASCO recommends.

Discussion with the patient and, if possible, scheduling the first appointment will increase the likelihood that the patient will follow through. Providing specificity (date, time, place, and person) helps circumvent avoidance.

Empirically support treatments

An accompanying podcast discusses cognitive behavioral treatments for GAD and MDD disorders of both low and high intensity. The podcast is available on iTunes, Google Play, and Libsyn. Search for "ASCO Daily News."

After Referral, Helping Patients Stay in Treatment

Sometimes we can be our own worst enemy. Cautiousness and a tendency to avoid threatening stimuli are cardinal features of anxiety pathology, making it common for persons to not follow through on referral or treatment recommendations. Persons with depressive symptoms can lack motivation and do the same. These characteristics and behaviors are disorder-based, and do not reflect personal failings or lack of responsibility.

With this in mind, oncology follow-up is critical. At the next oncology visit, determine the patient's follow-through. If it has been poor, reiterate the rationale and description of the provider's offering, discuss and address barriers, and provide support and encouragement to try again with rescheduling or redirecting to another option. If there is compliance though dissatisfaction, seek out the reasons and address as is possible, with referral to another provider considered. Request referral sources to provide monthly updates for the first 2 months as this is the period during which symptoms should remit, and if not, there is need for a treatment adjustment. Continue to monitor the patient's follow-through.

Conclusion

Cancer has modifiable psychological and behavioral patient elements capable of reducing risk, morbidity, and mortality. Identifying patients with moderate to high anxiety and depressive symptoms is the first step. Proper referral to empirically supported treatments is necessary, and continued monitoring will increase the likelihood that patients will receive services and be more successful in meeting cancer's challenges. This pathway is an achievable goal which offers huge returns for patients and oncology care systems. ●

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New Guidelines

Continued from page 9A

trastuzumab-based adjuvant therapy. Findings from the ExteNET trial showed that women who were randomly assigned to receive neratinib for 1 year after completing adjuvant trastuzumab had better invasive DFS than women who received placebo.

"We know that many patients do incredibly well with standard chemotherapy and trastuzumab alone, but these two agents—trastuzumab and neratinib—provide another therapeutic avenue for patients at highest risk," Dr. Denduluri said.

Practical for Practices?

The first recommendation regarding the use of adjuvant capecitabine helps address a gap in practice. It was previously unclear which intervention best reduces the high risk of disease recurrence in patients who underwent preoperative chemotherapy and had residual disease at surgery. The other two recommendations suggest escalating current approaches to therapy in hopes of providing incremental benefits.

However, all three recommendations are clear in suggesting these regimens are ones that oncologists may want to consider, not necessarily ones they should or must provide. As Dr. Giordano noted, that subtle distinction is intentional—and critical.

"Although the clinical trials were positive, they had smaller benefits than people were hoping for," she said. "So, it was reasonable to include them, but it wasn't on the level of 'everyone needs to get this.' We wanted to present these recommendations as options, something to discuss—especially for patients who are high-risk. But these recommendations aren't necessarily for everyone."

In determining whether to include the recommendations, the Expert Panel had to consider real-world effects of the adjuvant treatment regimens on patients.

"With any treatment decisions, the toxicity of the chemotherapy and/or biologic therapy and a patient's baseline risk of the cancer coming back need to be balanced with the potential benefits of these agents," Dr. Denduluri said.

But because the results from the trials were smaller than expected, achieving this balance may be challenging.

"We want to give patients the best treatments and best chances of being cured, but we also don't want to expose people to treatments unnecessarily if they might not have a substantial benefit," Dr. Giordano said. "We wanted the recommendations to be individualized so physicians and patients can make decisions based on factors like risk of recurrence and disease stage."

Although the new guidelines are not likely—nor intended—to be adopted for all patients, their likelihood of improving clinical outcomes is strong.

"I think there's a potential for these recommendations to impact many people because they address two specific subtypes of breast cancer—the HER2-positive and also patients at highest risk for recurrence," Dr. Denduluri said. ●

–Emily A. Kuhl, PhD

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Immunotherapy and CRC

Continued from page 1A

mutations, thus CRCs that are deficient in MMR have substantially increased tumor mutation burden. Because the types of errors recognized and repaired by MMR occur at areas of DNA repeats known as microsatellites, dMMR CRC is also termed microsatellite-instability high (MSI-H).

Because of the known differences in outcomes, as well as in effective therapies, guidelines have now shifted with regard to testing for MMR status. "Any patient with a colon or rectal cancer should be tested for deficient MMR," Dr. Overman said. This is true regardless of family history or other baseline characteristics.

Testing can be done using immunohistochemistry staining, polymerase chain reaction (PCR), or next-generation sequencing. Dr. Overman said that they all function reasonably well, although there are some downsides to each approach. PCR testing has a sensitivity and specificity of 97% and 95%, respectively, although it is known to be less accurate in noncolon cancers. IHC staining has a sensitivity of 92% and a specificity of 99%, but it cannot detect loss-of-function mutations. Next-generation sequencing is effective but there are multiple approaches using different microsatellite targets, with varying sensitivity and specificity.

"I think it is key that everyone understands the universal testing approach is now listed in guidelines," Dr. Overman said. "Everyone should be tested."


Dr. Michael J. Overman

Checkpoint Inhibitors

It has long been known that dMMR CRC has a unique immune tumor microenvironment consisting of tumor-infiltrating lymphocytes and a Crohn-like lymphoid reaction.[1] The immune activity is likely responsible for the favorable outcomes observed in resected dMMR CRC and led to the initial trials of immune checkpoint inhibitors in this setting.

In May 2017, the U.S. Food and Drug Administration (FDA) approved pembrolizumab for treatment of patients with dMMR CRC after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan, and who do not have satisfactory alternate treatment options.


Dr. Michael A. Morse

Soon afterward, in July 2017, the FDA also approved nivolumab for the treatment of dMMR CRC after the same prior treatment. This was based on results of the CheckMate-142 study, in which 74 patients with dMMR CRC were treated with single-agent nivolumab; that study showed a response rate of 31%, and 69% demonstrated disease control for 12 weeks or longer.[1] At 12 months, the progression-free survival (PFS) rate was 50%, and the overall survival (OS) rate was 73%.

The same study also examined the combination of nivolumab and ipilimumab in 119 patients with dMMR CRC.[1] The combination appeared effective, with an overall response rate of 55%, a 12-month PFS rate of 71%, and a 12-month OS rate of 85%.

Dr. Overman noted that the responses appear to be extremely durable. Long-term follow-up of several cohorts has revealed a flattening of both PFS and OS curves, suggesting the effect is a lasting one. This is true of nivolumab and pembrolizumab monotherapy, as well as the combination of an anti–PD-1 agent with an anti–CTLA-4 agent; the 12-month PFS rate in a cohort of patients receiving the combination was 77%, compared with 48% in a group receiving nivolumab monotherapy.

With pembrolizumab monotherapy, Dr. Overman noted that in 18 patients who stopped therapy at 2 years per the study protocol (11 with a response and seven with residual disease), the median time off therapy was 8 months and none have yet recurred. The 12-month PFS rates seen with both nivolumab and pembrolizumab are among the highest seen across the variety of tumor types in which these agents have been tested and approved.

Several phase III trials are now ongoing in this field. In one, atezolizumab is being tested alone and in combination with chemotherapy (mFOLFOX6) and bevacizumab in more than 300 patients with MSI-high metastatic CRC. Enrollment has completed for another study in the metastatic setting. A total of 270 patients will be randomly assigned to either mFOLFOX6 and bevacizumab or pembrolizumab monotherapy.

"Standard-of-care therapy for second-line [and after] for dMMR CRC is nivolumab or pembrolizumab," Dr. Overman said. "I think we do need more understanding of resistance mechanisms," he added, since not all patients with dMMR CRC respond to these immunotherapy approaches.

Proficient MMR Tumors

"We know that there is no benefit for anti–PD-1 antibody therapy in pMMR tumors," said Michael A. Morse, MD, MHS, FACP, of the Duke University Cancer Institute. "It's night and day." He spoke about why pMMR tumors do not respond and provided some potential approaches to change this situation.

"It does seem to be that having more T cells in the tumor may be important," Dr. Morse said. Having neoantigens or something else for the T cells to respond to may improve the response to immunotherapy. It is possible that WNT signaling could play a role in this, as it has been found to be inversely correlated with T-cell infiltration. Targeting WNT signaling is difficult, though, because it is mainly a protein-protein interaction, Dr. Morse said.

Still, some therapeutic approaches have been proposed. For example, in one ongoing clinical trial, the porcupine inhibitor CGX1321 is being tested along with pembrolizumab in patients with advanced gastrointestinal tumors.

There is also potential with approaches that modulate the cytokine environment since this can also induce an immune response. This could be accomplished by inducing inflammation in the tumor. A phase Ib study of talimogene laherparepvec along with atezolizumab is ongoing in patients with triple-negative breast cancer or colorectal cancer with liver metastases.

Dr. Morse said it could also be possible to focus on natural killer (NK) cells rather than on T cells as a way to improve pMMR responses to immunotherapy. Early results from a first-in-human trial of monalizumab, which suppresses inhibitory signaling by tumors on NK cells, plus durvalumab in metastatic pMMR CRC will be presented on Sunday (Abstract 3540). There were three partial responses out of 37 patients, while none would be expected with only the checkpoint inhibitor in this patient population.[2]

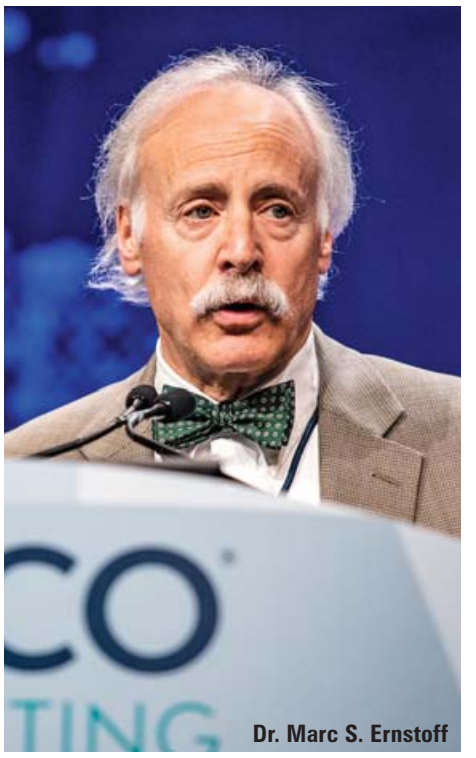
Looking toward the future, Dr. Morse said cancer vaccine approaches may be necessary. "It is likely that there will be patients who do not have adequate T-cell responses," he said. "If we could activate them with cancer vaccines, then we would have the substrate for checkpoint molecules to work on at the tumor site."

He stressed that the dramatic differences between dMMR and pMMR outcomes and responses suggest a new approach may be needed. "At some point we're going to have to diverge; they are biologically different," Dr. Morse said. "It may be that we have to forge our own path and study microsatellite-stable as a completely separate entity without considering what goes on in MSI-high."

Managing Toxicity

Since checkpoint inhibitors are now considered standard in some patients with dMMR CRC, considerations regarding toxicity have become more relevant. "It is important for us to recognize these toxicities and learn how to deal with them," said Marc S. Ernstoff, MD, of Roswell Park Comprehensive Cancer Center. He noted that a recent survey of oncologists found that only approximately half of respondents said they were somewhat or very comfortable managing immune-related adverse events (irAEs).

irAEs can be caused by several mechanisms, including the development of autoimmunity, expression of immune checkpoints, and inflammatory cytokine releases. Often, the toxicity can be delayed and it can affect nearly every organ.


Dr. Marc S. Ernstoff

Pruritus, rash, and diarrhea are among the most common irAEs. The timing can vary: skin reactions tend to occur early, and gastrointestinal, endocrine, and hepatic toxicities are usually seen within the first 12 weeks of therapy.

"About 10% to 20% of patients will have lasting, unresolved toxicities requiring ongoing management," Dr. Ernstoff said.

Some of the main principles of irAE management include ruling out other causes such as infection or comorbid diseases and consulting early on with organ-specific specialists when appropriate. Also, several established treatment algorithms have now been published that provide guidance for management. It is important to be aware of life-threatening AEs such as myocarditis, myositis, pneumonitis, and bowel perforation.

"Immune checkpoint inhibition of the PD-1/PD-L1 axis is, in general, well-tolerated and has an excellent safety profile compared to conventional chemotherapy," Dr. Ernstoff said. "Familiarize yourself and your community with the toxicity profile." ●

–Dave Levitan

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Much Work Remains to Determine Optimal Immunotherapy Combinations

The field of cancer immunotherapy has greatly advanced during the last 7 years. Agents approved for the treatment of advanced melanoma by the U.S. Food and Drug Administration include the anti–CTLA-4 antibody ipilimumab (2011), the anti–PD-1 antibodies nivolumab (2014) and pembrolizumab (2014), ipilimumab combined with nivolumab (2015), and the oncolytic virus vaccine talimogene laherparepvec (T-VEC; 2015). In addition, the combination of the kinase inhibitors dabrafenib and trametinib was approved in 2014 for *BRAF*-mutant melanoma. Disease remission has been achieved in many more patients thanks to these agents. The available evidence and continuing research for efficacious combinations of therapies for melanoma treatment was the topic of the Education Session "Rational Combinations With an Immuno-Oncology Backbone," held June 1.

Alexander M. Eggermont, MD, PhD, of Cancer Institut Gustave Roussy, France, provided an overview of treatment with multiple immunotherapies. Combining therapies does not always lead to a successful outcome. For example, the combination of dacarbazine with ipilimumab in patients with advanced melanoma was less successful than ipilimumab monotherapy. The immune-related adverse event profile of 3 mg/kg ipilimumab is well-characterized and includes colitis, hepatitis, hypophysitis, and rare cases of myocarditis and neuritis syndromes. Combination therapy may result in unforeseen events, further complicating the development of optimal treatment.


Dr. Alexander M. Eggermont

Anti–PD-1 and anti–PD-L1 antibodies have a more favorable toxicity profile compared with anti–CTLA-4 antibodies. Various combinations of ipilimumab with other immune-modulating, antiangiogenic, chemotherapeutic, or targeted agents have been investigated or are under evaluation, but nivolumab and pembrolizumab have taken center stage in the development of combination therapies.

"Monotherapy with anti–PD-1 agents has been phenomenally successful in melanoma and is actually an overachiever. Thus, it will be difficult to show that combining something with an anti–PD-1 agent in melanoma will be significantly better," Dr. Eggermont noted.

A small increase in overall survival has been observed when the anti–PD-1 agent nivolumab was combined with ipilimumab compared with nivolumab alone. More recently, anti–PD-1 agents combined with indoleamine 2,3-dioxygenase (IDO) inhibitors showed promising results. An interim analysis of a study of the IDO inhibitor epacadostat and pembrolizumab showed an overall response rate of 58%. This led to a phase III program that was stopped in April because of negative results. Combining the oncolytic vaccine T-VEC with pembrolizumab in patients with melanoma led to an overall response rate of 57%.

"Is this sufficient to be better than anti–PD-1 alone? I doubt it," Dr. Eggermont said. More research is needed to obtain better insight into the optimal mechanisms and timing of combining therapies.

Biomarkers to Monitor Disease Response

Jennifer A. Wargo, MD, MMedSc, of The University of Texas MD Anderson Cancer Center, discussed ways to optimize treatment regimens based on disease response to therapy. Reverse translation follows patients longitudinally using blood and tumor samples. This methodology was used to determine potential biomarkers in a cohort of 53 patients with melanoma who received treatment with ipilimumab.

Seven patients experienced a disease response; 46 patients experienced disease progression and subsequently received anti–PD-1 therapy. Of those 46 patients, 13 demonstrated disease response and 33 had disease progression. Baseline biopsies and biopsies during treatment were obtained from all patients with molecular and immune profiling conducted at each time point. The immune signatures in the pretreatment biopsy did not predict response to therapy, but the immune signatures in the biopsies obtained during treatment were highly predictive.

"If we stress the system and look for an adaptive response during treatment, we may get a better answer, suggesting that early on-treatment biomarkers may have more utility, at least in the short-term, until we can identify better pretreatment biomarkers," Dr. Wargo said.

Several lines of evidence suggest that the gut microbiome affects the response to immunotherapy. The microbiome is comprised of 100 trillion microbes, making up 3% of the human body mass. The gastrointestinal tract harbors the greatest number of microbes. Dr. Wargo and her team wanted to investigate the role of the gut microbiome in patients who received immune checkpoint blockade for melanoma.

Oral and gut microbiome samples and biopsies were obtained from 233 patients at baseline and after therapy. The samples underwent microbiome sequencing and immune profiling, revealing that patients who responded to anti–PD-1 therapy had a much greater diversity of gut bacteria and had prolonged progression-free survival. The results were recapitulated using fecal samples from the patients in mechanistic studies in germ-free mice. A collaborative effort is currently underway to conduct a clinical trial to further investigate the modification of the gut microbiome to elicit better response to therapy via fecal transplant and other methodologies.


Panelists from the Education Session "Rational Combinations With an Immuno-Oncology Backbone."

"Combination therapy holds tremendous promise, but there are a lot of complexities with regard to ideal combinations, dosing schedules, and optimal biomarkers of response. As we move forward, I think we need to embrace novel biomarkers and targets," Dr. Wargo concluded.

Radiation and Immunotherapy

Marka R. Crittenden, MD, PhD, of the Earle A. Chiles Research Institute, Providence Cancer Center, provided an update on the preclinical data of radiation with immunotherapy combinations and available clinical trial information. Several synergistic mechanisms exist that relate to radiation and the subsequent immune response. These include tumor antigen release and increased priming, tumor adjuvant release, the deletion of anergic and regulatory T cells, as well as T-cell activation, antigen processing machinery, death receptor upregulation, induction of cytokines and chemokines, and increased immune-cell trafficking.

Dr. Crittenden discussed two types of synergistic interactions between radiation therapy and the immune response. The first is the abscopal response, in which radiation acts as an in situ vaccine leading to increased control of distant disease sites. The second type of interaction is immunogenic modulation, in which changes occur in the tumor microenvironment and any residual cancer cells leading to immune-mediated clearance of remaining local disease.


Dr. Jennifer A. Wargo

Evidence to date indicates that a higher radiation dose may lead to a better endogenous vaccine effect, but an inflexion point may exist. To date, most clinical trials of combined radiation and immunotherapy have been early-phase studies. When combined with interleukin-2, the data indicate better response with ablative doses of radiation therapy. The response rates of radiation combined with immune checkpoint inhibitors in clinical studies have not been as high as those seen in the preclinical setting.

Recent reports indicate that responses to immune checkpoint inhibition combined with radiation therapy are dependent on preexisting immunity. Although there is a solid basis for combining radiation with immuno-oncology agents to boost abscopal responses, the details are still being researched. Preclinical studies will help guide the timing, appropriate immunotherapy combinations, and the amount of optimal fractionation. In addition, immuno-oncology agents other than immune checkpoint inhibition should be investigated in clinical trials.

"Radiation struggles a lot more when a patient does not have a competent immune system, suggesting that part of why radiation works is that the immune system helps clear the last residual cells," Dr. Crittenden said.

Patients receiving anti–PD-1 therapy have demonstrated enhanced local control of radiated tumors. PD-1 axis activation occurs following radiation as a result of PD-L1 upregulation.

"If you have patients receiving PD-1 inhibition, even if they are not responding systemically, they often show very good responses to the radiated tumor. Now we are starting to look at immunotherapy in the upfront neoadjuvant setting in combination with radiation to see if we can start reducing our doses and perhaps spare toxicity," Dr. Crittenden concluded. ●

–Muriel Cunningham

Patient-Reported Outcomes

Continued from page 4A

Thompson said. "Patients were randomly assigned into three groups for mode of survey collection. These groups were stratified by cancer state—active treatment, survivorship, and observation alone—as these groups were likely to have different PRO and activity levels."

Group 1 answered weekly surveys on paper only, Groups 2 and 3 answered weekly surveys on their iPhones, with Group 2 receiving daily emoji questions on their iPhone and Group 3 receiving daily emoji questions on the Apple Watch.

The weekly surveys included Patient-Reported Outcomes Measurement Information short forms: global health scale (physical and mental health); physical function, fatigue, sleep disturbance, social/role function; and anxiety. Additionally, patients were asked four single-item linear analog self-assessment questions: physical well-being, emotional well-being, fatigue, and quality of life.

The median age of the 294 patients was 53 (range, 20-79) and the median time since cancer diagnosis was 14.4 months. There were 99 patients in Group 1 (paper only), 98 patients in Group 2, and 97 patients in Group 3. The majority of patients were receiving active therapy, predominantly white, and predominantly female.

"In general, this was a computer-savvy group, but only 27% had used a smartwatch prior to the study," Dr. Thompson said. Patients wore the watches an average of 9.8 hours a day, meaning capturing the activity data on the device was feasible.

Response rates over the 12-week study varied: Group 1 had an average response rate of 76%, Group 2 had an average of 77%, and Group 3, who completed their weekly surveys on the iPhone app but the emoji component on the watch, had a 60% response rate. In all groups, the response rates decreased over time. In Group 3, the response rate decreased to about 40% by week 12; the other two groups had a response rate of more than 60% at week 12.

Activity levels were analyzed using square root of average daily values in order to minimize the effect of outliers. The associations between PROs and activity levels were analyzed with Spearman correlations (SC) for univariate analysis, stepwise linear regression models for multivariate associations, and mixed models for longitudinal associations; in all, the researchers collected more than 21.4 million discrete data points.


Dr. Manali I. Patel

"We found having more steps per day was associated with less fatigue, better physical function, better global physical well-being, better social function, and less sleep disturbance," Dr. Thompson said. "Having more minutes of exercise per day was associated with better global mental well-being and less sleep disturbance."

The researchers developed two emoji scales (one ordinal, one mood), each of which met the criteria for a valid ordinal scale. There was a high association between the emoji scale and fatigue (SC -0.80; $p < 0.0001$), between the emoji scale and physical function (SC 0.70; $p < 0.0001$), on the emotional scale (SC 0.68; $p < 0.0001$), and overall QOL (SC 0.75; $p < 0.0001$). Patients who selected the "happy face" emoji in the mood analysis had better overall ratings than other groups, whereas the "thinking face" group had the lowest QOL, physical health, and mental health, and the highest anxiety scores.

Dr. Thompson's group will continue following patients every 3 months for 24 months for events, including relapse, retreatment, hospitalization, and death to determine associations between activity level and PROs with clinical outcomes.

"In addition, we are performing further analysis to understand the discrepancies in response rates between groups," she said.

Lay Health Worker–Led Symptom Assessment

In the third study (Abstract 6502), Manali I. Patel, MD, MPH, MS, of Stanford University, said rising cancer costs "are demanding novel ways to deliver effective care." Numerous barriers to symptom management have been previously identified, including professional workforce shortages. Dr. Patel's group implemented a proactive symptom assessment conducted by a lay health worker supervised by a nurse practitioner.

Patients were enrolled if they were newly diagnosed with stage III or IV cancer, required medical oncology, planned to receive all of their care at the oncology practice where the assessment was implemented, and were enrolled in CareMore Medicare Advantage. The primary

See Patient-Reported Outcomes, Page 22A

FDA Commissioner Discusses How Agency Plans to Speed Access to Cancer Advances

"We are at a turning point in the history of cancer," said Scott Gottlieb, MD, commissioner of the U.S. Food and Drug Administration (FDA), addressing the crowded room of ASCO attendees during the Opening Session on June 2.

During his presentation, Dr. Gottlieb highlighted some of the new efforts that the FDA is pursuing across the entire drug development and regulatory process and how the FDA hopes to create policies that are as sophisticated as some of the treatments currently in development.

For example, in 2017, the FDA approved 16 new drugs and biologics including the first two CAR T-cell therapies. It also approved the first tissue-agnostic cancer treatment.

"Rather than require a separate development program for each disease site, which may have taken many years, we have created a single therapeutic approach based on the solid understanding of the underlying biology of microsatellite stability," Dr. Gottlieb said.

Dr. Gottlieb also announced the launch of two new FDA pilot programs. The first is aimed at focusing submissions more squarely on the most relevant data for assessing safety and efficacy.

"The goal is to improve the overall quality of drug applications and make sure that resource and review times are being focused on evaluating data that are most meaningful to clinicians and patients," Dr. Gottlieb said.

Under the pilot program, as soon as a sponsor locks its database and decides it wants to file with the FDA for drug approval, the FDA starts sharing data. This informed pre-analysis gives reviewers and sponsors an early opportunity to address data-quality issues.

Dr. Scott Gottlieb

"By the time the sponsor files the application, the agency review team will already be familiar with the data, and the analysis and review teams will be in a better position to conduct more efficient and thorough data review," Dr. Gottlieb said.

The second pilot program includes a new application assessment aid. This tool is a voluntary submission form that applicants can use to facilitate the FDA's assessment of the drug application. Under this templated approach to reviewing applications, the FDA will annotate the sponsor's drug file with its own assessment. The annotated application will be presented at the Oncology Drug Advisory Committee meeting as a single, combined background document that contains the applicant's position and the FDA's analysis of that position.

"A world is being created in many places where individual health and wellness are more clearly and rapidly becoming the beneficiary of technologic process," Dr. Gottlieb said. "We are challenging ourselves at the FDA to make sure we have the best approach to move these opportunities forward." ●

–Leah Lawrence

Cell-Free DNA Assays

Continued from page 7A

0.003% and 0.2%, thus a highly sensitive assay and tumor-informed approach are required for detection, Dr. Diehn noted.

Dr. Diehn also discussed ongoing work to develop a urine-based cfDNA assay to detect recurrence following localized bladder cancer treatment. Currently, surveillance in these patients requires repeated urine cytology and cystoscopy, which is limited by low sensitivity and high cost. He and colleagues modified the CAPP-Seq assay to detect ctDNA in the cell-free component of urine samples.

In a cohort of 64 patients with early-stage bladder cancer, ctDNA was detectable in the urine of patients who had disease recurrence following treatment months prior to the clinical diagnosis of recurrence, whereas ctDNA was detectable in only one patient who did not have recurrence. The sensitivity and specificity of a tumor-informed urine cfDNA approach were 91% and 100%, respectively, compared with a sensitivity of about 40% with urine cytology and cystoscopy.

Breast Cancer Monitoring and Management

Clinicians are deploying cfDNA assays to monitor disease burden in patients with metastatic breast cancer (mBC), and there is evidence that these assays could be used to stratify therapy, identify drug resistance–associated mutations, and detect heterogeneity between metastases. However, the question remains whether ctDNA could be used prospectively for early diagnosis of cancer, said Carlos Caldas, MD, FRCP, FRCPath, FMedSci, of the University of Cambridge, United Kingdom, during his presentation.

In 2013, Dr. Caldas and colleagues demonstrated using targeted or whole-genome sequencing that ctDNA levels fall when patients respond to treatment and rise when disease progresses. Therefore, they are a better biomarker of disease than circulating tumor cells or cancer antigen 15-3. Now, they can use ultra low pass whole-genome sequencing of plasma samples without any knowledge of tumor mutations, Dr. Caldas noted.


Dr. Carlos Caldas

In other applications, Dr. Caldas and colleagues conducted proof-of-principle studies that suggested they could identify mutations associated with resistance in patients with mBC using whole-exome sequencing. They were also able to capture the metastatic heterogeneity and evolution of mutations between metastases by exome and targeted amplicon sequencing, "opening up the possibility of liquid biopsies representing not one metastasis but all metastases," Dr. Caldas said.

Currently, Dr. Caldas and colleagues are carrying out a study of whole-genome sequencing to assay for structural variants such as translocations rather than point mutations. This approach has the advantage of being free of PCR and sequencing artifacts such that detection of even one copy of a structural variant in cfDNA would indicate the presence of tumor cells and thus could be a more sensitive way to detect MRD and track relapse, Dr. Caldas noted. "I hope that within the next 12 to 18 months we will have hard data on this," he said.

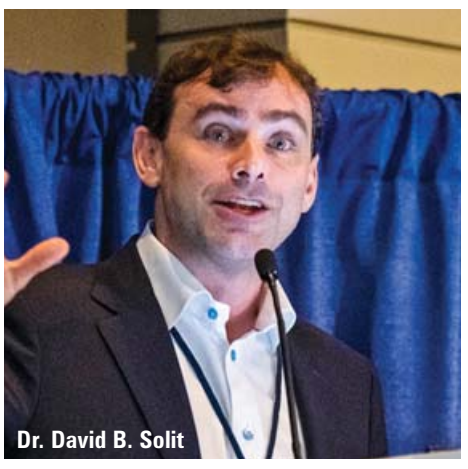
There is currently great excitement over developing cfDNA assays as a diagnostic tool. There has been some interesting research in this area suggesting that copy number gains and losses in cfDNA may allow presymptomatic tumor detection, Dr. Caldas said.

Bringing cfDNA Assays Into the Clinic

In his presentation, David B. Solit, MD, of Memorial Sloan Kettering Cancer Center, discussed how medical oncologists can use cfDNA assays in treating patients with advanced cancer either alongside other tests or instead of genomic profiling of tumor tissue.

Four years ago, an initiative at Memorial Sloan Kettering Cancer Center set out to molecularly profile tumor tissue for every patient with cancer to identify any actionable mutations and then match those patients with the appropriate therapy. For the molecular profiling, they use an assay called MSK-IMPACT, which captures regions in 468 cancer genes of interest using biotinylated DNA probes and sequences the regions for alterations.

To date, approximately 24,000 patients have received MSK-IMPACT testing. There is an effort now within the initiative to conduct molecular profiling at earlier stages of disease when matched therapies can be curative and treatment morbidity is lower, Dr. Solit said.


Dr. David B. Solit

Dr. Solit and colleagues have attempted to apply their MSK-IMPACT assay to plasma samples to determine if they could analyze 468 cancer genes in a cfDNA assay. In about two-thirds of cases, they are able to detect mutations in cfDNA, whereas no mutations can be detected in the remaining cases, suggesting their methods are not adequately sensitive for cfDNA assays, he said.

Nevertheless, Dr. Solit recounted a patient case to illustrate the urgent need to develop cfDNA. In a young patient with cancer, tumor profiling from a lung biopsy failed because of inadequate tissue for analysis, as it does in 5%-10% of cases. A cfDNA test was able to detect an actionable EML4-ALK fusion, but it was only done after the patient had died from the cancer. "We didn't have the technology at the time to identify the key molecular drivers in this individual patient," Dr. Solit said.

"To me, the first use of cfDNA going forward is in this population where we simply can't get good tumor tissue to do tumor genomic analysis, and cell-free will potentially provide an option," Dr. Solit said. "There are probably hundreds to thousands of patients like this in the country who are dying," especially patients with metastatic prostate cancer. ●

–Carina Storrs, PhD

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Karnofsky Memorial Award

Continued from page 3A

that some patients so affected should be amenable to a curative therapeutic strategy."[1] Their hypothesis was published in the *Journal of Clinical Oncology* in 1995, although it was consigned at that time to the editorial page.

The hypotheses underlying the subsequent research efforts were that metastasis represents a spectrum of disease, including the number of metastases, the involved organs, and the pace of progression. Additionally, subsets of patients with limited or oligometastatic disease are potentially curable with metastasis-directed therapies.

Randomized research has found that some patients with oligometastatic disease can be cured with ablative therapy and that these patients "can likely be identified through clinical features and molecular parameters," he said. Also, "some patients with oligo-progressive disease may be cured."

> One important area of Dr. Weichselbaum's research was defining, along with his colleague Samuel Hellman, MD, FASCO, the clinical state of oligometastasis, which they hypothesized refers to a distinct clinical entity.

Dr. Weichselbaum also highlighted research related to the "cytoreductive power of radiation therapy" and said that radiation is a "powerful cytotoxin" that can be used to boost antitumor immunity locally and "maybe systemically as well."

For the future, several avenues of investigation are promising, Dr. Weichselbaum said. These include clinical and molecular classification of the spectrum of metastasis, improved interaction of radiotherapy and immune therapy, and use of metastasis-directed ablative therapy to cure or decrease tumor cell burden. ●

–Kathy Holliman, MEd

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Patient-Reported Outcomes

Continued from page 20A

outcome was feasibility (retaining 75% of patients), with secondary outcomes of health care use, patient satisfaction, and self-reported health. There were a total of 186 patients in the intervention group and 102 patients in the control group. Baseline characteristics were similar between the two groups, but the intervention group had a higher risk adjustment factor (3.25 ± 1.78 vs. 2.80 ± 1.43, respectively).

Patients who received the proactive symptom assessment had significantly lower mean number of emergency department visits per quarter (0.60 vs. 0.92; p = 0.03) and lower mean number of inpatient admissions per quarter (0.72 vs. 1.02; p = 0.03).

"There was an almost $10,000 difference in total costs of care between the intervention group and the control group," she said.

Self-reported overall health and mental/emotional health also improved at the 5-month follow-up compared to the 1-week post-oncology visit.

'Important,' But Unanswered Questions Remain

Discussant Martin J. Taphoorn, MD, of Haaglanden Medical Center and Leiden University Medical Center, Netherlands, called all three papers "important," but he said they all left some unanswered questions. For instance, although web-mediated follow-up for PROs allows for easy assessment and earlier detection and treatment of symptoms, it's not applicable for all patients. "There may be cross-cultural differences in the use of a web-based system," he said.

Using mobile technologies or apps within the technology "may reduce the response burden and increase compliance," he said. "But it is important to see in the longer-term follow up that there was still a difference in OS with or without cross-over. This could be cost-effective because it may reduce the number of CT scans."

Although the Apple Watch activity data was associated with PROs and emojis are showing promise for PRO assessment, Dr. Taphoorn was concerned about the moderate response rate on the watch and with the lack of comparative data between the three groups.

"Emojis are easily interpretable, which could be beneficial for those with cognitive difficulties, illiteracy, or for children," Dr. Taphoorn said.

> "Emojis are easily interpretable, which could be beneficial for those with cognitive difficulties, illiteracy, or for children." –DR. MARTIN J. TAPHOORN

Using a lay health worker to assess symptoms can improve overall health and patient satisfaction while substantially reducing health care use and costs, but the short-term results and lack of control group should not be overlooked. ●

–Michelle Dalton, ELS

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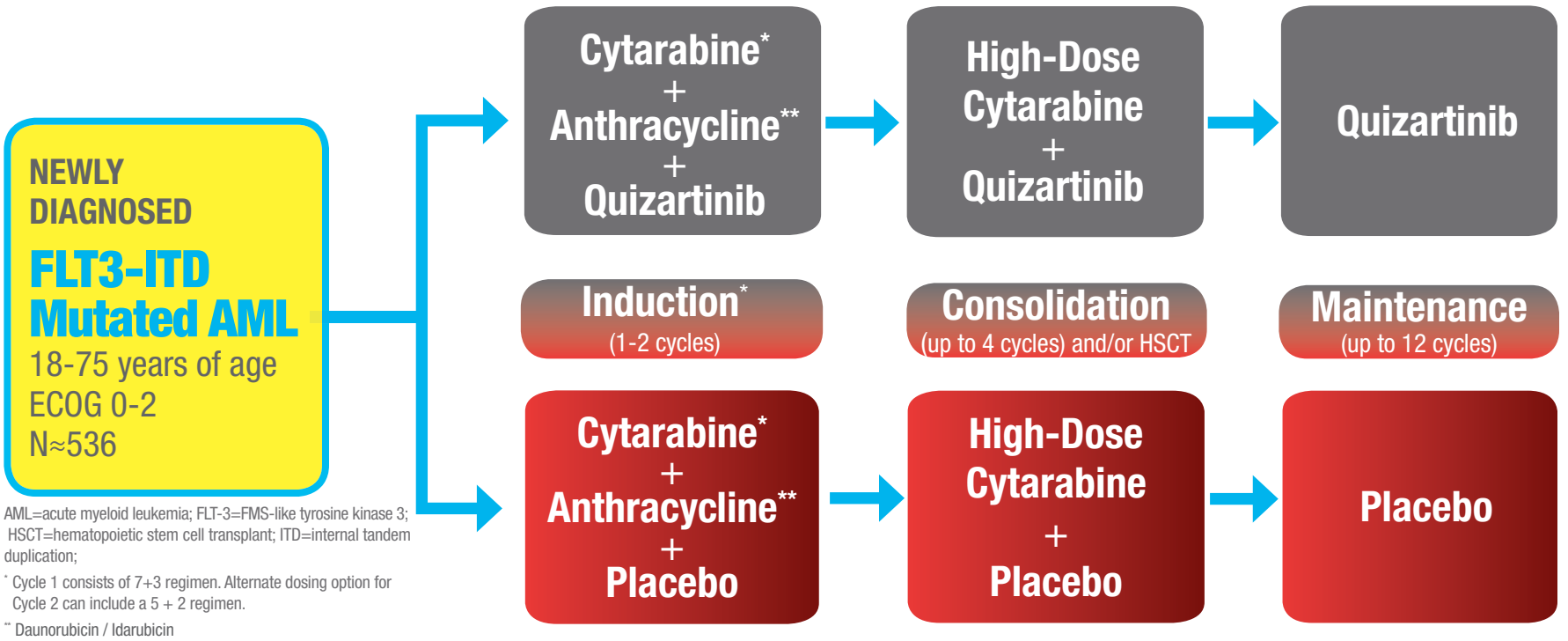

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SUNDAY · JUNE 3, 2018

Addressing Patient Communication Challenges

SESSION PREVIEW

There is no question that advances in cancer diagnostics and treatment have dramatically improved the cancer care landscape. However, these advances have led to increased costs and more complex treatments, causing oncologists to struggle with the sheer scope of information they're expected to know and communicate to patients.

For example, should oncologists ask patients about the potential financial burden of their cancer treatment? Should oncologists explain the results of complex genetic tests to patients or turn to specialists? How can oncologists manage patient expectations about targeted therapies and immunotherapies when only a subset of patients responds extremely well (so-called exceptional responders) to treatment?

Three Education Sessions during the 2018 Annual Meeting will delve into these topics, present the latest research, and provide practical solutions.*

Financial Burden of Cancer Care

During the Education Session "Communicating the Financial Burden of Treatment With Patients" on June 3, session Chair Ryan D. Nipp, MD, MPH, of Massachusetts General Hospital Cancer Center, will present the clinician's perspective on discussing cancer care costs with patients, concerns physicians and patients have about discussing financial issues, and practical strategies to alleviate financial distress.

"Immunotherapies and targeted therapies are new and exciting, but they can also be more expensive than the older treatments such as chemotherapy," Dr. Nipp

See Patient Communication, Page 3B

Dr. Douglas R. Lowy to Receive Science of Oncology Award

Douglas R. Lowy, MD, will receive the 2018 Science of Oncology Award. The award recognizes outstanding contributions to basic or translational research in cancer.

Dr. Lowy is deputy director of the National Cancer Institute (NCI) and chief of the NCI's Laboratory of Cellular Oncology. He is recognized for his work on HPV infection and was instrumental in developing the technology underlying the HPV vaccines that have been approved by the U.S. Food and Drug Administration (FDA). His contributions in this field have been recognized with the Lasker-DeBakey Clinical Medical Research Award in 2017 and the Szent-Gyorgyi Prize for Progress in Cancer Research in 2018.

In an interview with the *ASCO Daily News*, Dr. Lowy discussed the impact of his research efforts and ongoing investigations, the outlook for cancer research, and why this award is important to him and his colleagues.

Q: Can you talk about your previous and ongoing work in the development of the technology that underlies HPV vaccines against cervical cancer?

Dr. Lowy: Almost all the research that I have done has been in close collaboration with my longstanding colleague John Schiller, PhD, NIH distinguished investigator and deputy chief in the NCI's Laboratory of Cellular Oncology. He and I initially did basic research, and our first foray into translational research was the development of the virus-like particle vaccine used in HPV vaccination.

We were fortunate that this effort paid off in the laboratory very quickly when we determined that expressing just one gene from the papillomavirus could make particles that looked like papillomaviruses. When the particles were immunized into animals and then into people, they induced very high titers of neutralizing antibodies that are usually associated with protection from preventive vaccines.

Dr. Douglas R. Lowy

After that first translational research, we subsequently developed the standard serologic assays for measuring immune responses to HPV vaccination. One is

See Science of Oncology Award, Page 5B

PROs Bring Value to Routine Symptom Management and Clinical Trials

EXPERT EDITORIAL

Ethan Basch, MD, MSc, FASCO

Patient-reported outcomes (PROs) encompass data reported directly by people about how they feel and function—for example, symptoms, performance status, and quality of life.

PROs are collected through questionnaires that ideally have been rigorously developed and tested to assure that questions are clear, that they are measuring what we think they are measuring (i.e., "valid"), that they are reliable, and that the scores change as we might expect (i.e., "sensitive"). These questionnaires can be administered through good old-fashioned pencil and paper or electronically through the internet, an app, or automated telephone systems (Fig. 1).

Depending on the context of use, PRO questionnaires may be administered to patients on a regular basis, for example every 1, 2, or 3 weeks during active treatment from home between visits, or every cycle of therapy at visits. There are many different reasonable approaches that will depend on the goals for using the PRO data, as described below.

Fig. 1. Sample Patient PRO Interfaces for Mobile and Web

ARTICLE HIGHLIGHTS

- Patient-reported outcomes (PROs) reflect how patients feel and function and are measured through questionnaires.
- PROs can be collected through the internet, automated telephone systems, or downloadable applications.
- Multiple studies have tested whether it is feasible to integrate PROs into routine cancer care (it is) and whether outcomes are improved as a result (they are).
- PROs are the gold standard for assessing symptoms, physical functioning, and quality of life in clinical trials.

Using PROs for Symptom Monitoring in Routine Cancer Care

Multiple studies show that clinicians miss about half of their patients' symptoms during cancer treatment.[1,2] The downstream consequences of missing symptoms include patient suffering due to poor symptom control, missed treatments, emergency room (ER) visits and

See Patient-Reported Outcomes, Page 13B

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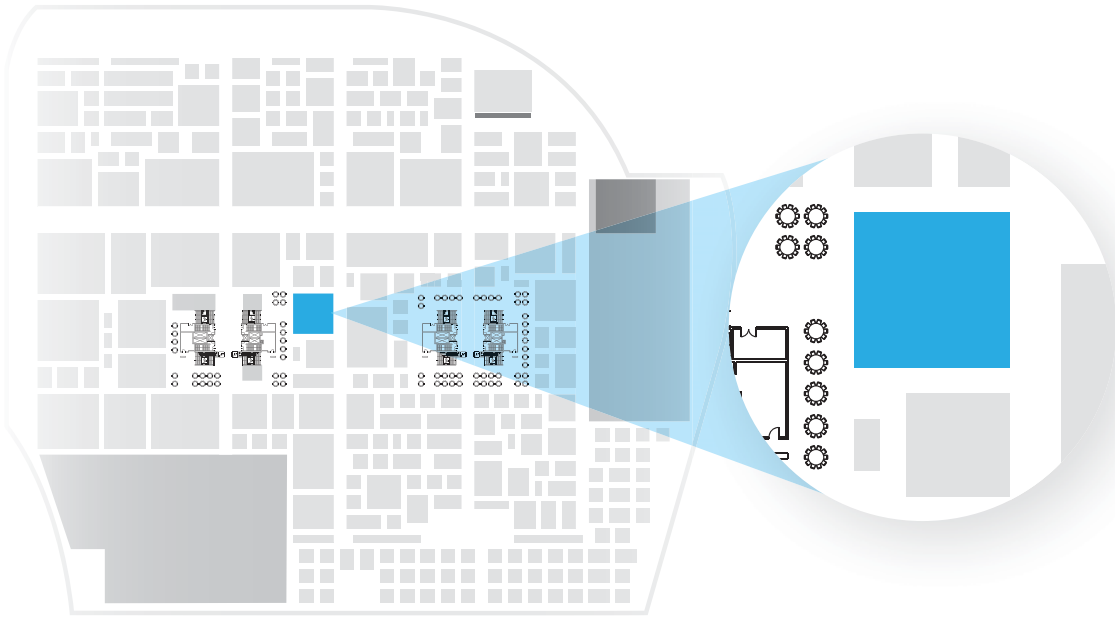

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Patient Communication

Continued from page 1B

said. From 1965 to 2013, the average monthly cost of cancer treatment increased from $100 to $10,000.[1] "Although patients with a good prognosis live longer, they may need to take their medications over a longer period of time, which can add to their financial burden," he explained.

To better understand the financial burdens faced by patients and their families, Gery P. Guy Jr., PhD, MPH, of the Centers for Disease Control and Prevention, will present the latest research on the costs of cancer care, share the publicly available data sources to examine the financial burden, and emphasize the need for more research in this area during his presentation, "Cost in the Era of Targeted Therapies and Immunotherapies for Cancer."

Studies show that when patients delay or forego care to defray costs, they may experience decreased quality of life, increased risk of depressed mood, and higher frequency of worrying about cancer recurrence.[2] However, research also shows that patients want to discuss the financial impact of care with their oncology team.[3,4] Therefore, medical organizations, including ASCO, recommend that clinicians discuss the cost of care with patients.

"We need to think of cost information as another piece of informed decision-making, which ultimately empowers patients," Dr. Nipp said.

Although oncologists can't be expected to navigate the maze of insurance coverage, just knowing which medications are more expensive than others can jumpstart the conversation. For example, Dr. Nipp may say to a patient, "I have heard this is an expensive medication. Let me know if you have any problems with your insurance coverage or trouble affording this prescription."

To round out the session, Ellen M. Sonet, MBA, JD, of Cancer*Care*, will discuss several strategies for assisting patients experiencing financial burdens including assessments, referrals, and interventions during her presentation, "Assisting Patients With the Cost Burden of Cancer Diagnosis and Treatment: Next-Generation Sequencing Testing, Off-Label Medications, and More."

Next-Generation Sequencing

Technology has dramatically improved the pace of genetic testing using DNA. It took more than a decade to sequence the first human genome; now a human genome can be sequenced in 1 or 2 days.

"We have seen a confluence of better, faster, and cheaper next-generation sequencing (NGS) technologies and more targeted therapies approved for cancers," Ben H. Park, MD, PhD, of the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, said. "However, NGS is a fast-moving target. Although some NGS platforms are now U.S. Food and Drug Administration (FDA)–approved to screen for many abnormalities, NGS technologies have outpaced FDA-approved therapies and are being used to guide therapeutic decision-making outside of these intended uses."

Dr. Park will chair the Education Session "Helping Our Patients Understand Molecular Testing and Its Implications" on June 4. He will discuss how academic medical centers and community molecular tumor boards can guide interpretation and analysis of test results and the differences between germline and somatic testing techniques, their limitations, and his recommendations.

"The results from NGS testing can vary significantly depending on the exact test performed and analysis of sequencing data," he said. "For example, the germline tests we do with a cheek swab specimen only look for heritable mutations, but the tumor tests we conduct predominantly look for mutations within the cancer. Using only one test can result in incomplete information."

Even when genetic mutations are identified, though, they may not have FDA-approved therapies. During his presentation, "Discussing Test Results: Understanding Actionable and Nonactionable Mutations," Michael P. Mullane, MD, of Aurora Cancer Care, will discuss how to prioritize actionable versus nonactionable mutations based on different levels of evidence, the challenges of false positives, and the reports that molecular tumor boards provide to referring physicians and their patients.

Finally, Aaron S. Mansfield, MD, of the Mayo Clinic, will discuss treatment recommendations, the identification of

Dr. Ryan D. Nipp

Dr. Ben H. Park

Dr. Thomas W. LeBlanc

FDA-approved therapies, label versus off-label use, clinical trials, and how to identify and prioritize molecular trials during his talk, "Identifying Appropriate Trials for Our Patients and Considering Compassionate Use Programs."

Communicating Prognosis

Shared decision-making requires that patients be informed azbout their prognosis. Although all oncologists talk with patients about what to expect, studies show that more than half of patients with advanced cancer surveyed have inaccurate perceptions of their prognosis and tend to overestimate the likelihood of a cure and their survival.[5-7]

"Other studies suggest that some oncologists avoid or rarely engage patients in these conversations unless patients explicitly ask about their prognosis," Thomas W. LeBlanc, MD, MA, MHS, FAAHPM, of Duke University School of Medicine, said. As chair of the session "How Much Time Do I Have, Doc? Communicating Prognosis in the Era of Exceptional Responders," on June 4, Dr. LeBlanc will set the stage for these topics by presenting research on prognostication involving patients and physicians' perceptions and biases.

For example, oncologists may be reluctant to communicate a negative prognosis when they have seen even a small number of patients in similar situations do much better than expected. "The research also shows that as oncologists get closer to patients and develop long-term relationships, they become less accurate in estimating patients' survival," Dr. LeBlanc said.

Communicating prognosis to patients is further complicated by the fact that only a minority of patients respond exceptionally well to immunotherapies. "Because we can't predict with any degree of certainty who will respond well, we may further avoid communicating prognostic information," Dr. LeBlanc said.

During her presentation, "Exceptional Responders, Hope, and Prognostication: Making a Tough Problem Even Tougher," Jennifer S. Temel, MD, of Massachusetts General Hospital, will discuss the impact of novel immunotherapies on oncologists' ability to formulate and communicate a prognostic estimate to their patients with advanced disease.

Paul R. Helft, MD, of Indiana University Melvin and Bren Simon Cancer Center, will present various strategies to improve communication skills, including training programs and pairing with palliative care specialists during his presentation, "Necessary Collusion: Prognostic Communication With Advanced Cancer Patients." ●

–Christine Lehmann, MA

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**Program information updated as of February 22. For session time and location information, please refer to the ASCO iPlanner on the Attendee Resource Center (am.asco.org/arc).*

Education Session to Highlight Novel Molecular Diagnostic Platforms

SESSION PREVIEW

The Education Session "Next-Generation Diagnostics Beyond Tissue" on June 4* promises to provide an in-depth look at the novel innovations in noninvasive cancer molecular diagnostic platforms as well as their potential and challenges.

The need for improvement of molecular cancer diagnostics "has never been more important" given the advent of cancer genomics and genomics-guided precision medicine and the arrival of cancer immunotherapies, session Chair Patrick C. Ma, MD, MSc, of the WVU Cancer Institute, said.

"We have seen an unprecedented pace of progress in expansion of cancer diagnostics on tumor tissues as well as beyond tissues in novel noninvasive molecular assays," he said.

Other speakers at the Education Session will be Sai-Hong Ignatius Ou, MD, PhD, of the University of California Irvine Chao Family Comprehensive Cancer Center, whose topic will be "Liquid Biopsy to Identify Actionable Genomic Alterations"; and Peter Kuhn, PhD, of the USC Michelson Center, whose topic will be "Noninvasive Biomarkers for Immunotherapy."

Noninvasive cancer diagnostics platforms have evolved and expanded in recent years because of practical limitations and risks associated with tissue-based biopsy diagnostics, Dr. Ma said. These next-generation molecular diagnostic assays—such as liquid biopsy interrogating circulating tumor DNA or circulating tumor cells; proteomics, metabolomics, and exosomes; urine biopsy to assay circulating tumor DNA; saliva and stool biopsies for molecular-genomic assays; and breath biopsy measuring volatile organic compounds—have transformed the utility of cancer diagnostics, according to Dr. Ma. Novel diagnostic tools are being used to longitudinally monitor therapy for early disease detection and for therapeutic response-resistance monitoring, he said.

Liquid Biopsies

A recent review article highlighted the potential and challenge of liquid biopsies for early detection of cancer.[1] Liquid biopsies are intended to provide information about the response to therapies, to detect relapse with lead time compared to standard measures, and to reveal mechanisms of resistance. The use of these biopsies for detection of early malignant disease stages, however, is not as well documented as the research and data available for advanced tumor stages.[1]

Dr. Ou's presentation will focus on the innovations in liquid biopsies that can identify actionable genomic alterations, the approved tests, next-generation plat-

See Molecular Diagnostic Platforms, Page 13B

ASCO Updates Guidelines for Use of Bone-Modifying Agents in Multiple Myeloma

In January, members of an Expert Panel updated ASCO Clinical Practice Guidelines on the role of bone-modifying agents in patients with multiple myeloma.[1] The update incorporates evidence that has become available since the guidelines were last published, including new information about denosumab and updated recommendations regarding indications for bone-modifying agents, duration of treatment, and potential complications.

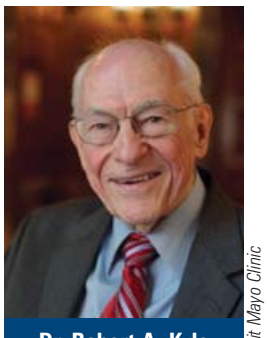
Indications for Bone-Modifying Agents

The updated guidelines have expanded the indications for bisphosphonate treatment. Whereas the previous guidelines recommended bone-modifying agents only for patients with lytic disease, the new guidelines state that any patient who receives treatment for active multiple myeloma should receive bisphosphonate therapy.

The benefit of the new recommendation is to decrease skeletal complications in patients with myeloma who have osteoporosis but no lytic disease, Expert Panel Co-Chair Kenneth Anderson, MD, of the Dana-Farber Cancer Institute, said. Dr. Anderson added that approximately 80% of patients with myeloma have osteoporosis or lytic disease of bone at diagnosis.

The expansion of the recommendation to use bone-modifying agents was based on the MRC IX trial, which demonstrated the benefit of bisphosphonate therapy in patients without lytic bone disease. In that trial, zoledronic acid was associated with a reduction in skeletal-related events at relapse and an improvement in progression-free survival. The MRC IX trial also demonstrated the superiority of intravenous zoledronic acid over clodronate (only approved outside the United States) for preventing skeletal complications.


Dr. Kenneth Anderson


Dr. Robert A. Kyle

Credit Mayo Clinic

Inclusion of Denosumab in Guidelines

Denosumab received U.S. Food and Drug Administration approval in January for the prevention of skeletal-related events in patients with multiple myeloma.[2] The approval was based on a large, international, phase III trial in which denosumab demonstrated noninferiority to zoledronic acid and was associated with less renal toxicity. The updated guidelines for bone-modifying agents note that denosumab provides an additional option, but it is substantially more expensive than zoledronic acid. "I would restrict denosumab to patients with myeloma with renal compromise," Dr. Anderson said.

Duration and Frequency of Bone-Modifying Agents

The updated guidelines also discuss the feasibility of less frequent dosing of bone-targeted treatments in selected patients, given the risk of osteonecrosis of the jaw associated with bone-targeting agents. For patients without active multiple myeloma who are receiving maintenance therapy, an every 3-month interval of bisphosphonates can be considered rather than monthly administration. Data from the single-arm Z-MARK study suggested that less-frequent dosing of zoledronic acid is associated with a low incidence of skeletal-related events.

In terms of duration of therapy, previous guidelines had suggested continuing bisphosphonates for 2 years, after which point discontinuation should be considered and further use should be left up to the physician's discretion. Recent data suggest a potential benefit with continued dosing beyond 2 years, although this has not been evaluated in a randomized study. The new guidelines note there are insufficient data to recommend a specific duration of bisphosphonate therapy. Therefore, it is recommended that bone-targeted treatment is continued for up to 2 years, resuming monthly treatment upon relapse with new-onset skeletal-related events.

For the subset of patients in remission who are not receiving maintenance therapy, "it is reasonable to discontinue bisphosphonates after 2 years, provided that the patient is in remission, [although] bisphosphonates should be reinstituted when the patient relapses," guideline co-author Robert A. Kyle, MD, of the Mayo Clinic, said.

See Bone-Modifying Agents, Page 30B

Science of Oncology Award

Continued from page 1B

the ELISA, and the other is a neutralization assay. The neutralization assay was enabled by another technology that we developed, papillomavirus pseudoviruses, which are authentic papillomavirus capsids or particles that can encapsidate any DNA. Both have become mainstay assays for measuring the immune response to papillomaviruses.

Using the papillomavirus pseudovirus technology, we developed a mouse genital tract challenge model for measuring the protection and immune response to papillomavirus challenge in the female mouse genital tract. The responses we saw were virtually identical to what we have seen in the international clinical trials that led to licensure for both vaccines.

Q: What did those clinical trials demonstrate?

Dr. Lowy: Early-phase trials demonstrated that the HPV vaccine was highly immunogenic and well tolerated in both young men and women. We subsequently worked with colleagues at the NCI who led a trial of the vaccine made by GlaxoSmithKline (GSK), a bivalent vaccine made of virus-like particles from different HPV types: HPV 16 and 18. The trial, conducted in Costa Rica, demonstrated that the vaccine had a high rate of efficacy. We also found in post-hoc analyses that the women who received just one or two doses of the vaccine were as well protected as the women who received all three doses. Those findings led to the approval and recommendation of only two doses of HPV vaccination for young adolescents.

The NCI began another clinical trial in Costa Rica in November 2017 with support from the Bill and Melinda Gates Foundation, which will determine whether one dose of the HPV vaccine in young adolescents is sufficient to induce strong, long-term protection. The trial will include about 20,000 adolescent girls who will be followed for 4 years after vaccination. Two FDA-approved HPV vaccines are being tested: the bivalent (types 16 and 18) vaccine[1] and the HPV 9-valent vaccine.[2]

Q: What are the potential implications of this trial?

Dr. Lowy: Although the vaccine is highly effective, costs and logistics combine to make the HPV vaccine less widely deployed in low- and middle-income countries. This is where the big public health problem resides for HPV-associated cancer, mainly cervical cancer. If one dose were shown to be effective, it would be far easier and much less expensive. That could expand the widespread deployment of the vaccine in less-developed countries, while at the same time saving a tremendous amount of money in the industrialized world, because you would not need to give as many doses.

Q: What is the focus of other research at the NCI, including the impact of funding due to the Cancer Moonshot?

Dr. Lowy: The NCI supports a broad range of research, including basic and investigator-initiated research. We support research on the causes of cancer, pathogenesis of cancer, the training of the next-generation cancer researchers, cancer health disparities, and a broad range of research in cancer prevention, screening, treatment, and survivorship. Fortunately, there is strong bipartisan support in Congress for biomedical research. In addition, our strong and committed cancer advocacy community plays an indispensable role in advocating strongly and effectively for funding on behalf of cancer research.

The NCI has been going full-tilt on implementing the recommendations of the Cancer Moonshot Blue Ribbon Panel, and we have created numerous funding opportunities that can be found on the NCI website at cancer.gov.

We have been going out regularly to our extramural colleagues to get their input on how to prioritize funding. Those efforts have led directly to a public-private partnership between the NCI and more than a dozen pharmaceutical companies to conduct research in the area of immunotherapy in what we call precompetitive collaboration. We are developing standard operating procedures and standardized assays that we are confident will be able to move the field forward.

Q: What is the importance of the Science of Oncology Award to you?

Dr. Lowy: One reason I am so pleased to accept this award is that it highlights how precision medicine and immunology can come together in important ways to prevent cancer from developing in the first place. Because ASCO is an organization of oncologists and oncology care providers, it is principally focused on the treatment of cancer. I am especially grateful to ASCO for highlighting our translational research, which is outside the area of treatment but instead is in an area earlier than treatment—in this case, primary prevention.

Although these awards are given to individuals, research is a group activity. I wouldn't be here if it were not for the excellent research that came before the research that Dr. Schiller and I have done. ●

–Tim Donald, ELS

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2018 GU Cancers Symposium Focuses on Translating Evidence to Multidisciplinary Care

The 2018 Genitourinary Cancers Symposium took place on February 8-10, in San Francisco, and featured the most up-to-date research and its translation to clinical, multidisciplinary care for prostate, renal, urothelial, testicular, and adrenal cancers.

Read on for a summary of some of the top research presented at the meeting, including data from long-term phase III trials, early-phase results of novel approaches, and the newest genomic and biomarker studies.

Advances in Prostate Cancer Therapy

Prostate cancer therapy continues to evolve. Several abstracts focused on androgen signaling inhibition, the use of immunotherapy options, and some of the specifics of radiotherapy in this malignancy.

- The phase III PROSPER trial (Abstract 3) showed that the androgen signaling inhibitor enzalutamide resulted in significantly better metastasis-free survival (MFS) compared with placebo in patients with metastatic castration-resistant prostate cancer (mCRPC). It included 1,401 patients, and the median MFS was 36.6 months with enzalutamide and only 14.7 months with placebo (HR 0.29, 95% CI [0.24, 0.35]; p < 0.0001). Subgroup analyses showed benefit across all subgroups, and there is an early, though nonsignificant, trend toward an overall survival (OS) benefit with enzalutamide as well.
- Similarly, the phase III SPARTAN trial (Abstract 161) demonstrated that the next-generation androgen signaling inhibitor apalutamide also offered much better MFS than placebo. In the study of 1,207 patients, the median MFS was 40.5 months with the study drug and 16.2 months with placebo (HR 0.28, 95% CI [0.23, 0.35]; p < 0.0001). The median time to symptomatic progression was also better with apalutamide. The trial was unblinded, allowing patients who originally received the placebo to receive apalutamide.
- As the era of immunotherapy has progressed, prostate cancer has proved a difficult malignancy for this field. A phase II study of mCRPC (Abstract 163) found that combining the immune checkpoint inhibitor durvalumab with the PARP inhibitor olaparib is well tolerated with some promising activity. Among 17 unselected patients with mCRPC, eight (47%) had prostate-specific antigen responses greater than 50%; notably, six of those patients had mutations in the DNA damage repair pathways. The combination was reasonably well tolerated, with the most common grade 3/4 adverse events including anemia (24%), lymphopenia (12%), and infection (12%).


More than 4,000 individuals attended the 2018 Genitourinary Cancers Symposium.

- Daily image-guided radiation therapy (IGRT) resulted in a lower risk of recurrence and late rectal toxicity compared with weekly IGRT in localized prostate cancer, but it was also associated with an increased risk of second cancer. A phase III trial (Abstract 4) randomly assigned 470 patients with N0 localized disease to daily or weekly IGRT. After a median follow-up of 4.1 years, the recurrence-free survival was nonsignificantly better with daily IGRT (HR 0.81, 95% CI [0.52, 1.25]; p = 0.330). The second cancer-free interval was worse with daily IGRT (HR 2.21, 95% CI [1.10, 4.44]; p = 0.026). OS was also worse with daily IGRT.

Advances in Bladder Cancer Treatment

Several studies highlighted major advances in the treatment of urothelial carcinoma, including some that should change standards of care.

- Adjuvant chemotherapy following nephroureterectomy significantly improves outcomes in upper tract urothelial cancer. The phase III POUT trial (Abstract 407), the largest randomized study in this setting to date, included 248 patients who were randomly assigned to either surveillance or chemotherapy with four cycles of gemcitabine-cisplatin or gemcitabine-carboplatin. After a median follow-up of 17.6 months, progression-free survival (PFS) favored chemotherapy (HR 0.49, 95% CI [0.30, 0.79]; p = 0.003). The 2-year disease-free survival rate was 51% with surveillance and 70% with chemotherapy; the trial stopped early due to the significant benefit seen with chemotherapy.
- Two bladder-sparing chemoradiation therapy regimens showed promise in a phase II trial of muscle invasive bladder cancer. The study (Abstract

See 2018 GU Cancers Symposium, Page 15B

Genitourinary Cancers Symposium
2018 HIGHLIGHTS

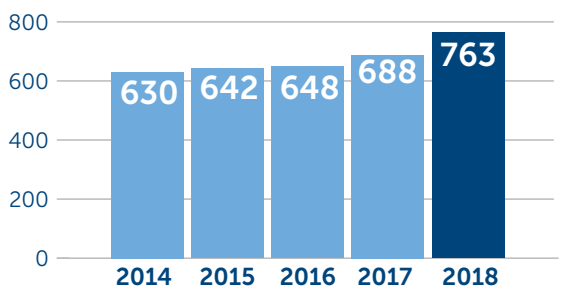
gucasym.org

The Genitourinary (GU) Cancers Symposium brings together a diverse group of international leaders in GU cancers from multiple specialties to debate and exchange the latest strategies in the prevention, screening, diagnosis, and multidisciplinary management of prostate, renal, testicular, penile, urethral, and urothelial cancers. Marking the Symposium's 14th year, the 2018 meeting had record-breaking abstract submissions and registration and featured the latest in systemic therapy, exploration of biomarkers, and genomic analysis. The Symposium was cosponsored by ASCO, ASTRO, and the Society of Urologic Oncology.

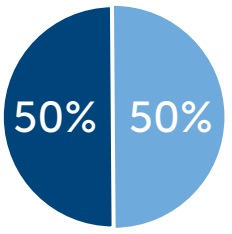
ABSTRACT SUBMISSIONS: TOP 5 COUNTRIES

USA	452
JAPAN	47
CANADA	46
UNITED KINGDOM	36
FRANCE	28

ABSTRACTS SUBMITTED BY YEAR



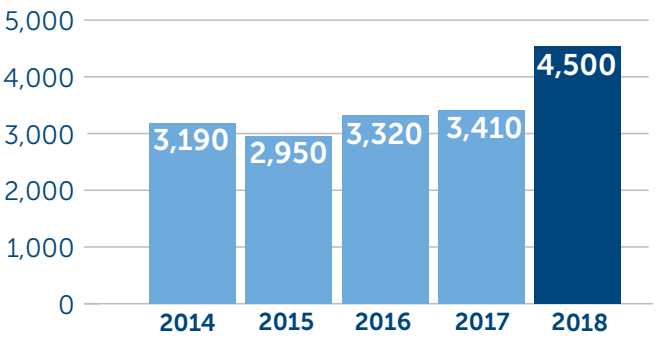
DOMESTIC VS. INTERNATIONAL ATTENDANCE



2,057
Domestic Professional Attendees

2,083
International Professional Attendees

TOTAL ATTENDANCE OVER TIME



ATTENDEE FEEDBACK

SOCIAL MEDIA #GU18

During the meeting,

2,020 users sent **7,928** tweets using the hashtag #GU18,

which garnered **16.4 million** potential impressions.

Could targeting specific PI3K isoforms be the key for patients with relapsed/refractory CLL/SLL and FL?

Explore **booth 2016** where Verastem will showcase an innovative look at:

- **PI3K isoforms and their distinct functions**
- **Potential inhibition of the tumor and its microenvironment**
- **The importance of targeted therapies**

Visit PI3Kinhibition.com for in-depth discussion and resources on a variety of topics in CLL/SLL and FL prior to the meeting.

Verastem Oncology

We are a clinical-stage biopharmaceutical company focused on developing therapies to improve the lives of patients diagnosed with cancer.

THESE ARE PATIENTS WITH METASTATIC GASTRIC, NON-SMALL CELL LUNG, OR COLORECTAL CANCER.

PATIENTS WHOSE DISEASE HAS PROGRESSED ON PRIOR TREATMENT.*

PATIENTS WHO KNOW THEIR SITUATION, BUT ARE NOT SURRENDERING TO IT.

PATIENTS WHO, IN THE FACE OF ADVERSITY, **REMAIN DETERMINED.**

LEARN MORE ABOUT THE APPROPRIATE PATIENTS FOR CYRAMZA AT **CYRAMZAHCP.COM**

*Hypothetical patient example.

SELECT IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

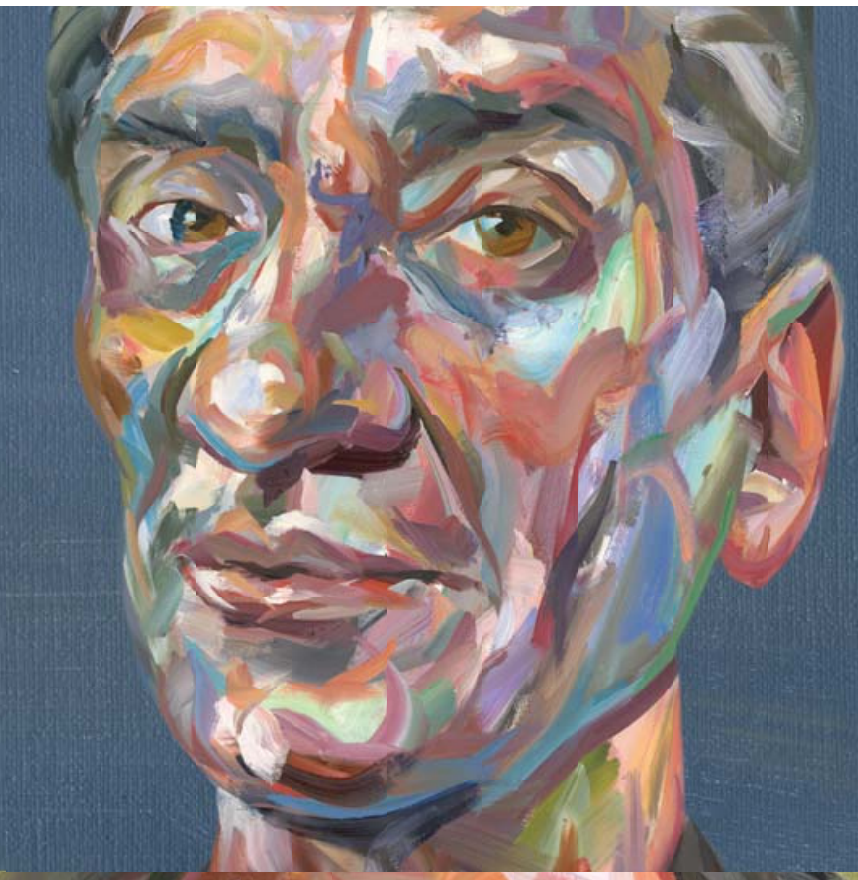
Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Please see additional Important Safety Information for CYRAMZA, including Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on adjacent page.
Also see the Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.

Lilly

CYRAMZA®
ramucirumab injection
10 mg/mL solution

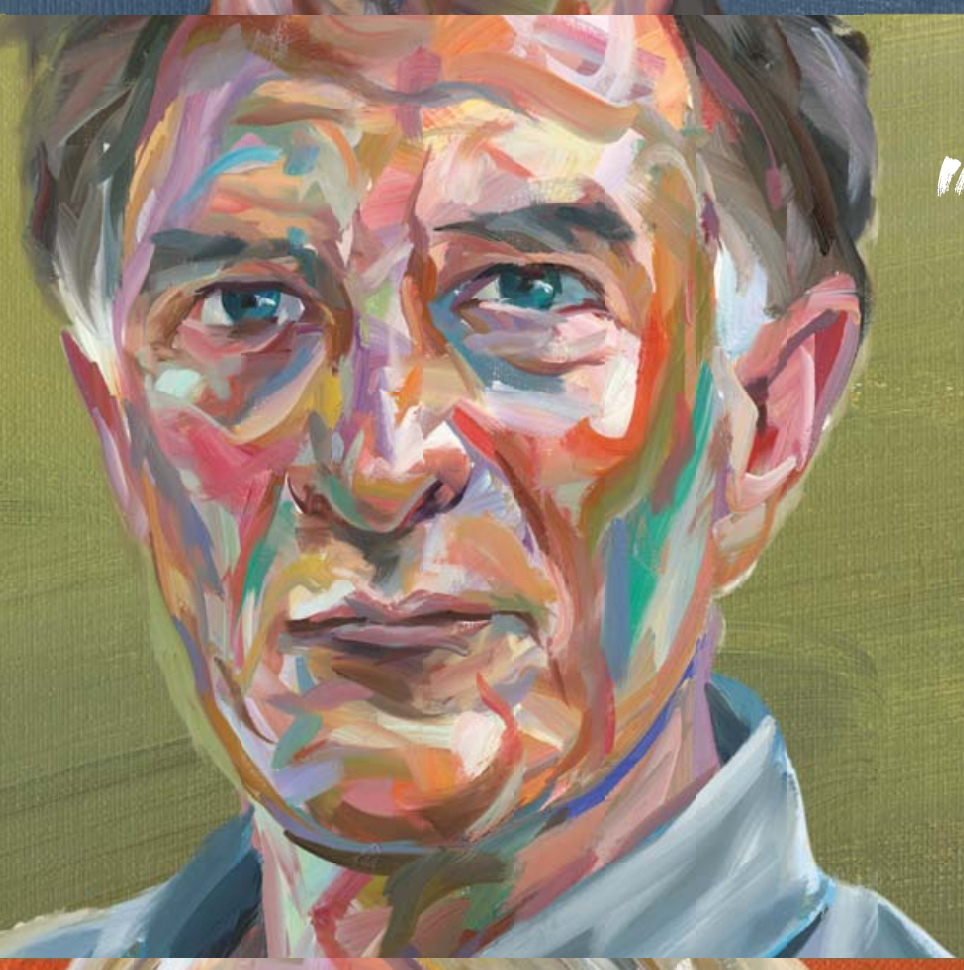


"We have some unfinished business."

METASTATIC GASTRIC OR GEJ ADENOCARCINOMA

INDICATION

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.



"Whatever's next, I want to be all in."

METASTATIC NON-SMALL CELL LUNG CANCER

INDICATION

CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

"I'm ready to do what it takes."

METASTATIC COLORECTAL CANCER

INDICATION

CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

INDICATIONS

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Warnings and Precautions

Hemorrhage

- In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel in advanced gastric cancer, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3. In study 4, which evaluated CYRAMZA plus FOLFIRI in metastatic colorectal cancer, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%), in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), and in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- Four of 570 patients (0.7%) who received CYRAMZA as a single agent in advanced gastric cancer clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforation was 1.2% for CYRAMZA plus paclitaxel as compared to 0.3% for placebo plus paclitaxel. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel as compared to 0.3% for placebo plus docetaxel. In study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- In study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA. In study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the CYRAMZA plus FOLFIRI-treated patients and 0.9% in the placebo plus FOLFIRI-treated patients.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse events with CYRAMZA in study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients vs placebo in study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

Most Common Adverse Reactions—Combination With Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel and ≥2% higher than placebo plus paclitaxel in study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs 0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Most Common Adverse Reactions—Combination With Docetaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lacrimation increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).
- The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- In patients ≥65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA in study 3 were infusion-related reaction (0.5%) and epistaxis (0.3%).
- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel-treated patients in study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Most Common Adverse Reactions—Combination With FOLFIRI

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus FOLFIRI and ≥2% higher than placebo plus FOLFIRI in study 4 were diarrhea (60% vs 51%; 11% vs 10%), neutropenia (59% vs 46%; 38% vs 23%), decreased appetite (37% vs 27%; 2% vs 2%), epistaxis (33% vs 15%; 0% vs 0%), stomatitis (31% vs 21%; 4% vs 2%), thrombocytopenia (28% vs 14%; 3% vs <1%), hypertension (26% vs 9%; 11% vs 3%), peripheral edema (20% vs 9%; <1% vs 0%), proteinuria (17% vs 5%; 3% vs <1%), palmar-plantar erythrodysesthesia syndrome (13% vs 5%; 1% vs <1%), gastrointestinal hemorrhage events (12% vs 7%; 2% vs 1%), hypoalbuminemia (6% vs 2%; 1% vs 0%). Twenty percent of patients treated with CYRAMZA plus FOLFIRI received granulocyte colony-stimulating factors.
- The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
- Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA plus FOLFIRI-treated patients (29%) than in placebo plus FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA plus FOLFIRI as compared to placebo plus FOLFIRI were neutropenia (12.5% versus 5.3%) and thrombocytopenia (4.2% versus 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%) and gastrointestinal perforation (1.7%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus FOLFIRI-treated patients in study 4 consisted of gastrointestinal perforation (1.7% CYRAMZA plus FOLFIRI versus 0.6% for placebo plus FOLFIRI).
- Thyroid-stimulating hormone (TSH) was evaluated in 224 patients (115 CYRAMZA plus FOLFIRI-treated patients and 109 placebo plus FOLFIRI-treated patients) with normal baseline TSH levels. Increased TSH was observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and paclitaxel, between ramucirumab and docetaxel, or between ramucirumab and irinotecan or its active metabolite, SN-38.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and pediatric development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see Brief Summary of Prescribing Information for CYRAMZA, including Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on adjacent pages.

RB-P-HCP ISI 16FEB2017

CYRAMZA®
ramucirumab injection
10 mg/mL solution

CYRAMZA® (ramucirumab) injection

BRIEF SUMMARY:
For complete safety, please consult the full Prescribing Information.

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

INDICATIONS AND USAGE

Gastric Cancer

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic, gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Non-Small Cell Lung Cancer

CYRAMZA in combination with docetaxel, is indicated for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

Colorectal Cancer

CYRAMZA in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hemorrhage

CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In Study 1, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In Study 2, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in Studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. In Study 3, the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDS or other antiplatelet therapy other than once daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from Study 3; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown. In Study 4, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in Study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions

Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including two severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Gastrointestinal Perforations

CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In Study 2, the incidence of gastrointestinal perforations was also increased in patients that received CYRAMZA plus paclitaxel (1.2%) as compared to patients receiving placebo plus paclitaxel (0.3%). In Study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel and 0.3% for placebo plus docetaxel. In Study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or non-healing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Patients with Child-Pugh B or C Cirrhosis

Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported with a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

In Study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

Monitor thyroid function during treatment with CYRAMZA. In Study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the CYRAMZA plus FOLFIRI treated patients and 0.9% in the placebo plus FOLFIRI treated patients.

Embryofetal Toxicity

Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Gastric Cancer

Safety data are presented from two randomized, placebo controlled clinical trials in which patients received CYRAMZA: Study 1, a randomized (2:1), double-blind, clinical trial in which 351 patients received either CYRAMZA 8 mg/kg intravenously every two weeks or placebo every two weeks and Study 2, a double-blind, randomized (1:1) clinical trial in which 656 patients received paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle plus either CYRAMZA 8 mg/kg intravenously every two weeks or placebo every two weeks. Both trials excluded patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or greater, uncontrolled hypertension, major surgery within 28 days, or patients receiving chronic anti-platelet therapy other than once daily aspirin. Study 1 excluded patients with bilirubin ≥1.5 mg/dL and Study 2 excluded patients with bilirubin >1.5 times the upper limit of normal.

CYRAMZA Administered as a Single Agent

Among 236 patients who received CYRAMZA (safety population) in Study 1, median age was 60 years, 28% were women, 76% were White, and 16% were Asian. Patients in Study 1 received a median of 4 doses of CYRAMZA; the median duration of exposure was 8 weeks, and 32 (14% of 236) patients received CYRAMZA for at least six months.

In Study 1, the most common adverse reactions (all grades) observed in CYRAMZA-treated patients at a rate of ≥10% and ≥2% higher than placebo were hypertension and diarrhea. The most common serious adverse events with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients versus 8.7% of patients who received placebo.

Table 1 provides the frequency and severity of adverse reactions in Study 1.

Table 1: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 1

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA (8 mg/kg) N=236		Placebo N=115	
	All Grades (Frequency %)	Grade 3-4 (Frequency %)	All Grades (Frequency %)	Grade 3-4 (Frequency %)
Gastrointestinal Disorders				
Diarrhea	14	1	9	2
Metabolism and Nutrition Disorders				
Hyponatremia	6	3	2	1
Nervous System Disorders				
Headache	9	0	3	0
Vascular Disorders				
Hypertension	16	8	8	3

Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in Study 1 were: neutropenia (4.7% CYRAMZA versus 0.9% placebo), epistaxis (4.7% CYRAMZA versus 0.9% placebo), rash (4.2% CYRAMZA versus 1.7% placebo), intestinal obstruction (2.1% CYRAMZA versus 0% placebo), and arterial thromboembolic events (1.7% CYRAMZA versus 0% placebo).

Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including Grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In Study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria versus 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in Study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

CYRAMZA Administered in Combination with Paclitaxel

Among 327 patients who received CYRAMZA (safety population) in Study 2, median age was 61 years, 31% were women, 63% were White, and 33% were Asian. Patients in Study 2 received a median of 9 doses of CYRAMZA; the median duration of exposure was 18 weeks, and 93 (28% of 327) patients received CYRAMZA for at least six months.

In Study 2, the most common adverse reactions (all grades) observed in patients treated with CYRAMZA plus paclitaxel at a rate of ≥30% and ≥2% higher than placebo plus paclitaxel were fatigue, neutropenia, diarrhea, and epistaxis. The most common serious adverse events with CYRAMZA plus paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors. Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in Study 2 were neutropenia (4%) and thrombocytopenia (3%).

Table 2 provides the frequency and severity of adverse reactions in Study 2.

Table 2: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA plus Paclitaxel in Study 2

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus Paclitaxel (N=327)		Placebo plus Paclitaxel (N=329)	
	All Grades (Frequency %)	Grade ≥3 (Frequency %)	All Grades (Frequency %)	Grade ≥3 (Frequency %)
Blood and Lymphatic System Disorders				
Neutropenia	54	41	31	19
Thrombocytopenia	13	2	6	2
Gastrointestinal Disorders				
Diarrhea	32	4	23	2
Gastrointestinal hemorrhage events	10	4	6	2
Stomatitis	20	1	7	1
General Disorders and Administration Site Disorders				
Fatigue/Asthenia	57	11	44	6
Peripheral edema	25	2	14	1
Metabolism and Nutrition Disorders				
Hypoalbuminemia	11	1	5	1
Renal and Urinary Disorders				
Proteinuria	17	1	6	0
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	31	0	7	0
Vascular Disorder				
Hypertension	25	15	6	3

Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel treated patients in Study 2 were sepsis (3.1% CYRAMZA plus paclitaxel versus 1.8% placebo plus paclitaxel) and gastrointestinal perforations (1.2% CYRAMZA plus paclitaxel versus 0.3% for placebo plus paclitaxel).

Non-Small Cell Lung Cancer

CYRAMZA Administered in Combination with Docetaxel

Study 3 was a multinational, randomized, double-blind study conducted in patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease. Patients received either CYRAMZA 10 mg/kg intravenously plus docetaxel 75 mg/m^2 intravenously every 3 weeks or placebo plus docetaxel 75 mg/m^2 intravenously every 3 weeks. Due to an increased incidence of neutropenia and febrile neutropenia in patients enrolled in East Asian sites, Study 3 was amended and 24 patients (11 CYRAMZA plus docetaxel, 13 placebo plus docetaxel) at East Asian sites received a starting dose of docetaxel at 60 mg/m^2 every 3 weeks. Study 3 excluded patients with an ECOG PS of 2 or greater, bilirubin greater than the upper limit of normal (ULN), uncontrolled hypertension, major surgery within 28 days, radiographic evidence of major airway or blood vessel invasion by cancer, radiographic evidence of intra-tumor cavitation, or gross hemoptysis within the preceding 2 months, and patients receiving therapeutic anticoagulation or chronic anti-platelet therapy other than once daily aspirin. The study also excluded patients whose only prior treatment for advanced NSCLC was a tyrosine kinase (epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) inhibitor. The data described below reflect exposure to CYRAMZA plus docetaxel in 627 patients in Study 3. Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 84% were White and 12% were Asian; 33% had ECOG PS 0; 74% had non-squamous histology and 25% had squamous histology. Patients received a median of 4.5 doses of CYRAMZA; the median duration of exposure was 3.5 months, and 195 (31% of 627) patients received CYRAMZA for at least six months.

In Study 3, the most common adverse reactions (all grades) observed in CYRAMZA plus docetaxel-treated patients at a rate of ≥30% and ≥2% higher than placebo plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related reaction (0.5%) and epistaxis (0.3%). For patients with non-squamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of ≥Grade 3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for ≥Grade 3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of ≥Grade 3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for ≥Grade 3 pulmonary hemorrhage for placebo plus docetaxel. The most common serious adverse events with CYRAMZA plus docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel. In patients ≥65 years, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.

Table 3 provides the frequency and severity of adverse reactions in Study 3.

Table 3: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 3

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus docetaxel (N=627)		Placebo plus docetaxel (N=618)	
	All Grades (Frequency %)	Grade 3-4 (Frequency %)	All Grades (Frequency %)	Grade 3-4 (Frequency %)
Blood and Lymphatic System Disorders				
Febrile neutropenia	16	16	10	10
Neutropenia	55	49	46	40
Thrombocytopenia	13	3	5	<1
Gastrointestinal Disorders				
Stomatitis/Mucosal inflammation	37	7	19	2
Eye Disorders				
Lacrimation increased	13	<1	5	0
General Disorders and Administration Site Disorders				
Fatigue/Asthenia	55	14	50	11
Peripheral edema	16	0	9	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	19	<1	7	<1
Vascular Disorders				
Hypertension	11	6	5	2

Clinically relevant adverse drug reactions reported in ≥1% and <5% of the CYRAMZA plus docetaxel-treated patients in Study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Colorectal Cancer

CYRAMZA Administered in Combination with FOLFIRI

Study 4 was a multinational, randomized, double-blind study conducted in patients with metastatic colorectal cancer with disease progression on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients received either CYRAMZA 8 mg/kg intravenously plus FOLFIRI intravenously every 2 weeks or placebo plus FOLFIRI intravenously every 2 weeks.

Study 4 excluded patients with an ECOG PS of 2 or greater, uncontrolled hypertension, major surgery within 28 days, and those who experienced any of the following during first-line therapy with a bevacizumab-containing regimen: an arterial thrombotic/thromboembolic event; Grade 4 hypertension; Grade 3 proteinuria; a Grade 3-4 bleeding event; or bowel perforation.

Demographics and baseline characteristics for the treated population were similar between treatment arms (n=1057). Median age was 62 years; 57% of patients were men; 76% were White and 20% were Asian; 48% had ECOG PS 0.

The data described in this section reflect exposure to CYRAMZA plus FOLFIRI in 529 patients in Study 4. Patients received a median of 8 doses (range 1-68) of CYRAMZA; the median duration of exposure was 4.4 months, and 169 (32% of 529) patients received CYRAMZA for at least six months. The most common adverse reactions (all grades) observed in CYRAMZA plus FOLFIRI-treated patients at a rate of ≥30% and ≥2% higher than placebo plus FOLFIRI were diarrhea, neutropenia, decreased appetite, epistaxis, and stomatitis. Twenty percent of patients treated with CYRAMZA plus FOLFIRI received granulocyte colony-stimulating factors. Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA plus FOLFIRI-treated patients (29%) than in placebo plus FOLFIRI-treated patients (13%).

The most common adverse reactions leading to discontinuation of any component of CYRAMZA plus FOLFIRI as compared to placebo plus FOLFIRI, were neutropenia (12.5% versus 5.3%) and thrombocytopenia (4.2% versus 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%) and gastrointestinal perforation (1.7%).

The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).

Table 4 provides the frequency and severity of adverse reactions in Study 4.

Table 4: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 4

Adverse Reactions (MedDRA) System Organ Class	CYRAMZA plus FOLFIRI N=529		Placebo plus FOLFIRI N=528	
	All Grades (Frequency %)	Grade ≥3 (Frequency %)	All Grades (Frequency %)	Grade ≥3 (Frequency %)
Blood and Lymphatic System Disorders				
Neutropenia	59	38	46	23
Thrombocytopenia	28	3	14	<1
Gastrointestinal Disorders				
Decreased appetite	37	2	27	2
Diarrhea	60	11	51	10
Gastrointestinal hemorrhage events	12	2	7	1
Stomatitis	31	4	21	2
General Disorders and Administration Site Disorders				
Peripheral edema	20	<1	9	0
Metabolism and Nutrition Disorders				
Hypoalbuminemia	6	1	2	0
Renal and Urinary Disorders				
Proteinuria[a]	17	3	5	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	33	0	15	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia syndrome	13	1	5	<1
Vascular Disorders				
Hypertension	26	11	9	3

[a]Includes 3 patients with nephrotic syndrome in the CYRAMZA plus FOLFIRI treatment group.

Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus FOLFIRI-treated patients in Study 4 consisted of gastrointestinal perforation (1.7% CYRAMZA plus FOLFIRI versus 0.6% for placebo plus FOLFIRI).

Thyroid stimulating hormone (TSH) levels were evaluated in 224 patients (115 CYRAMZA plus FOLFIRI-treated patients and 109 placebo plus FOLFIRI-treated patients) with normal baseline TSH levels. Patients underwent periodic TSH laboratory assessments until 30 days after the last dose of study treatment. Increased TSH levels were observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In 23 clinical trials, 86/2890 (3.0%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

DRUG INTERACTIONS

No pharmacokinetic interactions were observed between ramucirumab and paclitaxel, between ramucirumab and docetaxel, or between ramucirumab and irinotecan or its active metabolite, SN-38.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. The background risk of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

Animal Data

No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryofetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and feto-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels.

Lactation

Risk Summary

There is no information on the presence of ramucirumab in human milk, the effects on the breast-fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, CYRAMZA can cause fetal harm. Advise females of reproductive potential to use effective contraception while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Infertility

Females

Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Pediatric Use

The safety and effectiveness of CYRAMZA in pediatric patients have not been established. In animal studies, effects on epiphyseal growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epiphyseal growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

Geriatric Use

Of the 563 CYRAMZA-treated patients in two randomized gastric cancer clinical studies, 36% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 1253 patients in Study 3, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA plus docetaxel in Study 3, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of Study 3, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years or older was 1.10 (95% CI: 0.89, 1.36).

Of the 529 patients who received CYRAMZA plus FOLFIRI in Study 4, 209 (40%) were 65 and over, while 51 (10%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger subjects.

Renal Impairment

No dose adjustment is recommended for patients with renal impairment based on population pharmacokinetic analysis.

Hepatic Impairment

No dose adjustment is recommended for patients with mild (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or total bilirubin >1.0-1.5 times ULN and any AST) or moderate (total bilirubin >1.5-3.0 times ULN and any AST) hepatic impairment based on population pharmacokinetic analysis. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

DOSAGE AND ADMINISTRATION

Do not administer CYRAMZA as an intravenous push or bolus.

Recommended Dose and Schedule

Gastric Cancer

The recommended dose of CYRAMZA either as a single agent or in combination with weekly paclitaxel is 8 mg/kg every 2 weeks administered as an intravenous infusion over 60 minutes. Continue CYRAMZA until disease progression or unacceptable toxicity. When given in combination, administer CYRAMZA prior to administration of paclitaxel.

Non-Small Cell Lung Cancer

The recommended dose of CYRAMZA is 10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue CYRAMZA until disease progression or unacceptable toxicity.

Colorectal Cancer

The recommended dose of CYRAMZA is 8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes prior to FOLFIRI administration. Continue CYRAMZA until disease progression or unacceptable toxicity.

Premedication

Prior to each CYRAMZA infusion, premedicate all patients with an intravenous histamine H_1 antagonist (e.g., diphenhydramine hydrochloride).

For patients who have experienced a Grade 1 or 2 infusion-related reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion.

Dose Modifications

Infusion-Related Reactions (IRR)

- Reduce the infusion rate of CYRAMZA by 50% for Grade 1 or 2 IRRs.
- Permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

Hypertension

- Interrupt CYRAMZA for severe hypertension until controlled with medical management.
- Permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy.

Proteinuria

- Interrupt CYRAMZA for urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose (see Table 5) once the urine protein level returns to <2 g/24 hours. If the protein level ≥2 g/24 hours reoccurs, interrupt CYRAMZA and reduce the dose (see Table 5) once the urine protein level returns to <2 g/24 hours.
- Permanently discontinue CYRAMZA for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome.

Table 5: CYRAMZA Dose Reductions for Proteinuria

Initial CYRAMZA Dose	First Dose Reduction to:	Second Dose Reduction to:
8 mg/kg	6 mg/kg	5 mg/kg
10 mg/kg	8 mg/kg	6 mg/kg

Wound Healing Complications

- Interrupt CYRAMZA prior to scheduled surgery until the wound is fully healed.

Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding

- Permanently discontinue CYRAMZA.

For toxicities related to paclitaxel, docetaxel, or the components of FOLFIRI, refer to the current prescribing information.

PATIENT COUNSELING INFORMATION

- **Hemorrhage:**
Advise patients that CYRAMZA can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.

- **Arterial thromboembolic events:**
Advise patients of an increased risk of an arterial thromboembolic event.

- **Hypertension:**
Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.

- **Gastrointestinal perforations:**
Advise patients to notify their health care provider for severe diarrhea, vomiting, or severe abdominal pain.

- **Impaired wound healing:**
Advise patients that CYRAMZA has the potential to impair wound healing. Instruct patients not to undergo surgery without first discussing this potential risk with their health care provider.

- **Pregnancy and fetal harm:**
Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.

- **Lactation:**
Advise patients not to breastfeed during CYRAMZA treatment.

- **Infertility:**
Advise females of reproductive potential regarding potential infertility effects of CYRAMZA.

Additional information can be found at www.CYRAMZAHCP.com.

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Patient-Reported Outcomes

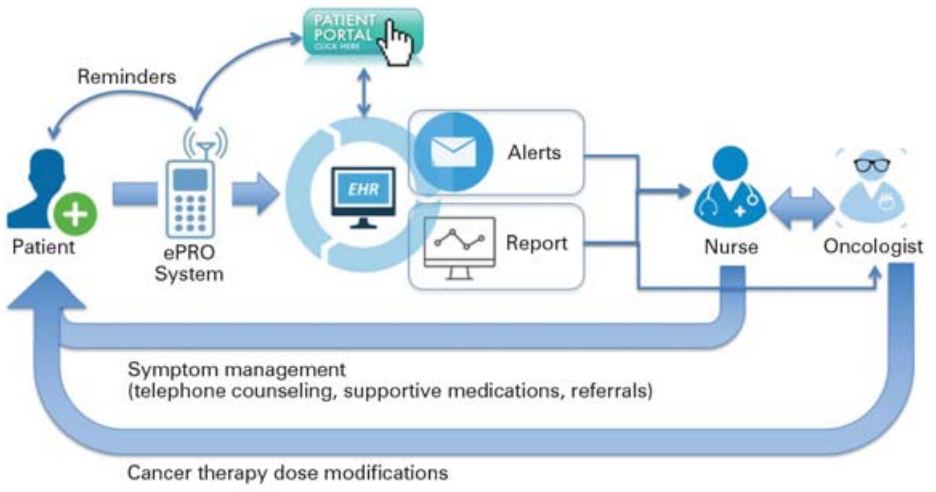
Continued from page 1B

hospitalizations, and physical debility. Indeed, poorly controlled symptoms are a principal driver of preventable ER visits for pain, dyspnea, dehydration, nausea/vomiting, diarrhea, and fatigue.[3,4]

Multiple studies show that systematic monitoring of patients' symptoms using PROs closes this gap, improving patient-clinician communication, clinician awareness of symptoms, symptom management, patient satisfaction, and quality of life.[5,6] Most patients with cancer (about 80%) are willing and able to self-report PROs on a regular basis during treatment. Presentations during the 2016 and 2017 ASCO Annual Meetings reported that PRO monitoring can significantly reduce ER visits and improve survival:

- In 2016, Fabrice Denis, MD, PhD, presented "Overall survival in patients with lung cancer using a web application–guided follow-up compared to standard modalities: Results of phase III randomized trial" during the ASCO Annual Meeting (Abstract LBA9006). In this multicenter French study, 121 patients were randomly assigned to one of two post-treatment surveillance strategies: PRO symptom monitoring versus standard care with scheduled follow-up scans. Compared to standard care, survival was significantly improved by 8 months among patients in the PRO arm.[7]
- In 2017, my research group presented "Overall survival results of a randomized trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment" during the ASCO Annual Meeting Plenary Session (Abstract LBA2). In this study, 766 patients with metastatic solid tumors at Memorial Sloan Kettering Cancer Center were randomly assigned to weekly PRO symptom monitoring with alerts to nurses for severe/worsening symptoms versus usual care. Compared to usual care, patients in the PRO arm experienced significantly better quality of life, reduced ER visits by 7%, longer tolerability of cancer treatment by 2 months, improved physical functioning, and a 5-month overall survival benefit.[8]

Fig. 2. Generic Model for Integrating Patient-Reported Outcomes Into Clinical Workflow



Abbreviation: ePRO, electronic patient-reported outcomes.

How does this all work in a practice? Figure 2 illustrates a model for bringing PROs into usual workflow processes for symptom management in cancer care.

There are many variations of workflow considerations when bringing PROs online in a practice, but most models share three common elements:

1. A cross-disciplinary governance group to make decisions and implement the system (usually including clinicians, administrators, patient representatives, and information technology experts).
2. A PRO software system that includes:
   - An interface for patients to self-report (connected to the electronic health record [EHR]/patient portal or free-standing);
   - Automated reminders to patients to self-report (usually by email, text message, or automated phone call);
   - Automated alerts to clinicians when severe or worsening symptoms are reported (usually to nurses, via email or EHR in-basket messages); and
   - The ability to visualize PRO values longitudinally (either through the EHR or a free-standing PRO system).
3. A standardized quality improvement process for implementing PROs in the workflow, including patient training and monitoring, staff training, and project monitoring.

A more in-depth description of the various considerations for bringing PROs into a practice can be found in two excellent Users' Guides, which are freely available online and are highly recommended: the "User's Guide to Implementing Patient-Reported Outcomes Assessment in Clinical Practice," from the International Society for Quality of Life Research,[9] and the "Users' Guide to Integrating Patient-Reported Outcomes in Electronic Health Records" supported by the Patient-Centered Outcomes Research Institute (PCORI).[10]

Like any quality improvement project, there is a risk of failure if implementation is not done thoughtfully with ongoing monitoring and adjustment—particularly in early phases. There are a few steps that can be helpful toward success. It should be clear to patients that this is something that is important to the center and to the clinicians. Invitations to patients to participate should come from a clinician or staff member they know or recognize. Staff should remind patients at all visits about self-reporting. Clinicians should use the information and make it clear to patients that they are referencing it for care. Technical support should be available for patients and clinicians.

A question that many institutions ponder is whether to use a PRO functionality native to their EHR system patient portal or to build or license a free-standing PRO system. There is no right answer, and the decision will depend on the desired use of the data and the quality of the available EHR PRO functionality. Unfortunately, many of the widely used EHR systems still only include rudimentary PRO functionality, with unappealing clinician visualization of patient-reported data. Hopefully this will change in the near future.

There is support for research on implementing PROs in clinical practice and within EHR systems from multiple agencies, including the National Cancer Institute (NCI), PCORI, and the Agency for Healthcare Research and Quality. Notably, one of the recent NCI Cancer Moonshot announcements specifically focused on implementing PROs into EHRs and clinical workflow of practice networks.[11]

Increasing Focus on PROs in Clinical Trials and Drug Development

Drug development trials are perhaps the most well-traveled context in which PROs have been used in oncology. Many of the PRO questionnaires in use today were developed for trials. PROs are commonly collected in publicly funded research (e.g., through the NCI-supported National Clinical Trials Network of cooperative groups) and in industry sponsored research.

See Patient-Reported Outcomes, Page 15B

Molecular Diagnostic Platforms

Continued from page 3B

forms, and other mutations that are outside lung and colon cancers, he said.

"The future is next-generation sequencing," he said. His presentation will give an overview of the two most common next-generation sequencing platforms used in the United States, as well as others, and "the genes they are testing, when they were launched, and the types of alterations they target," he said. "This field is moving so fast. New tests are being approved and developed, and they keep improving the current platforms."

His talk will update attendees with the latest information about these emerging platforms.

Noninvasive Biomarkers

Dr. Kuhn, the third speaker at the session, will focus on noninvasive biomarkers for immunotherapy. "Our goal in cancer therapy is to identify consequential cancer and treat effectively to avoid its lethality within the healthy lifespan of a patient. There are two distinct steps: separating consequential from inconsequential and treating effectively, which both have a time-space challenge. The disease evolves over time and through 'space'; i.e., the body as a system," he said. "Assessing this time-space correlation and tracking its evolution requires an extension of our traditional approach to the tissue biopsy."

Dr. Kuhn noted that next-generation diagnostic methods "have to support each and every decision point that a patient is facing with both accuracy and precision. This can be achieved with the appropriate implementation of high-content liquid biopsy approaches that use single-cell proteogenomics. The results can be validated and reproduced, and the final tests can be shrink-wrapped and launched to impact globally," he said.

Dr. Kuhn will discuss recent research by the USC Michelson Center for Convergent Bioscience Bridge Institute. By imaging metal-tagged antibodies on biopsies from patients with metastatic prostate cancer, Dr. Kuhn and colleagues created detailed digital facsimiles of cancer cells. The researchers established the proof of concept for the metal-detection technique that allows for detection of tumor cells at a molecular level, he said. According to Dr. Kuhn, the research published recently in *Convergent Science Physical Oncology* will help researchers understand how cancer moves from its initial location to other organs and will hopefully lead toward development of more precise treatment plans for patients.[2]

Using the Fluidigm Hyperion Imaging System, Dr. Kuhn and his team could see protein biomarkers that may determine how a tumor cell would potentially respond or not to therapy, how it could metastasize, and how it could affect the patient's immune system response. This new approach, now a technique available with Fluidigm, uses metal-tagged antibodies and a laser ablation system, along with a mass spectrometer, which can provide 35 distinct views of the cancer cell's biology, Dr. Kuhn said.

Their research using metal-targeted antibodies expands on the pioneering research of Bernd Bodenmiller, PhD, of the University of Zurich, in Switzerland, by using his approach with the liquid biopsy he had previously developed.[3] "We simply add the antibody cocktail, wait for binding, and then wash off the excess and see what sticks. Then we use a laser to atomize the sample and a mass spectrometer to look for each of the metals," Dr. Kuhn said. ●

—Kathy Holliman, MEd

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**Program information updated as of March 12. For session time and location information, please refer to the ASCO iPlanner on the Attendee Resource Center (am.asco.org/arc).*

CLINICAL CORNER

Duration of Adjuvant Chemotherapy for Early-Stage Breast Cancer

Sayeh Lavasani, MD, MSc, FRCPC, answers a question posed by an attendee during a Best of ASCO® Meeting. Dr. Lavasani is a breast medical oncologist at Memorial Cancer Institute.

Question: How many cycles of combination docetaxel/cyclophosphamide do you recommend in the adjuvant setting for patients with breast cancer?

Answer: This remains an area of controversy. Many studies have compared standard-dose doxorubicin/cyclophosphamide (AC) to docetaxel/cyclophosphamide (TC; 75 mg/m^2 and 600 mg/m^2, respectively) at four and six cycles. TC administered every 3 weeks for four cycles (TC4) is a chemotherapy regimen used for the treatment of early-stage breast cancer in an adjuvant setting and is gaining popularity due to the lack of cardiotoxicity and decreased risk of acute leukemia compared to an anthracycline-based regimen.

USOR 9735 was the first trial to reveal efficacy and improved toxicity of TC over AC.[1] This phase III study by Jones et al compared TC4 with standard-dose AC for four cycles (AC4) with the primary endpoint of disease-free survival (DFS). In this report, TC was associated with a superior DFS and different toxicity profile compared to AC.

The 7-year follow-up showed that TC4 was superior to AC4.[2] DFS was 81% versus 75%, respectively (HR 0.74, 95% CI [0.56, 0.98]; p = 0.03). The overall survival (OS) was 87% versus 82%, respectively (HR 0.69, 95% CI [0.50, 0.97]; p = 0.032).

There are no head-to-head comparisons between TC4 versus TC for six cycles (TC6). The first study comparing four versus six cycles of therapy of the same regimen was the CALGB 40101 trial.[3] Using a 2 x 2 factorial design, the study compared four and six cycles of AC (AC4 vs. AC6) or single-agent paclitaxel in early-stage breast cancer and zero to three positive axillary nodes. The study found no difference in 4-year relapse-free survival or OS between four and six cycles with more toxicities in six-cycle treatment arms.

TC6 has been compared to the taxane anthracycline (TaxAC) combination chemotherapy regimen. The joint analysis of the Anthracyclines in Early Breast Cancer (ABC) trials reported by Blum et al pooled patients from three large randomized trials to compare TaxAC with a nonanthracycline taxane-based control arm (TC6).[4] The study's primary endpoint was invasive DFS. Four-year invasive DFS was 88.2% in the TC arm versus 90.7% for the TaxAC arm (HR 1.23; p = 0.04), demonstrating that TC6 is inferior to TaxAC.

According to the ASCO adaptation of the Cancer Care Ontario Program in Evidence-Based Care guideline, TC4 is recommended as an alternative to AC4 and offers improved DFS and OS.[5] The National Comprehensive Cancer Network guideline also recommends TC4.[6]

In summary, current data illustrates that TC4 is better than AC4. We also know that AC6 is equal to AC4 with more toxicities, and we know that TC6 is inferior to TaxAC, particularly in patients who are triple-negative or hormone-positive and who have multiple positive axillary nodes.

Some medical oncologists believe that by adding two more cycles to TC4, they can compensate for the TaxAC regimen; therefore, they are replacing the dose-dense AC/paclitaxel with TC6. However,

Dr. Sayeh Lavasani

we know from the recent data that TC6 is inferior to AC/paclitaxel. The truth is that we do not have any scientific evidence that TC needs to be given for six cycles. In my practice, if I feel that I can avoid anthracyclines and decide that I want to use the TC regimen, I use four cycles only—otherwise I use the TaxAC combination regimen. ●

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Tantalizingly Close: Global Health Equity and the Influence of Socioeconomic Disparities on Cancer Care Outcomes

EXPERT EDITORIAL

Robert Ali, MBBS; Jonas A. de Souza, MD; Bijou Hunt, MA; Fredrick Chite Asirwa, MD; Clement Adebamowo, BM, ChB Hons, FACS, FWACS, ScD; and Gilberto Lopes Jr., MD, MBA, FAMS

It is an easy place to reach; the problem has always been returning home. From most world capitals, airliners will take you to Athens, Greece, and from there a short flight north will get you to Thesprotia in the region of Epirus. Locals will be happy to point you in the direction of the cave known as Charonium, one of the gates to our destination. Do not forget to bring a gold coin or two to pay the ferryman, Charon (yes, you guessed where his name comes from). Once on the river Styx, at the bifurcation, do not take the road to Elysium (appropriately for our story, in Greek mythology, heaven was actually in the underworld as well); keep going. Hades' most appropriate metaphor for cancer control in low-resource settings in both rich and poor countries alike is Tantalus. Here, there is water to quench your thirst and sweet fruit to satiate your hunger. But try to bow down and drink or stretch your arm to pick an apple, and the water will seep through the rock while the branches move away. Close enough, but always tantalizingly out of reach.

Such is the current situation in resource-constrained settings when we fight for cancer control. The last few decades have been brimming with major breakthroughs in care initiatives including novel immunotherapy options, molecular testing, targeted therapies, greater public awareness, and improved national cancer control plans. Nonetheless, a significant disparity in the accessibility to care among various socioeconomic settings exists. For those among the low- and middle-income strata, these advancements remain an aspiration. This editorial focuses on health disparities using specific countries across the income spectrum to highlight the challenges encountered by health officials, physicians, and patients at each level.

Defining Health Care Disparities and Cancer Control

Multiple definitions for health care disparities have been proposed; however, the consensus put forward by Healthy People 2020 offers a nicely rounded description. The Healthy People 2020 program defines a health disparity as "a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage."[1] It includes differences among the most advantaged group in a given category, such as the most wealthy or powerful, and all others, not only between the best- and worst-off groups. Furthermore, inherent in this designation is that those disadvantaged social groups who persistently experience social discrimination systematically experience worse health or greater health risks than their more advantaged social counterparts. Pursuing health equity implies pursuing the elimination of such health disparities and inequalities.

Per the Union for International Cancer Control (UICC), cancer control is defined as "a public health approach aimed at reducing the burden of cancer in a population."[2] This concept includes the planning of integrated, evidence-based, and cost-effective interventions across the cancer continuum, including research, prevention, early detection, treatment, and palliation.

So why bother with a global initiative? During the 2014 World Cancer Leaders' Summit, cancer advocates argued that it makes economic sense to invest in global cancer control, particularly in low- and middle-income countries (LMICs). In 2010, the annual global

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ARTICLE HIGHLIGHTS

- A significant disparity exists in the accessibility to cancer care among various socioeconomic settings.
- Only one in five low- or middle-income countries have the data needed to drive cancer policies.
- Although a considerable financial emphasis is placed on health care initiatives, high-income countries still face challenges with ensuring equitable distribution of cancer care resources.
- Middle-income countries have been partially successful through measures such as tax-funded health care. However, low-income countries continue to struggle with providing sufficient resources and may require international support.

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Continued from page 6B

408) included 66 patients with T2-4a bladder cancer, randomly assigned to receive either twice-daily radiation plus 5-fluorouracil/cisplatin (FCT) or daily radiation plus gemcitabine (GD). The rate of distant metastasis at 3 years was 22% with FCT and 16% with GD (the study was not designed for direct comparisons of the two groups). Complete response rates in the two groups were 88% and 78%, respectively, and there was less toxicity seen in the GD arm of the study.

- Interim results of the KEYNOTE-045 trial led to the approval of pembrolizumab for treatment of locally advanced or metastatic urothelial carcinoma that progressed during or after platinum-based chemotherapy. Now, 2-year results confirm the benefits (Abstract 410). Among the 542 patients randomly assigned to pembrolizumab or investigator's choice chemotherapy and followed for a median of 27.7 months, the median OS was 10.3 months with the immune checkpoint inhibitor and 7.3 months with chemotherapy (HR 0.70; p < 0.0002). The benefit was seen in all PD-L1 expression subgroups, and adjustments for multiple variables did not change the findings, confirming the use of this agent in this setting.

Renal Cell Carcinoma Highlights

Studies were also presented that demonstrate advances in renal cell carcinoma (RCC), including less well-understood settings such as patients with papillary histology.

- A retrospective analysis of 353 patients with papillary metastatic RCC found that cytoreductive nephrectomy could improve survival outcomes (Abstract 581). After a median follow-up of 57.1 months, the median OS in patients who underwent cytoreductive nephrectomy was 16.3 months, compared with 8.6 months in those who did not (p < 0.0001). After adjustment for individual risk factors, the hazard ratio for death was 0.62 (95% CI [0.45, 0.85]; p = 0.0031).
- Combining a PD-1/PD-L1 pathway inhibitor with an anti-VEGF agent offered improved outcomes in patients with metastatic RCC, especially in those who are PD-L1–positive. The phase III IMmotion151 trial (Abstract 578) included 915 patients in an intention-to-treat analysis, and 362 who were PD-L1–positive were randomly assigned to receive either sunitinib or atezolizumab plus bevacizumab. The median PFS was 11.2 months with the combination compared with 7.7 months with sunitinib in patients with advanced clear cell RCC of intermediate or poor risk (Abstract 583). The TemPa trial included 69 patients, and the median PFS was 5.2 months with pazopanib and 2.6 months with temsirolimus. The median OS was 12.0 months with pazopanib, compared with 7.4 months with temsirolimus (p = 0.61). The response rate was significantly better with pazopanib, at 26%, compared with 6% with temsirolimus (p = 0.046). Safety profiles were similar to that seen with these drugs in other trials.
- The VEGFR tyrosine-kinase inhibitor pazopanib improved outcomes over temsirolimus in a study of patients

The 2018 Genitourinary Cancers Symposium featured robust panel discussions, putting the science presented into real-world context.

Testicular Cancer Therapies and Phenotypes

- A case control study of 30 individuals including 15 with testicular cancer treated with chemotherapy found a "senescence phenotype" in the survivors of the malignancy (Abstract 548). They had a significantly higher expression of *p16INK4a*, which has been dubbed a biomarker of aging, than the control individuals (p = 0.031). Differences in lymphocyte populations were also observed, suggesting survivors of these cancers treated with chemotherapy could be at increased risk of infection; the findings reinforce the importance of surveillance in this survivor population.
- A prospective study found that treatment for germ cell tumors can result in long-term sexual function problems (Abstract 549). The study included 155 survivors who filled out a Sexual Function Questionnaire after a median of 10 years of follow-up. Survivors who were treated with chemotherapy and radiotherapy, or with any therapy, had difficulty maintaining erection during intercourse compared to control patients (p = 0.04), and those treated with the combination reported difficulty in achieving orgasm during intercourse (p = 0.04). Those patients treated with both chemotherapy and radiotherapy also reported disappointment with overall quality of sex life (p = 0.002).
- The expansion of Medicaid has had an effect on the diagnosis of testicular cancer. An analysis using the Surveillance Epidemiology and End Results database identified 12,731 cases of testicular cancer from 2010 to 2014 (Abstract 551). In the states that expanded Medicaid after passage of the Affordable Care Act, Medicaid coverage for testicular cancer increased from 14.8% to 19.4% of patients (p < 0.001), and the uninsured rate for these patients decreased from 8.7% to 4.3% (p < 0.001). No such trends were seen in states that did not expand Medicaid. The number of cases diagnosed at stage I also increased in expansion states, whereas in nonexpansion states there was an increase in stage III cases. No change in management of the malignancy has yet been observed.

Save the date for the 2019 Genitourinary Cancers Symposium, to be held February 14-16, in San Francisco. ●

–David Levitan

Patient-Reported Outcomes

Continued from page 13B

For more than a decade, regulatory agencies, particularly the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), have championed the value of directly collecting information from patients through PRO questionnaires. Indeed, the term "patient-reported outcome" was popularized by the FDA in the late 2000s when it published a highly influential PRO methods guidance,[12] which was reinforced by an equally influential reflections document from the EMA.[13] A recent accomplishment is a framework for PRO data collection presented by the FDA, which focuses on three domains: cancer-related symptoms, physical functioning, and symptomatic adverse events.[14]

Understanding patients' symptom and physical functioning experiences is vital to appreciating the properties of cancer treatments, and PRO questionnaires are the gold standard for assessing these areas. For example, in early-phase trials, patient symptoms and physical functioning can reflect tolerability and inform decisions about dosing. In phase III trials, PROs can be useful to understand the impact of therapy on disease-related symptoms, such as pain or fatigue.

Ideally, the PRO component of a clinical trial will be planned early. This starts with identifying outcomes that are meaningful in a given context or population through literature reviews or qualitative (patient interview) work, then choosing or developing a rigorous questionnaire that maps to those outcomes. Investigators should ideally partner with an expert in PRO methods to assist with the design. Increasingly, there are efforts to standardize approaches to PROs in various contexts side by side with other endpoints. For example, the Prostate Cancer Clinical Trials Working Group has recommended standards for outcomes in clinical trials, including biomarkers, imaging, and PROs.

The Patient Version of the CTCAE

Recently, the NCI released a patient-reported version of the Common Terminology Criteria for Adverse Events (the PRO-CTCAE). The PRO-CTCAE is a library of items for patient self-reporting of 78 different symptomatic adverse events that are common in cancer care such as nausea, diarrhea, dyspnea, etc. Like the CTCAE, individual adverse events can be elicited in trials or during routine care depending on the context of use. The PRO-CTCAE was rigorously developed for the NCI by a group of multidisciplinary investigators, including myself.[15]

The PRO-CTCAE is free and available from the NCI for use in any clinical trial or real-world setting, and it can be downloaded in multiple languages at healthcaredelivery.cancer.gov/pro-ctcae. This tool is designed to bring the patient voice into research and care and to reduce the frequency of missing vital symptoms experienced by patients.

Summary

PROs enable patients to report how they are feeling and functioning. This is essential information for cancer clinicians and investigators. Without PROs, we generally have an incomplete picture of the patient experience, which can impair our ability to make informed decisions about treatments. Technologies for collecting PROs are improving, and there is rapidly growing interest to routinely include PROs in care and research processes. ●

About the Author

Dr. Basch is a UNC Lineberger Comprehensive Cancer Center member, director of Cancer Outcomes Research Program, and professor of medicine at the University of North Carolina, Chapel Hill.

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ASCO Guideline Addresses Palliative Care in the Global Setting

Integrating palliative care into overall oncology care is critical, and ASCO has published a new resource-stratified guideline to address this issue worldwide. The new "Palliative Care in the Global Setting: American Society of Clinical Oncology Resource-Stratified Practice Guideline," is intended to complement the "Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update" of 2016. The purpose of the new resource-stratified guideline "is to provide expert guidance to clinician policymakers on implementing palliative care in resource-constrained settings."[1]

"It came to our attention that the 2016 guidelines were beneficial for very well-resourced, high-income countries," James F. Cleary, MD, of the University of Wisconsin School of Medicine and Public Health, said. "The previous guidelines work well in countries that already have excellent oncology care and the resources to provide that care." Dr. Cleary co-chaired the guideline Expert Panel along with Hibah Osman, MD, MPH, of the Lebanese Center for Palliative Care-Balsam.

> Palliative care "should be initiated as early as possible and should not be reserved until the patient is no longer a candidate for curative therapies."
>
> –DR. HIBAH OSMAN

When the nonresource-stratified guidelines were first published, everyone agreed they were useful. "They redefined the role of palliative care in cancer treatment, and they were an extremely helpful resource in our advocacy efforts as we work to get palliative care integrated into our health care systems," Dr. Osman said. "Unfortunately, it was easy for decision-makers in countries with limited resources like mine [Lebanon] to dismiss the U.S.-based guidelines as standards that cannot be realistically applied in our setting."

Globally, the push for palliative care has increased over the years, Dr. Cleary said. For example, a World Health Organization resolution in 2014 recommended that nations look to improve their palliative care efforts.[2] Last year, a *Lancet* Commission report noted an "access abyss in palliative care," saying the lack of global access is a global crisis.[3]

ASCO's resource-stratified guideline "sets an achievable standard for any setting, regardless of how limited resources may be," Dr. Osman said. "This makes it an extremely useful tool for palliative care advocates globally and will encourage policymakers to implement the recommendations in the guideline."

Dr. James F. Cleary

Dr. Hibah Osman

She added a key point of the ASCO guideline is that palliative care "should be initiated as early as possible and should not be reserved until the patient is no longer a candidate for curative therapies."

Although clinician mindset is slowly embracing that philosophy, Dr. Osman said it's still common to hear oncologists say a patient "isn't at the palliative stage yet," even as patients are receiving second-, third-, and fourth-line chemotherapy treatments. "I'm hopeful that this guideline will help us change that," she said.

Key Concepts

This guideline addresses two critical components: accessibility of opioids in lower-income countries and the role of spiritual care. ASCO's guideline recommends a coordinated system where the palliative care needs of patients and families are identified and met at all levels, in collaboration with the team providing oncology care. The health care system "should have trained personnel who are licensed to prescribe, deliver, and dispense opioids at all levels."[1]

According to Dr. Cleary, 80% of the world's population lacks access to morphine, making palliative care crucial in areas where oncology care resources are stretched by budgetary constraints.

These guidelines are "the very basic level that should actually come, or be provided, for the low-income countries or least-resourced countries," he said. "This provides a roadmap for countries as they develop health care policies."

Accessibility of opioids remains a major issue in lower-income parts of the world.

"The *Lancet* Commission report on palliative care and pain relief estimated

See Guideline Addresses Palliative Care, Page 30B

Because not every colorectal cancer (CRC) tumor will present itself,

WE ARE WORKING TO BRING IMMUNE RESPONSE TO THE SURFACE

The majority of CRC tumors may go undetected by the immune system

≈5% of stage IV CRC tumors are microsatellite instability-high (MSI-H) and exhibit high mutational burden[1-5]

The remaining ≈95% are microsatellite stable (MSS) or microsatellite instability-low (MSI-L) and exhibit low mutational burden. This leads to limited generation of tumor-directed T cells, allowing tumors to escape immune surveillance[2-4,6,7]

Genentech is leading cancer immunotherapy research to enhance immune detection of CRC tumors regardless of mutational burden

- MEK pathway inhibition may expose tumors by increasing antigen presentation on the surface of tumor cells[8]
- PD-L1 pathway inhibition may activate T cells to attack tumor cells[9]

PD-L1=programmed death-ligand 1.

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WHY I ATTEND DR. LESLIE SAMUEL

Long-time ASCO Annual Meeting attendee Leslie Samuel, MD, provides advice to new attendees on how to get the most out of the Meeting.

Q: Why are you attending the ASCO Annual Meeting this year?
Dr. Samuel: It is an opportunity to hear the results from a number of clinical trials, some of which I've been involved with, being presented and discussed. It is also an opportunity to catch up with oncologists whom I know, as well as industry colleagues about present or future trials.

Q: How do you plan your time during the Meeting?
Dr. Samuel: I use the iPlanner app and online abstracts for planning. It's important to spend time going through the program and note what is happening and when, as well as the location within McCormick Place. The silver lining for those of us with long wait times in airport departure lounges or long flights to Chicago is that there is plenty of time to make plans.

Q: Do you have any tips for new attendees who may feel overwhelmed by all the on-site options?
Dr. Samuel: There are bound to be times where you want to be in two places at once. My advice is to use the Annual Meeting Videos & Slides tool to help prioritize. You can watch recorded presentations of sessions you may have missed in person.

Q: Apart from the science presented, what are the benefits of attending the Meeting?
Dr. Samuel: There are quite a few, apart from the obvious one of spending a few days in Chicago. It is an opportunity to meet other oncologists, particularly at the Poster Sessions, and discuss results, which may lead to other studies. In the same vein, it is an opportunity to meet industry colleagues, as it is always good to put a face to a name. This may lead to future trial collaborations to the benefit of your patients and your career.

Q: Have you made any connections at the Meeting that have impacted your career?
Dr. Samuel: I've made some very interesting connections that have led to clinical trial collaborations, which have enriched my career. If you know of a study that you would like to be involved with, contact the sponsor, commercial company, or a lead investigator, and ask to meet for coffee. You may find opportunities flow from these meetings.

Q: This year's theme is focused on precision medicine. What do you think the Meeting will be most focused on 10 years from now?
Dr. Samuel: That's a very good question, particularly given the rapid change in knowledge over the past few years. Our understanding of the interaction between cancer cells and other normal tissue function, such as stromal tissue, for example, will increase yet pose challenges to how we interpret the information from biopsies. Bioinformatics will need to be (and I'm sure will be) more user-friendly for clinicians, but I suspect our training will need to embrace the bioinformatic analysis and pitfalls.

Q: What do you always make sure to include when packing for the Meeting?
Dr. Samuel: As I'm coming from the United Kingdom with a 5- to 6-hour time difference, I always make sure to pack some melatonin tablets. I usually also bring my cycling shorts, as there are some great urban cycling routes in Chicago. I also bring business cards.

Q: Any other tips for attendees?
Dr. Samuel: The Poster Sessions can be an excellent opportunity to get up-to-date information about studies from someone involved. Engage the presenters, and make sure to bring some business cards to exchange. ●

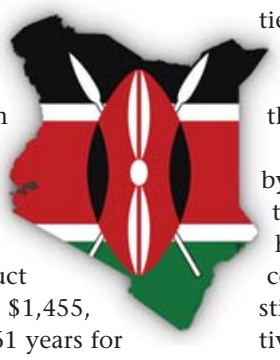
Leslie Samuel, MD, is the Macmillan Consultant Oncologist at the Aberdeen Royal Infirmary, United Kingdom, and honorary senior lecturer in the Health Service Research Unit, Aberdeen University. He's involved with academic and commercial clinical research, particularly in lower gastrointestinal cancers.

Global Health Equity

Continued from page 14B

cost of cancer was up to $2.5 trillion, accounting for costs related to prevention and treatment, economic value of morbidity and mortality, and longer-term costs to patients and families.[3] By 2012, there was an estimated 14.1 million new cases of cancer, with 8.2 million cancer deaths occurring worldwide. Sixty-five percent of these occurred in low-income countries.[4] Cancer has been designated the second leading cause of death internationally and is responsible for nearly one in six deaths.[5] In 2015, the World Health Organization (WHO) estimated that 8.8 million deaths related to cancer occurred, with 70% of these in LMICs.[5] More than 90% of high-income countries report available treatment services versus less than 30% in low-income settings. Furthermore, only one in five LMICs have the necessary data to drive cancer policies. Implementing prevention, early detection, and treatment strategies could potentially save between 2.4 to 3.7 million lives annually, translating to an economic benefit in excess of $400 billion.[3]

Kenya



Kenya is a lower-middle income East African country in sub-Saharan Africa with a population of about 48.5 million.[6] As of 2016, the gross domestic product (GDP) per capita is $1,455, life expectancy was 61 years for men and 66 years for women, and health expenditures accounted for 4.7% GDP.[7] The estimated annual incidence of cancer is 28,000 cases, with 22,000 deaths. As with many middle-income countries, an inequitable distribution of finances, expertise, and resources portends a poor health care foundation. In 2004, the country's health care policy was revised, mandating free basic health care at the primary level to all citizens. That being said, cancer screening, diagnostics, and treatment are still not covered by the government-funded insurance, and routine vaccinations for HPV and hepatitis B are not included in the immunization schema. By 2013, only 4.5 million (11%) of the Kenyan population had health care coverage.[7]

Access to medications, surgery, and radiation therapy is cost-prohibitive. Kenya's oncology drug list consists of only 18 of the 52 essential cancer medicines outlined by WHO.[7] Chemotherapy is available, but because of the high cost of drugs and lack of coverage of the cost of cancer treatments by the National Hospital Insurance Fund, it is inaccessible to most. This quandary also extends to narcotic agents, making pain control a major obstacle. Use of other complimentary services is also curtailed by cost restraints. Kenya has only two cobalt radiation machines for patients with public health care, with appointments booked for several months in advance. For patients with private health care, there are four linear accelerators in Nairobi, with prompt initiation of therapy for those who can afford it.

This lack of resources is compounded by limited education and exacerbates the difficulty in accessing efficient health care. In 2011, the National Cancer Prevention and Control Programme stipulated provisions to making preventive, curative, and palliative care services accessible to all Kenyans.[7] Unfortunately, such an undertaking proved overly ambitious; screening occurs only in a few selected sites, rather than as a cohesive national program. Access to cervical, breast, and colon cancer screening is also impaired because of a lack of community awareness on the importance of screening, as well as low levels of health literacy. Other contributing factors include inadequate skill among service providers, lack of equipment and supplies, and scant monitoring.

As is typical of many middle-income countries, health policy and resources are primarily focused on communicable diseases. The most common cancers are breast and cervical—malignancies that can be prevented or detected early, benefiting from the implementation of dedicated vaccination and screening programs. Cancer-related mortality is the third most common cause of death in Kenya.[7] Circumstances such as inadequate public education and awareness, scarce oncology services, and poorly trained personnel, compounded by low prioritization by political parties have resulted in these inferior outcomes.

Brazil

Brazil is an upper-middle-income country, with a population of 200 million, a GDP per capita of $8,650 (in 2016), and a general life expectancy of 70 years for men and 77 years for women.[7] Total health expenditure accounts for about 9.3% of the GDP, with 46% of this in the public sector. Sistema Único de Saúde is a public, tax-funded health scheme that covers the population; however, about one-quarter of the population still subscribes to private medical insurance. Brazil instituted a national cancer control plan in 2005, with a heavy emphasis on public education and screening. Smoking, as well as its advertising, is banned in public places, federal policies have been implemented to combat obesity and the harmful effects of alcohol. HPV and hepatitis B vaccines are freely available. Additionally, screening for both cervical and breast cancers has been advocated, and protocols comply with standard international guidelines.

Despite implementation of these initiatives, there are still significant problems with access to cancer care. For instance, the average time between mammography and diagnostic biopsy is 72 days.[7] Or, in the case of patients diagnosed with oral cancer, it takes an average of 41 days to commence treatment. Traditional imaging and surgical and pathology services are available, but delays are common and molecular analyses are not always available. Similarly, while there are more than 250 radiation machines in the country, access is limited based on geography and income, and wait times can be up to 3 months.

Policies differ in terms of the provision of anticancer medicines. The Brazilian essential medicine list is mostly congruent with the WHO essential medicine list.[7] Moreover, once a drug is approved by the local regulatory agency, coverage is mandatory in the private health care system. As such, citizens (usually the more affluent) can sue the federal government for access to cancer medications. This creates the conundrum where distribution of scarce resources in the public system becomes imbalanced in favor of those belonging to higher socioeconomic levels.

Brazil is a model for health care in middle-income countries. Execution of screening programs and public education emphasizing risk reduction strategies constitute the mainstay of their cancer control plan.[7] Establishment

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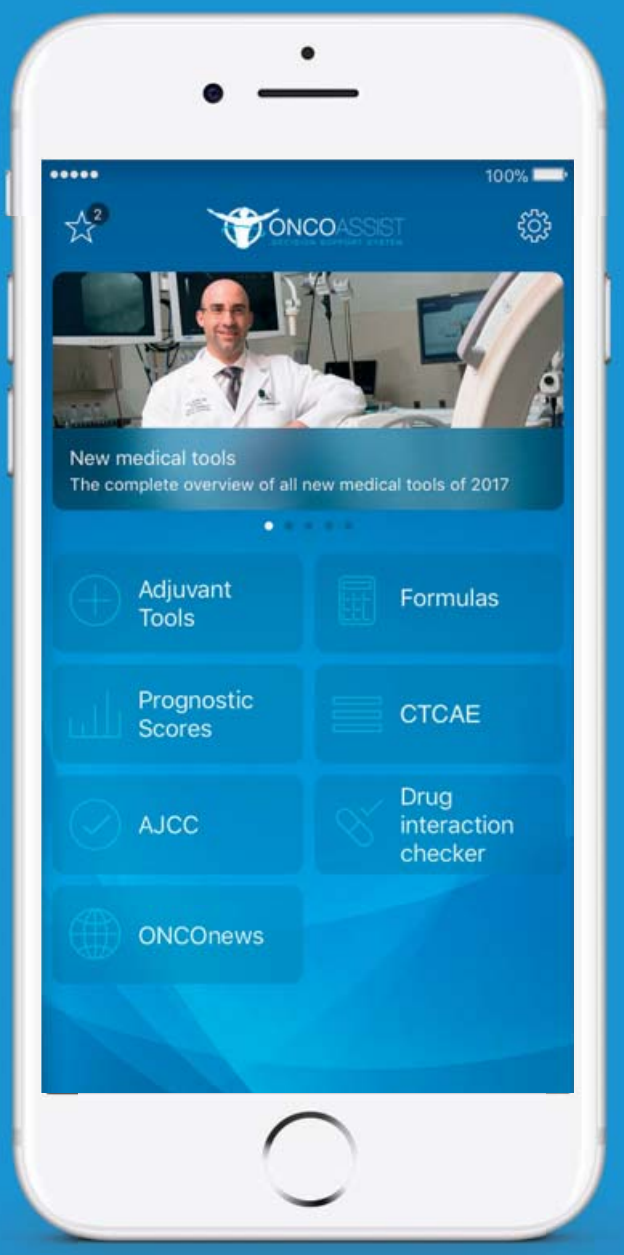

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Global Health Equity

Continued from page 18B

of this basic health care system has resulted in improved outcomes and decreased cancer mortality over the past decade. Nonetheless, challenges still exist with the distribution of resources among various social echelons, as well as geographic locations. Also, the routine acquisition and implementation of advanced technologies and medicines continues to be a struggle.

The United States

The United States is a federal presidential republic with a population of 323 million, as of 2016.[7] The GDP is $15 trillion, establishing it as a high-income country. Health care accounts for 17% of the GDP. Both public and private financing contribute to the health care system, with up to 65% of funds sourced from the government. The life expectancy is 76 years for men and 81 years for women. The annual incidence of cancer is just over 1.6 million cases, with a mortality-to-incidence ratio of 0.36.

A national cancer control plan has been implemented since 2010.[7] Similar to Brazil, smoking is banned in indoor public places, and policies are in place

to prevent obesity and alcohol abuse. Screening for preventable cancers, including cervical, breast, and colon, is widely available. Hepatitis B and HPV vaccinations are ubiquitous, and there is increased public awareness regarding vaccinations, with 91% and 32% of the target populations being vaccinated, respectively. Advanced imaging, surgical services, and pathology are also available, as are radiation services, with more than 2,700 machines nationwide. Novel and inherently more expensive chemotherapeutic agents are accessible through health care coverage.

Despite the high-income standing of the United States, socioeconomic status, access to health care services, and individual behaviors continue to adversely affect health care equity. The highest cancer incidence rate among men is observed within the black community.[7] Overall rates are 15% higher than those of whites and nearly twice the rates among Asians/Pacific Islanders. Conversely, non-Hispanic and white women have the highest overall cancer incidence rates among females. These disparities among racial groups are also reflected in the all-cancer mortality rates. The highest rate is noted among non-Hispanic blacks (208.8 per 100,000 population), followed by whites (176.5), Hispanics (119.7), and Asians (108.9).

Mitigating Disparities Moving Forward

Although considerable emphasis is placed on the role of finances on health care initiatives, high-income countries still face the challenge of ensuring equitable distribution of resources among their population including minorities and vulnerable groups. Additionally, with the landscape of oncology shifting toward targeted therapies and biologic agents, the cost of these agents must be factored in when attempting to deliver equitable care.

Several strategies can be employed at every level to mitigate the disparities among countries of various income classes[7]:

- **Low-Income Countries**—Prevention and risk reduction should be the primary focus via the establishment of a national cancer control plan and database to track trends in disease patterns. Additionally, investment in basic health care infrastructure and education, as well as efforts to expand coverage to remote areas, is paramount.
- **Middle-Income Countries**—Investment in prevention and early detection programs should be the objective. Access to basic pathology, imaging, and other ancillary services, as well as striving toward compliance with the WHO Model List for Essential Medications, are also pivotal for progress.
- **High-Income Countries**—Capitalizing on advancing interventions and services should form the backbone of care at this level. These include, for example, genomic assays, higher-resolution and nuclear studies, and advanced radiation and surgical techniques. Also, with the continuum extending to include more innovative and consequently expensive medications, efforts should extend to make these available nationwide and to all persons regardless of minority or economic background.

Notwithstanding the obvious disparities highlighted here, basic challenges persist that are common among all strata of socioeconomic standing. Poverty has been a relentless obstacle to receiving cancer care.[7] This prevents people from practicing good lifestyle habits and accessing preventive and curative medical care promptly. Cancer care financing is a global challenge. In high-income countries, the high cost of new treatments is straining the system while LMICs struggle with the cost of providing the minimum set of cancer prevention and treatment services for the majority of their population.

Cancer treatment is often multifaceted, including the need for readily available and high-quality pathologic and imaging studies. Treatments often include a careful mixture of surgery, radiation, and chemotherapy, followed by a long period of follow-up. The typical health care coverage that is available is not always able to accommodate these expenses, causing patients to forfeit some components of their care.

The distribution of screening and treatment centers are not always even within countries because of funding and geography. Accessibility to cancer care is often worse in rural compared to urban communities, regardless of the income level of the country.

The Institute of Medicine, the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries, WHO, and other groups have created frameworks detailing the most important stepping stones in improving the fight against cancer.[7] Some of these include establishing universal health care coverage, creating national cancer registries and data repositories on risk factors and treatment outcomes, providing tobacco control programs, vaccinating against the most common viruses that cause cancer, creating reference cancer centers, ensuring access to essential cancer medicines and palliative care, and other steps detailed throughout this review. That being said, economic growth may be the ultimate remedy in the long run. Middle-income countries have been at least partially successful through measures such as tax-funded health care; however, their low-income counterparts may require international support to achieve these targets.

The financial impact of cancer across all socioeconomic levels has been demonstrated ad nauseam, particularly to those in low-income countries. Consequently, from both an economic and a pragmatic standpoint, it is pivotal to invest in measures to alleviate this burden. This task would entail the consolidated effort of governments, private stakeholders, and nonprofit organizations. Furthermore, from a humanistic standpoint, all endeavors should be made to curb this suffering. Following the United Nations summit on noncommunicable disease in 2011, the worldwide plight of cancer has come to the forefront in global public health.[7] Indeed, it will take a global initiative to have these ambitions brought to fruition.

Like Orpheus, son of Apollo and the muse Calliope, we must venture into the underworld to rescue cancer control in underserved areas, our Eurydice, from the reign of Hades. Let us not look back lest our dream vanishes in front of us before we reach our goal. ●

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Credit Neil Thomas

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CLINICAL CORNER

Complete Resection for Second-Line Ovarian Cancer Treatment

Elizabeth L. Dickson Michelson, MD, FACOG; Colleen Rivard Hunt, MD, FACOG; Melissa Geller, MD, MS, FACOG; and Deanna Teoh, MD, FACS, FACOG, answer a question posed by an attendee during a Best of ASCO® Meeting. Dr. Dickson Michelson is a gynecologic oncologist with Aurora Health Care, and Dr. Rivard Hunt, Dr. Geller, and Dr. Teoh are gynecologic oncologists with the University of Minnesota.


Dr. Elizabeth L. Dickson Michelson


Dr. Colleen Rivard Hunt


Dr. Melissa Geller

Question: Why is complete resection valuable in second-line ovarian cancer treatment but not in first-line treatment?

Answer: Ovarian cancer, which will be diagnosed in more than 21,000 women and be responsible for 14,000 deaths in 2017,[1] continues to be the most deadly gynecologic malignancy facing women today. The mainstay of treatment combines aggressive surgical debulking with chemotherapy, and now targeted therapies are used as well.

Several studies have shown that patients who undergo primary cytoreductive surgery, what is referred to as "optimal debulking," have the best survival outcomes in ovarian cancer.[2,3] The definition of optimal debulking has evolved over time, from less than 3 cm of residual disease to more recent studies showing that if a patient can be debulked to no gross residual disease they have even better survival.[2] If a surgeon believes that optimal cytoreductive surgery will not be possible, neoadjuvant chemotherapy may be the next best step in order to reduce the burden of disease before attempting cytoreductive surgery. There have been mixed results from studies evaluating patients who had suboptimal debulking surgery, then received chemotherapy, and then a second attempt at debulking.[4-10]

The DESKTOP III trial interim analysis was presented during the 2017 ASCO Annual Meeting.[9] The data showed improved progression-free survival (PFS) with secondary cytoreduction. At the time of a first platinum-sensitive ovarian cancer recurrence in which complete resection is deemed feasible, patients were randomly selected to receive secondary cytoreductive surgery (204 patients) followed by chemotherapy versus standard platinum-based chemotherapy alone (203 patients). Whereas the study was powered for overall survival (OS) analysis, the PFS data were promising, with a PFS advantage of 19.6 months versus 14.0 months for the secondary cytoreductive surgery group. The most striking finding, though, was that the cytoreductive surgery had to achieve complete resection to obtain the benefit of increased PFS (a median increase of 7.2 months). This study seems to confirm what is already believed about primary debulking surgery: If a complete resection to no visible disease can be achieved, there is likely to be a survival advantage; however, we must await the final OS analysis.

Overall, ovarian cancer acts differently than other metastatic solid tumor types—even though ovarian cancer can be chemosensitive, numerous studies have shown that surgical cytoreduction of tumor volume to no visible disease is significantly correlated to improved patient outcomes.[10] We continue to strive to find the best combination modality treatment for patients with ovarian cancer, and surgical cytoreduction will continue to be the cornerstone of this therapy. ●

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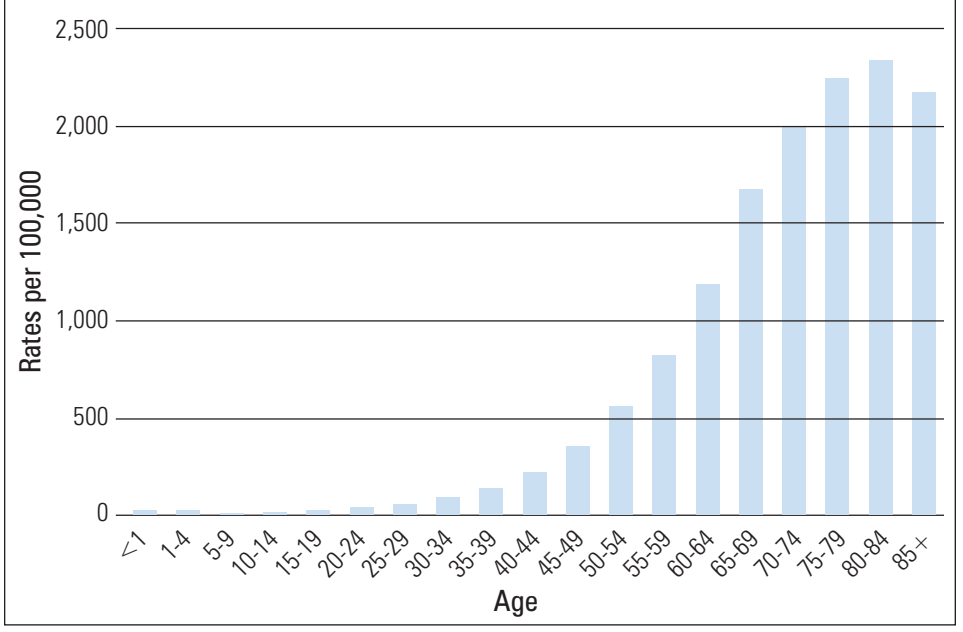
Assessing the Older Adult With Cancer

EXPERT EDITORIAL

Grant R. Williams, MD, and Ronald J. Maggiore, MD

Cancer is predominantly a disease of older adults, with the majority of new cancer diagnoses occurring in adults over age 65 and the cancer incidence rate peaking around the eighth decade of life (Fig. 1).[1] Given changing demographics, approximately 70% of all new cancer diagnoses will be in older adults by 2030, yet the same treatment options are not appropriate for each individual patient.[2] Older adults with cancer vary in health status irrespective of age, and it is paramount to use a comprehensive assessment to adequately weigh the risks and benefits of treatment options. In this review, we highlight best practices in evaluating older adults to better individualize cancer therapies.

Fig. 1. Age-Specific Cancer Incidence Rates



How to Assess the Older Patient

Chronologic age alone is insufficient in evaluating older adults given the significant variability in physiologic ability between individuals. Although the use of performance status assessments may help in evaluating the overall level of physical functioning of our patients, it is subjective and may miss many important factors that are known to influence treatment outcomes.[3] More systematic and comprehensive evaluations are needed in order to appropriately individualize therapies in older adults with cancer.

Geriatric assessment is a multidimensional and interdisciplinary assessment of an older person's medical, functional, and psychosocial abilities.[4] Geriatric assessment evaluates a broad range of health domains including physical function, functional status, nutrition, cognition, psychological health, comorbidity, and social support to develop a coordinated and integrated plan for treatment (Table 1, page 21B). Although these assessments are traditionally performed by geriatricians and, ideally, as part of a multidisciplinary evaluation, shortened versions that are primarily patient-reported have been developed for ease of use in oncology clinics.[5] These abbreviated assessments take about 20 to 30 minutes to complete and only about 5 minutes of health care provider time, and they have been shown to be feasible in different clinical settings. A variety of well-validated measures can be used to assess the domains of the geriatric assessment, and deciding which measures to employ can be tailored to the provider and local resources. The exact tools employed may vary, but should assess the following do-

See Assessing the Older Adult, Page 28B

ARTICLE HIGHLIGHTS

- Older adults with cancer vary in health status irrespective of age, and it is paramount to use a comprehensive assessment to adequately weigh the risks and benefits of treatment options.
- Geriatric assessment evaluates a broad range of health domains including physical function, functional status, nutrition, cognition, psychological health, comorbidity, and social support to develop a coordinated and integrated plan for treatment.
- For busier oncology practices or those with limited access to formal geriatrics specialty clinics or resources, a geriatric screening tool may be able to help cancer therapy providers discern higher-risk patients for treatment-related toxicities, other complications, and/or worse prognosis.

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INDICATIONS

BAVENCIO is indicated for the treatment of:

- Adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC)
- Patients with locally advanced or metastatic urothelial carcinoma (UC) who:
  - Have disease progression during or following platinum-containing chemotherapy
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

These indications are approved under accelerated approval based on tumor response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

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IMPORTANT SAFETY INFORMATION

BAVENCIO can cause **immune-mediated pneumonitis**, including fatal cases. Monitor patients for signs and symptoms of pneumonitis, and evaluate suspected cases with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% (21/1738) of patients, including one (0.1%) patient with Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3.

BAVENCIO can cause **immune-mediated hepatitis**, including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis was reported in 0.9% (16/1738) of patients, including two (0.1%) patients with Grade 5, and 11 (0.6%) with Grade 3.

BAVENCIO can cause **immune-mediated colitis**. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold BAVENCIO until resolution for moderate or severe (Grade 2 or 3) colitis, and permanently discontinue for life-threatening (Grade 4) or recurrent (Grade 3) colitis upon reinitiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including seven (0.4%) with Grade 3.

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IMPORTANT SAFETY INFORMATION (continued)

BAVENCIO can cause **immune-mediated endocrinopathies**, including adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus.

Monitor patients for signs and symptoms of **adrenal insufficiency** during and after treatment, and administer corticosteroids as appropriate. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Adrenal insufficiency was reported in 0.5% (8/1738) of patients, including one (0.1%) with Grade 3.

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone replacement therapy and hyperthyroidism with medical management. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Thyroid disorders, including hypothyroidism, hyperthyroidism, and thyroiditis, were reported in 6% (98/1738) of patients, including three (0.2%) with Grade 3.

Type 1 diabetes mellitus including diabetic ketoacidosis: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer antihyperglycemics or insulin in patients with severe or life-threatening (Grade ≥ 3) hyperglycemia, and resume treatment when metabolic control is achieved. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients, including two cases of Grade 3 hyperglycemia.

BAVENCIO can cause **immune-mediated nephritis and renal dysfunction**. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to Grade 1 or lower. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% (1/1738) of patients.

BAVENCIO can result in **other severe and fatal immune-mediated adverse reactions** involving any organ system during treatment or after treatment discontinuation. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending on the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high-dose corticosteroids, and initiate hormone replacement therapy, if appropriate. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or lower following a corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening (Grade 4) immune-mediated adverse reaction. The following clinically significant immune-mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO: myocarditis with fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response.

BAVENCIO can cause severe (Grade 3) or life-threatening (Grade 4) **infusion-related reactions**. Patients should be premedicated with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent doses based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. Permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% (439/1738) of patients, including three (0.2%) patients with Grade 4 and nine (0.5%) with Grade 3.

BAVENCIO can cause **fetal harm** when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman **not to breastfeed** during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

The most common adverse reactions (all grades, ≥ 20%) in patients with **metastatic Merkel cell carcinoma (MCC)** were fatigue (50%), musculoskeletal pain (32%), diarrhea (23%), nausea (22%), infusion-related reaction (22%), rash (22%), decreased appetite (20%), and peripheral edema (20%).

Selected treatment-emergent laboratory abnormalities (all grades, ≥ 20%) in patients with **metastatic MCC** were lymphopenia (49%), anemia (35%), increased aspartate aminotransferase (34%), thrombocytopenia (27%), and increased alanine aminotransferase (20%).

The most common adverse reactions (all grades, ≥ 20%) in patients with **locally advanced or metastatic urothelial carcinoma (UC)** were fatigue (41%), infusion-related reaction (30%), musculoskeletal pain (25%), nausea (24%), decreased appetite/hypophagia (21%), and urinary tract infection (21%).

Selected laboratory abnormalities (Grades 3-4, ≥ 3%) in patients with **locally advanced or metastatic UC** were hyponatremia (16%), increased gamma-glutamyltransferase (12%), lymphopenia (11%), hyperglycemia (9%), increased alkaline phosphatase (7%), anemia (6%), increased lipase (6%), hyperkalemia (3%), and increased aspartate aminotransferase (3%).

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BRIEF SUMMARY: Please see package insert for Full Prescribing Information

INDICATIONS AND USAGE

- BAVENCIO (avelumab) is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).
- BAVENCIO is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

These indications are approved under accelerated approval based on tumor response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Immune-Mediated Pneumonitis: BAVENCIO can cause immune-mediated pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis and evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) for Grade 2 or greater pneumonitis. Withhold BAVENCIO for moderate (Grade 2) pneumonitis, and permanently discontinue for severe (Grade 3), life-threatening (Grade 4), or recurrent moderate (Grade 2) pneumonitis. Pneumonitis occurred in 1.2% (21/1738) of patients receiving BAVENCIO including one patient (0.1%) with Grade 5, one (0.1%) with Grade 4, and five (0.3%) with Grade 3 pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% (6/1738) patients. Among the 21 patients with immune-mediated pneumonitis, the median time to onset was 2.5 months (range: 3 days to 11 months) and the median duration of pneumonitis was 7 weeks (range: 4 days to 4+ months). All 21 patients were treated with systemic corticosteroids; 17 (81%) of the 21 patients received high-dose corticosteroids for a median of 8 days (range: 1 day to 2.3 months). Resolution of pneumonitis occurred in 12 (57%) of the 21 patients at the time of data cut-off.

Immune-Mediated Hepatitis: BAVENCIO can cause immune-mediated hepatitis including fatal cases. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids (initial dose of 1- to 2 mg/kg/day prednisone or equivalent, followed by a corticosteroid taper) for Grade 2 or greater hepatitis. Withhold BAVENCIO for moderate (Grade 2) immune-mediated hepatitis until resolution and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.9% (16/1738) of patients receiving BAVENCIO including two patients (0.1%) with Grade 5 and 11 patients (0.6%) with Grade 3 immune-mediated hepatitis. Immune-mediated hepatitis led to permanent discontinuation of BAVENCIO in 0.5% (9/1738) of patients. Among the 16 patients with immune-mediated hepatitis, the median time to onset was 3.2 months (range: 1 week to 15 months), and the median duration of hepatitis was 2.5 months (range: 1 day to 7.4+ months). All 16 patients were treated with corticosteroids; 15 (94%) of the 16 patients received high-dose corticosteroids for a median of 14 days (range: 1 day to 2.5 months). Resolution of hepatitis occurred in nine (56%) of the 16 patients at the time of data cut-off.

Immune-Mediated Colitis: BAVENCIO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) for Grade 2 or greater colitis. Withhold BAVENCIO for moderate or severe (Grade 2 or 3) colitis until resolution. Permanently discontinue BAVENCIO for life-threatening (Grade 4) or for recurrent (Grade 3) colitis upon re-initiation of BAVENCIO. Immune-mediated colitis occurred in 1.5% (26/1738) of patients receiving BAVENCIO including seven (0.4%) patients with Grade 3 colitis. Immune-mediated colitis led to permanent discontinuation of BAVENCIO in 0.5% (9/1738) of patients. Among the 26 patients with immune-mediated colitis, the median time to onset was 2.1 months (range: 2 days to 11 months) and the median duration of colitis was 6 weeks (range: 1 day to 14+ months). All 26 patients were treated with corticosteroids; 15 (58%) of the 26 patients received high-dose corticosteroids for a median of 19 days (range: 1 day to 2.3 months). Resolution of colitis occurred in 18 (70%) of the patients at the time of data cut-off.

Immune-Mediated Endocrinopathies: BAVENCIO can cause immune-mediated endocrinopathies. ***Adrenal Insufficiency:*** Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment. Administer corticosteroids as appropriate for adrenal insufficiency. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Adrenal insufficiency occurred in 0.5% (8/1738) of patients receiving BAVENCIO including one patient (0.1%) with Grade 3 adrenal insufficiency. Immune-mediated adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% (2/1738) of patients. Among the 8 patients with immune-mediated adrenal insufficiency, the median time to onset was 2.5 months (range: 1 day to 8 months). All eight patients were treated with corticosteroids; four (50%) of the eight patients received high-dose corticosteroids for a median of 1 day (range: 1 day to 24 days). ***Thyroid Disorders (Hypothyroidism/Hyperthyroidism):*** BAVENCIO can cause immune-mediated thyroid disorders. Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage hypothyroidism with hormone-replacement therapy. Initiate medical management for control of hyperthyroidism. Withhold BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) thyroid disorders. Immune-mediated thyroid disorders occurred in 6% (98/1738) of patients receiving BAVENCIO including 3 (0.2%) Grade 3 immune-mediated thyroid disorders. Immune-mediated thyroid disorders led to discontinuation of BAVENCIO in 0.1% (2/1738) of patients. Hypothyroidism occurred in 90 (5%) patients; hyperthyroidism in seven (0.4%) patients; and thyroiditis in four (0.2%) patients treated with BAVENCIO. Among the 98 patients with immune-mediated thyroid disorders, the median time to onset was 2.8 months (range: 2 weeks to 13 months) and the median duration was not estimable (range: 6 days to more than 26 months). Immune-mediated thyroid disorders resolved in seven (7%) of the 98 patients. ***Type 1 Diabetes Mellitus:*** BAVENCIO can cause type 1 diabetes mellitus, including diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Withhold BAVENCIO and administer anti-hyperglycemics or insulin in patients with severe or life-threatening (Grade $\geq$ 3) hyperglycemia. Resume treatment with BAVENCIO when metabolic control is achieved on insulin replacement or anti-hyperglycemics. Type 1 diabetes mellitus without an alternative etiology occurred in 0.1% (2/1738) of patients including two cases of Grade 3 hyperglycemia that led to permanent discontinuation of BAVENCIO.

Immune-Mediated Nephritis and Renal Dysfunction: BAVENCIO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a corticosteroid taper) for Grade 2 or greater nephritis. Withhold BAVENCIO for moderate (Grade 2) or severe (Grade 3) nephritis until resolution to $\leq$ Grade 1. Permanently discontinue BAVENCIO for life-threatening (Grade 4) nephritis. Immune-mediated nephritis occurred in 0.1% (1/1738) of patients receiving BAVENCIO; BAVENCIO was permanently discontinued in this patient.

Other Immune-Mediated Adverse Reactions: BAVENCIO can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. Most immune-mediated reactions initially manifest during treatment with BAVENCIO; however, immune-mediated adverse reactions can occur after discontinuation of BAVENCIO. For suspected immune-mediated adverse reactions, evaluate to confirm or rule out an immune-mediated adverse reaction and to exclude other causes. Depending upon the severity of the adverse reaction, withhold or permanently discontinue BAVENCIO, administer high dose corticosteroids, and if appropriate, initiate hormone replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper. Resume BAVENCIO when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue BAVENCIO for any severe (Grade 3) immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of 1738 patients treated with BAVENCIO for each of the following adverse reactions: immune-mediated myocarditis including fatal cases, immune-mediated myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response. The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), pancreatitis, rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, hypophysitis, iritis, and encephalitis.

Infusion-Related Reactions: BAVENCIO can cause severe or life-threatening infusion-related reactions. Premedicate with antihistamine and acetaminophen prior to the first 4 infusions. Monitor patients for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Infusion-related reactions occurred in 25% (439/1738) of patients treated with BAVENCIO including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Ninety-three percent (1615/1738) of patients received premedication with antihistamine and acetaminophen. Eleven (92%) of the 12 patients with Grade $\geq$ 3 reactions were treated with intravenous corticosteroids. Fourteen percent of patients (252/1738) had infusion-related reactions that occurred after the BAVENCIO infusion was completed.

Embryo-Fetal Toxicity: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 signaling pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking BAVENCIO, inform the patient of the potential risk to a fetus. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least one month after the last dose of BAVENCIO.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-mediated pneumonitis
- Immune-mediated hepatitis
- Immune-mediated colitis
- Immune-mediated endocrinopathies
- Immune-mediated nephritis and renal dysfunction
- Other immune-mediated adverse reactions
- Infusion-related reactions

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the WARNINGS AND PRECAUTIONS section are based on two trials, in which 1738 patients received BAVENCIO at doses of 10 mg/kg intravenously

every two weeks. This included 88 patients with metastatic MCC (JAVELIN Merkel 200 trial) and 242 patients with locally advanced and metastatic UC within the JAVELIN Solid Tumor trial. In the JAVELIN Solid Tumor trial, 1650 patients were treated with BAVENCIO at doses of 10 mg/kg. The following criteria were used to classify an adverse reaction as immune-mediated: onset within 90 days after last dose of BAVENCIO, no spontaneous resolution within 7 days of onset, treatment with corticosteroids or other immunosuppressant or hormone replacement therapy, biopsy consistent with immune-mediated reaction, and no other clear etiology. The study population characteristics of the 1738 patients were: median age of 64 years (range: 19 to 91 years), 52% male, 78% White, 9% Asian, 5% Black or African American and 8% other ethnic groups, ECOG performance score of 0 (38%), 1 in (62%), and > 1 (0.4%) and the underlying malignancies were non-small cell lung cancer (20%), gastric and gastroesophageal cancer (15%), urothelial cancer (14%), ovarian cancer (13%), metastatic breast cancer (10%), head and neck cancer (9%), metastatic MCC (5%), mesothelioma, renal cell carcinoma, melanoma, adrenocortical carcinoma (3% each), colorectal cancer, castrate-resistant prostate cancer, and unknown (1% each). In this population, 24% of patients were exposed to BAVENCIO for ≥ 6 months and 7% were exposed to BAVENCIO for ≥ 12 months.

Metastatic Merkel Cell Carcinoma

The data described below reflect exposure to BAVENCIO 10 mg/kg intravenously every 2 weeks in 88 patients with metastatic MCC enrolled in the JAVELIN Merkel 200 trial. Patients with any of the following were excluded: autoimmune disease; medical conditions requiring systemic immunosuppression; prior organ or allogeneic stem cell transplantation; prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies; central nervous system (CNS) metastases; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score ≥ 2. The median duration of exposure to BAVENCIO was 4 months (range: 2 weeks to 21 months). Forty percent of patients received BAVENCIO for more than 6 months and 14% were treated for more than one year. The study population characteristics were: median age of 73 years (range: 33 to 88), 74% male, 92% White, ECOG performance score of 0 (56%) or 1 (44%), and 65% of patients had one prior anti-cancer therapy for metastatic MCC and 35% had two- or more prior therapies. BAVENCIO was permanently discontinued for adverse reactions in six (7%) patients; adverse reactions resulting in permanent discontinuation were ileus, Grade 3 transaminitis, Grade 3 creatine kinase elevation, tubulointerstitial nephritis, and Grade 3 pericardial effusion. BAVENCIO was temporarily discontinued in 21 (24%) patients for adverse events, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. The most common adverse reaction requiring dose interruption was anemia. Serious adverse reactions that occurred in more than one patient were acute kidney injury, anemia, abdominal pain, ileus, asthenia, and cellulitis. The most common adverse reactions (≥ 20%) were fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema.

Table 2: Adverse Reactions in ≥ 10% of Patients Receiving BAVENCIO in the JAVELIN Merkel 200 Trial

Adverse Reactions	BAVENCIO (N = 88)	
	All Grades (%)	Grade 3-4 (%)
General Disorders		
Fatigue[a]	50	2
Infusion-related reaction[b]	22	0
Peripheral edema[c]	20	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	32	2
Arthralgia	16	1
Gastrointestinal Disorders		
Diarrhea	23	0
Nausea	22	0
Constipation	17	1
Abdominal pain[e]	16	2
Vomiting	13	0
Skin and Subcutaneous Tissue Disorders		
Rash[f]	22	0
Pruritus[g]	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	20	2
Decreased weight	15	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	18	0
Dyspnea[h]	11	1
Nervous System Disorders		
Dizziness	14	0
Headache	10	0
Vascular Disorders		
Hypertension	13	6

[a]Fatigue is a composite term that includes fatigue and asthenia; [b]Infusion-related reaction is a composite term that includes drug hypersensitivity, hypersensitivity, chills, pyrexia, back pain, and hypotension; [c]Peripheral edema is a composite term that includes peripheral edema and peripheral swelling; [d]Musculoskeletal pain is a composite term that includes back pain, myalgia, neck pain, pain in extremity; [e]Abdominal pain is a composite term that includes abdominal pain and abdominal pain upper [f]Rash is a composite term that includes rash maculo-papular, erythema, and dermatitis bullous; [g]Pruritus is a composite term that includes pruritus and pruritus generalized; [h]Dyspnea is a composite term that includes dyspnea and dyspnea exertional

Table 3 Selected Treatment-Emergent* Laboratory Abnormalities in Patients receiving BAVENCIO in the JAVELIN Merkel 200 Trial

Laboratory Tests	Any Grade (N = 88) %	Grade 3-4 (N = 88) %
Chemistry		
Increased aspartate aminotransferase (AST)	34	1
Increased alanine aminotransferase (ALT)	20	5
Increased lipase	14	4
Increased amylase	8	1
Increased bilirubin	6	1
Hyperglycemia**	-	7
Hematology		
Anemia	35	9
Lymphopenia	49	19
Thrombocytopenia	27	1
Neutropenia	6	1

*Treatment emergent consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality

**Hyperglycemia limited to Grade ≥ 3 events since fasting measurements were not obtained routinely

Locally Advanced or Metastatic Urothelial Cancer

Table 4 describes adverse reactions reported in 242 patients with locally advanced or metastatic UC receiving BAVENCIO at 10 mg/kg every 2 weeks in the UC cohorts of the JAVELIN Solid Tumor trial. Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. The median duration of exposure to BAVENCIO was 12 weeks (range: 2 weeks to 92 weeks). Fourteen patients (6%) who were treated with BAVENCIO experienced pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death. BAVENCIO was permanently discontinued for Grade 1-4 adverse reactions in 30 (12%) patients. The adverse reaction that resulted in permanent discontinuation in >1% of patients was fatigue. BAVENCIO was temporarily discontinued in 29% of patients for adverse reactions, excluding temporary dose interruption for infusion-related reactions where infusion was restarted on the same day. The adverse reactions that resulted in temporary discontinuation in >1% of patients were diarrhea, fatigue, dyspnea, urinary tract infection, and rash.

Grade 1-4 serious adverse reactions were reported in 41% of patients. The most frequent serious adverse reactions reported in ≥ 2% of patients were urinary tract infection/urosepsis, abdominal pain, musculoskeletal pain, creatinine increased/renal failure, dehydration, hematuria/urinary tract hemorrhage, intestinal obstruction/small intestine obstruction, and pyrexia. The most common Grade 3 and 4 adverse reactions (≥ 3%) were anemia, fatigue, hyponatremia, hypertension, urinary tract infection, and musculoskeletal pain.

The most common adverse reactions (≥ 20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. Eleven (4.5%) patients received an oral prednisone dose equivalent to ≥ 40 mg daily for an immune-mediated adverse reaction.

Table 4: All Grade Adverse Reactions in ≥ 10% of Patients with Locally Advanced or Metastatic UC in the JAVELIN Solid Tumor Trial

Adverse Reactions	BAVENCIO (N = 242)	
	All grades (%)	Grade 3-4 (%)
Any	98	59
Gastrointestinal Disorders		
Nausea	24	1
Abdominal pain[a]	19	2
Diarrhea	18	2
Constipation	18	1
Vomiting/Retching	14	1
General Disorders and Administration Site Conditions		
Fatigue[b]	41	7
Infusion-related reaction[c]	30	0.4
Peripheral edema[d]	17	0.4
Pyrexia/Temperature increased	16	1
Infections		
Urinary tract infection[e]	21	5
Investigations		
Weigh decreased	19	0
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	21	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[f]	25	3

Adverse Reactions	BAVENCIO (N = 242)	
	All grades (%)	Grade 3-4 (%)
Renal Disorders		
Creatinine increased/Renal failure[g]	16	3
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea/Exertional dyspnea	17	2
Cough/Productive cough	14	0
Skin and Subcutaneous Tissue Disorders		
Rash[h]	15	0.4
Pruritus/Generalized pruritus	10	0.4
Vascular Disorders		
Hypertension/Hypertensive crisis	10	5

[a] Includes abdominal discomfort, abdominal pain upper and lower, and gastrointestinal pain; [b] Includes asthenia and malaise; [c] Infusion-related reaction is a composite term that includes chills, pyrexia, back pain, flushing, dyspnea, and hypotension; [d] Includes edema, generalized edema, and peripheral swelling; [e] Includes urosepsis, cystitis, kidney infection, pyuria, and urinary tract infection due to fungus, bacterial, and enterococcus; [f] Includes back pain, myalgia, neck pain, and pain in extremity; [g] Includes acute kidney injury and glomerular filtration rate decreased; [h] Includes dermatitis acneiform, eczema, erythema, erythema multiforme, erythematous, macular, maculopapular, papular, and pruritic rash.

Table 5: Selected Laboratory Abnormalities* (Grade 3-4) in ≥1% of Patients with Locally Advanced or Metastatic UC Receiving BAVENCIO in the JAVELIN Solid Tumor Trial

Laboratory Tests	Grade 3-4 (N = 242)** %
Chemistry	
Hyponatremia	16
GGT increased	12
Hyperglycemia	9
Increased alkaline phosphatase	7
Increased lipase	6
Hyperkalemia	3
Increased aspartate aminotransferase (AST)***	3
Increased creatinine	2
Increased amylase	2
Increased bilirubin	1
Hematology	
Lymphopenia	11
Anemia	6

* Including Grade 3 and 4 lab abnormalities worsening from and unchanged since baseline.
**The number of patients with on study available laboratories varies between 188 and 235.
*** Increased alanine aminotransferase (ALT) was reported in 0.9% (Grade 3-4) of platinum-pretreated patients with locally advanced or metastatic UC.

Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to avelumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Of the 1738 patients treated with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks, 1558 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 64 (4.1%) tested positive. The development of treatment-emergent ADA against avelumab did not appear to alter the pharmacokinetic profile or risk of infusion-related reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy, Risk Summary: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of BAVENCIO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Human IgG1 immunoglobulins (IgG1) are known to cross the placenta. Therefore, BAVENCIO has the potential to be transmitted from the mother to the developing fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data: Animal reproduction studies have not been conducted with BAVENCIO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering BAVENCIO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to BAVENCIO may increase the risk of developing immune related disorders or altering the normal immune response.

Lactation, Risk Summary: There is no information regarding the presence of avelumab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

Females and Males of Reproductive Potential, Contraception: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO.

Pediatric Use: Safety and effectiveness of BAVENCIO have been established in pediatric patients aged 12 years and older for metastatic MCC. Use of BAVENCIO in this age group is supported by evidence from adequate and well-controlled studies of BAVENCIO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of avelumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MCC is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater is the same as that in adults. Safety and effectiveness of BAVENCIO have not been established in pediatric patients less than 12 years of age.

Geriatric Use

Metastatic Merkel Cell Carcinoma: Clinical studies of BAVENCIO in MCC did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Locally Advanced or Metastatic Urothelial Cancer: Of the 226 patients with locally advanced or metastatic UC treated with BAVENCIO, 68% were 65 years or over and 29% were 75 years or over. Among patients 65 years or over who were followed for at least 13 weeks, 14% (22/153) responded to BAVENCIO and 58% (89/153) developed a Grade 3-4 adverse reaction. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

OVERDOSAGE: No information on BAVENCIO overdosage is available.

PATIENT COUNSELING INFORMATION: Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions: Inform patients of the risk of immune-mediated adverse reactions requiring corticosteroids or hormone replacement therapy, including, but not limited to:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus.
- Nephritis and Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction

Infusion-Related Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Embryo-Fetal Toxicity: Advise females of reproductive potential that BAVENCIO can cause fetal harm. Instruct females of reproductive potential to use highly effective contraception during and for at least one month after the last dose of BAVENCIO.

Lactation: Advise nursing mothers not to breastfeed while taking BAVENCIO and for at least one month after the final dose.

Manufacturer: EMD Serono, Inc. Rockland, MA 02370 U.S.A. US License No: 1773
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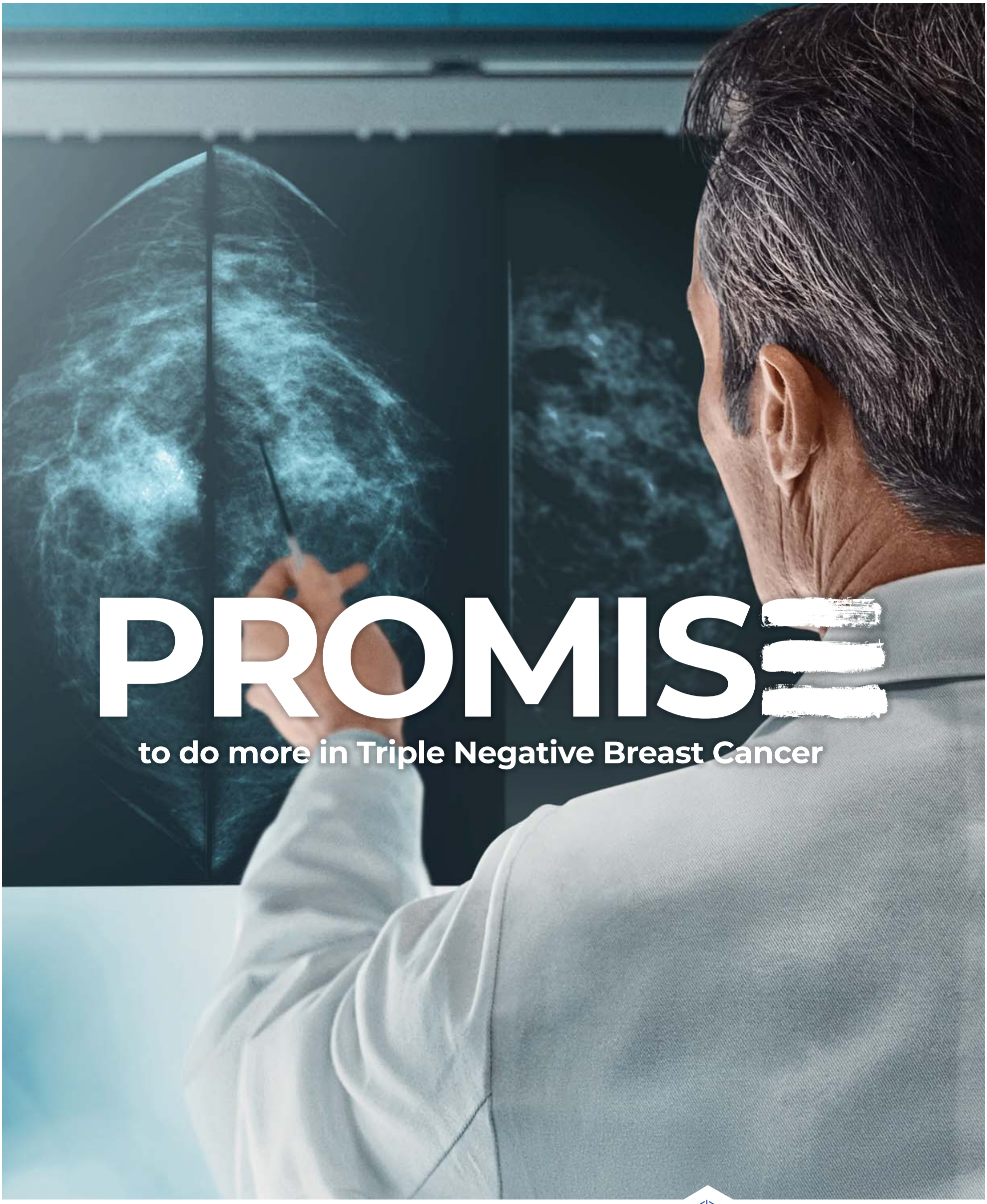

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Assessing the Older Adult

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mains: functional status, physical performance, comorbidity/polypharmacy, cognition, nutrition, psychological status, and social support.[6]

Why Perform a Geriatric Assessment?

There are several benefits to performing a geriatric assessment in older adults with cancer. First, a geriatric assessment can reveal areas of vulnerability that often go unnoticed during a routine oncologic evaluation. For example, the presence of falls and/or impairments in Instrumental Activities of Daily Living (IADL) are frequently overlooked by traditional evaluations, yet are important health indicators. In one study of older patients with cancer and normal performance status, more than two-thirds of patients had a geriatric assessment–identified impairment, and one-quarter of older patients had three or more impairments.[3] Second, these identified areas of vulnerability and impairments can aid in prediction of several important outcomes such as prognosis, risk of surgical complications, and tolerability of systemic chemotherapy.[7] Using falls and IADL impairments as examples, both are independently predictive of grade 3-5 chemotherapy toxicity.[8] Better understanding the likelihood of severe chemotherapy toxicities, complications, and survival can help in the decision-making process when weighing the risks and benefits of certain cancer treatments.

Lastly, geriatric assessment can identify impairments that are amenable to interventions, such as physical and occupational therapy, nutritional guidance, and improved management of comorbid conditions. How these interventions impact long-term outcomes in older adults with cancer is an area of active investigation, but promising results in noncancer populations suggest improved health-related quality of life and, potentially, survival.

Incorporating Geriatric Assessment Into Routine Oncologic Practice

As chronological age does not always correlate with physiologic age, defining a threshold age for performing a geriatric assessment is challenging. Experts recommend performing a geriatric assessment in all patients age 75 or older or in younger patients with specific age-related concerns ("geriatric syndromes"), such as cognitive impairment or a history of falls.[6] Although many of these assessments have been streamlined and designed specifically for use in busy oncology clinics, performing a geriatric assessment in all older adults with cancer can be time- and resource-consuming, since this includes nearly half of all new cancer diagnoses.

Screening tools have been developed to aid in identifying which patients may benefit the most from undergoing a full geriatric assessment. Using screening tools such as the Geriatric 8 (G8) or the Vulnerable Elders Survey takes only a few minutes to complete and provides useful and prognostic information.[9] For patients who test positive on a screening tool, a full geriatric assessment should be pursued. In settings with available specialty care for older adults with cancer, referral and consultation is preferred; however, as most areas lack this specialized care, using a patient-reported geriatric assessment survey is recommended, such as the Cancer and Aging Research Group (CARG)'s geriatric assessment. Table 2 highlights some selected online resources for geriatric oncology that include access to the CARG geriatric assessment in a variety of different languages, as well as further educational resources.

Case Examples

To demonstrate how geriatric assessments can aid in patient care, we present two cases of stage III colon cancer. Mr. Jones and Mr. Smith are 74-year-old men who presented to urgent care with bright red blood in their stool, and on subsequent colonoscopy were found to have invasive adenocarcinoma of the sigmoid colon. Both patients undergo CT staging without any identification of metastatic disease and undergo laparoscopic colectomy with pathology later revealing pT3N1 (stage IIIb) disease and microsatellite stability. Both patients were referred for consultation with their medical oncologist to discuss possible adjuvant therapy.

Upon consultation with their medical oncologist to discuss adjuvant therapy, Mr. Jones undergoes a G8 screening tool and scores a 16 out of 17 (notable only for more than three daily medications), indicating a negative screen for vulnerability (total score ≤ 14 = vulnerable). He has minimal comorbid conditions and remains active with no functional status limitations, and is recommended to undergo adjuvant therapy with capecitabine.

On the other hand, Mr. Smith undergoes the same screening assessment but scores a 9 out of 17 (below the ≤ 14 cutoff), and therefore has a full geriatric assessment performed that reveals significant weight loss, history of falls, limitations in ability to walk one block, impairments in IADL, and polypharmacy related to the ongoing care of his heart failure. His CARG chemotherapy toxicity score is calculated at 94% risk of developing a grade 3-5 toxicity. After discussion of the risks/benefits of adjuvant therapy, Mr. Smith decides to forgo adjuvant therapy and instead is referred for physical and occupational therapy (for his IADL and mobility limitations) and to see a nutritionist (for weight loss).

Table 1. Domains Assessed in a Typical Geriatric Assessment

Domain	What Is Measured?
Functional Status	Activities of daily living and instrumental activities of daily living
Physical Function	Ability to ambulate, walk stairs, and history of falls
Comorbidity	Number of any coexisting conditions in addition to cancer, hearing/vision
Psychological State	Assessment of anxiety and depression
Social Support	Availability of social support
Nutritional Status	History of weight loss, BMI
Cognition	Measure of cognitive function
Medications	Number and type of medications including potential interactions

Abbreviation: BMI, body mass index.

Table 2. Selected Online Resources for Geriatric Oncology

Site	What It Contains	URL
International Society of Geriatric Oncology	• Links to numerous published guidelines on management of older adults with cancer • Further information on screening tools and geriatric assessment measures • Information regarding more advanced educational courses on geriatric oncology	siog.org
Cancer & Aging Research Group	• Access to geriatric assessments (in a variety of different languages) and an online chemotherapy toxicity calculator • Updates on grant and job opportunities related to cancer and aging research	mycarg.org
ASCO: Geriatric Oncology Website	• Geriatric oncology resources and updates with links on a variety of different aging-related topics including cancer-specific information	asco.org
Portal of Geriatric Online Education	• Free public repository of a growing collection of geriatric educational materials in various e-learning formats	pogoe.org

Conclusion

Performing a geriatric assessment can not only provide useful prognostic information to aid decision-making, but also guide intervention strategies for patients with identified impairments. It's important to note, however, that chronologic age and physiologic age are distinct entities, and there is significant heterogeneity in aging between individuals of the same age; therefore, the determination of fitness for more versus less intense cancer treatment strategies requires a comprehensive evaluation of an individual's health status. A geriatric assessment may benefit cancer care providers in assessing fitness of older adults and/or those with geriatric syndromes such as functional and cognitive impairments for cancer treatments and facilitate their treatment decision-making with older adults with cancer and their caregivers. For busier oncology practices or those with limited access to formal geriatrics specialty clinics or resources, a geriatric screening tool (e.g., G8 and Vulnerable Elders Survey) may help cancer therapy providers discern higher-risk patients for treatment-related toxicities, other complications, and/or worse prognosis. ●

About the Authors: *Dr. Williams is a geriatrician and medical oncologist at the University of Alabama at Birmingham. Dr. Maggiore is a geriatrician and medical oncologist at the University of Rochester.*

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Continued from page 15B

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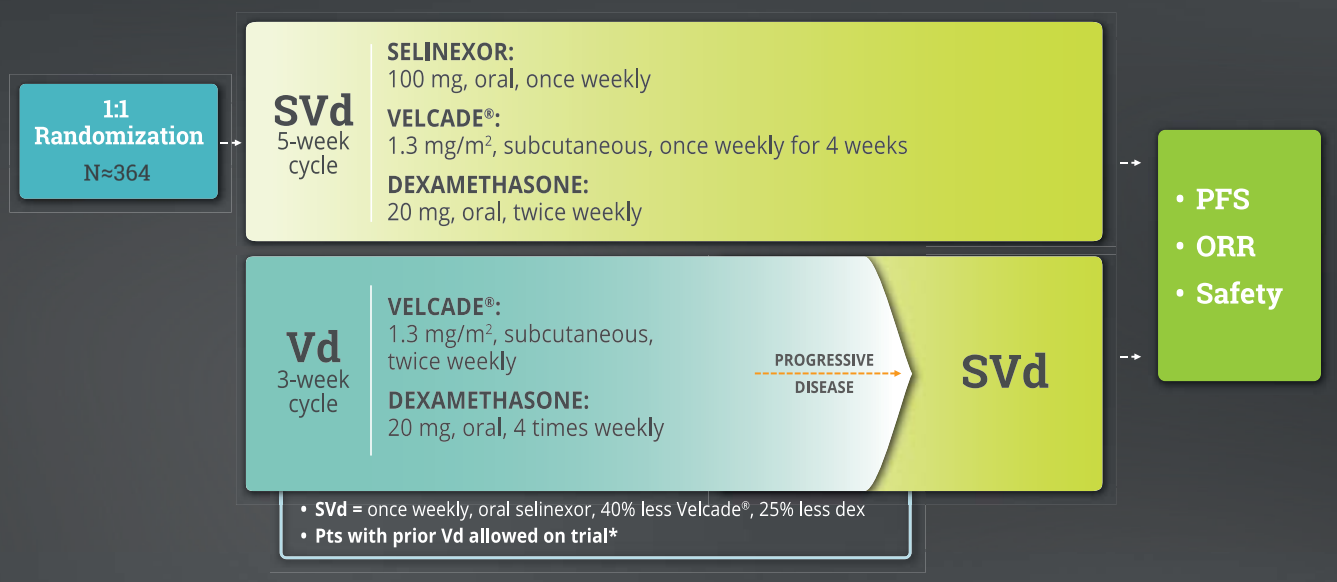

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In the Journals

Real-World Treatment of mRCC in Low-Resource Settings

"Assessment of Treatment Patterns for Metastatic Renal Cell Carcinoma in Brazil"

Journal: *Journal of Global Oncology*
DOI: 10.1200/JGO.17.00113

Abstract

Purpose: Although multiple therapies have emerged for the treatment of metastatic renal cell carcinoma (mRCC), it is unclear whether application of these agents is consistent in high-income and developing countries. We sought to determine patterns of care for mRCC in Brazil as a representative developing country.

Methods: A commercial database was used to acquire information pertaining to patients with mRCC receiving treatment at private or public hospitals in Brazil between March 2013 and October 2016. Basic clinical and demographic criteria were available, as well as information to ascertain the International Metastatic Renal Cell Carcinoma Database Consortium risk. Treatment-related data across multiple lines of therapy were collected.


Dr. Paulo G. Bergerot

Results: Of 4,379 patients assessed, 3,990 (91%) had metastatic disease, and 26%, 48%, and 26% of patients had good, intermediate, and poor International Metastatic Renal Cell Carcinoma Database Consortium risk disease, respectively. Although 3,149 patients (79%) received first-line therapy, only 641 (20%) and 152 (5%) received second- and third-line therapy, respectively. In the first-line setting, vascular endothelial growth factor–directed agents represented the most commonly used therapy, whereas in the second-line setting, vascular endothelial growth factor–directed and mammalian target of rapamycin–directed agents were used with similar frequency. Marked differences were seen in receipt of systemic therapy on the basis of treatment in private or public hospitals.

Conclusion: Relative to high-income countries, marked attrition is noted between each subsequent line of therapy in Brazil. Patterns of care also vary greatly in private and public settings, pointing to financial constraints as a potential cause for discordances in treatment.

Author Perspective

Paulo G. Bergerot, MD, City of Hope Comprehensive Cancer Center

Q: Technically, Brazil is a higher-middle income country, but its public health system is equivalent to that of a low-income country. Within this context, what did your study reveal about mRCC in Brazil?

Dr. Bergerot: Our study brings real-world evidence about treatment patterns for patients with mRCC in Brazil. Our findings show a large dichotomy between public and private practices that suggests a strong limitation on resources in the public system—maybe reflecting the socioeconomic disparity of a country in a low-resource setting. Furthermore, we compared our data from a low-resource setting with findings from high-income countries that were previously published.[1,2]

Our dataset included 4,379 patients, 3,990 of whom presented with metastatic disease. We identified that patients with mRCC in Brazil have some overlap in treatment with patients in high-income countries, especially in the first-line setting. Nevertheless, there was marked attrition from first- to second-line therapy and also from second- to third-line therapy. There was also a significant disparity between public and private institutions in that patients who were treated in private settings received systemic therapy in the first- and second-line setting more frequently than those treated within a public setting. Finally, we found a substantial difference in the type of treatment given to patients with mRCC in Brazil, as many received quite unconventional therapies. Some notable examples of these included imatinib or erlotinib, as well as older cytotoxic drugs such as dacarbazine, doxorubicin, and other cytotoxic regimens that have little evidence base in mRCC.

Q: How does your study seek to improve mRCC treatment in Brazil, and possibly other low-resource settings, going forward?

Dr. Bergerot: Our study reflects the largest experience related to treatment patterns for patients with mRCC in Brazil and fills an incredible gap that exists in the literature about kidney cancer epidemiology there. These findings are crucial for proper public health management and can be applied to daily practice. Although it is encouraging to see many practitioners adhering to treatment guidelines in the first-line setting, our results suggest important opportunities for improving care across scientific evidence that could be translated to the reality of a low-resource setting.

The challenges faced in Brazil are similar to those experienced in other low-resource settings, such as lack of access to certain types of treatment. We hope that our findings can inform and guide the improvement of quality cancer care in these countries.

Q: Have you seen any significant changes in treatment decisions in the wake of your study?

Dr. Bergerot: Our findings are thought-provoking. Although it is too early to see changes in treatment decisions, we have received interesting feedback, which has opened a dialogue with physicians across many different countries. This, we believe, is the first step in a long and important journey that was previously unexplored. This constructive conversation, without doubt, is the greatest outcome from our study.

Q: What about these data surprised you?

Dr. Bergerot: We were pleasantly surprised to find that some treatment patterns in Brazil were similar to those used in high-income countries. However, the discrepancies seen in second- and third-line therapies between low-resource settings and high-income countries was a concerning observation. Although surprising, these findings are encouraging and will hopefully convince providers to access biosimilars, participate in clinical trials, and prioritize training opportunities they may not have considered previously. ●

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Guideline Addresses Palliative Care

Continued from page 16B

28 million people with serious health-related suffering are in low- and middle-income countries, and they suffer inadequate pain management," Dr. Osman said. "So unlike in the U.S. guideline, we felt it was very important to address the opioid issue in the resource-stratified guideline."

Spirituality is another "very important dimension of palliative care, but when we are concerned about resources, it often becomes the first element of palliative care to be cut," Dr. Osman said. "The panel wanted to ensure that the spiritual dimension retained some importance even in areas with low resources." Very little published literature exists on the topic, she added, making the panel "feel more strongly about highlighting spiritual care as an important part of palliative care."

ASCO's guideline notes that in addition to providing direct patient care, "spiritual care providers may advise and support the care team to support the patients and their families," and suggests nurses or counselors can be trained to provide this support. These providers should be sensitive to the religious norms of patients and families. Dr. Cleary noted some religious sects do not allow the use of intoxicants or alcohol, but allow use for pain relief.

> "There is increasing evidence that supports the view that palliative care is an essential part of cancer care."
> –DR. JAMES F. CLEARY

"It's the intention of the medicine," he said. "This becomes critical as we look and address many African and Asian countries. There is increasing evidence that supports the view that palliative care is an essential part of cancer care."

Integrating the Guideline

Dr. Cleary said integrating palliative care on the level of some resource-constrained communities "is going to be very tough" in situations where there may only be four social workers in the entire country or when local health centers may not have someone dedicated to palliative care.

Dr. Osman uses the nonresource-stratified guidelines in her teaching and advocacy work, she said, and will now include this guideline's recommendations.

"I don't think I've given a single presentation without the ASCO statement about providing palliative care concurrent with treatment since the guideline came out in 2016," she said. "The resource-stratified guidelines will help us approach policymakers to lobby for change that is realistic and feasible in our setting."

"The clinical officer, the nursing community—these are the people who can start providing this type of care," Dr. Cleary said. "Palliative care is truly specialized care. We're really coming back to the importance of primary palliative care and the benefits it provides to patients and their caretakers and/or families." ●

–Michelle Dalton, ELS

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Bone-Modifying Agents

Continued from page 4B

Management of Complications

Guidelines note that the risk for osteonecrosis of the jaw appears to increase with the use of more potent bisphosphonates and is also observed with denosumab. Patients should undergo a comprehensive dental examination with appropriate preventive measures before starting bone-modifying therapy. Active oral infections should be treated and high-risk sites should be eliminated. Clinicians should talk with patients about the importance of oral hygiene and avoiding invasive dental procedures if possible. ●

–Melinda Tanzola, PhD

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SUNDAY · JUNE 3, 2018

Dr. Gabriel Hortobagyi Receives 2018 Gianni Bonadonna Breast Cancer Award

Gabriel N. Hortobagyi, MD, FACP, FASCO, is the recipient of the 2018 Gianni Bonadonna Breast Cancer Award for his leadership and contribution in the field of translational medicine in breast cancer, with an exceptional record of mentorship. A past ASCO president, Dr. Hortobagyi is professor and chair emeritus of the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center. He will deliver a lecture accepting his award on June 4.

A Lifetime of Mentoring

Dr. Hortobagyi has been affiliated with MD Anderson since the completion of his fellowship training in 1976. He has enjoyed a lifetime of mentorships and professional associations from a long list of achievers and colleagues in the oncology field, including Gianni Bonadonna, MD, after whom the award was named.

"My parents were my first mentors," Dr. Hortobagyi said. "We lived in a very tumultuous era of the 21st century, and their example of standing up after adversity was very inspirational through emigration and political discrimination," he said, referring to his family's emigration from Hungary and eventually to Colombia, where Dr. Hortobagyi earned his medical degree.

In kind, Dr. Hortobagyi has been an active mentor to younger colleagues in the field of oncology, beginning with his time as director of residency training at MD Anderson in 1978. "I enjoy interacting with younger people," he said, commenting that he must have trained more than 500 to 600 fellows over the years. "I have always been surrounded by restless young minds. Working with them not only expands your own, but also provides you the opportunity to distribute the work and train your younger colleagues."

Research Contributions

Dr. Hortobagyi has personally led or helped guide dozens of clinical trials. Starting from his work optimizing doxorubicin hydrochloride into the treatment of breast cancer, to the development of new drugs—especially paclitaxel and docetaxel—in the neoadjuvant setting, to his work with gene therapy, to the control of bone metastases with bisphosphonates and strategies to prevent resistance to endocrine treatment of breast cancer, he has become an international leader in developing new breast cancer treatments.

He is widely acknowledged as a leader in the field of neoadjuvant chemotherapy. "I did much of the early work of neoadjuvant chemotherapy, but by the time I came to MD Anderson, one of my predecessors had been administering chemotherapy before surgery to some [patients with] locally advanced breast cancers," Dr. Hortobagyi said.

It was not intended as a research strategy but was done out of desperation, because the disease was responding so poorly to standard treatment.

In the early 1980s, he remembers becoming frustrated with the lack of therapies for patients with metastatic breast cancer that spread to bone. That frustration led to conducting some of the pivotal trials with bisphosphonates, which ultimately resulted in the availability of pamidronate, zoledronate, and denosumab for prevention of bone-related complications in that setting. He is particularly satisfied that this approach later went through the hands of his trainees into adjuvant bisphosphonate therapy in early-stage breast cancer.


Dr. Gabriel Hortobagyi

See Gianni Bonadonna Award, Page 8C

SESSION PREVIEW

Incorporating Immunotherapy in Frail Adults With Common Malignancies

Although immunotherapy drugs may now provide a treatment option for older patients with cancer who are ineligible for, or whose disease fails, chemotherapy, there are many unanswered questions about the efficacy and adverse effects of immunotherapy in this patient population. Highlighting these knowledge gaps, as well as discussing ways to reconcile those gaps in clinical practice, will be the focus of an Education Session on June 4 titled "Treating Frail Adults With Common Malignancies: Best Evidence to Personalize Therapy."*

"People should come to the session to get a deep dive into the current existing evidence base for older or more vulnerable adults who are receiving immunotherapy," said session Chair Ronald J. Maggiore, MD, of the University of Rochester Medical Center. Older adults are often not candidates for standard chemotherapeutic treatments because of comorbidities and poor performance status, Dr. Maggiore said.

The session will focus on non–small cell lung cancer (NSCLC), which Dr. Maggiore will discuss, as well as bladder cancer and lymphoma. The session will also cover immunotherapy recently approved by the U.S. Food and Drug Administration (FDA) for these cancer types, including pembrolizumab for patients with bladder cancer, Hodgkin lymphoma, and NSCLC.[1]

However, the clinical trials that led to many of the immunotherapy drug approvals included younger patients than oncologists typically see, Dr. Maggiore

See Immunotherapy in Frail Adults, Page 3C

Medical Marijuana: Efficacy, Toxicity, and Legality

EXPERT EDITORIAL

Wesley M. Durand, ScB, and Tina Rizack, MD, MPH

Cannabis use in Western medicine was initially popularized by Irish physician William B. O'Shaughnessy in 1840.[1-3] It was included in the U.S. Pharmacopeia shortly afterward and was often prescribed for rheumatism, cholera, tetanus, rabies, and labor pain.[1,4] In the early 20th century, however, cannabis was outlawed in several states.[5] Access was further reduced with the passage of the Harrison Narcotics Tax Act in 1914, defining drug use as a crime de facto.[1,6] The Marijuana Tax Act was passed in 1936, declaring nonmedical cannabis illegal.[1,5] It was removed from the U.S. Pharmacopeia in 1942, justified by a lack of recognized medical value.[4,5] The 1950s saw passage of the Boggs Control Act and Narcotics Control Acts codifying mandatory penalties for those caught possessing or distributing marijuana.[1] Although laws were temporarily eased in the 1970s, the Reagan administration's Anti-Drug Abuse Act (1986) reestablished a tough federal stance on marijuana use.[1,7]

The modern trend toward state-level legalization of medical marijuana started with California in 1996.[1] Despite growing nationwide support for marijuana legalization, it remains classified as a Schedule I substance: one with high

See Medical Marijuana, Page 3C

ARTICLE HIGHLIGHTS

- A wide variety of formulations exist for medical marijuana use, including dried cannabis flowers, resins, extracts, and oils.
- The legalization and use of cannabis for medical purposes is an evolving issue, and physician perspectives are likely evolving in tandem.
- At present, there is limited but evolving support for the use of cannabinoids as anticancer therapies; the largest evidence base exists in gliomas.
- A growing proportion of state legislatures have voted in favor of medical marijuana use, although tension between state and federal laws persists.

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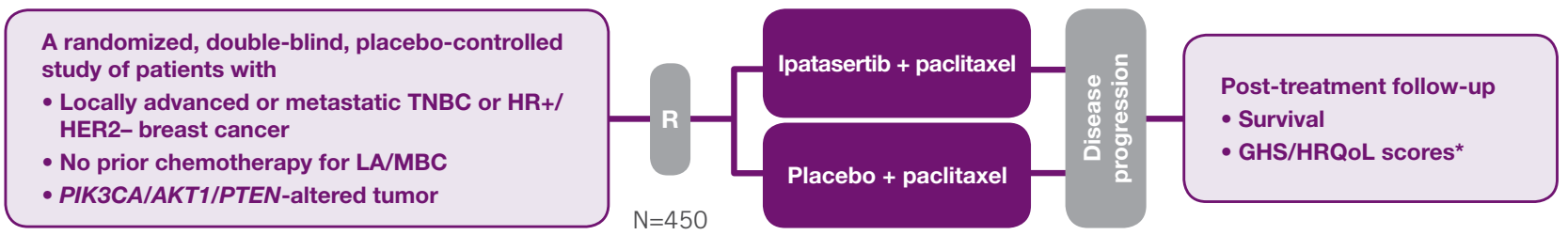

Study Endpoints

Primary Outcome Measure:

- Progression-free survival, defined as the time from randomization to the first occurrence of disease progression or death from any cause†

Selected Secondary Outcome Measures:

- Objective response rate, defined as a complete response or partial response on 2 consecutive occasions ≥4 weeks apart†
- Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause
- Overall survival, defined as the time from randomization to death from any cause
- GHS/HRQoL scores*

Selected Eligibility Criteria

- Histologically documented TNBC or HR+/HER2– adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to resection with curative intent
- Measurable disease according to RECIST v1.1
- Valid results confirming *PIK3CA*/*AKT1*/*PTEN*-altered status in tumor tissue
- No prior treatment with chemotherapy for inoperable LA/MBC
- No history of diabetes requiring insulin
- ECOG performance status of 0 or 1

*As assessed using selected questions from EORTC QLQ-C30.
†As determined by the investigator through the use of RECIST v1.1.

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www.ClinicalTrials.gov Identifier: NCT03337724; Sponsor Study Identifier: CO40016.

ATP=adenosine triphosphate; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS=global health status; HER=human epidermal growth factor receptor; HR=hormone receptor; HRQoL=health-related quality of life; LA=locally advanced; MBC=metastatic breast cancer; *PIK3CA*=phosphoinositide-3-kinase, catalytic, alpha polypeptide; PTEN=phosphatase and tensin homolog; RECIST=Response Evaluation Criteria In Solid Tumors; TNBC=triple-negative breast cancer.

This compound and the combination of agents and their uses are investigational and have not been approved by the US Food and Drug Administration. Efficacy and safety have not been established. The information presented should not be construed as a recommendation for use. The relevance of findings in preclinical studies to humans is currently being evaluated.

Information is consistent with www.ClinicalTrials.gov as of February 1, 2018.

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Medical Marijuana

Continued from page 1C

potential for abuse and lacking a currently accepted medical use.[8] Perhaps in response to this trend, in 2009 the Obama administration recommended against prosecution of marijuana for medical purposes.[9,10] In 2013, the U.S. Department of Justice clarified that, although marijuana remained illegal on a federal level, it would presently refrain from challenging state-level legalization.[11] As of January 2018, 29 states, the District of Columbia, and Puerto Rico permit medical marijuana use; an additional 18 states permit use of "low delta 9-tetrahydrocannabinol (THC), high cannabidiol (CBD)" products in medical circumstances (Fig. 1).[12] Finally, although the National Institutes of Health provided $111 million for research on cannabinoid compounds in 2016, others have charged that the pace of cannabis research is hampered by restrictions on scientific marijuana acquisition and distribution.[13,14]

Cannabis Pharmacology

Formulation

A wide variety of formulations exist for medical marijuana use, including dried cannabis flowers, resins, extracts, and oils.[13] Cannabis oils may be particularly potent; evidence supports that oils may contain up to 75% THC, as compared to 20% in other formulations.[15] Importantly, cannabis products may be composed of either THC, CBD, or both. THC is generally considered responsible for the psychoactive effects of cannabis, whereas CBD lacks such activity. This discrepancy may be attributable to differential binding affinity of CBD versus THC for the CB_1 and CB_2 cannabinoid receptors.[13,16,17]

Online purchasing is possible, and a recent *JAMA* research letter purchased and examined 84 cannabinoid products online and found that with respect to CBD, only 31% (±10%) were labeled accurately: 43% had more cannabinoids than labeled, whereas 26% had less or no active ingredient. THC was found in 21%. Oils were the most likely to be labeled accurately (45%), whereas vaporization liquids were the least likely.[18]

Route of administration

Cannabis products can be inhaled, ingested, or administered topically, vaginally, or rectally.[13,19] These diverse routes of administration are associated with distinct pharmacologic profiles. Evidence suggests that inhaled cannabis (typically smoked or vaporized) is associated with more rapid and predictable effects, although ingestion of cannabis yields more variable results.[13] Smoke or inhaled cannabis act quickly, with usual onset in minutes, and lasts 2 to 4 hours. Pills and edible forms of cannabis take longer to achieve a therapeutic effect and last longer (4 to 12 hours). They can be perceived as not working and lead to increased doses and potential cumulative overdose. Novel, synthetic cannabinoid products are generally administered orally via capsules.[13]

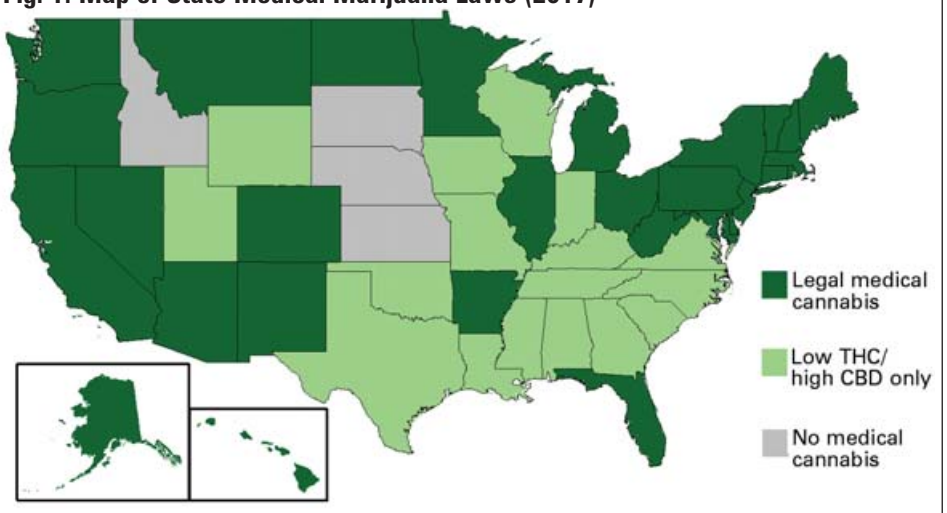
FDA-approved cannabinoid products

At present, the U.S. Food and Drug Administration (FDA) has approved three cannabinoid products for medical use.[13] Dronabinol is a synthetic THC isomer available in both oral capsular and liquid formulations. Both are indicated for anorexia associated with weight loss in adult patients with AIDS and treatment of chemotherapy-associated nausea and vomiting (CINV) in nonresponders to conventional antiemetic therapies.[20] Nabilone is a synthetic cannabinoid derivative also available in an oral capsular formulation.[21] Nabilone is indicated for second-line treatment of CINV, and its prescribing information indicates that the product is limited to refractory CINV due to "psychotomimetic reactions not observed with other antiemetic agents."[21]

Several additional cannabinoid products may also be on the horizon. Ajulemic acid is an nonpsychoactive synthetic endocannabinoid analog that is being developed in a range of indications related to inflammation and fibrosis.[13,21] Cannabidiol (an oral solution of CBD extract) was submitted for consideration by the FDA in late 2017.[13] Nabiximol is an oromucosal spray with THC/CBD extracts; although it is currently marked ex-U.S., the company has yet to file for approval with the FDA.[13,22] These latter two are notable in that they are composed of cannabis extracts rather than synthetic cannabinoids. The FDA's response to these products will likely

See Medical Marijuana, Page 14C

Fig. 1. Map of State Medical Marijuana Laws (2017)[12]



Abbreviations: THC, tetrahydrocannabinol; CBD, cannabidiol.

Immunotherapy in Frail Adults

Continued from page 1C

said. Most of the patients enrolled in the seminal studies of immunotherapy for NSCLC were in their early to mid-60s, yet 50% of patients diagnosed with lung cancer in the United States are older than 70.[2] These trials also excluded patients with poor performance status from participation a priori,[3,4] although post-marketing and FDA safety analyses have been somewhat encouraging for single-agent checkpoint inhibitors in older adults or those with poorer performance status, Dr. Maggiore added.

It can be challenging to apply data from these trials to clinical decision-making for older patients, particularly if they have other comorbidities, Dr. Maggiore said. One of the issues is that, as patients age and develop comorbidities, immune function may decline and there may be changes in the tumor microenvironment, all of which could affect the efficacy of immunotherapy drugs.

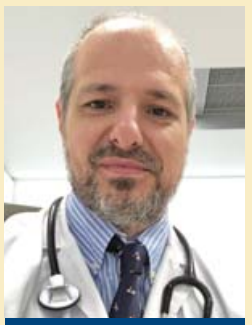
The session will feature a clinical vignette to illustrate some of the key challenges in deciding how to treat older patients with immunotherapy, Dr. Maggiore said.

Older Patients in Advanced Bladder Cancer Trials

During his presentation, Ravindran Kanesvaran, MD, of the National Cancer Centre Singapore, will discuss the characteristics of older patients with advanced bladder cancer who could benefit from immunotherapy drugs.

Dr. Ronald J. Maggiore

Dr. Ravindran Kanesvaran



Dr. Raul Cordoba

Patients who are frail or who have poor renal function are ineligible for cisplatin-based chemotherapy, which is the standard of care for advanced bladder cancer. "Thanks to immunotherapy, patients who may not have received the current standard of care can potentially get some treatment that can prolong their life and give them good quality of life," Dr. Kanesvaran said.

The recent approvals of pembrolizumab and atezolizumab in the first-line treatment of patients with advanced bladder cancer who were cisplatin-ineligible were based on single-arm phase II clinical trials that reported good tolerability and antitumor activity.[5,6] Moreover, because trial participants were ineligible for cisplatin treatment because of poor performance status or comorbidities such as kidney dysfunction, neuropathy, or hearing loss, they tended to be elderly (median age: 74 and 73 years for the pembrolizumab and atezolizumab studies, respectively).

"Now we know these data specifically apply to older patients with advanced bladder cancer. In general, clinical trial enrollments are biased toward younger populations, and it is a challenge to decide how to extrapolate those data to the older patient," Dr. Kanesvaran said.

Immunotherapy for Older Patients With Lymphoma in the First-Line and Relapsed Settings

As is the case with most cancer types, clinical trials of immunotherapy drugs for Hodgkin and non-Hodgkin lymphoma have included few patients older than 65. Raul Cordoba, MD, PhD, MS, of the Fundacion Jimenez Diaz University Hospital, in Madrid, Spain, will review data on PD-1 inhibitors and CAR T-cell therapy for patients with aggressive relapsed lymphoma.

"So far, clinical data on efficacy and safety of immunotherapy in older patients with lymphoma seem to be similar to younger patients, but we need longer follow-up," Dr. Cordoba said. Research should be conducted to understand the relationship between baseline immune function, as evaluated through a comprehensive immune assessment, and outcomes of immunotherapy in older patients, he said.

Dr. Cordoba will also discuss early clinical studies testing combination nivolumab and brentuximab vedotin as first-line treatment of patients with advanced Hodgkin lymphoma. "This strategy seems to be attractive in older patients with Hodgkin lymphoma who are not candidates for conventional chemotherapy because of frailty or comorbidities," Dr. Cordoba said. ●

–Carina Storrs, PhD

References:

1. National Cancer Institute. FDA Expands Approval of Pembrolizumab for First-Line Treatment of Non-Small Cell Lung Cancer. cancer.gov/news-events/cancer-currents-blog/2017/fda-pembrolizumab-lung-expanded. Published June 6, 2017. Accessed February 21, 2018.
2. Ferrara R, et al. *Cancer Treat Rev.* 2017;60:60-8.
3. Reck M, et al. *N Engl J Med.* 2016;375:1823-33.
4. Brahmer J, et al, *N Engl J Med.* 2015;373:123-35.
5. Balar AV, et al. *Lancet Oncol.* 2017;18:1483-92.
6. Balar AV, et al. *Lancet.* 2017;389:67-76.

**Program information updated as of February 22. For session time and location information, please refer to the ASCO iPlanner on the Attendee Resource Center (am.asco.org/arc).*

YES CAR T IS HERE

YESCARTA®, THE FIRST CAR T THERAPY FOR CERTAIN TYPES OF RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA

The following data reflect results from the ZUMA-1 pivotal trial*[1]

// PROVEN EFFICACY

51%

Patients achieved a best response of complete remission (CR) (52/101)

NR

Response duration was not reached at a median follow-up of 7.9 months in patients who achieved CR

// CYTOKINE RELEASE SYNDROME

13%

Grade ≥3 incidence

94%

Overall incidence

// NEUROLOGIC TOXICITIES

31%

Grade ≥3 incidence

87%

Overall incidence

// RAPID & RELIABLE MANUFACTURING

17 DAYS

Median turnaround time†

99%

Manufacturing success of CAR T cells engineered and expanded ex vivo

VISIT YESCARTAHCP.COM/CENTERS TO FIND A LIST OF AUTHORIZED TREATMENT CENTERS

*ZUMA-1 was an open-label, single-arm study in 101 adult patients who received YESCARTA® therapy. Patients received lymphodepleting chemotherapy prior to a single infusion of YESCARTA® at a target dose of 2 x 10^6 viable CAR T cells/kg body weight (maximum of 2 x 10^8 viable CAR T cells). Patients had refractory disease to their most recent therapy, or had relapsed within 1 year after autologous hematopoietic stem cell transplantation.

†The median time from leukapheresis to product delivery.

INDICATION

YESCARTA® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA® is not indicated for the treatment of patients with primary central nervous system lymphoma.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®. Do not administer YESCARTA® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA®. Provide supportive care and/or corticosteroids as needed.**
- **YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS.**

Important Safety Information continued on adjacent page.

VISIT US AT THE
GILEAD BOOTH #18063

YESCARTA®
(axicabtagene ciloleucel) Suspension for IV infusion

IMPORTANT SAFETY INFORMATION (continued)

CYTOKINE RELEASE SYNDROME (CRS): CRS occurred in 94% of patients, including 13% with ≥ Grade 3. Among patients who died after receiving YESCARTA®, 4 had ongoing CRS at death. The median time to onset was 2 days (range: 1-12 days) and median duration was 7 days (range: 2-58 days). Key manifestations include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA®. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

NEUROLOGIC TOXICITIES: Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks, with a median time to onset of 4 days (range: 1-43 days) and a median duration of 17 days. Grade 3 or higher occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA®. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA®. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly.

YESCARTA® REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS. The required components of the YESCARTA® REMS are: Healthcare facilities that dispense and administer YESCARTA® must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA® infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA® are trained about the management of CRS and neurologic toxicities. Further information is available at www.YESCARTAREMS.com or 1-844-454-KITE (5483).

HYPERSENSITIVITY REACTIONS: Allergic reactions may occur. Serious hypersensitivity reactions including anaphylaxis may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA®.

SERIOUS INFECTIONS: Severe or life-threatening infections occurred. Infections (all grades) occurred in 38% of patients, and in 23% with ≥ Grade 3. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA® should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA® infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

PROLONGED CYTOPENIAS: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA® infusion. Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA® infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA® infusion.

HYPOGAMMAGLOBULINEMIA: B-cell aplasia and hypogammaglobulinemia can occur. Hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA® treatment, and until immune recovery following treatment.

SECONDARY MALIGNANCIES: Patients may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Due to the potential for neurologic events, including altered mental status or seizures, patients are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA® infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages.

Reference: 1. YESCARTA™ [package insert]. Santa Monica, CA: Kite Pharma; 2017.

Kite
A GILEAD Company
Santa Monica, CA

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR YESCARTA®
(axicabtagene ciloleucel) suspension for intravenous infusion

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)]*.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)]*.**
- **YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

2.2 Administration: YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient *[see Dosage and Administration(2.2.3)]*.

Preparing Patient for YESCARTA Infusion: Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. *Pre-treatment:* Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously on the fifth, fourth, and third day before infusion of YESCARTA. *Premedication:* Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion: Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready. Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette. Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient. Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label. Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE). Place the infusion bag inside a second sterile bag per local guidelines. Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion. Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration: For autologous use only. Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period. Do NOT use a leukodepleting filter. Central venous access is recommended for the infusion of YESCARTA. Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag. Prime the tubing with normal saline prior to infusion. Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw. Gently agitate the product bag during YESCARTA infusion to prevent cell clumping. After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered. YESCARTA contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring: Administer YESCARTA at a certified healthcare facility. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome (CRS): Identify CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 1. CRS Grading and Management Guidance

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.

Table 1. CRS Grading and Management Guidance (continued)

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

(a) Lee et al 2014, (b) Refer to Table 2 for management of neurologic toxicity, (c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity: Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS): CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA. In Study 1, CRS occurred in 94% (101/108) of patients receiving YESCARTA, including ≥ Grade 3 (Lee grading system) CRS in 13% (14/108) of patients. Among patients who died after receiving YESCARTA, four had ongoing CRS events at the time of death. The median time to onset was 2 days (range: 1 to 12 days) and the median duration of CRS was 7 days (range: 2 to 58 days). Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) *[see Adverse Reactions (6)]*. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (17)]*. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated *[See Dosage and Administration (2.3)]*.

5.2 Neurologic Toxicities: Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA. Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks of YESCARTA infusion, with a median time to onset of 4 days (range: 1 to 43 days). The median duration of neurologic toxicities was 17 days. Grade 3 or higher neurologic toxicities occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor

patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly *[see Management of Severe Adverse Reactions (2.3); Neurologic Toxicities]*.

5.3 YESCARTA REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS *[see Boxed Warning and Warnings and Precautions (5.1 and 5.2)]*. The required components of the YESCARTA REMS are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions: Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

5.5 Serious Infections: Severe or life-threatening infections occurred in patients after YESCARTA infusion. In Study 1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 23% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients after YESCARTA infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. *Viral Reactivation:* Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In Study 1, Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In Study 1, hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies: Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS: The following adverse reactions are described in Warnings and Precautions: Cytokine Release Syndrome, Neurologic Toxicities, Hypersensitivity Reactions, Serious Infections, Prolonged Cytopenias, Hypogammaglobulinemia.

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based *[see Clinical Trials (14)]* . Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was 43% with ECOG 0, and 57% with ECOG 1. The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (> 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia. The most common (≥ 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections. Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.

Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

Adverse Reaction		Any Grade (%)	Grades 3 or Higher (%)
Cardiac disorders	Tachycardia	57	2
	Arrhythmia	23	7
Gastrointestinal disorders	Diarrhea	38	4
	Nausea	34	0
	Vomiting	26	1
	Constipation	23	0
	Abdominal pain	14	1
	Dry mouth	11	0
General disorders and administration site conditions	Fever	86	16
	Fatigue	46	3
	Chills	40	0
	Edema	19	1
Immune system disorders	Cytokine release syndrome	94	13
	Hypogammaglobulinemia	15	0
Infections and infestations	Infections-pathogen unspecified	26	16
	Viral infections	16	4
	Bacterial infections	13	9
Investigations	Decreased appetite	44	2
	Weight decreased	16	0
	Dehydration	11	3

Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1 (continued)

Adverse Reaction		Any Grade (%)	Grades 3 or Higher (%)
Musculoskeletal and connective tissue disorders	Motor dysfunction	19	1
	Pain in extremity	17	2
	Back pain	15	1
	Muscle pain	14	1
	Arthralgia	10	0
Nervous system disorders	Encephalopathy	57	29
	Headache	45	1
	Tremor	31	2
	Dizziness	21	1
	Aphasia	18	6
Psychiatric disorders	Delirium	17	6
Respiratory, thoracic and mediastinal disorders	Hypoxia	32	11
	Cough	30	0
	Dyspnea	19	3
	Pleural effusion	13	2
Renal and urinary disorders	Renal insufficiency	12	5
Vascular disorders	Hypotension	57	15
	Hypertension	15	6
	Thrombosis	10	1

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxemia, renal insufficiency, and hypotension. For a complete list of events that contributed to the incidence of certain adverse reactions, please see footnote below Table 3 in Section 6.1 of the Full Prescribing Information.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following: blood and lymphatic system disorders: coagulopathy (2%); cardiac disorders: cardiac failure (6%) and cardiac arrest (4%); immune system disorders: hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%); infections and infestations disorders: fungal infections (5%); nervous system disorders: ataxia (6%), seizure (4%), dyscalculia (2%), and myoclonus (2%); respiratory, thoracic and mediastinal disorders: pulmonary edema (9%); skin and subcutaneous tissue disorders: rash (9%); vascular disorders: capillary leak syndrome (3%).

Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

Lymphopenia 100%, Leukopenia 96%, Neutropenia 93%, Anemia 66%, Thrombocytopenia 58%, Hypophosphatemia 50%, Hyponatremia 19%, Uric acid increased 13%, Direct Bilirubin increased 13%, Hypokalemia 10%, Alanine Aminotransferase increased 10%.

6.2 Immunogenicity: YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: *Risk Summary*: There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

8.2 Lactation: *Risk Summary*: There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential: *Pregnancy Testing*: Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA. *Contraception:* See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA. *Infertility:* There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use: The safety and efficacy of YESCARTA have not been established in pediatric patients.

8.5 Geriatric Use: Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Ensure that patients understand the risk of manufacturing failure (1% in clinical trial). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period. Advise patients to seek immediate attention for any of the following: Cytokine Release Syndrome, Neurologic Toxicities, Serious Infections, Prolonged Cytopenia *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.5) and Adverse Reactions (6) for more information and signs and symptoms]*. Advise patients for the need to: Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion until at least 8 weeks after infusion *[see Warnings and Precautions (5.2)]*, Have periodic monitoring of blood counts. Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy *[see Warnings and Precautions (5.8)]*.

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Looking Back: First Antibody-Drug Conjugate Changed Practice in Breast Cancer Treatment

During the 2012 ASCO Annual Meeting Plenary Session, Kimberly L. Blackwell, MD, of Duke University Medical Center, presented the primary results of the EMILIA trial.[1] In that phase III clinical trial, in patients with previously treated HER2-positive locally advanced or metastatic breast cancer, investigators demonstrated that trastuzumab emtansine (T-DM1) conferred a significant and clinically meaningful improvement in progression-free survival (PFS) over its comparator regimen.

To assess the effect of the study on the practice of breast cancer treatment in the 6 years since that presentation, the *ASCO Daily News* recently spoke to Dr. Blackwell and Louis M. Weiner, MD, of Georgetown Lombardi Comprehensive Cancer Center.

In 2012, Dr. Weiner—who was the discussant for the abstract during the Plenary Session—called T-DM1 "an important new weapon in the therapeutic armamentarium for breast cancer." He said the results of the trial served as justification to explore other antibody-drug conjugates, and he congratulated the study authors for their "excellent and very important accomplishment."

Contacted in 2018 for this retrospective article, Dr. Weiner told the *ASCO Daily News*, "I find my opinions remarkably unchanged from back then. The drug lived up to its promise. It adds to the therapeutic armamentarium, as predicted. It's being widely employed. Breast cancer oncologists have learned how and when to use it."

Dr. Blackwell agreed that T-DM1 met expectations. "This was the first antibody-drug conjugate approved for the treatment of solid tumors, and it has definitely been practice-changing in the metastatic setting," she said. "It's wonderful to have a drug that is well tolerated and does not have the traditional toxicity we saw with the previous chemotherapy regimen. It's a demonstration of what we all strive for in the treatment of patients facing cancer, which is to not hurt the patient as much as we hurt their cancer."

Based primarily on the strength of the EMILIA findings, T-DM1, also known ado-trastuzumab emtansine, was approved by the U.S. Food and Drug Administration (FDA) in 2013.[2,3] T-DM1 is an antibody-drug conjugate comprising trastuzumab, a linker, and the cytotoxic agent derivative emtansine, or DM1. It combines the antitumor activities of trastuzumab and the HER2-targeted delivery of DM1, a microtubule inhibitor. The drug is indicated for the treatment of patients with HER2-positive metastatic breast cancer who have previously received trastuzumab and a taxane.

Last June, 5 years after the Plenary presentation, the final overall survival (OS) results of EMILIA were published in

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Gianni Bonadonna Award

Continued from page 1C

Working with long-time MD Anderson collaborator Mien-Chie Hung, PhD, Dr. Hortobagyi started some of the initial clinical trials on gene modification in the early 1990s. "At the time the tools were very primitive, but now it is so satisfying for me to see how, indirectly from earlier trials, we have the ability to harvest CAR T cells and implement newer gene therapy programs that are actually working," he said.

Current Research Efforts

For the past 5 to 6 years, Dr. Hortobagyi has been working on developing improved endocrine therapy in breast cancer. Having earlier discovered a number of genomic abnormalities that were commonly associated with breast cancer, among them activation or abnormalities of the AKT/mTOR pathway, he developed the idea that some of those abnormalities might be involved in the development of resistance to endocrine therapy.

The next step was to look for drugs that were far enough in development to test the hypothesis. Working with José Baselga, MD, PhD, on the BOLERO-2 trial, everolimus, one of the first mTOR inhibitors, emerged. From that trial, two adjuvant trials are now ongoing with everolimus.

Dr. Hortobagyi has been deeply involved in development of the cyclin CDK4/6 inhibitors, such as ribociclib, which represent another pathway for preventing endocrine therapy resistance in breast cancer. He designed the successful MONALEESA-2 clinical study with ribociclib and is now conducting adjuvant ribociclib trials.

"Progress in any field, including breast cancer, is a process of who builds on what and how to take advantage of existing knowledge, whether positive or negative, and move forward," Dr. Hortobagyi said. ●

–Alice McCarthy

Oncologists in the Philippines Determined to Make Palliative Care the Norm

As one of the world's largest archipelago nations—comprising more than 7,100 individual islands—the Philippines is disparate by nature. Among its population of 100.9 million people, demographics, economic standing, and living conditions vary considerably. Although the country's rich natural resources and environmental assets secured a 6.6% economic growth rate in 2012, 26.5% of the population still lives below the poverty line, and with a gross national income per capita of $3,580 in 2016, the Philippines is classified as a low- to middle-income nation.[1,2]

Nowhere is this disparity so clearly reflected as in the Philippines' health care system—and, accordingly, its cancer care.

"In the private hospitals—which are mostly concentrated in major cities—the level of cancer care is on par with comprehensive cancer hospitals in the United States and other high-resource settings," Marie Belle Francia, MD, MSc, a medical oncologist at St. Luke's Medical Center, in Manila, and a 2014 recipient of ASCO's International Development and Education Award in Palliative Care (IDEA-PC), said. "But then in government hospitals, cancer care is less developed due to a lack of government funding."

The comprehensive care offered at private hospitals comes at a much higher expense than the care offered at government hospitals. Coupled with the fact that there are 98,200 new cases of cancer diagnosed in the Philippines each year, this expense results in a significant financial burden nationwide.[3]

"Here in the Philippines, families and loved ones often pay for treatment themselves," said Maria Diana Aileen Bautista, MD, a medical oncologist at the University of Santo Tomas Hospital, in Manila, and a 2017 International Development and Education Award (IDEA) recipient.

See Oncologists in the Philippines, Page 20C

First Antibody-Drug Conjugate

Continued from page 8C

The Lancet Oncology.[4] That publication confirmed that T-DM1 "improved OS in patients with previously treated HER2-positive metastatic breast cancer even in the presence of crossover treatment." The safety profile was similar to that seen in previous reports.

Recapping the Trial

Dr. Kimberly L. Blackwell

Dr. Louis M. Weiner

EMILIA was a phase III clinical trial comparing T-DM1 with the chemotherapy regimen of lapatinib plus capecitabine in patients with HER2-positive locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane. Lapatinib plus capecitabine was, at that time, the only approved chemotherapy combination for trastuzumab-refractory HER2-positive metastatic breast cancer.[1]

Patients in the trial were randomly assigned to receive lapatinib plus capecitabine or T-DM1. The primary endpoints were PFS, OS, and safety. In 991 patients, there was a significant improvement in PFS favoring T-DM1 (median 9.6 vs. 6.4 months; HR for death from any cause 0.65, 95% CI [0.55, 0.77]; $p < 0.001$).[2]

At the time of the Plenary Session, the median OS for T-DM1 had not been reached.[1] When the study results were published later in 2012, the authors reported that median OS crossed the stopping boundary for efficacy at the second interim analysis (30.9 vs. 25.1 months; HR for death from any cause 0.68, 95% CI [0.55, 0.85]; $p < 0.001$).[2]

T-DM1 was well tolerated in the study, with no unexpected safety signals. Thrombocytopenia and increased serum aminotransferase levels were more common in those receiving T-DM1, but diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus capecitabine.[1]

The authors concluded that T-DM1 conferred a significant and clinically meaningful improvement in PFS compared with lapatinib plus capecitabine, and that the drug was an active and well-tolerated novel therapy for HER2-positive breast cancer.[1]

Changing Mindset

Dr. Blackwell said she sees the findings of the EMILIA trial as a pivotal point in her career.

"The reason EMILIA was accepted as a Plenary abstract, in my opinion, was not so much the trial itself, but the demonstration of the power of antibody-drug conjugates and, for that matter, of targeted drug delivery," she said. "It was a demonstration that we had reached a point in oncology where we were no longer going to accept giving nontargeted poisons for the treatment of patients facing cancer.

"Look what doors have opened since then," Dr. Blackwell continued. "Now we have all these immuno-oncology agents that represent a similar paradigm. I think it was that moment in 2012 when people realized that this might actually happen during our lifetimes."

She spoke about the investigators' misgivings during the trial—wondering whether the drug was working because patients were not exhibiting toxicities.

"We were giving these patients drugs every 3 weeks, and they weren't getting sick," Dr. Blackwell said. "Our mindset up to that point was, if the patient doesn't have some toxicity, maybe it wasn't working. Looking at the practice of oncology today, I think EMILIA allowed us to say that there can be drugs that work but that don't cause harm to patients. That was the practice-changing component of EMILIA."

Dr. Blackwell said she has now treated more than 100 patients with T-DM1 outside the clinical trial setting, and the results mirror what the investigators saw during the EMILIA trial. "The toxicities are things that patients don't even know about, unlike traditional chemotherapy where they get diarrhea, lose their hair, and throw up," Dr. Blackwell said. "These toxicities are lab findings."

The Legacy

Several antibody-drug conjugates are now available for the treatment of hematologic malignancies, but T-DM1 remains the only such agent approved for treatment of solid tumors.[5] That status may not last long, however. Blackwell noted that two antibody-drug conjugates in advanced stages of development for TDM1-refractory breast cancer have been granted accelerated approval status by the FDA. "They both have a trastuzumab-antibody component, but different cytotoxins," she said. "This lays the groundwork for other very promising drugs."

One of these compounds, DS-8201, is a humanized HER2 antibody attached to a novel topoisomerase I inhibitor payload by a tetrapeptide linker. It was granted accelerated review based on preliminary clinical evidence of potential clinical benefit for the treatment of patients with HER2-positive locally advanced or metastatic breast cancer who have been treated with trastuzumab and pertuzumab and have disease progression after T-DM1, according to the manufacturer.[6] The other, [vic-]trastuzumab duocarmazine (SYD985), received the Fast Track designation based on promising data from heavily pretreated patients with HER2-positive metastatic breast cancer in a phase I clinical trial.[7,8]

In addition to these, multiple other antibody-drug conjugates are in development. It has been only 6 years since the presentation of the EMILIA Plenary abstract demonstrated the promise of this type of drug targeting system. As Dr. Weiner pointed out, 6 years "would be an awfully quick turnaround to a useful drug if one was only getting started" at the time of the abstract presentation, based on the promising results demonstrated by T-DM1 in EMILIA.

Dr. Weiner noted that, during his discussion of the abstract, he "ruminated about the possibility that T-DM1 might be acting, at least in part, by stimulating host immune responses." Subsequent to that Plenary discussion, "it's become quite clear that checkpoint-focused antibodies have a very powerful role to play in the treatment of human cancers," he said. "I've been gratified to hear of a number of different strategies to explore the induction of host immunity by immunoconjugates. I think it's too soon to know if these studies will turn out to be as potentially transformational as the development of an effective immunoconjugate was, but I think they point to a direction for future investigation that appears to be extremely promising." ●

–Tim Donald, ELS

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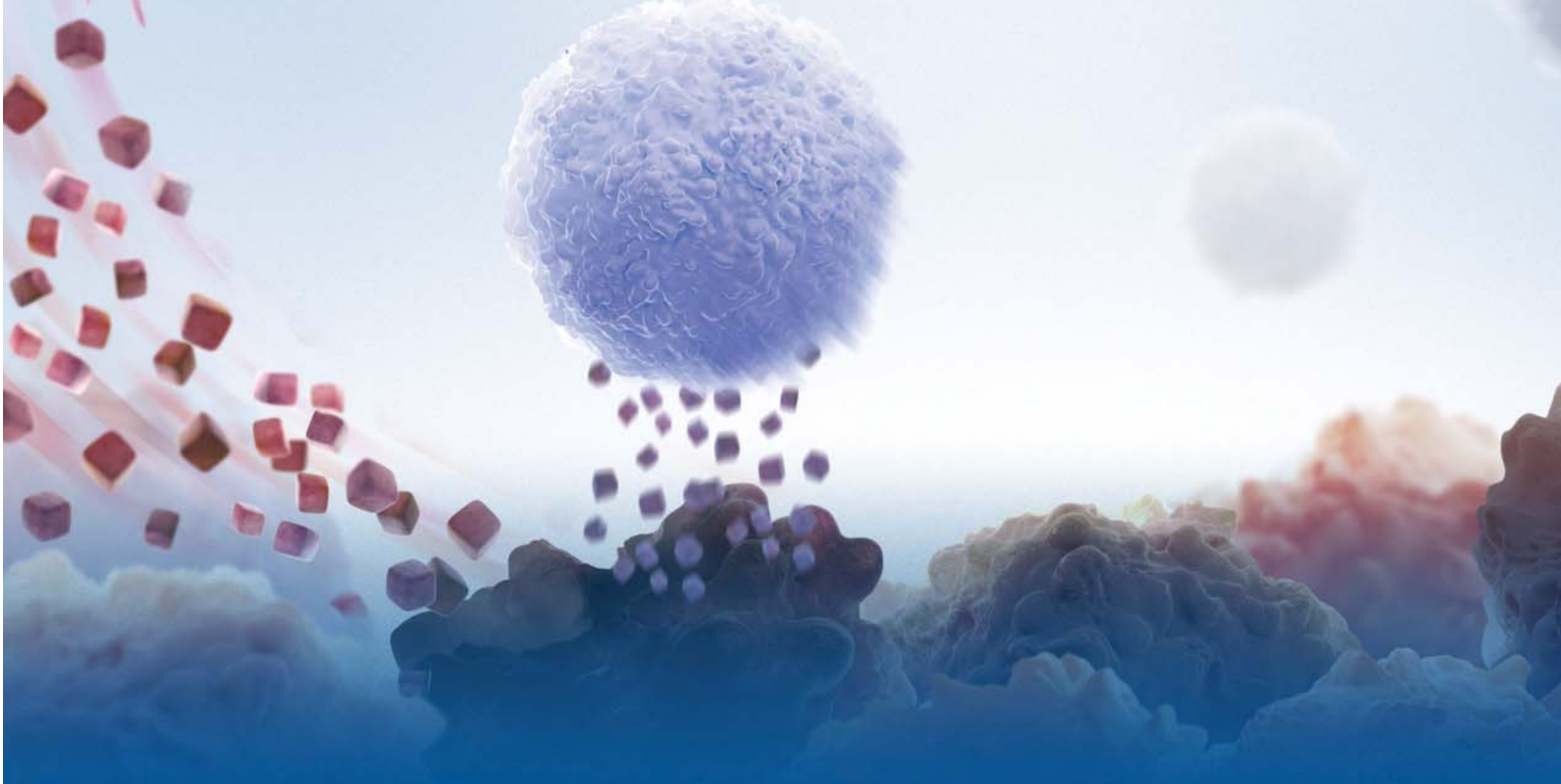
Investigating multiple mechanisms of immune escape in cancer

Genentech is exploring new possibilities by researching pathway combinations with PD-L1



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Reference: US National Institutes of Health. ClinicalTrials.gov. https://www.clinicaltrials.gov. Accessed January 28, 2018.

Patient-Reported Outcomes in Oncology Practices

EXPERT EDITORIAL

Donna L. Berry, RN, PhD, and
William B. Lober, MD, MS

Evidence from multiple positive trials, support from literature reviews and editorials, and the endorsements of professional societies and funding agencies all promote the use of patient-reported outcomes (PROs) in clinical cancer care. And yet, relatively few cancer care settings have implemented consistent methods of PRO assessment and integrated interventions.

What are the reasons for the lack of widespread adoption? In other words, why is this easier said than done? The pros and cons of a comprehensive PRO supportive program are complex, and solutions to address the barriers are largely unknown.

Why PROs?

Communication

Patient-clinician communication is required for adequate symptom management. Assessment and monitoring of an individual's health status and delivery of cutting-edge interventions require engagement of patients and direct care clinicians, as well as technology experts, innovators, and support staff. However, our current health system is characterized by limited face-to-face patient-clinician contact. Time constraints during clinic visits and patients' hesitancy to verbally report certain symptoms can result in missed or under-communicated, but significant, symptoms.[1,2] Unreported adverse outcomes may have even led to chemotherapy overdose.[3] Medical oncologists value patient-reported toxicities for planning safe and effective doses of chemotherapy, notably self-administered oral agents.[4]

What patients want

Qualitative work has described patients' and caregivers' experiences with cancer symptoms, reporting, and management.[5-7] Study participants identified their own methods of tracking symptoms, as they lacked the proper tools from the cancer treatment institution. Findings from focus groups, individual interviews, and cognitive and usability testing all suggest common desired features for PRO systems: tracking symptoms on custom calendars that incorporate medications (both self- and clinic-administered) and tracked laboratory values; information regarding how to manage symptoms at home; and timely electronic communication between patients, caregivers, and clinicians. Perhaps most importantly, patients and caregivers want to know when and who to call for help, for which symptom, and what to expect in terms of a response.

Evidence

Various strategies to enhance patient-clinician communication have been studied. Trials in the United States, Canada, Australia, and Northern Europe have shown symptom management and quality-of-life clinical screening to be feasible and clinically beneficial with regard to communication and, most importantly, patient outcomes. Several large trial interventions included substantial in-person contact by research personnel, limiting applicability to many clinical settings.[8-11] In more automated trial interventions, evidence suggests clinicians can readily use PRO summaries in practice to significantly enhance communication and improve patient experience.[8,12-14] Howell et al conducted a scoping review of the use, impact on health outcomes, and implementation factors related to PRO use in practice, concluding that PRO use is likely acceptable to patients, enables earlier assessment and identification of symptoms, and may improve patient-clinician communication.[15] Basch and colleagues established that PROs extend life in patients with advanced disease.[16] Given the longer survival, coupled with the efficacy of other systems to reduce symptom distress and depression during treatment in patients of all stages of cancer, there is no question that PRO collection and intervention is beneficial.[17]

Professional opinions and funding

Thought leaders and investigators have called for the implementation of PROs, ranging from Bruner's 2007 suggestion that every cancer clinical trial include PROs, to Basch and Snyder's commentary on how to tackle PRO integration in clinical practice and electronic medical records (EMRs).[18,19] The International Society for Quality of Life Research produced the "User's Guide to Implementing Patient-Reported Outcomes Assessment in Clinical Practice," including practical steps for planning PRO assessments.[20] Subsequently, the Patient-Centered Outcomes Research Institute developed the "Users' Guide to Integrating Patient-Reported Outcomes in Electronic Health Records."[21] ASCO and the Oncology Nursing Society have also featured columns highlighting the importance of clinically integrated PRO systems.[22,23] Subsequent to the Beau Biden Cancer Moonshot Initiative, the National Cancer Institute released a UM1 opportunity for funding (RFA-CA-17-042) to test PRO implementation and use.

Barriers and Recommendations

Many of the barriers to effective PRO implementation and use relate either to value perceived by specific stakeholders (patients, clinic staff, clinicians, health care organizations, etc.) or to the integration of PROs with existing workflows. For instance, low PRO response by patients may result from their belief that the data aren't used in clinical care or from inadequate support for PRO completion.

Technical capabilities of PRO systems may substantially impact barriers. For instance, access to a standalone computerized PRO system may require the administration of patient usernames and passwords. Using PRO tools within patient portals lessens those barriers, but low adoption of an organization's patient portal or underdeveloped or inflexible questionnaire software creates new problems. Emerging technologies address these problems by allowing tighter, more seamless integration of PRO apps into EMR software, using the same standards and strategies across multiple vendors.[24,25]

Barriers and recommendations below are organized by the primary stakeholders they impact. We have referenced evidence where we are aware of it; additional discussion is based on our experience with approximately 40 PRO implementations in research and usual care settings, cancer, HIV/AIDS, chronic pain, orthopedics, general surgery, and primary care/behavioral health integration.

The patient

The lack of consistent endorsement by clinicians or clinic staff undermines patients' perceptions of PRO value. Endorsement by the physician and reporting reminders were shown to be the two factors most associated with high PRO response rates in one study.[26] Clinicians should ensure patients know that PRO data supports their care and remind patients to report their experiences and outcomes.

Inadequate support for using PRO tools may limit patients' abilities to complete reporting. The ability of patients to use computerized PRO systems varies widely, and introductory material and hands-on training should be available. Patients, or those assisting patients—whether family members or staff—need to be supported when using PRO tools.

Limited options for PRO reporting increases patient effort, complicates scheduling, and decreases engagement. Although clinic-based reporting may seem easier to support than home use, patients may need to arrive earlier for appointments or schedule the use of limited tablets or kiosks. PROs should be offered to the patient on their own computer or device, meeting them in the times and places most convenient. Some will need device access or additional support, and in-clinic access should also be available. In one clinic with both home and clinic access, unpublished data show half of patients with chronic pain will complete their PROs on their own device, before return visits, and half require clinic devices and/or support. PRO systems should be available to the patient in both settings.

Diverse health, computer, and reading literacy present challenges for those who need support. For savvy computer users, simplistic navigation may be frustrating, arguing for a customized interface based on previous technology use. PROs should be designed to ensure that patients are engaged at an appropriate literacy level and in the language most appropriate to them. We use a fourth-grade reading level for survey items and responses, with medical terms at a higher reading level accompanied by definitions. Computer adaptive surveys offer the opportunity for personalization to support those patients with higher literacy levels and is an area that should be explored.

No access to data may decrease the value perceived by patients. Patients value longitudinal summaries of their PRO data, which they can use for shared symptom management strategies during a clinical visit and view outside the visit as a reminder of progress or associations with treatment days and peak symptomatology.[7] The potential value of PRO data as a "health diary" should be investigated further.

High patient burden from frequent or long assessments can occur when PROs satisfy research interests in longitudinal outcomes data or regulatory requirements for the health care organization. PRO assessments may encompass the union of all stakeholder requirements, resulting in long assessments that patients perceive as tangential to their care and burdensome. PRO assessments should be relevant to the patient's care and easily perceived as such.

The clinician

Information overload may be concerning to clinicians who are faced with a new route for unmoderated feedback from patients.[27] This can take several forms: increased patient access to clinicians, poorly summarized data, and data that are not clinically actionable. PRO data should support clinical decision-making and be presented to emphasize longitudinal changes.

See Patient-Reported Outcomes, Page 24C

ARTICLE HIGHLIGHTS

- Assessment and monitoring of an individual's health status and delivery of cutting-edge interventions require engagement of patients, direct care clinicians, technology experts, innovators, and support staff.
- Thought leaders and investigators have called for the implementation of patient-reported outcomes (PROs), ranging from suggestions that every cancer clinical trial include PROs, to commentary on how to tackle PRO integration in clinical practice.
- PRO data should support clinical decision-making and be presented to emphasize longitudinal changes.
- PROs are desired by patients, enable clinicians to efficiently address the whole patient, and impact clinical outcomes and patients' experience of disease.

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Medical Marijuana

Continued from page 3C

signal its receptivity to further, nonsynthetic cannabis derivatives.

Toxicity and adverse reactions

Medical cannabis exhibits a very favorable toxicity profile. The lethal dose of THC has been estimated to be far greater than amounts consumed in either medical or recreational use.[3,23-25] The same is true for synthetic cannabinoids; monkeys administered nabilone at 2 mg/kg/day experienced no significant adverse effects.[26]

Nevertheless, cannabis use is associated with a variety of side effects. In the acute phase, these may include euphoria, altered judgment, paranoia, amnesia, difficulty concentrating, hallucinations, panic attacks, sedation, unsteadiness, dizziness, dry mucous membranes, and headache.[27-29] There is also substantial evidence of an association between chronic cannabis use and the development of schizophrenia in a dose-dependent manner.[30] Evidence of a link between marijuana use and other mental health disorders exists, but is less understood.[13] Although many cannabinoids are used in treatment of nausea and vomiting, select patients may experience cannabinoid hyperemesis syndrome, characterized by persistent nausea, vomiting, and abdominal pain, and frequent hot bathing to relieve symptoms.[31-33]

The risk of substance dependence may also be considered a potential side effect of medical cannabis use. The risk of addiction among those experimenting with marijuana has been cited as 9%, and although the vast majority of medical cannabis patients may use marijuana daily, this statistic may be less relevant to these patients.[29,34,35] Coffey et al's 2002 study of Australian young adults observed DSM-IV cannabis dependence rates of 53% among those using cannabis "weekly or more often"; the proportion increased to 72% among those using cannabis "almost daily."[36] The most common dependence symptoms included persistent desire, unintentional use, and withdrawal. Further research on the long-term safety profile of medical cannabis use is warranted; such studies should ideally be conducted among both patients with intended long-term versus limited-term use (e.g., chronic pain vs. CINV, respectively).

Medical Cannabis: Patients and Providers

Who is using medical cannabis?

Several surveys have sought to understand demographics among patients using medical cannabis. In 2006, Reiman et al surveyed 130 patients from medical marijuana facilities in the San Francisco Bay Area.[37] They observed a mean age of 40 years and male predominance (74%) among their sample. Medi-Cal (38%) was the most represented insurance type, followed by no insurance (24%), and 59% of those surveyed indicated an annual income of less than $20,000.

A 2014 study by Webb et al surveyed 100 patients in Hawaii, 97% of whom were prescribed cannabis for chronic pain.[38] All patients had been certified for 1 year or less and were surveyed upon reapplication for use. The median age was 51 years, and patients reported a 64% average relative decrease in pain (7.8 out of 10 at baseline, 2.8 post-treatment). Additional reported benefits included reduction in stress and insomnia, and the vast majority of patients (71%) reported no adverse reactions.

Reinarman et al reviewed data from 1,746 consecutive admissions to a network of California medical cannabis assessment clinics from July to September of 2006.[35] A relative underrepresentation of Latino patients was also observed (14% of the cohort, compared to 32% in California overall as of 2000 Census data). The authors hypothesized that this may be due to the "undocumented status of many Latinos in California." The majority of patients reported that medical marijuana relieved pain (83%) and improved sleep (71%). Many patients reported substituting marijuana for another prescription medication (51%) or alcohol (13%). Importantly, most patients reported using medical cannabis daily (67%), and the vast majority reported administration via smoke inhalation at least some of the time (86%).

Physician opinions

The legalization and use of cannabis for medical purposes is an evolving issue, and physician perspectives are likely evolving in tandem. A 2005 study by Charuvastra et al found that 36% of a national sample of physicians believed that medically prescribed marijuana should be legal.[39] In 2013, Adler et al published results from a poll of *New England Journal of Medicine* readers; in total, 76% of respondents favored use of medical cannabis.[40] Among U.S. respondents, however, the results differed strongly by state. For example, whereas 96% (103 of 107) respondents from Pennsylvania had favorable views of medical marijuana, only about 1% of those from Utah (1 of 76) responded favorably. Notably, neither Pennsylvania nor Utah had legalized marijuana for medical use at the time of this survey.[12] If accurate, these results suggest that federal-level efforts to legislate medical marijuana use will need to reconcile diverse regional perspectives.

Therapeutic Uses

Chronic pain

There is a large body of evidence supporting the efficacy of cannabinoids in the treatment of chronic pain. In 2015, Whiting et al published a meta-analysis of trials evaluating cannabinoids for a wide range of indications; chronic pain and CINV were among those with the greatest number of included studies.[32] Studied cannabinoid modalities included nabiximols, smoked and vaporized THC, nabilone, THC oromucosal spray, dronabinol, and oral THC capsules, and almost all studies used a placebo comparator. Diagnoses included neuropathic pain, cancer pain, and diabetic peripheral neuropathy, among others. In aggregate, cannabinoids exhibited superior reduction in pain as compared to placebo. Although no differences were observed between diagnosis types or cannabinoid modalities, the ability to adequately detect differences may have been hampered by limited statistical power.

A separate meta-analysis by Andreae et al studied inhaled cannabis specifically, pooling data from five randomized controlled trials in chronic neuropathic pain.[41] Using a hierarchical Bayesian model, they aggregated data from trials with differing designs and outcomes. The results indicated a statistically significant benefit of inhaled cannabis in the reduction of chronic neuropathic pain, with a number-needed-to-treat of 5.6 (95% CI [3.4,14]). Nevertheless, the authors caution that further long-term studies are required to evaluate the long-term efficacy and safety profile of inhaled medical marijuana.

Cannabinoids are known to enhance the potency of opioids, and when used synergistically they can allow for reduced doses of opioids and better pain control. When used alone, cannabinoids have shown efficacy in neuropathic pain but appear to be less effective when used alone for other types of pain. The 2017 *National Academies of Sciences, Engineering, and Medicine* report concluded that adults with chronic pain treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms, adding that the effect is modest.[13]

Chemotherapy-induced nausea and vomiting (CINV)

A large number of studies have assessed the efficacy of cannabinoids in the treatment of CINV. Whiting et al's recent meta-analysis analyzed 28 studies with 1,772 total patients, ultimately finding that patients receiving dronabinol or nabiximols had significantly greater odds of exhibiting a complete nausea and vomiting response, as compared to placebo (OR 3.82, 95% CI [1.55, 9.42]). A recent Cochrane review similarly found substantial evidence supporting efficacy of cannabinoids over placebo in CINV (complete absence of nausea and vomiting RR 2.9, 95% CI [1.8, 4.7]).[42]

A 2001 meta-analysis by Tramèr et al found that cannabinoids (including nabilone, dronabinol, and levonantradol) were more effective as first-line antiemetics as compared to prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride (complete control of nausea and vomiting RR 1.38, 95% CI [1.18, 1.62]).[43] These effects, however, were not observed among patients receiving chemotherapy with very low or very high emetogenic potential. Further, evidence from crossover trials suggested that patients strongly preferred cannabinoids. However, Smith et al's recent Cochrane review found differently; although they observed a trend toward superior efficacy of cannabinoids over prochlorperazine, the results were not statistically significant.[42] Additionally, the authors noted the lack of studies comparing cannabinoids to 5-HT_3 antagonists and NK-1 inhibitors, indicating the need for additional studies of cannabinoid efficacy against modern antiemetic agents.

Sleep disorders

Whiting et al's meta-analysis identified two large-scale randomized controlled trials studying cannabinoids in sleep disorders specifically, reporting significant improvement in the sleep quality with nabilone as compared to both placebo and amitriptyline.[13,32] A more recent trial by Carley et al compared dronabinol to placebo in the treatment of moderate-to-severe obstructive sleep apnea.[44] Treatment with dronabinol (10 mg/day) was associated with significantly improved apnea/hypopnea index and Epworth Sleepiness Scale as compared to placebo.

Additional studies suggest that these results may be generalizable to improved sleep among patients without sleep disorders. Whiting et al analyzed 19 chronic pain and multiple sclerosis trials that included sleep-related outcomes.[32] In total, patients treated with cannabinoids (including nabiximols, nabilone, dronabinol, THC/CBD capsules, and smoked THC) exhibited superior sleep quality as compared to placebo.

Anticancer agent

At present, there is limited but evolving support for the use of cannabinoids as anticancer therapies; the largest evidence-base exists in gliomas. A wide range of preclinical in vivo and in vitro studies have observed that cannabinoids exhibit substantial antitumoral activity through a wide range of mechanisms, including necrosis, apoptosis, cytotoxicity, antiproliferation, and oxidative stress-induced cellular damage.[45] At present, clinical evidence is limited to a single phase I trial conducted on surgery- and radiotherapy-refractory glioblastoma multiforme patients; Guzman et al administered intracranial THC to nine patients, observing minimal adverse effects.[46] A reduction in tumor growth was observed in two patients.

Conclusions

Medical cannabis is an evolving and potentially divisive issue. A growing proportion of state legislatures have voted in favor of medical marijuana use, although tension between state and federal laws persists. Cannabis is associated with a number of potential adverse reactions and risk of dependence; addressing these issues may be crucial for those seeking broader cannabinoid utilization. Nevertheless, medical cannabis has demonstrated efficacy as a treatment for a wide range of conditions, including chronic pain, CINV, and sleep disorders. It may also have potential as an anticancer agent, although the evidence for this

See Medical Marijuana, Page 22C

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Examining Smoking Cessation in Current Practice

EXPERT EDITORIAL

Carolyn M. Dresler, MD, MPA, and
Matthew A. Steliga, MD

When we were asked to write an Expert Editorial about smoking cessation in patients with cancer, our first thought was, isn't this topic settled and already well understood? But, then, that is what our "expert" thinking is—versus what actually exists in the field. There are a few interesting updates in the arena for smoking cessation, but let's first make sure that everyone is on the same page.

First, we all know that using tobacco causes many cancers, as well as other diseases, and that there is no safe use of tobacco products. Second, as oncologists, we should all know that continued smoking after cancer diagnosis significantly affects cancer treatment outcomes and survival. In the 2014 Surgeon General Report, the evidence base was assessed regarding continued tobacco use by people with cancer, with the following key outcomes in patients with cancer and survivors:[1]

1. The evidence is sufficient to infer a causal relationship between cigarette smoking and adverse health outcomes. Quitting smoking improves the prognosis of patients with cancer.
2. The evidence is sufficient to infer a causal relationship between cigarette smoking and increased all-cause and cancer-specific mortality.
3. The evidence is sufficient to infer a causal relationship between cigarette smoking and increased risk for second primary cancers known to be caused by cigarette smoking, such as lung cancer.
4. The evidence is suggestive but not sufficient to infer a causal relationship between cigarette smoking and the risk of recurrence, poorer response to treatment, and increased treatment-related toxicity.

Third, oncologists need to do better at addressing tobacco cessation. In an ASCO membership survey several years ago, respondents indicated that at initial visit, most physicians routinely ask patients about tobacco use (90%), ask patients to quit (80%), and advise patients to stop using tobacco (84%). However, only 44% routinely discuss medication options with patients, and only 39% provide cessation support.[2] As this is self-reported data of survey respondents, the actual, real-world implementation is likely even less. We must be better at identifying persistent tobacco users when they come to us for treatment and at intervening to help them stop tobacco use.

Addressing Addiction

Tobacco use, particularly by inhalation of combusted tobacco, is the most deadly—and, the most addictive—drug we have in our societies. Big tobacco engages in massive marketing campaigns targeting youth to initiate and become addicted.[3,4] It is not a "choice" to be addicted. Many people who use tobacco want to quit, and have probably tried at least several times. It is terrifically difficult to quit, so there should never be "blame" or "shame" to anyone who uses or is addicted to tobacco. No one "deserves" to get cancer.

Thus, when implementing a tobacco cessation program in your practice, be very sensitive to this blame or shame that our patients might feel when addressing their need for cessation. We need to make it very clear that the reason for addressing cessation is because it really matters for their health and treatment outcome. We choose the best treatment protocol or regimen with the least side effects while maximizing the outcome and survival, and tobacco cessation is a critical piece of this effort. Also, quitting tobacco is a process. Tobacco addiction is a chronic disease, and any blame goes to the tobacco industry that promulgates these products without any shame on their part.

Program Implementation

To implement a program that addresses tobacco use and cessation, visit ASCO's webpage on Tobacco Cessation Tools and Resources, which lays out the data and process.[5] Look for resources that can help you implement such a program in your setting. We found from surveys that most oncologists are not trained and/or do not feel comfortable or competent in addressing tobacco cessation.[2,6] Tobacco cessation is an integral part of a patient's treatment, and there are experts who are knowledgeable and trained in this practice. As physicians, we are dedicated and caring, and our message to the patient is crucial, but we cannot be the only tobacco cessation resource for the patient. Just as we involve respiratory therapists, physical therapists, and other medical specialists in a multidisciplinary fashion, we need to recognize that tobacco cessation is an area with specialized resources and experts who can help our patients, and we need to integrate these resources into patient care.

The National Cancer Institute (NCI) launched the Cancer Center Cessation Initiative as part of the NCI Cancer Moonshot program to help cancer centers build and implement sustainable tobacco cessation programs to target patients with cancer.[7] Twenty-two leading cancer centers received funding, and this initiative demonstrates NCI's understanding of the necessity for this type of program in cancer treatment. Perhaps there will be more funding for expanded programs at non–NCI-designated cancer centers in the future.

If your cancer center or clinic participates in a lung cancer screening program, does it already have a smoking cessation program within it? It should. Is there a way to access that tobacco cessation program? (We assume that if you have a lung cancer screening program, you also address smoking cessation.) We believe that cancer centers or large clinical oncology clinics should design and implement their own program that comprehensively addresses tobacco cessation and integrates cessation into the clinical care of all patients. The National Comprehensive Cancer Network (NCCN) has published one example of smoking cessation guidelines in cancer care,[8] and the most recent updates are always available at NCCN.org.

Telephone-Based Resources

For practices without tobacco cessation programs, there are outside available resources, often at low cost or free to patients. Many oncologists are unaware of tobacco cessation programs that all U.S. states have in the form of telephone-based quitlines. These quitlines provide evidence-based strategies including free telephone counseling and often free or reduced-cost nicotine replacement therapy to support quit attempts. Quitlines are cost-effective programs and typically have acceptable cessation rates. However, they are funded by state departments of health with assistance from the Centers for Disease Control and Prevention. These programs may be in a challenging funding status, which impacts what a particular state quitline can actually provide. The best way to know what your state offers is to call your state department of health and ask to speak with the person in their tobacco control program who works with the state quitline and who can share their tools to access and successfully use the quitline. Many quitlines accept referrals from physicians in the form of fax or online referrals, and integration of quitline resources through electronic health records should be explored.

Other countries address tobacco

See Smoking Cessation, Page 21C

ARTICLE HIGHLIGHTS

- When implementing a tobacco cessation program in your practice, be sensitive to the blame or shame that our patients might feel when addressing their need for cessation.
- For practices without tobacco cessation programs, there are outside available resources, often at a low cost or free to patients.
- We likely have a few more years of assessment of intensive research on the topic of electronic cigarettes.
- At each visit with your patient, discuss their tobacco use status just like you check for adverse events or other symptoms.

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY

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FDA approved for metastatic CRPC since 2012

In the US alone, 106,000 patients have been prescribed XTANDI—and counting†[2]

†Estimate based on US sales and use data from September 2012 to December 2017.
Reference: Astellas. XTANDI. Data on File. Source: Symphony Health.[2]

Indication and Important Safety Information

Indication

XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

Important Safety Information

Contraindications

XTANDI is not indicated for women. XTANDI can cause fetal harm and potential loss of pregnancy.

Warnings and Precautions

Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors, seizures were reported in 2.2% of patients. See section 5.1 of the Prescribing Information for the list of predisposing factors. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)
In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Adverse Reactions

The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI patients from the two placebo-controlled clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. In the bicalutamide-controlled study of chemotherapy-naïve patients, the most common adverse reactions (≥ 10%) reported in XTANDI patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, upper respiratory tract infection, diarrhea, and weight loss.

In the placebo-controlled study of patients taking XTANDI who previously received docetaxel, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In the placebo-controlled study of chemotherapy-naïve patients, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups. In the bicalutamide-controlled study of chemotherapy-naïve patients, Grade 3-4 adverse reactions were reported in 38.8% of XTANDI patients and 37.6% of bicalutamide patients. Discontinuations due to adverse events were reported for 7.6% of XTANDI patients and 6.3% of bicalutamide patients.

Supported by 3 randomized, controlled trials

AFFIRM TRIAL

1199 patients with metastatic CRPC who were previously on docetaxel therapy were randomized to XTANDI + GnRH therapy* (n = 800) or placebo + GnRH therapy* (n = 399).[1]

PREVAIL TRIAL

1717 patients with metastatic CRPC who were asymptomatic or mildly symptomatic were randomized to XTANDI + GnRH therapy* (n = 872) or placebo + GnRH therapy* (n = 845).[1,3]

TERRAIN TRIAL

375 patients with metastatic CRPC who were asymptomatic or mildly symptomatic were randomized to XTANDI + GnRH therapy* (n = 184) or bicalutamide + GnRH therapy* (n = 191).[1,4]

GnRH therapy, gonadotropin-releasing hormone therapy; mCRPC, metastatic castration-resistant prostate cancer.

***Or after bilateral orchiectomy.**[1]

Visit XtandiHCP.com to learn more about XTANDI in metastatic CRPC patients

Lab Abnormalities: In the two placebo-controlled trials, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients (0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).

Infections: In the study of patients taking XTANDI who previously received docetaxel, 1% of XTANDI patients compared to 0.3% of placebo patients died from infections or sepsis. In the study of chemotherapy-naïve patients, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls (including fall-related injuries) occurred in 9% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.

Hypertension occurred in 11% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI.

Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

Effect of XTANDI on Other Drugs Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

References: 1. XTANDI [package insert]. Northbrook, IL: Astellas, Inc. **2.** Astellas. XTANDI. Data on File. **3.** Beer TM, Armstrong AJ, Rathkopf DE, et al; for the PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371(5):424-33. **4.** Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol 2016;17(2):153-63.

astellas

Pfizer Oncology

Xtandi®
(enzalutamide)
40 mg capsules

Xtandi® (enzalutamide) 40 mg capsules

XTANDI® (enzalutamide) capsules for oral use
Initial U.S. Approval: 2012

BRIEF SUMMARY OF PRESCRIBING INFORMATION

The following is a brief summary. Please see the package insert for full prescribing information.

INDICATIONS AND USAGE

XTANDI is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

CONTRAINDICATIONS

Pregnancy

XTANDI can cause fetal harm and potential loss of pregnancy.

WARNINGS AND PRECAUTIONS

Seizure

Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In these trials patients with predisposing factors for seizure were generally excluded. Seizure occurred from 31 to 603 days after initiation of XTANDI. Patients experiencing seizures were permanently discontinued from therapy and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 366 (2.2%) XTANDI-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTANDI after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all < 5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTANDI in patients who develop PRES.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Three randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchiectomy), a disease setting that is also defined as metastatic CRPC. Two trials were placebo-controlled (Studies 1 and 2), and one trial was bicalutamide-controlled (Study 3). In Studies 1 and 2, patients received XTANDI 160 mg or placebo orally once daily. In Study 3, patients received XTANDI 160 mg or bicalutamide 50 mg orally once daily. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids.

The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI-treated patients from the two randomized placebo-controlled clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

Study 1: XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

Study 1 enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in Study 1 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in Study 1

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[b]	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal And Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness[c]	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[d]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections And Infestations				
Upper Respiratory Tract Infection[e]	10.9	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection[f]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal And Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning And Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin And Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

a CTCAE v4.
b Includes asthenia and fatigue.
c Includes dizziness and vertigo.
d Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
e Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
f Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Study 2: XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

Study 2 enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients and 6% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in Study 2 that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in Study 2

	XTANDI N = 871		Placebo N = 844	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[b]	46.9	3.4	33.0	2.8
Peripheral Edema	11.5	0.2	8.2	0.4
Musculoskeletal And Connective Tissue Disorders				
Back Pain	28.6	2.5	22.4	3.0
Arthralgia	21.4	1.6	16.1	1.1
Gastrointestinal Disorders				
Constipation	23.2	0.7	17.3	0.4
Diarrhea	16.8	0.3	14.3	0.4
Vascular Disorders				
Hot Flush	18.0	0.1	7.8	0.0
Hypertension	14.2	7.2	4.1	2.3
Nervous System Disorders				
Dizziness[c]	11.3	0.3	7.1	0.0
Headache	11.0	0.2	7.0	0.4
Dysgeusia	7.6	0.1	3.7	0.0
Mental Impairment Disorders[d]	5.7	0.0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0.0
Respiratory Disorders				
Dyspnea[e]	11.0	0.6	8.5	0.6
Infections And Infestations				
Upper Respiratory Tract Infection[f]	16.4	0.0	10.5	0.0
Lower Respiratory Tract And Lung Infection[g]	7.9	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8.2	0.1	5.7	0.0
Renal And Urinary Disorders				
Hematuria	8.8	1.3	5.8	1.3
Injury, Poisoning And Procedural Complications				
Fall	12.7	1.6	5.3	0.7
Non-Pathological Fracture	8.8	2.1	3.0	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	18.9	0.3	16.4	0.7
Investigations				
Weight Decreased	12.4	0.8	8.5	0.2
Reproductive System and Breast Disorders				
Gynecomastia	3.4	0.0	1.4	0.0

a CTCAE v4.
b Includes asthenia and fatigue.
c Includes dizziness and vertigo.
d Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
e Includes dyspnea, exertional dyspnea, and dyspnea at rest.
f Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
g Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

Study 3: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

Study 3 enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI

and 5.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.6% of XTANDI-treated patients and 6.3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥ 10%) in XTANDI-treated patients.

Table 3. Adverse Reactions in Study 3

	XTANDI N = 183		Bicalutamide N = 189	
	Grade 1-4[a] (%)	Grade 3-4 (%)	Grade 1-4[a] (%)	Grade 3-4 (%)
Overall	94.0	38.8	94.2	37.6
General Disorders				
Asthenic Conditions[b]	31.7	1.6	22.8	1.1
Musculoskeletal And Connective Tissue Disorders				
Back Pain	19.1	2.7	18.0	1.6
Musculoskeletal Pain[c]	16.4	1.1	14.3	0.5
Vascular Disorders				
Hot Flush	14.8	0.0	11.1	0.0
Hypertension	14.2	7.1	7.4	4.2
Gastrointestinal Disorders				
Nausea	14.2	0.0	17.5	0.0
Constipation	12.6	1.1	13.2	0.5
Diarrhea	11.5	0.0	9.0	1.1
Infections And Infestations				
Upper Respiratory Tract Infection[d]	12.0	0.0	6.3	0.5
Investigational				
Weight Loss	10.9	0.5	7.9	0.5

a CTCAE v 4.
b Including asthenia and fatigue.
c Including musculoskeletal pain and pain in extremity.
d Including nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.

Laboratory Abnormalities

In the two randomized placebo-controlled clinical trials, Grade 1-4 neutropenia occurred in 15% of patients treated with XTANDI (1% Grade 3-4) and in 6% of patients treated with placebo (0.5% Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was 6% of patients treated with XTANDI (0.3% Grade 3-4) and 5% of patients treated with placebo (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of patients treated with XTANDI (0.2% Grade 3-4) and 16% of patients treated with placebo (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients treated with XTANDI (0.1% Grade 3-4) and 2% of patients treated with placebo (no Grade 3-4).

Infections

In Study 1, 1% of patients treated with XTANDI compared to 0.3% of patients treated with placebo died from infections or sepsis. In Study 2, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls and Fall-related Injuries

In the two randomized placebo-controlled clinical trials, falls including fall-related injuries, occurred in 9% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and hematomas.

Hypertension

In the two randomized placebo-controlled trials, hypertension was reported in 11% of patients receiving XTANDI and 4% of patients receiving placebo. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Post-Marketing Experience

The following additional adverse reactions have been identified during post approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Body as a Whole: hypersensitivity (tongue edema, lip edema, and pharyngeal edema)
Gastrointestinal Disorders: vomiting
Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)
Skin and Subcutaneous Tissue Disorders: rash

DRUG INTERACTIONS

Drugs that Inhibit CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Induce CYP3A4

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with XTANDI should be avoided if possible. St John's wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

XTANDI is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. XTANDI is not indicated for use in females. There are no human data on the use of XTANDI in pregnant women. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose.

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

Lactation

Risk Summary

XTANDI is not indicated for use in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Enzalutamide and/or its metabolites were present in milk of lactating rats.

Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of XTANDI.

Infertility

Based on animal studies, XTANDI may impair fertility in males of reproductive potential.

Pediatric Use

Safety and effectiveness of XTANDI in pediatric patients have not been established.

Geriatric Use

Of 1671 patients who received XTANDI in the two randomized placebo-controlled clinical trials, 75% were 65 and over, while 31% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Renal Impairment

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCL] ≤ 89 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed.

Patients with Hepatic Impairment

Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment.

OVERDOSAGE

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

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Oncologists in the Philippines

Continued from page 9C

In 2011, out-of-pocket expenditures in the Philippines accounted for 52.7% of total household health expenditures, which is over the World Health Organization's threshold for catastrophic expenditure leading to impoverishment.[4] The financial disparity is exacerbated by the fact that not all medications are marketed and available in the country, which drives up the prices of those that are available. This often leads patients with cancer little choice but to discontinue or abandon treatment.

Barriers to Palliative Care

Pauline Cauton, MD, also a medical oncologist at St. Luke's Medical Center and a 2018 IDEA-PC recipient who works alongside Dr. Francia, said the public-private dichotomy dictates priorities for Filipino oncologists and their patients.

"In general, just getting the chance to receive treatment is the presumed goal. When all energy and focus is poured into getting the patient from one cycle of chemotherapy to the next, it can get quite difficult to start talking about, say, options for palliative care," Dr. Cauton said.

Palliative care is a complicated topic for oncologists in the Philippines. For Dr. Francia and Dr. Cauton, both of whom have taken a special interest in helping patients with cancer manage pain and distressing symptoms, palliative care's lack of integration into the broader Filipino oncology landscape has posed a distinct challenge.

"Here, the primary physician or medical oncologist handles palliative care," Dr. Bautista explained. "But there is a lack of confidence in handling pain medications, and there is a lack of community understanding about what palliative care can offer."

Dr. Cauton added that to most Filipinos, the term "palliative care" simply means "we've run out of options."

"There are few Filipinos who understand what [palliative care] is and what it can do for patients and physicians," she said.

Internationally, published studies show that integrating palliative care early on in the course of a patient's treatment can result in myriad positive results; doing so has proven beneficial to patients' overall survival and quality of life in certain cancers.[5] But these studies have yet to proliferate the Filipino oncology landscape.

The lack of understanding when it comes to palliative care is coupled with challenges to access. Although there are several large hospitals in the Philippines with established palliative care services, Dr. Francia said the majority don't offer palliative care to patients with cancer during the course of their treatment.

"We need places to refer patients who would benefit from palliative care," Dr. Cauton said. "We hope that exposure to palliative care education will inspire and embolden more Filipino oncologists to ride against the waves of convention and establish these services—even if they start with their own private practices."

That's exactly what Dr. Francia and Dr. Cauton are pushing for in their own institution, and with the help of mentorship and exposure facilitated through ASCO's IDEA-PC program, they're on their way to making this a reality.

Mentorship From Abroad

Janet Lee Abrahm, MD, former chief of the Division of Adult Palliative Care at the Dana-Farber Cancer Institute/Brigham and Women's Hospital and professor of medicine at Harvard Medical School, was matched through the IDEA-PC program as a mentor to both Dr. Francia and Dr. Cauton.

Today, Dr. Abrahm has an official palliative care specialization—but that wasn't always the case. In the early days of her career, before hospice and palliative medicine became a formal subspecialty in 2006, Dr. Abrahm struggled with many of the same issues facing Filipino oncologists today. Having experienced the transition firsthand, Dr. Abrahm is an effective mentor for Dr. Francia and Dr. Cauton.

Dr. Marie Belle Francia

Dr. Maria Diana Aileen Bautista

Dr. Pauline Cauton

Dr. Janet Lee Abrahm

Dr. Abrahm cited several difficulties she faced while providing palliative care without a specialization, all of which are concerns in the Philippines today. Prior to 2006, palliative care was no different than general oncology in the eyes of insurance companies. "The billing was awkward," she said. "It looked like two oncologists were seeing the same patient, even though I was providing palliative care—a completely different service. We had to meet with insurance companies and prove that all of our consultations were different."

Even once palliative care became a subspecialty in the United States, Dr. Abrahm continued to struggle with the same stigmas and lack of understanding that Dr. Francia, Dr. Cauton, and Dr. Bautista described. "We needed to show that we could help patients finish curative chemoradiotherapy for cancer of the head and neck by controlling their pain and secretions, not just help at the end-of-life stage," Dr. Abrahm said.

Over the next decade, exposure, integration, and frequent conversations began to move the culture in the United States toward accepting and integrating palliative care. "I'm hoping I can help with that in the Philippines," Dr. Abrahm said. "But first, they need to establish a culture in which multidisciplinary care is the norm."

Moving Toward Multidisciplinary Care

Dr. Abrahm's first foray into mentorship in the Philippines came in 2014, when she accompanied several colleagues who were traveling there to lead an ASCO Multidisciplinary Care Management Course (MCMC), a program intended to improve cancer care globally by promoting interdisciplinary cancer management through mock tumor boards and education on different aspects of treatment. But Dr. Abrahm's palliative care expertise wasn't actually integrated into the mock tumor boards and panels on that first trip; she was instead making rounds in the local hospitals as Dr. Francia's mentor and serving in the faculty of ASCO's Palliative Care Train-the-Trainer program, led by Frank Douglas Ferris, MD, of OhioHealth.

The program offered MCMC attendees and select nurses from throughout the Philippines the option to attend workshops focusing on strategies for implementing palliative care as well as teaching symptom management and patient communication. "We were separate from the MCMC, so the physicians had to choose which one to go to," Dr. Abrahm said.

Despite the separation, Dr. Abrahm's trip to the Philippines in 2014 opened many Filipino oncologists' eyes to palliative care integration. Dr. Abrahm recalled the impact of a suggestion she made for one of the patients in the charity hospital during the rounds that trip. "The patient had cancer all throughout their lungs, and I suggested using an opioid for shortness of breath, which no one had thought of doing before," she said. "The next day, the oncologists treating that patient told me they had tried my suggestion and that it had really worked—the patient felt much more comfortable. They were so excited and encouraged."

It was during this first visit that Dr. Abrahm drew a strong connection between palliative care in the Philippines and her early years of practicing in the Unites States, thereafter shaping her role as a mentor.

Visible Progress

When she returned to the Philippines to join another MCMC in October 2017, Dr. Abrahm was fully integrated into the mock tumor boards as a palliative care consultant—a palpable change she found extremely promising.

"In just 3 years, you could really tell the difference," Dr. Abrahm said of integrating palliative care into multidisciplinary education. "I had the same number of slides as the medical, surgical, and radiation oncologists, and the attendees were very receptive to my input."

When Dr. Abrahm met with Dr. Francia during this recent trip, she was thrilled to see that Dr. Francia and her colleagues—including Dr. Cauton—had taken the initiative to establish a full palliative care program at St. Luke's Medical Center. In just 3 years, Dr. Francia and her colleagues had been able to make a case for a palliative care program and get approval from the hospital's board to begin implementation.

Table. Top Five Incidences of Cancer in the Philippines, Age-Standardized[3]

Males	Females
Lung	Breast
Liver	Cervix
Prostate	Colorectal
Colorectal	Lung
Leukemia	Ovary

Areas for Improvement

The progress Dr. Abrahm noticed when she returned to the Philippines in 2017 is reflective of an overall effort to establish multidisciplinary cancer care in the Philippines, but the country still has a long way to go.

"Multidisciplinary care for patients with cancer is still not standard in the Philippines," Dr. Francia said, pointing out that the promising integration under way at her hospital in Manila does not necessarily go hand-in-hand with improvement across the disparate country. "It is not mandatory in all hospitals."

"We try to coordinate with a multitude of specialties, including surgery, rehabilitation medicine, and psychiatry," Dr. Bautista said. "But there are still so many things needed."

The Power of Exposure

As part of the IDEA-PC program, Dr. Francia and Dr. Bautista both traveled to the Unites States—as will Dr. Cauton this June—to attend the ASCO Annual Meeting and spend a week shadowing their mentors at their institutions.

"Exposure to integrated cancer management allowed me to appreciate the level of care offered at a comprehensive cancer center and bring that back to my hospital," Dr. Francia said of the experience.

"Seeing the juxtaposition of how things are [in other countries] will move Filipino oncologists to resolve to make things better," Dr. Cauton added. "We cannot just accept things the way they are without trying to do things differently. We just need to start doing it, even in the littlest of steps."

Dr. Francia, Dr. Cauton, and Dr. Bautista all agreed that perhaps the most valuable benefit of the educational programs ASCO has brought—and continues to bring—to the Philippines is simply exposure to how multidisciplinary care teams can collaborate to treat patients from a full spectrum of approaches. Although oncologists can read about multidisciplinary care and consume didactic materials available through online learning and textbooks, it is difficult to truly grasp its benefits and understand how it works without experiencing it in person.

In multidisciplinary cancer care, "coordination is a key to progress," Dr. Bautista said. "As a country, we are getting there, step by step, with the help of our

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In the Journals

High Mutational Burden Linked With Sensitivity to Immune Checkpoint Inhibition

"Identifying a Clinically Applicable Mutational Burden Threshold as a Potential Biomarker of Response to Immune Checkpoint Therapy in Solid Tumors"

Journal: *JCO Precision Oncology*
DOI: 10.1200/PO.17.00146

Abstract

Purpose: An association between mutational burden and response to immune checkpoint therapy has been documented in several cancer types. The potential for such a mutational burden threshold to predict response to immune checkpoint therapy was evaluated in several clinical datasets, where mutational burden was measured either by whole-exome sequencing or by using commercially available sequencing panels.

Methods: Whole-exome sequencing and RNA sequencing data of 33 solid cancer types from The Cancer Genome Atlas (TCGA) were analyzed to determine whether a robust immune checkpoint–activating mutation (iCAM) burden threshold associated with evidence of immune checkpoint activation exists in these cancers that may serve as a biomarker of response to immune checkpoint blockade therapy.

Results: We found that a robust iCAM threshold, associated with signatures of immune checkpoint activation, exists in eight of 33 solid cancers: melanoma, lung adenocarcinoma, colon adenocarcinoma, endometrial cancer, stomach adenocarcinoma, cervical cancer, estrogen receptor–positive/human epidermal growth factor receptor 2–negative breast cancer, and bladder-urothelial cancer. Tumors with a mutational burden higher than the threshold (iCAM positive) also had clear histologic evidence of lymphocytic infiltration. In published datasets of melanoma, lung adenocarcinoma, and colon cancer, patients with iCAM-positive tumors had significantly better response to immune checkpoint therapy compared with those with iCAM-negative tumors. Receiver operating characteristic analysis using TCGA predictions as the gold standard showed that iCAM-positive tumors are accurately identifiable using clinical sequencing assays, such as FoundationOne (Foundation Medicine, Cambridge, MA) or StrandAdvantage (Strand Life Sciences, Bangalore, India). Using the Foundation One-derived threshold, an analysis of 113 melanoma tumors showed that patients with iCAM-positive disease have significantly better response to immune checkpoint therapy. iCAM-positive and iCAM-negative tumors have distinct mutation patterns and different immune microenvironments.

Conclusion: In eight solid cancers, a mutational burden threshold exists that may predict response to immune checkpoint blockade. This threshold is identifiable using available clinical sequencing assays.

Author Perspective

Anshuman Panda, PhD, Rutgers Cancer Institute of New Jersey

Q: What are the major findings from the research discussed in the paper?
Dr. Panda: When we analyzed data from more than 9,000 samples from 33 solid tumor types from TCGA, we found eight solid cancer types where mutation burden may be a predictor of response to immune checkpoint therapy. They included four known cancer types (melanoma, lung adenocarcinoma, colon adenocarcinoma, and bladder-urothelial cancer) and four novel cancer types (endometrial cancer, stomach adenocarcinoma, cervical cancer, and ER-positive HER2-negative breast cancer). Additionally, serous ovarian cancer warrants further investigation.


Dr. Anshuman Panda

Moreover, a substantial fraction of tumors in these eight cancer types have a mutation burden above the identified threshold, showing that our results can potentially impact a clinically significant fraction of patients in these cancer types.

Further, we showed that in these cancer types, it is possible to define a threshold on mutation burden, also known as an iCAM threshold, such that tumors with mutation burden above this threshold show evidence of immune activation and checkpoint pathway up-regulation and are significantly more likely to respond to immune checkpoint therapy. This iCAM threshold can be identified with high accuracy using routinely used clinical sequencing assays.

Q: What is the significance of this research?
Dr. Panda: The results of this paper suggest that a high mutation burden is associated with immune checkpoint activation, and potentially, with response to immune checkpoint therapy more generally than previously known. Additionally, the above mechanism is likely operative in four novel cancer types as well as the four known cancer types, but is not operative in every cancer type. This demonstrates that mutation burden, although clearly a very important marker of response to immune checkpoint therapy, is not the only mechanism of local immune checkpoint activation in cancer.

Q: How may this new research influence or impact clinical practice?
Dr. Panda: Although immune checkpoint therapy can lead to dramatic responses in some patients with advanced solid cancers, only a minority of treated patients have durable clinical benefit. Therefore, there is a clear need to develop methods to identify which patients are most likely to benefit from immune checkpoint therapy.

Once refined and validated in prospective trials, iCAM threshold analysis may be useful as a robust biomarker of response in multiple solid cancer types, for prioritizing patients who are likely to benefit from immune checkpoint therapy. Moreover, because this threshold can be identified with routinely used clinical sequencing assays, it can be used in the clinic without requiring the development of additional new assays. ●

Smoking Cessation

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cessation in a variety of ways, but many do have quitlines and some countries even mandate that the national quitline number be printed on the tobacco package warning label.[9] The details country by country are too lengthy to list within this article, and resources do change over time, so clinicians are encouraged to investigate what local resources are available to their patient population. A positive example is the United Kingdom, which has successfully integrated a tobacco cessation program with specialists into general care.

Electronic Cigarettes

Patients commonly ask about the role of electronic cigarettes in cessation. Electronic cigarettes were first developed by a pharmacist in China to stop smoking after his father, who smoked heavily, died of lung cancer.[10] Since then, electronic cigarettes, or electronic nicotine delivery systems (ENDS), have swept the world with rapid uptake in many countries. ENDS are variably regulated around the world and in a state of change in many places. The regulation of ENDS varies

from a complete ban (but, admittedly smuggled in) in Australia, to banned if it has nicotine in it in Japan, to "regulated" in the European Union, to going to be regulated in the United States, to endorsed usage in the United Kingdom. The regulation of ENDS almost varies by the day, depending on which country you are reviewing.

The science is not yet conclusive, and unsettled topics of concern include the following: Are ENDS less harmful than cigarettes? Do people quit by using ENDS? Do ENDS make it more difficult to quit? Do people reduce or quit cigarettes completely? Do young adults use ENDS and then use cigarettes (thus perpetuating nicotine addiction, using cigarettes)? Are there nononcologic disease outcomes from ENDS such as cardiovascular risk and/or inflammatory lung diseases?

Two recent reports presented a review of the available literature, and interestingly have a bit different results. In the United States, the federal legislature required the U.S. Food and Drug Administration to fund the National Academies of Science and Engineering to comprehensively and systematically review the literature on the health effects of ENDS.[11] The second report from Public Health England can be found on the U.K. government website.[12]

The conclusions between the two reports are not identical. The U.S.-sponsored report has some mixed results in its statements including, "Overall, the evidence suggests that while e-cigarettes might cause youth who use them to transition to use of combustible tobacco products, they might also increase adult cessation of combustible tobacco cigarettes."[11] The U.K. report goes so far as to say, "Stop-smoking practitioners and health professionals should provide behavioural support to smokers who want to use an e-cigarette to help them quit smoking. Stop-smoking service practitioners and health professionals supporting smokers to quit should receive education and training in use of e-cigarettes in quit attempts."[12]

The general feel is that:

- ENDS have short-term scientific findings that they are probably less harmful than cigarettes.
- People do and have quit smoking cigarettes with ENDS. However, the question of how many quit versus how many "dual use" (smoke cigarettes and ENDS) appears to still be dependent on the country examined, the survey methods, and timelines.
- Young people are using ENDS and progressing to cigarettes.

We likely have a few more years of assessment and intensive research on the topic of ENDS, and equally intensive efforts to regulate them.

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Medical Marijuana

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effect is currently limited. Additional research on the medical use of cannabinoids is strongly warranted. The pace of such research is likely to accelerate as states continue to approve cannabis for medical purposes. ●

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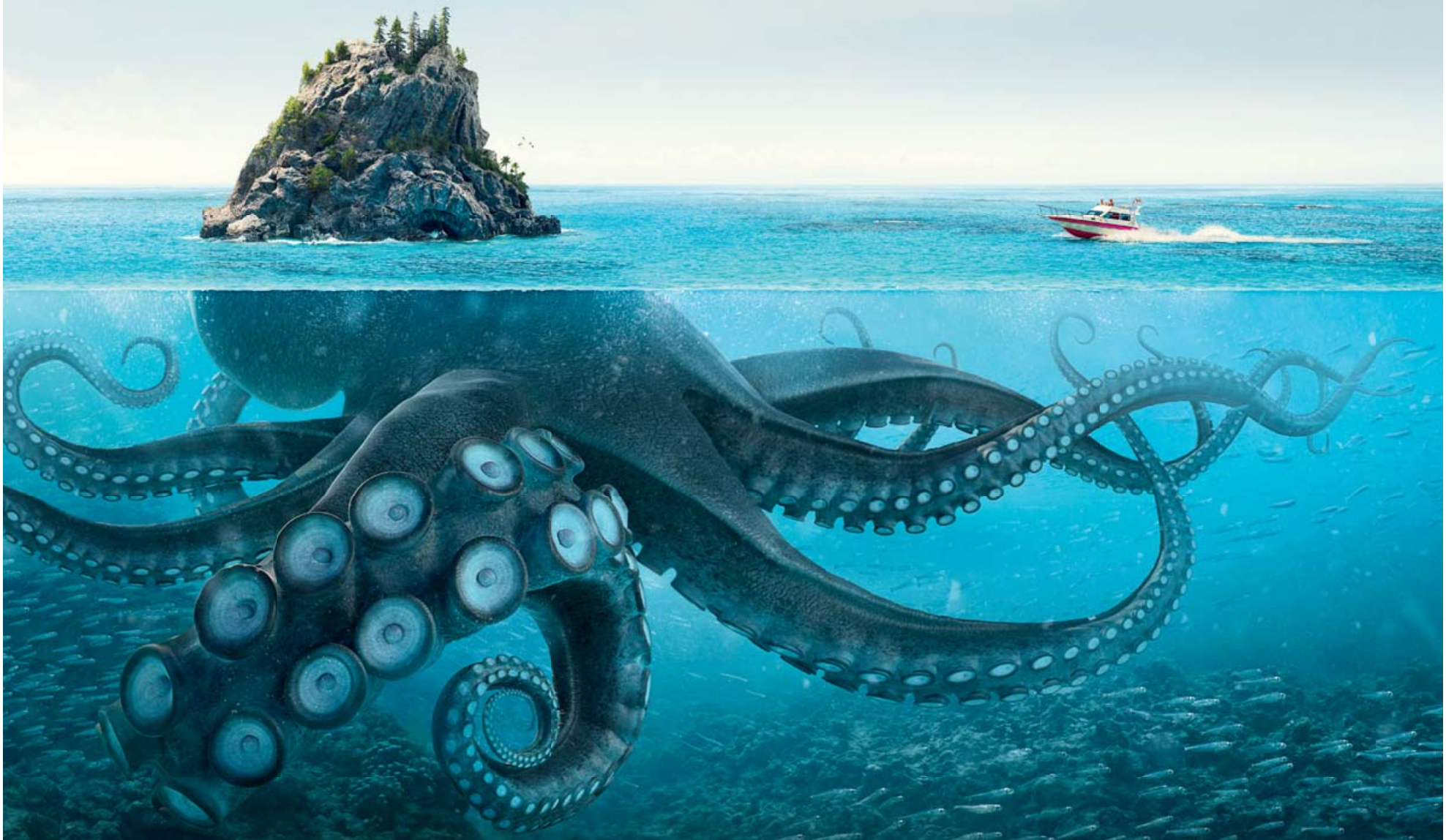
THERE'S MORE TO SOME CANCERS THAN MEETS THE EYE

TRK FUSION PROTEINS ARE A PRIMARY ONCOGENIC DRIVER ACROSS MULTIPLE TUMORS IN ADULTS AND CHILDREN[1,2]



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TRK, tropomyosin receptor kinase.

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Patient-Reported Outcomes

Continued from page 12C

Limited data utility may occur when PRO data are not timely enough for clinical encounters or are not consistently available due to a low completion rate. Clinicians may see little value in supporting PRO collection among their patients. PRO data must be timely and consistently available. Data must accurately reflect the patient's experiences and outcomes and must be relevant to the clinician's care of the patient. Explicit monitoring of timeliness, accuracy, completeness, and clinical utility supports specific activities to understand and improve PRO data quality.

Poor presentation of PRO data may make it difficult for clinicians to effectively use PROs for shared decision-making. Clinicians may not always respond meaningfully to verbal reports or to electronic summaries of symptom management and quality-of-life issues, sometimes interrupting the patient and changing the subject.[28] Shared review of PRO data should support collaborative discussion and shared decision-making. A paper printout with summarized responses and trends may facilitate discussion and serve the patient as a reminder of the clinical visit.

Poorly timed information is a common concern when PRO assessments include suicidality, making clinicians and health care organizations wary of liability for failing to act when a patient endorses suicidality, severe depression, or a desire to harm others. PRO systems should assess the full range of responses from patients, but the response should be appropriate for the setting. In the clinic, endorsing self-harm on the suicidality item of the PHQ-9 should trigger an alert to clinic staff.[29] A similar endorsement while using a home-based tool might offer the patient an alert identifying both the concern and an action to take, with appropriate after-hours notification to the clinic. When used in an anonymous public screening tool, the PHQ-9 suicidality item triggers only a message of concern and a general recommendation.[30]

The idea that the patient may feel worse has inhibited some clinicians from sharing comparative data about patients' symptom burden relative to that of similar patients. Urology patients with worse-than-average urinary symptoms may feel worse about their incontinence after realizing other post-treatment patients do better. However, there are a range of interventions to impact incontinence, and the clinician's concern for the patient's self-image is not sufficient reason to deny patients the opportunity and motivation to seek out treatments that may improve their symptoms.

The health care organization

Labor-intensive activities with PRO methods such as paper collection are expensive and more so when accompanied by manual data entry. Computerized PRO systems used directly by the patient avoid the associated expense and error, but add costs of information technology (IT) system implementation and maintenance. However, PRO systems may offer significant savings in workflow, with the potential to reduce labor costs. These could include facilitating asynchronous or message-based communications and the inclusion of self-management strategies, such as automated self-care responses to patients with symptoms at the minimal to moderate level of severity.

Disruption to clinic flow may occur because PROs add more uncertainty to already numerous factors. Clinic wait times are highly variable, and PROs add variations both in time and support required for in-clinic completion. Tracking times for individual components of the assessment, focusing PROs on clinically actionable domains, and dynamically tailoring PRO assessments to current clinic flow all address these concerns.[31] In addition, shifting from fixed kiosks to portable tablets lets patients begin reporting in the waiting room and continue in the exam room, with results still immediately available. But perhaps the greatest impact is the ability to shift PRO completion outside the clinic to the patient's own preferred device, place, and time.

PROs introduce IT complexity, but patient and clinician interests are not always best served by minimizing this. In one example, nurses in the bone marrow transplant service at the Seattle Cancer Care Alliance sustained use of a PRO system for 8 years after the end of a PRO trial because of perceived value of PRO screening.[32] The practice ended only when a new enterprise EMR was introduced at the institution. However, the new electronic system lacked a PRO component, and the service began using paper PROs, decreasing functionality and potentially increasing cost.

The EMR is almost universally the medico-legal record, supporting and documenting health care delivery. Risks of performance impact to the EMR can be addressed with application programming interface management software, managing information flow into and out of the EMR, which also helps address data privacy and security risks, in concert with the IT governance policies of a health care organization.

PRO systems can be labor intensive and thus costly. A recent article estimated and compared requirements of several methods of PRO collection using institutionally developed systems, EMR embedded version of the third-party PROMIS-CAT system and vendor-based systems.[33] The estimates were necessarily uncertain; the authors do not include either the "built-in" questionnaire systems offered by the EMR vendors themselves or other noncommercial EMR embedded systems. However, when planning implementation of computerized PROs into clinical practice, it is important to delineate the range of possible methods and to understand acquisition, implementation, and operating costs of these systems.

Competing and overlapping PRO content may be desired by different clinical services and clinicians. There may be legitimate benefit to addressing similar domains with different instruments in different situations, or clinicians may simply prefer familiar instruments. Strong governance, tied to clinical services, ensures conflicts are managed at the same level as other workflows and policies, as part of the same processes that encourage uniform clinical care standards, rather than as IT questions.

Societal concerns

Health care access and equity can be eroded by technology unless sufficient support is provided to ensure that there is no widening of the "digital divide" that separates patients by resources and literacy.[34] Neither lack of technology nor lack of proficiency should result in diminished attention to the symptoms and preferences of patients with less access. Although patients across all ages and socioeconomic statuses increasingly have access to smartphones as well as the PRO tools and support to use them, they should still be available in the clinic setting for those who need them.[35]

Patient-centered care is increasingly a priority at a societal level, evidenced by funding initiatives from federal agencies and institutes to better understand PRO implementations and effects; by the efforts to shift care to better satisfy, engage, and empower patients in their own care; by regulatory requirements to share health information with patients; and by myriad statements from health care organizations. At the same time, patient-centered care can be challenging to all stakeholders, including patients, accustomed to a more traditional model. PROs have the potential to organize and strengthen the patient's voice in the clinical conversation and be a cornerstone of patient-centered care.

Successful Clinical Implementation

Given the barriers enumerated above, a clinician may wonder if real-world implementation is feasible, sustainable, and worth the effort. Published examples and reports of PRO implementation without research team coordination are few. Cancer Care Ontario has used screening PROs since 2007 and published reports of significantly reduced emergency department visits in women receiving

See Patient-Reported Outcomes, Page 30C

About the Authors

Dr. Berry is the director of the Phyllis F. Cantor Center of the Dana-Farber Cancer Institute.

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CLINICAL CORNER

Anthracycline Chemotherapy in Breast Cancer

Megan Kruse, MD, and Jame Abraham, MD, FACP, answer a question posed by an attendee during a Best of ASCO® Meeting. Drs. Kruse and Abraham are medical oncologists in the breast cancer program at the Cleveland Clinic Taussig Cancer Institute, where Dr. Abraham also serves as director.

Question: What patients with early-stage breast cancer should be treated with anthracyclines?

Answer: When choosing an adjuvant chemotherapy regimen for a patient with early-stage breast cancer, one must balance the potential benefit of therapy with risk of long-term toxicities, as the goal of therapy in such patients is cure. As anthracycline chemotherapy agents are known to have a risk of treatment-related cardiomyopathy, myelodysplastic syndrome, and acute leukemia, much effort has gone into determining which patients benefit most from anthracycline-based therapy in hopes of sparing those patients who will not derive significant benefit from potentially devastating long-term toxicities.

Dr. Megan Kruse

Dr. Jame Abraham

A US Oncology Research, Inc. (USOR) study of more than 1,000 women with early-stage breast cancer compared doxorubicin plus cyclophosphamide (AC) for four cycles with docetaxel plus cyclophosphamide (TC) for four cycles and found an overall survival (OS) benefit of TC over AC (HR 0.69, 95% CI [0.50, 0.97]; p = 0.032) at a median follow-up of 7 years.[1] This study demonstrated that a non-anthracycline regimen is a viable and potentially superior approach to treatment of early-stage breast cancer compared to AC; however, many patients in clinical practice are treated with AC and taxane, so the practical application of this data was unclear.

The recently published Anthracyclines in Early Breast Cancer trials, consisting of a combined analysis of USOR 06-090, NSABP B-46-I/USOR 07132 and NSABP B-49, help to address the efficacy of TC compared to AC plus taxane. In these trials, patients with HER2 nonamplified early-stage breast cancer were randomly selected to receive TC for six cycles or one of several AC plus taxane regimens.[2] These studies were designed to assess for non-inferiority of TC compared with AC plus taxane. Approximately 4,200 patients were enrolled and randomly assigned by the number of positive lymph nodes and hormone receptor status.

At interim analysis, a statistically significant 2.5% difference in 4-year invasive disease-free survival was found favoring AC plus taxane over TC (HR 1.23, 95% CI [1.01, 1.5]; p = 0.04). In exploratory analyses, the addition of anthracycline to taxane-based chemotherapy was found to be more substantial for patients with hormone receptor–negative disease, particularly those with positive lymph nodes. For hormone receptor–positive disease, the benefit was greatest for those with four or more lymph nodes involved.

Although these analyses were not preplanned and thus not powered for, they do suggest patient populations who may derive meaningful benefit from anthracycline and taxane–containing chemotherapy. Of note, five patients in the anthracycline-containing chemotherapy arm developed leukemia compared to zero in the TC arm.

There is also controversy regarding use of anthracyclines in the treatment of HER2-amplified early-stage breast cancer. The BCIRG-006 trial evaluated three different chemotherapy regimens (AC plus docetaxel [AC-T]; AC plus docetaxel and trastuzumab [AC-TH]; and docetaxel plus carboplatin and trastuzumab [TCH]) in this treatment setting and found no statistically significant difference in disease-free survival (DFS, 84% for AC-TH vs. 81% for TCH) or OS (92% for AC-TH vs. 91% for TCH) between the two trastuzumab-containing regimens, although both were statistically better than AC-T (DFS 75% and OS 87%).[3] The study was not powered to compare the two trastuzumab-containing arms to each other, so limited conclusions can be drawn regarding superiority of one regimen over another. There were numerically more breast cancer recurrences in the TCH arm compared to the AC-TH; however, there were more cases of leukemia and congestive heart failure with anthracycline-containing chemotherapy.

Based on these data, there continues to be a role for anthracycline-containing chemotherapy in the treatment of certain patients with early-stage breast cancer. For patients with hormone receptor–positive disease, those with aggressive biologic features (especially those with at least four lymph nodes involved) should be considered for anthracycline plus taxane chemotherapy. Those patients with strongly hormone receptor–positive disease who have no lymph node involvement or limited lymph node involvement may be better served with a non-anthracycline chemotherapy regimen, particularly those with risk factors for cardiomyopathy, including diabetes mellitus, hypertension, and coronary artery disease.

For patients with hormone receptor–negative disease, the threshold for including anthracycline is lower given the greater risk of recurrence, although patients with small tumors that are lymph node–negative may be good candidates for non-anthracycline–containing chemotherapy. For HER2-amplified patients, a non-anthracycline treatment is generally preferred due to increased risk of cardiomyopathy with sequential anthracycline plus trastuzumab therapy, but use of anthracycline can be considered for those patients at very high risk for disease recurrence. ●

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Oncologists in the Philippines

Continued from page 20C

local and international colleagues, our patients, and the whole community."

In collaboration with the Benavides Cancer Institute University of Santo Tomas Hospital, ASCO will be hosting another MCMC in Manila, November 14-16, 2018. For more information, visit asco.org/international-programs. ●

–Caroline Hopkins

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Smoking Cessation

Continued from page 21C

The Tobacco Market

On a final note, we would be remiss if we did not address a gorilla in the room. Philip Morris International (the largest transnational tobacco industry with cigarette market leader Marlboro) has launched their new product iQOS (or, I quit ordinary smoking) in a number of countries. It has seen remarkable market growth, particularly in Japan. The other large transnational tobacco companies have their own "heated tobacco products" (they are supposedly not combusting tobacco, but only heating it), with British American Tobacco marketing "glo" and Japan Tobacco International marketing "Ploom." As with ENDS, there are many questions surrounding these products. Are these heated tobacco products less likely to kill when used as intended (as cigarettes do)? Will adults who want to quit, completely quit, or just be addicted to a different product? And will young people, or people who had previously quit smoking, take up these new technologically attractive products?

It is too early and we have too little science to know if we should be recommending heated tobacco products for our patients with cancer—the products are just too new and variable. We view them in the same category as ENDS for now, and recommend that your patients use approved tobacco cessation products first. If they can't quit, consider ENDS until they can also quit ENDS. These new technologies are a moving target and we may never get clear, simple data. However, on a different level, the profits from the sale of these products supports the tobacco industry, which continues to undermine efforts at effective tobacco control.[13,14]

Most importantly: Ask all patients if they use tobacco. Advise them that it is the most important thing they can do to help with their cancer treatment. Tell them that this intervention has nothing to do with blame or shame, and that no one deserves to get cancer. Refer them to an effective tobacco cessation program with which you have established a relationship. At each visit with your patient, discuss their tobacco use status, just like you check for adverse events or other symptoms. Be sure to congratulate them for quitting. It is probably the hardest thing they've ever done, and maybe one of the things they are most proud of doing.

We are passionate about having fewer people die from tobacco. We are part of a cadre of providers who work in the oncology area including many international organizations that share similar interests, such as ASCO, the American Association for Cancer Research, the International Association for the Study of Lung Cancer, Society of Thoracic Surgeons, and the American College of Chest Physicians. As tobacco is a worldwide problem, so is tobacco control. We work globally, and offer to help any oncologist who would like brief advice on how to help their practice address tobacco cessation. Obviously we cannot do it for you, but we will enlist our global colleagues to see if we can provide helpful advice or connections. First, read ASCO's materials[5] and then, just start! ●

About the Authors: *Dr. Dresler is a member of ASCO and the International Association for the Study of Lung Cancer. Dr. Steglia is associate professor of surgery at the Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences.*

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ASCO'S TOBACCO CESSATION RESOURCES

The *Tobacco Cessation Guide for Oncology Providers* is an evidence-based booklet to help oncology providers integrate tobacco cessation strategies into their practices by offering practical tips for tobacco use assessment and treatment, as well as information about how to be reimbursed for these services. ASCO's patient companion booklet, *Stopping Tobacco Use After a Cancer Diagnosis,* aims to provide clear, practical information for patients and their caregivers on the benefits of quitting tobacco use after a cancer diagnosis, as well as tips for talking with health care professionals about tobacco cessation. Learn more at asco.org. ●

ASCO University® Unveils New Imaging Course

Understanding basic medical imaging modalities is essential to any oncologist, from new physicians to those reviewing this fundamental aspect of oncology.

ASCO University®, wanting to assist medical professionals with this task, has launched a new course on medical imaging. The course was designed by imaging experts—with specialties including interventional radiology, diagnostic radiology, and nuclear medicine—to create a foundational curriculum, especially for those new to practice.

"Emerging companion diagnostic imaging and therapeutic agents have the potential to become hallmarks of precision medicine, optimizing selection of patients for individual therapies and how these drugs are delivered," said course faculty member Heather Jacene, MD, of the Dana-Farber Cancer Institute.

Course faculty member Richard Marshall, MD, of LSU Health, noted, "Interventional radiology [IR] is an integral component of precision medicine that uses imaging technology to extend cancer care to patients in a minimally invasive way. IR procedures help patients who are eligible for surgical treatment, as well as those who may not be eligible for surgery, and offers palliation of cancer related symptoms."

The slide-based course with an audio overlay is divided into four sections along with a post-test. Designed for advanced practitioners, this course benefits anyone wanting to learn more about interpreting medical imaging, including when to order and when not to order.

Upon completing the course, users will have a better understanding of how to use imaging to guide therapy, including the best ways to optimize drug therapies, demonstrate targets prior to therapy, and evaluate the response to certain therapies.

The four sections of the course are as follows:

- **Diagnostic Imaging** will help learners identify common imaging modalities used in oncology, explain how radiologists use Response Evaluation Criteria in Solid Tumors (RECIST) reporting, discuss the basic concepts of liver imaging, and describe the basic concepts of rectal cancer staging.
- **Interventional Radiology** will help learners describe how an interventional radiologist can see inside patients without opening them up, discuss some of the treatments interventional radiology can offer to diagnose and treat cancers of the liver, lung, and kidney, and explain the two ways drug-eluting beads (used in DEB TACE) treat hepatocellular carcinoma.
- **Radiologic Response** will help learners identify issues and challenges with response assessment, explain different methods of response assessment, discuss the interpretation of each method in clinical context, and describe future research considerations.
- **New and Emerging Imaging Modalities** will help learners define theranostics, discuss prognostic versus predictive biomarkers, discuss applications of molecular imaging for theranostics and as imaging biomarkers, and explain other applications where imaging can be used to guide therapy.

The Imaging course is offered as part of the Advanced Practitioner Certificate Program: Basics 102 through ASCO University. Certificate and credit types available for the course include 4 *AMA PRA Category 1 Credits*™, ABIM MOC Points, CNE Contact Hours, CPE Credits, ONCC ILNA Points, a Certificate of Participation, and a Certificate of Completion. All final decisions regarding the awarding of credits will be made by the licensing organization to which the credits are submitted.

The course is also available for purchase as part of the ASCO University Essentials package, which provides unlimited access to more than 100 courses in the ASCO University course catalog. An annual subscription also includes a Personalized Learning Dashboard, an enhanced self-assessment tool that supports a more individualized approach to oncology education, utilizing the enhanced self-assessment to offer tailored content recommendations based on identified knowledge gaps.

For more information on the ASCO University imaging course, visit university.asco.org. ●

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Dr. Bishoy M. Faltas Takes on Bladder Cancer

Bladder cancer is the fourth most common cancer among men. Like many cancers, it can be challenging to treat—especially when the cancer develops resistance to chemotherapy or immunotherapy treatments. In such cases, there is often not much else doctors can offer.

Happily, that is beginning to change thanks to the work of researchers like Bishoy M. Faltas, MD.

Dr. Faltas, an assistant professor at Weill Cornell Medicine, has been studying the changes in bladder cancer that lead to treatment resistance. He has also been developing strategies to reverse or prevent resistance so that patients continue responding to treatment. In 2015, a Young Investigator Award from ASCO's Conquer Cancer Foundation, supported by the John and Elizabeth Leonard Family Foundation, helped make this work possible.

Dr. Bishoy M. Faltas

"Even with the new immunotherapy agents, less than one-quarter of patients will respond at any given time," Dr. Faltas said. "I'm trying to identify alternative strategies to target the other three-quarters of patients."

Dr. Faltas and his team are now building on the findings of their Conquer Cancer–funded study; they are developing a small clinical trial to test a new treatment approach. Eventually, their research could lead to better outcomes and increased survival for patients with bladder cancer.

"This work was really critical for my career—but also for our understanding of the biology of the disease," Dr. Faltas said. "I'm hopeful that it will lead to significant therapeutic advances in the future.

"To me, conquering cancer means translating the laboratory discoveries to new therapies that we can give to patients to hopefully cure them," Dr. Faltas said. ●

Dr. Faltas' 2015 ASCO's Conquer Cancer Foundation Young Investigator Award was supported by the John and Elizabeth Leonard Family Foundation.

ASCO Develops Professional Resources for Pain Management

When it comes to helping patients with cancer manage pain, education and communication are critical. ASCO University® has developed two resources for providers to help facilitate educated clinical decision-making skills for pain management and feedback from patients in the forms of the Pain Management Program and the Pain Management Safety Survey.

ASCO University's Pain Management Program

Updated in February, the Pain Management Program is designed to:

- Apply personalized patient assessment and follow-up for multidimensional symptoms;
- Define the principles of opioid initiation and titration, including recognizing indications and process of rotation;
- Use general management strategies of opioid-related adverse effects and ensure safety, tolerance, and compliance with analgesic regimens; and
- Implement multimodal, multidisciplinary approaches and universal precautions when caring for all patients with cancer experiencing pain, including patients with substance use disorder.

The program explores case scenarios using an interactive question format to select a course of action in managing the patient's pain. The purpose is to provide a safe opportunity where the learner can make clinical decisions without real-world consequences. After every decision the learner makes, they will receive feedback on whether the choice was clinically optimal, clinically suitable, or incorrect. To access the program, visit university.asco.org.

ASCO's Pain Management Safety Survey

ASCO offers the Pain Management Safety Survey, an activity designed to identify gaps in pain management communication. Available free of charge to ASCO members, providers download a 26-question survey and administer it to 25 patients, who answer anonymously. Questions, which are directly related to pain management, follow a yes/no format and fall into three sections:

- Aspects the provider explained to the patient;
- Questions the provider asked the patient; and
- Whether the patient felt the communication was effective.

After collecting responses, providers then determine any areas in which they need to improve communication. Once this improvement plan has had adequate time to be implemented, providers administer an identical survey to a different cohort of 25 patients. Comparing responses before and after implemented changes, providers then assess improvements as well as areas that still need work.

"The survey taught us that patients need to be told directly by their clinical team that they're supposed to keep pain medications in safe spots—possibly even lock boxes if that is appropriate for the home situation," Eric Roeland, MD, of the University of California, San Diego, who participated in the Pain Management Safety Survey's pilot alongside his palliative care team, said.

For both the Pain Management Program and the Pain Management Survey, participating providers can obtain continuing medical education certificates (including *AMA PRA Category 1 Credits™* to physicians), ABIM MOC points, CNE certificates, certificates of participation, or certificates of completion. To access the survey, visit university.asco.org and search "Pain Management." ●

–Caroline Hopkins

Patient-Reported Outcomes

Continued from page 24C

adjuvant chemotherapy for breast cancer, as well as significantly fewer adverse emotional and physical outcomes.[36,37] Also in Canada, clinical PRO screening was associated with increased clinician documentation of pain outcomes as patient-reported pain severity increased.[38] Dutch clinicians reported long-term success of nurse-coordinated PRO screening with patients with head and neck cancer.[39] The notable absence of the United States in success stories has much to do with the barriers reviewed above.

Conclusions

PROs are desired by patients, enable clinicians to efficiently address the whole patient, and make a difference in clinical outcomes and patients' experience of disease. There are many ways in which suboptimal implementation may increase cost and decrease the value of PROs, eroding their timeliness, accuracy, completeness, and personalization, and may limit their utility. Computerized PRO collection easily available to the patient, increased integration of access and data with the EMR, and the ability to personalize the PRO experience for individual patients all contribute to maximizing feasibility and value. ●

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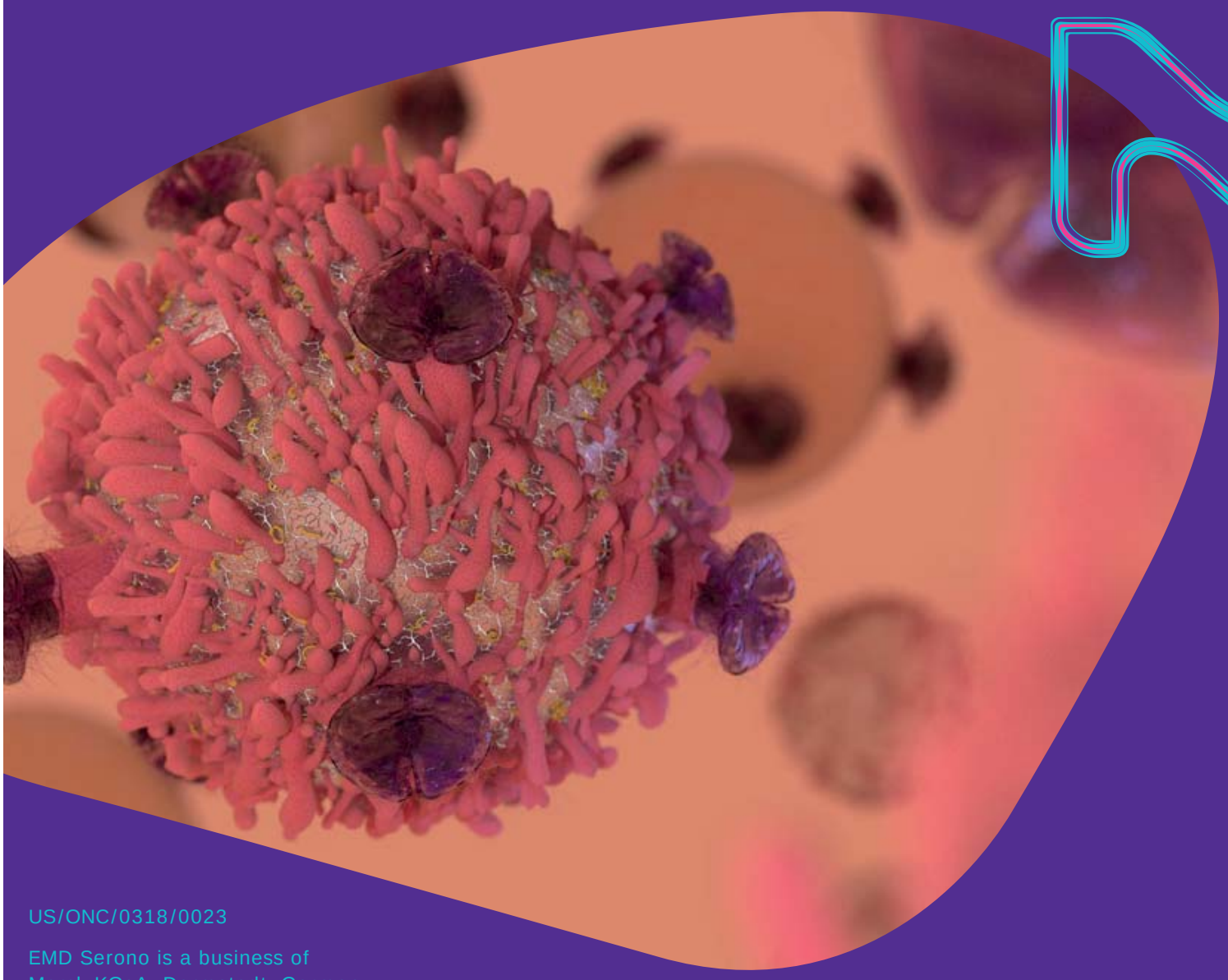

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ASCO Daily News®
SUNDAY · JUNE 3, 2018

Inside: **LATE-BREAKING ABSTRACTS** ▸ PAGES 8D-9D

2018 ASCO Annual Meeting Plenary Session Preview

The 2018 ASCO Annual Meeting Plenary Session, which will take place on June 3 from 1 PM to 4 PM in Hall B1, is the most anticipated event of the Meeting. The session includes 15-minute didactic presentations highlighting abstracts of scientific research deemed to have the highest merit and greatest impact on oncology research and practice. In addition to the abstract presentations, experts in the field serve as discussants, placing the research findings into context.

Prior to the abstract presentations, Douglas R. Lowy, MD, will receive the 2018 Science of Oncology Award. The award honors outstanding contributions to basic or translational research in cancer. Dr. Lowy, the deputy director of the National Cancer Institute (NCI) and chief of the NCI's Laboratory of Cellular Oncology, is being recognized for his work in developing the technology underlying the U.S. Food and Drug Administration approval of the HPV vaccines for cervical cancer prevention. "I am especially grateful to ASCO for highlighting our translational research, which is on primary prevention," Dr. Lowy said.


Dr. Ann H. Partridge

As for the abstracts chosen for this year's Plenary Session, Ann H. Partridge, MD, MPH, FASCO, of the Dana-Farber Cancer Institute and chair of the Plenary Session, said the science will impact how oncologists care for patients going forward. "I was so excited when these abstracts came in," Dr. Partridge said. "I was even more excited to see that the highest-ranking abstracts covered a range of cancer types and specialties."

The first Plenary abstract, LBA1, is "TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score," presented by first author Joseph A. Sparano, MD, of Montefiore Medical Center. The prospective randomized trial looked at endocrine therapy versus chemoendocrine therapy in women with HR-postive, HER2-negative, axillary node-negative breast cancer who had a mid-range Oncotype DX Recurrence Score of 11 to 25 and tumors 1.1 to 5.0 cm in size. The primary endpoint was invasive disease-free survival, and the trial was designed to show noninferiority for endocrine therapy alone.

"For any breast cancer clinician—or anyone who cares for women with breast cancer—this abstract may be one of the most important studies to come out in recent years," Dr. Partridge said, adding that the abstract results will inform how oncologists care for a large proportion of patients with early-stage breast cancer. "We've all been anxiously waiting for these data," Dr. Partridge said. Lisa A. Carey, MD, of UNC Lineberger Comprehensive Cancer Center, will discuss the abstract.

The second Plenary Abstract, LBA2, is titled, "Maintenance low-dose chemotherapy in patients with high-risk rhabdomyosarcoma: A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG)," and will be presented by first author Gianni Bisogno, MD, of the University of Padova, in Italy. Approximately 20% to 30% of patients with localized rhabdomyosarcoma experience disease relapse after standard treatment, and the prognosis is poor. This study tested whether adding maintenance metronomic chemotherapy after standard chemotherapy would improve the survival for patients with nonmetastatic rhabdomyosarcoma

See Plenary Session Preview, Page 16D

Early-Morning Sessions

7:30 AM–9:15 AM

HIGHLIGHTS OF THE DAY SESSION

Highlights of the Day Session I
Hall D1

David R. Spigel, MD—Chair
Sarah Cannon Research Institute, Tennessee Oncology

7:30 AM
Joon H. Uhm, MD
Mayo Clinic
Central Nervous System Tumors

7:45 AM
Christophe Le Tourneau, MD, PhD
Institut Curie
Developmental Therapeutics—Clinical Pharmacology and Experimental Therapeutics

8:00 AM
Patrick Hwu, MD
The University of Texas MD Anderson Cancer Center
Developmental Therapeutics—Immunotherapy

8:15 AM
Ethan M. Basch, MD, FASCO
The University of North Carolina at Chapel Hill
Health Services Research, Clinical Informatics, and Quality of Care

8:30 AM
Guillermo Garcia-Manero, MD
The University of Texas MD Anderson Cancer Center
Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant

8:45 AM
Amrita Y. Krishnan, MD
City of Hope
Hematologic Malignancies—Plasma Cell Dyscrasia

7:30 AM–9:30 AM

EDUCATION SESSION

Training Program Directors' Breakfast
(Training Program Directors and Associate Directors Only)
S103
Professional Development

7:30 AM
Breakfast and Networking

7:45 AM
Julia Lee Close, MD
University of Florida
Welcome and Introductions

7:55 AM
Frank P. Worden, MD
University of Michigan Comprehensive Cancer Center
Review of Programs and Resources for Program Directors

8:10 AM
Frances A. Collichio, MD
University of North Carolina School of Medicine
Milestones 2.0 and Harmonized Milestones

8:25 AM
Roberto Antonio Leon-Ferre, MD
Mayo Clinic
Trainee Council Updates and Sharing

Surbhi Sidana, MD
Mayo Clinic
Trainee Council Updates and Sharing

Evelyn Mary Brosnan, MD, MBA
Dartmouth Hitchcock Medical Center
Trainee Council Updates and Sharing

8:45 AM
Julia Lee Close, MD, and
Adaeze Nwosu-Iheme, MD
University of Florida
Implementation of a Bias Curriculum

9:10 AM
Frank P. Worden, MD
University of Michigan Comprehensive Cancer Center
Open Discussion: What Keeps You Up at Night?

8:00 AM–9:15 AM

EDUCATION SESSION

Beyond Chemotherapy: Checkpoint Inhibition and Cell-Based Therapy in Non-Hodgkin Lymphoma
E450
Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia; Developmental Therapeutics and Translational Research; Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant; Immunotherapy

Catherine Bollard, MD, MBChB
Children's National Medical Center
The Landscape of Anti–CD-19 CAR T Cells in the Management of Non-Hodgkin Lymphoma

Leo I. Gordon, MD—Chair
Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Cell Therapy in Lymphoma: Practical Applications and New Targets

Loretta J. Nastoupil, MD
The University of Texas MD Anderson Cancer Center
Checkpoint Inhibitors in Lymphoma: When and How

Panel Question and Answer

EDUCATION SESSION

Overcoming Unique Obstacles to Implementing Precision Medicine Trials in the Community Setting
S100bc
Developmental Therapeutics and Translational Research; Care Delivery and Practice Management; Clinical Trials; Ethics

Edward S. Kim, MD—Chair
Levine Cancer Institute, Atrium Health
Identify Strategies and Best Practices for Precision Medicine Trials

Michael A. Thompson, MD, PhD, FASCO
Aurora Advanced Healthcare
Challenges Conducting Precision Medicine Trials in the Community

Lora Jane Black, RN, MPH, OCN, CCRP
Sanford Research
Technologies and Resources for Implementing Precision Medicine Trials in Community-Based Settings

Panel Question and Answer

EDUCATION SESSION

Thinking Beyond RECIST
S100a
Tumor Biology; Clinical Trials; Developmental Therapeutics and Translational Research

Mizuki Nishino, MD, MPH
Dana-Farber Cancer Institute
Is It Time to Move Beyond RECIST Criteria for Tumor Response Evaluation?

Prateek Prasanna, PhD
Case Western Reserve University
Novel Quantitative Tumor Imaging: Techniques and Clinical Applications

Lawrence Howard Schwartz, MD—Chair
Columbia University Medical Center, NewYork-Presbyterian Hospital
Incorporating Novel Imaging Techniques and Novel Imaging Study End Points in Clinical Trials: Opportunities and Challenges

Panel Question and Answer

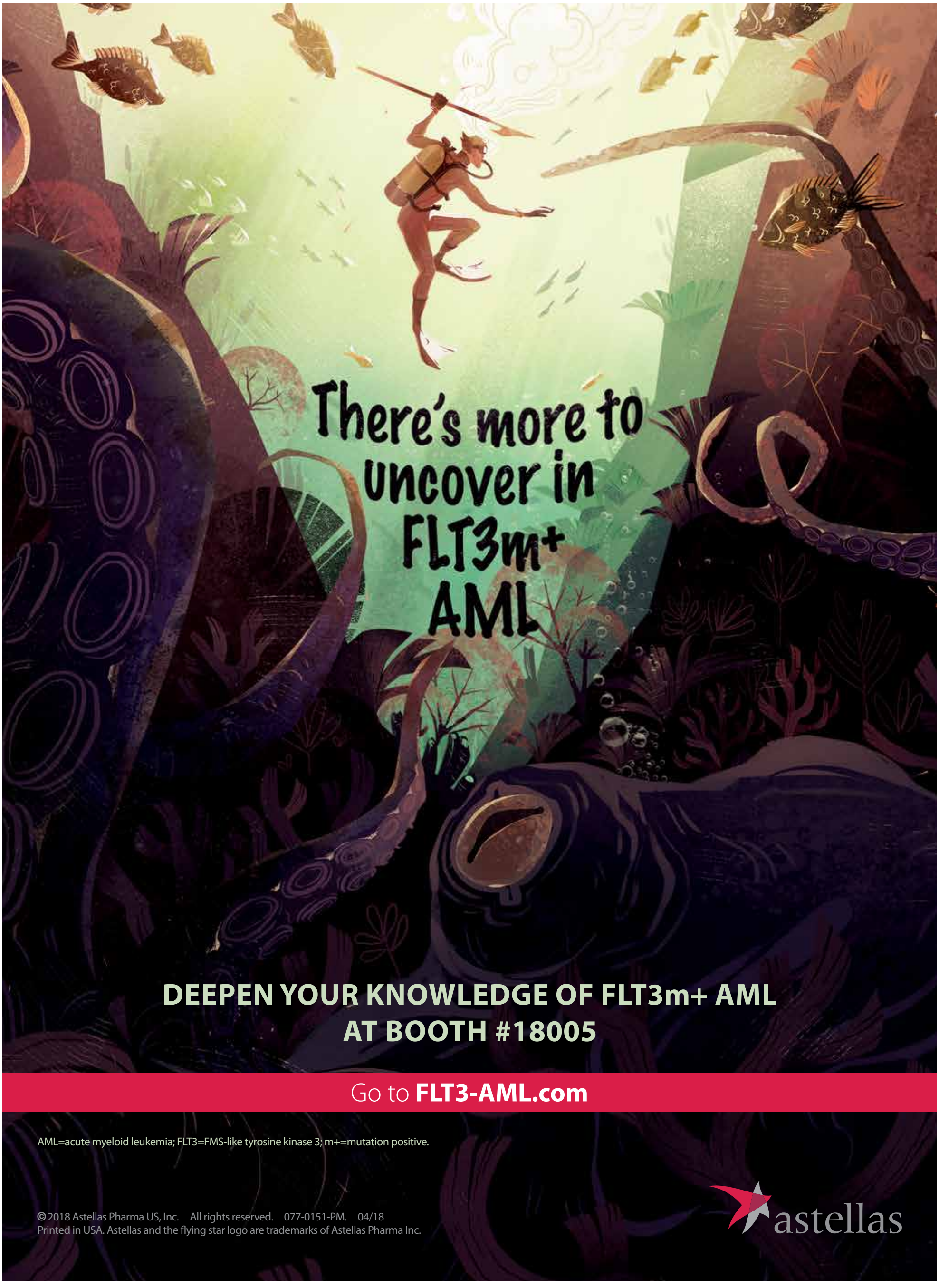
MEET THE PROFESSOR SESSION

Adjuvant/Neoadjuvant Treatment in Melanoma: Where Surgery Meets Medical Oncology— Ticketed Session
E253c
Melanoma/Skin Cancers

Amod Sarnaik, MD
Moffitt Cancer Center
Is Neoadjuvant Treatment for Stage III Melanoma Ready for Prime Time?

Georgina V. Long, MD, PhD, FRACP
Melanoma Institute Australia, The University of Sydney, Mater Hospital, and Royal North Shore Hospital
What Is the Rationale for (Neo-)Adjuvant Therapy in Stage III Melanoma?

See Sessions, Page 10D



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SUNDAY: SESSIONS AT A GLANCE

CSS = Clinical Science Symposium **ED** = Education Session **ORAL** = Oral Abstract Session
MTP = Meet the Professor Session (ticketed) **CPO** = Clinical Problems in Oncology Session (ticketed)

Primary Track	7:30 AM	8:00 AM	9:00 AM	10:00 AM	11:00 AM	12:00 PM
Special Sessions	Highlights of the Day Session I | *Hall D1*			**CSS:** Compelling Combinations: Raising the Bar With Immunotherapy | *Hall D1* **ED:** ASCO/European CanCer Organization (ECCO) Joint Session: Access and Innovation With Multiplex Genomic Testing | *S100a*		
Breast Cancer		**ORAL:** Breast Cancer–Metastatic | *Hall D2*				
Cancer Prevention, Hereditary Genetics and Epidemiology		**ORAL:** Cancer Prevention, Hereditary Genetics, and Epidemiology | *S404*			**ED:** Lynch Syndrome 360 | *S404*	
Care Delivery and Practice Management					**ED:** Filling the Gap: Creating an Outpatient Palliative Care Program in Your Institution | *S504*	
Central Nervous System Tumors				**MTP:** Biology and Therapeutic Promise of Exploiting IDH Mutations in Gliomas | *E253c*		
Developmental Therapeutics and Translational Research		**ED:** Overcoming Unique Obstacles to Implementing Precision Medicine Trials in the Community Settings | *S100bc*				**MTP:** Primary and Acquired Resistance to Checkpoint Inhibitors | *E253d*
GI (Colorectal) Cancer		**POSTER:** Gastrointestinal (Colorectal) Cancer | *Hall A*				**POSTER DISCUSSION:** Gastrointestinal (Colorectal) Cancer | *Hall D2*
GI (Noncolorectal) Cancer		**MTP:** How Do I Treat Hepatocellular Carcinoma? | *E253d* **POSTER:** Gastrointestinal (Noncolorectal) Cancer | *Hall A*				
GU (Nonprostate) Cancer		**ORAL:** Genitourinary (Nonprostate) Cancer | *Arie Crown Theater*				
GU (Prostate) Cancer						**ED:** Management of Biochemically Recurrent Prostate Cancer: Which Imaging, Which Treatment, and When? | *S406*
Geriatric Oncology				**MTP:** How to Bring Geriatric Assessment Into Your Practice | *E253d*		
Global Health						
Gynecologic Cancer				**CSS:** Engaging the Immune System in Ovarian Cancer | *S406*		**ED:** Moving From Mutation to Actionability | *S100bc*
Head and Neck Cancer		**ORAL:** Head and Neck Cancer | *E451*				**MTP:** Treatment Strategies for Locoregionally Advanced Nasopharyngeal Cancer: Making Sense of Recent Studies | *E253c*
Health Services Res, Clinical Informatics, and Quality of Care						**ED:** Collecting and Using Real-World Evidence: Supplementing and Perhaps Replacing Clinical Trials (Includes Presentation of Public Service Award) | *S100a*
Heme Malignancies—Leukemia, MDS, and Allotransplant						
Heme Malignancies—Lymphoma and CLL		**ED:** Beyond Chemotherapy: Checkpoint Inhibition and Cell-Based Therapy in Non-Hodgkin Lymphoma | *E450*		**ORAL:** Hematologic Malignancies–Lymphoma and Chronic Lymphocytic Leukemia | *E450*		
Heme Malignancies—Plasma Cell Dyscrasia						
Lung Cancer		**POSTER:** Lung Cancer–Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers | *Hall A* **POSTER:** Lung Cancer–Non-Small Cell Metastatic | *Hall A*				**POSTER DISCUSSION:** Lung Cancer–Non-Small Cell Metastatic | *Arie Crown Theater*
Melanoma/ Skin Cancers		**MTP:** Adjuvant/Neoadjuvant Treatment in Melanoma: Where Surgery Meets Medical Oncology | *E253c*		**ED:** A New Era in the Management of Melanoma Brain Metastases | *S100bc*		
Patient and Survivor Care		**ORAL:** Patient and Survivor Care | *S102*				**ED:** How Can Genetics Personalize Cancer Survivorship? | *S102*
Pediatric Oncology		**ORAL:** Pediatric Oncology II | *S504*				
Professional Development	**ED:** Training Program Directors' Breakfast (Training Program Directors and Associate Training Program Directors Only) | *S103*					**CSS:** Innovative Approaches to Oncology Education | *S103*
Sarcoma						**ED:** Controversies in Adjuvant/ Neoadjuvant Chemotherapy in Localized Soft Tissue Sarcoma | *E451*
Tumor Biology		**ED:** Thinking Beyond RECIST | *S100a*				

SUNDAY: SESSIONS AT A GLANCE

CSS = Clinical Science Symposium **ED** = Education Session **ORAL** = Oral Abstract Session
MTP = Meet the Professor Session (ticketed) **CPO** = Clinical Problems in Oncology Session (ticketed)

Primary Track	1:00 PM	2:00 PM	3:00 PM	4:00 PM		5:00 PM	
Special Sessions	**Plenary Session Including the Science of Oncology Award and Lecture** | *Hall B1* *(With Simulcast in Hall D1)*			Post-Plenary Discussion Session I: Breast Cancer | *S100a*	Post-Plenary Discussion Session II: Rhabdomyosarcoma | *S100bc*	Post-Plenary Discussion Session III: Kidney Cancer | *S100a*	Post-Plenary Discussion Session IV: Lung Cancer | *S100bc*
Breast Cancer					**ED:** Innovative Strategies Targeting Subtypes in Metastatic Breast Cancer | *Hall B1*		
Cancer Prevention, Hereditary Genetics and Epidemiology					**ED:** Lifestyle Modifications for Primary and Secondary Cancer Prevention: Diet, Exercise, Sun Safety, and Alcohol Reduction | *S102*		
Care Delivery and Practice Management							
Central Nervous System Tumors							
Developmental Therapeutics and Translational Research							
GI (Colorectal) Cancer							
GI (Noncolorectal) Cancer					**POSTER DISCUSSION:** Gastrointestinal (Noncolorectal) Cancer | *Hall D2*		
GU (Nonprostate) Cancer							
GU (Prostate) Cancer					**ED:** The Winds of Change: Optimizing Immunotherapy, Radiopharmaceuticals, and PARP Inhibition in Prostate Cancer | *Hall D1*		
Geriatric Oncology							
Global Health							
Gynecologic Cancer							
Head and Neck Cancer							
Health Services Res, Clinical Informatics, and Quality of Care					**ED:** Communicating the Financial Burden of Treatment With Patients | *S404*		
Heme Malignancies—Leukemia, MDS, and Allotransplant							
Heme Malignancies—Lymphoma and CLL					**ED:** Common Themes in Uncommon Lymphomas: How Biology and Novel Treatments Are Changing the Landscape | *E450*		
Heme Malignancies—Plasma Cell Dyscrasia					**ED:** Global Myeloma, Health Disparities, and the Cost of Drugs | *E451*		
Lung Cancer					**POSTER DISCUSSION:** Lung Cancer-Non-Small Cell Local–Regional/Small Cell/Other Thoracic Cancers | *Arie Crown Theater*		
Melanoma/ Skin Cancers							
Patient and Survivor Care					**MTP:** Addressing Fertility in Young Adult Cancer Survivors | *E253d*		
Pediatric Oncology					**ED:** Pediatric Clinical Trials: Economics, Cost, and Value of Investment | *S504*		
Professional Development					**MTP:** The Peer-Review Process and Writing an Outstanding Manuscript | *E253c*		
Sarcoma					**ED:** Novel Approaches in Bone and Soft Tissue Sarcomas: The Emerging Role of Precision Medicine | *S103*		
Tumor Biology					**ED:** Precision Medicine for a Single Patient: What Does It Really Mean and How Do We Do It? | *S406*		

The Plenary Session includes abstract presentations of the top practice-changing science, with commentary from expert discussants.

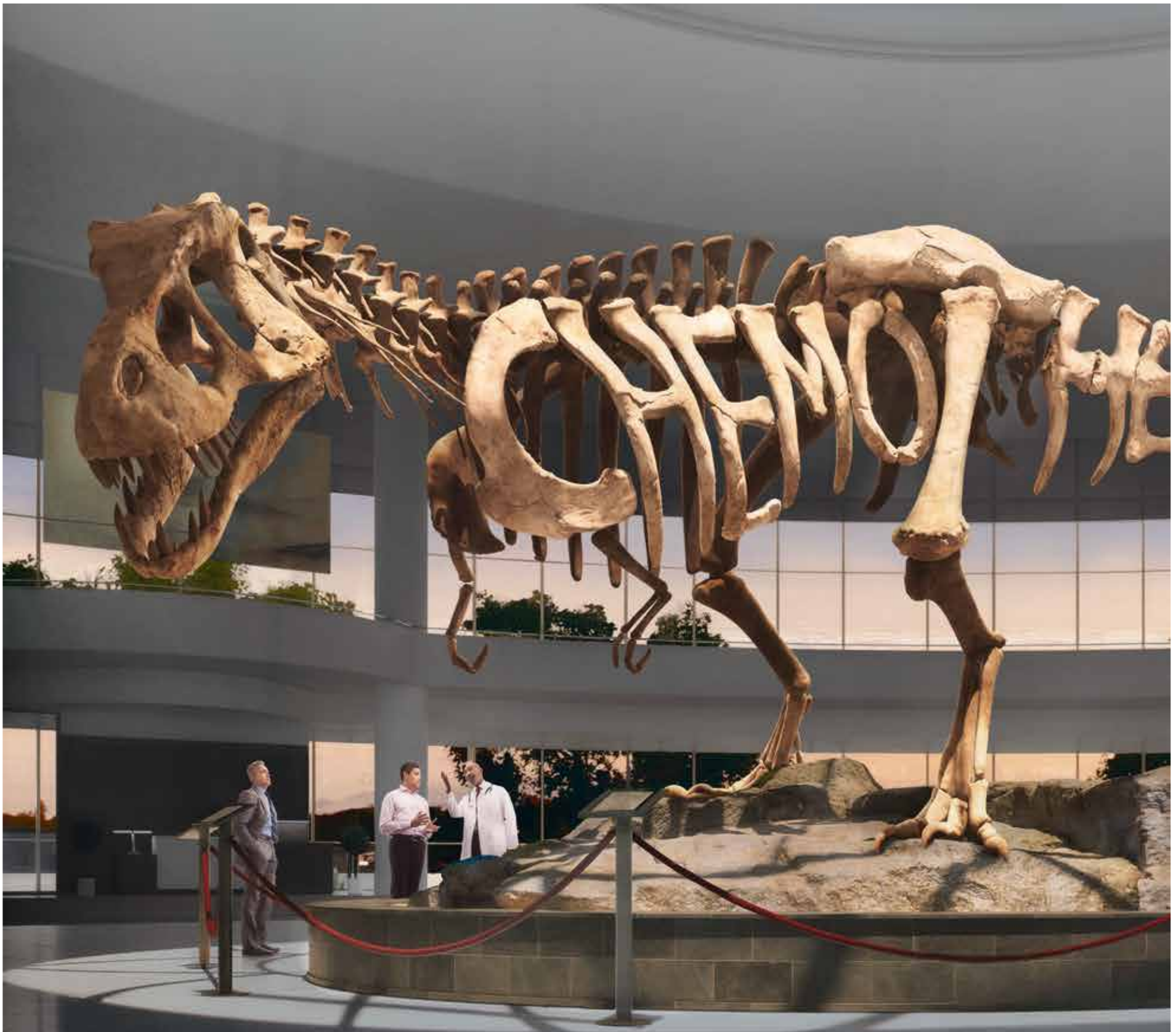
ABSTRACT 1: Breast Cancer
ABSTRACT 2: Rhabdomyosarcoma
ABSTRACT 3: Kidney Cancer
ABSTRACT 4: Lung Cancer

TODAY'S PLENARY SESSION

Plenary Session Abstracts: Page 9D
Plenary Session Program Information: Page 18D

ATTEND THE POST-PLENARY DISCUSSIONS

Breast Cancer | 4:00 PM-4:30 PM, *S100a*
Rhabdomyosarcoma | 4:30 PM-5:00 PM, *S100bc*
Kidney Cancer | 5:00 PM-5:30 PM, *S100a*
Lung Cancer | 5:30 PM-6:00 PM, *S100bc*



In indolent NHL…

As our knowledge evolves, so should our approach

Our understanding of indolent non-Hodgkin lymphoma (NHL), which includes follicular lymphoma (FL) and marginal zone lymphoma (MZL), has improved greatly. We know that indolent NHL is characterized in part by dysfunction within the tumor microenvironment that drives changes to the immune system.[1,2]

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References: 1. Yang ZZ, Ansell SM. The tumor microenvironment in follicular lymphoma. *Clin Adv Hematol Oncol*. 2012;10(12):810-818. **2.** Kridel R, Sehn LH, Gascoyne RD. Pathogenesis of follicular lymphoma. *J Clin Invest*. 2012;122(10):3424-3431.

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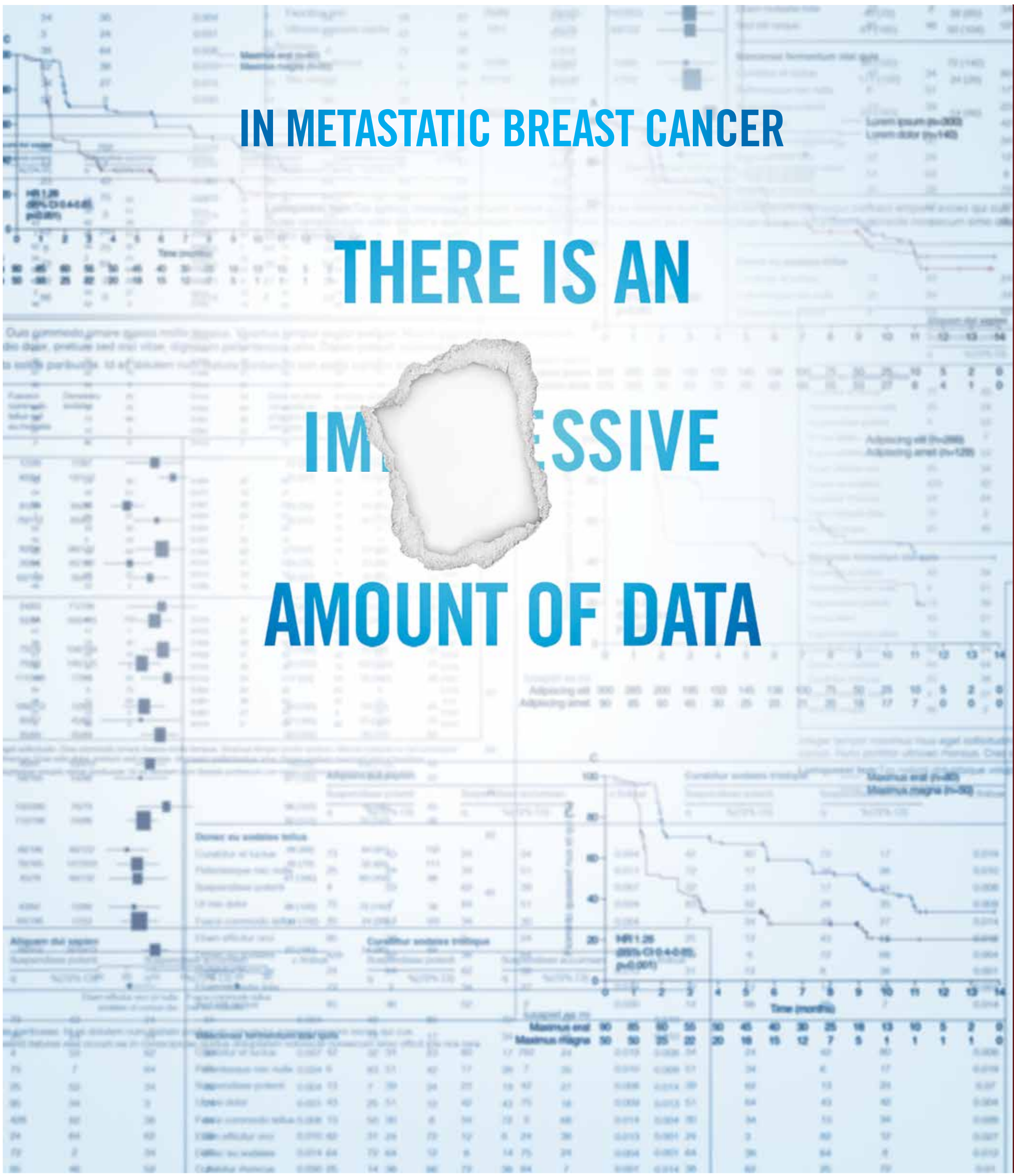
IN METASTATIC BREAST CANCER

THERE IS AN IMPRESSIVE AMOUNT OF DATA



mBC=metastatic breast cancer.

References: 1. ClinicalTrials.gov. Search results for premenopausal metastatic breast cancer studies recruiting; not yet recruiting; active, not recruiting, completed, enrolling by invitation, suspended, terminated, withdrawn, unknown status; phase 3. Search results for postmenopausal metastatic breast cancer studies recruiting; not yet recruiting; active, not recruiting, completed, enrolling by invitation, suspended, terminated, withdrawn, unknown status; interventional studies; studies with female participants; phase 3. Accessed April 2, 2018. **2.** Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the number of women living with metastatic breast cancer in the United States. *Cancer Epidemiol Biomarkers Prev.* 2017;26(6):809-815.

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PREMENOPAUSAL

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*Large clinical trials were defined as Phase III trials of 200 or more women. Dated April 2018.

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LATE-BREAKING ABSTRACTS: LBA1006

Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) *v* FULV in patients (pts) with estrogen receptor (ER)-positive, *PIK3CA*-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER.

BREAST CANCER—METASTATIC

Oral Abstract Session
Sunday, 8:00 AM-11:00 AM
Location: Hall D2

First Author: Jose Baselga, MD, PhD, FASCO
Memorial Sloan Kettering Cancer Center
Discussant: Cynthia X. Ma, MD, PhD
Washington University School of Medicine in St. Louis

Background: Taselisib, a potent, selective PI3K inhibitor, has enhanced activity in *PIK3CA*-MUT BC cell lines and confirmed partial responses in *PIK3CA*-MUT BC as a single-agent or with FULV. We assessed taselisib + FULV in pts with ER-positive, HER2-negative, *PIK3CA*-MUT locally advanced or MBC. **Methods:** SANDPIPER (NCT02340221) is a double-blind, placebo (PBO)-controlled, randomized, phase III study. Postmenopausal pts with disease recurrence or progression during or after an aromatase inhibitor were randomized 2:1 to receive taselisib (4 mg oral, qd) or PBO + FULV (500 mg). Stratification factors were: visceral disease, endocrine sensitivity, and geographic region. Pts with *PIK3CA*-MUT tumors, assessed by central cobas PIK3CA Mutation Test, were randomized separately from non-MUT tumors. The primary endpoint was investigator-assessed progression-free survival (INV-PFS) in pts with *PIK3CA*-MUT tumors. Secondary endpoints included objective response rate (ORR), overall survival (OS), clinical benefit rate (CBR), duration of objective response (DoR), PFS by blinded independent central review (BICR-PFS), and safety. **Results:** 516 pts were randomized in the *PIK3CA*-MUT intention-to-treat (ITT) population. Efficacy is shown in the Table. Taselisib + FULV significantly improved INV-PFS (hazard ratio [HR] 0.70) as confirmed by BICR-PFS (HR 0.66). OS is immature. The most common grade ≥3 adverse events (AEs; preferred terms) in the taselisib + FULV arm in safety-evaluable pts who received ≥ 1 dose of treatment were diarrhea (12%), hyperglycemia (10%), colitis (3%), and stomatitis (2%). AEs led to more taselisib discontinuations (17% *v* 2%) and dose reductions (37% *v* 2%), *v* PBO. **Conclusions:** Taselisib + FULV significantly improved INV-PFS, *v* PBO + FULV, in pts with ER-positive, HER2-negative, *PIK3CA*-MUT locally advanced or MBC. The safety profile is largely consistent with previous studies. Clinical trial information: NCT02340221.

ITT	PBO + FULV	Taselisib + FULV
Median INV-PFS, mo	N=176 5.4	N=340 7.4
HR	0.70 (p=.0037)	
Baseline measurable disease ORR, %	n=134 11.9	n=264 28.0
	p=.0002	
CBR, %	37.3	51.5
DoR, mo	n=16 7.2	n=74 8.7

See full session details p. 10D

LATE-BREAKING ABSTRACTS: LBA3579

Comparison of chemotherapy use, cost, and survival in patients with metastatic colorectal cancer in Western Washington and British Columbia.

GASTROINTESTINAL (COLORECTAL) CANCER

Poster Session (Board #72)
Sunday, 8:00 AM-11:30 AM
Location: Hall A

First Author: Todd Yezefski, MS, MD
University of Washington School of Medicine

Background: Few studies have directly compared health care utilization, costs, and outcomes between geographically similar patients (pts) treated in the U.S.' multi-payer health system versus Canada's single-payer system. Using cancer registry and claims data, we assessed systemic therapy (ST) use, cost, and survival for metastatic colorectal cancer (mCRC) pts in Western Washington (WW) and British Columbia (BC). **Methods:** Pts age ≥ 18 diagnosed with mCRC in 2010 and later were identified from 1) the BC Cancer Agency database and 2) a regional database linking WW SEER to claims from two large commercial insurers. Demographic and treatment characteristics for the two populations were compared using two-sample T tests. ST costs (first-line and lifetime) were expressed as mean per patient per month costs; Canadian costs were expressed in US dollars using the Purchasing Power Parity for Health in 2009. Median survival was reported for both populations. **Results:** 1622 BC pts and 575 WW pts were included in the analysis. BC pts were more likely to be older (median age 60 vs 66) and male (57% vs 48%, p = < 0.01). A greater proportion of WW versus BC pts received ST (79% vs. 68%, p < 0.01). FOLFIRI plus bevacizumab was the most common first-line regimen in BC (32%) while FOLFOX was the most common first-line regimen in WW (39%). The mean monthly cost of first-line therapy per patient was significantly higher in WW than BC ($12,345 vs $6,195, p = < 0.01), and this was true for all regimens assessed. Mean lifetime monthly ST costs were significantly higher in WW ($7,883 vs $4,830, p = < 0.01). There was no difference in median overall survival between populations among those receiving ST (21.4 months (95% CI 18.0-26.2) in WW and 22.1 months (20.5-23.7) in BC) or among those not receiving ST (5.4 months (2.4-7.7) WW versus 6.3 months (5.2-7.3) BC). **Conclusions:** Utilization and cost of ST for mCRC was significantly higher for patients in WW compared to BC without differences in overall survival in treated and untreated patients.

See full session details p. 16D

LATE-BREAKING ABSTRACTS: LBA6002

Are women with head and neck cancer undertreated?

HEAD AND NECK CANCER

Oral Abstract Session
Sunday, 8:00 AM-11:00 AM
Location: E451

First Author: Annie Park, MD
Kaiser Permanente
Discussant: Faye M. Johnson, MD, PhD
The University of Texas MD Anderson Cancer Center

Background: Generalized competing event (GCE) models have been used to stratify patients with cancer according to their relative hazard for cancer death versus death from other causes. We evaluated outcomes for head and neck cancer (HNC) patients treated at Kaiser Permanente Northern California (KPNC) based on demographic data and comorbidities using a GCE model. **Methods:** We identified 884 HNC patients diagnosed 2000-2015 from the KPNC cancer registry, age 18-85 and stage II-IVB by AJCC 7th edition. Using the GCE proportional relative hazards model, controlling for age, sex, tumor site, and Charlson comorbidity index (CCI), we identified associations between these factors and the relative hazard for HNC-specific mortality (ω+ ratio, 'gcerisk' package in R). Death, disenrollment, and end of study (12/31/2016) were used as censoring events. Logistic regression models estimated the odds of receiving intensive treatment (platinum based regimen), adjusting for the same covariates plus stage, smoking, and alcohol abuse history. **Results:** With a median follow-up of 2.9 years, 271 patients died of cancer, and 93 of non-cancer causes. Compared to male, females were less likely to receive intensive chemotherapy (35% vs. 46%, p = 0.006) and radiation (60% vs. 70%, p = 0.008). On GCE analysis, female patients had an increased relative hazard ratio (RHR) for death from HNC vs. other causes (adjusted RHR 1.92; 95% CI 1.07-3.43), indicating they may be relatively undertreated. **Conclusions:** Female patients in our cohort may be undertreated in clinical practice, potentially missing the opportunity to aggressively treat their HNC. This study supports the use of a GCE methodology to objectively identify patients more likely to benefit from treatment intensification. These findings may help guide future research in health disparities.

ω+ ratio and odd ratio for select variables.

Covariate	Adjusted RHR (ω+ ratio) for cancer vs. non-cancer mortality (95% CI)	Intensive chemotherapy OR (95% CI)	Radiation OR (95% CI)	Surgery OR (95% CI)
Female	1.92 (1.07-3.43)	0.68 (0.48, 0.98)	0.79 (0.56, 1.11)	1.04 (0.72, 1.53)
CCI > = 1	0.75 (0.46-1.24)	0.78 (0.68-0.89)	0.96 (0.86-1.07)	1.02 (0.91-1.15)
Age (per 10 years)	0.78 (0.62-0.99)	0.88 (0.75-1.02)	0.90 (0.77-1.05)	0.70 (0.59-0.82)

See full session details p. 10D

LATE-BREAKING ABSTRACTS: LBA10003

Improving communication with older patients with cancer using geriatric assessment (GA): A University of Rochester NCI Community Oncology Research Program (NCORP) cluster randomized controlled trial (CRCT).

PATIENT AND SURVIVOR CARE

Oral Abstract Session
Sunday, 8:00 AM-11:00 AM
Location: S102

First Author: Supriya Gupta Mohile, MD, MS
University of Rochester Medical Center
Discussant: Ethan M. Basch, MD, FASCO
The University of North Carolina at Chapel Hill

Background: GA includes validated measures that assess age-related health domains (e.g., function, cognition) known to increase adverse outcomes. In this PCORI and NCI funded CRCT, we evaluated if providing a GA summary and recommendations for GA-guided interventions improves communication about age-related concerns for older patients (pts) with cancer. **Methods:** Pts aged ≥ 70 with advanced solid tumors or lymphoma and at least 1 impaired GA domain were enrolled. Oncology practices were randomized to intervention (oncologists received GA summary) or usual care (no summary provided). The primary outcomes were: 1) number of discussions about age-related concerns (the clinic visit after GA was audio-recorded and transcribed; 2 blinded coders evaluated quality of communication and plan for follow-up interventions) and 2) telephone surveys of patient satisfaction (modified Health Care Climate Questionnaire [HCCQ-age] scored 7-35). Outcomes were analyzed using linear mixed models with arm as the fixed effect, controlling for practice. **Results:** From 2014-17, 544 pts (295 in GA) were enrolled from 31 practices. There were no differences in demographics by arm (mean age 77 yrs; 49% female). More patients in usual care had impaired physical performance (96% vs 92%, p = 0.03) and social support (33% vs 25%, p = 0.05). In 530 evaluable pts, the overall mean number of discussions was 6.3 (SD: 4.0). The GA arm had 3.5 more discussions about age-related concerns (95% CI: 2.28-4.72, p = 10-6; intraclass correlation coefficient [ICC] = 0.24) compared to usual care; of these, in the GA arm, 2.0 more discussions on average had higher quality communication (95% CI: 1.20-2.69; $p = 6x10^{-6}$) and 1.9 more led to interventions (95% CI: 1.14-2.73; $p = 1.6x10^{-5}$). The GA arm had significantly more discussions for almost all GA domains. In 511 pts with HCCQ-age, the mean score was 22.9 (SD 4.5); the score was 1.12 points higher in the GA arm (95% CI: 0.23-2.03; p = .027; ICC = 0.02). **Conclusions:** Providing a GA summary to oncologists increases the number and quality of discussions about age-related concerns and improves pt satisfaction. Clinical trial information: NCT02107443.

See full session details p. 15D

LATE-BREAKING ABSTRACTS: LBA1

TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score.

BREAST CANCER—LOCAL/REGIONAL/ADJUVANT

Plenary Session
Sunday, 1:00 PM-4:00 PM
Location: Hall B1

First Author: Joseph A. Sparano, MD
Montefiore Medical Center
Discussant: Lisa A. Carey, MD
The University of North Carolina at Chapel Hill

Background: In hormone receptor (HR)-positive, HER2-negative, axillary node (AN)-negative breast cancer, the 21-gene expression assay (Oncotype DX Recurrence Score [RS]) is prognostic for distant recurrence, prognostic for low recurrence with endocrine therapy alone if low (0-10), and predictive of chemotherapy benefit if high (26 or higher). We performed a prospective, randomized trial of endocrine therapy (ET) versus chemoendocrine therapy (CET) in women with a mid-range RS of 11-25. **Methods:** Eligibility criteria included women 18-75 years of age with HR-positive, HER2-negative, axillary node (AN)-negative breast cancer and tumors 1.1-5.0 cm in size (or 0.6-1.0 cm and int/high grade) and agreed to have chemotherapy assigned or randomized based on the RS. Women with a mid-range RS (11-25) were randomized to receive ET or CET. The primary endpoint was invasive disease-free survival (iDFS), and the trial was designed to show non-inferiority for ET alone by not rejecting equality (hazard ratio [HR] margin up to 1.322 for omission of chemotherapy, 1-sided type I error rate 10%, type II error rate 5%). The target sample size was adjusted to compensate for non-adherence to randomized treatment, and the protocol-specified final analysis was triggered after 835 iDFS events. **Results:** Of the 10,253 eligible women enrolled between 4/7/06-10/6/10, 6711 (65.5%) had a RS of 11-25 and adequate information. There were 836 iDFS events at final analysis with a median followup of 90 months. ET was non-inferior to CET for iDFS (HR 1.08, 95% confidence intervals [CI] 0.94, 1.24, p=0.26) in the intention-to-treat (ITT) population. ET was also non-inferior for distant recurrence-free interval (DRFI; HR 1.03, p=0.80), recurrence-free interval (RFI; HR 1.12, p=0.28), and overall survival (OS; HR 0.97, p=0.80). Nine year rates were similar for iDFS (83.3% vs. 84.3%), DRFI (94.5% vs. 95.0%), RFI (92.2% vs. 92.9%), and OS (93.9% vs. 93.8%). Recurrence accounted for 338 (41.6%) the first iDFS event, of which 199 (23.8%) were distant recurrences. Treatment interaction tests were significant for age (iDFS p=0.03; RFI p= 0.02), but not menopause, tumor size, grade, or RS (continuous or RS 11-15, 16-20, 21-25). **Conclusions:** In women with HR-positive, HER2-negative, AN-negative breast cancer and a RS of 11-25, adjuvant ET was not inferior to CET in the ITT analysis. (Funded by NCI, BCRF, and Komen Foundation.) Clinical trial information: NCT00310180.

See full session details p. 20D

LATE-BREAKING ABSTRACTS: LBA2

Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG).

PEDIATRIC ONCOLOGY

Plenary Session
Sunday, 1:00 PM-4:00 PM
Location: Hall B1

First Author: Gianni Bisogno, MD
University Hospital of Padova
Discussant: Douglas S. Hawkins, MD
Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center

Background: Most patients with localized RMS achieve complete remission during standard (std) treatment but approximately 20-30% of them relapse and chance of salvage is poor. We tested whether adding maintenance metronomic chemotherapy after std chemotherapy would improve survival for patients with non metastatic RMS defined as HR according to EpSSG stratification. **Methods:** Patients (pts) age >6 months <21 years, with N0 alveolar (A)RMS or incompletely resected (Group II or III) embryonal (E)RMS arising in an unfavorable primary site and/or N1 in complete remission after std treatment including 9 cycles of ifosfamide, vincristine and actinomycin D +/- doxorubicin, surgery and/or radiotherapy were eligible for randomization to stop treatment (Std-arm) or receive maintenance chemotherapy (M-arm) with 6 28-day cycles of iv vinorelbine 25 mg/m^2 on day 1,8,15 of each cycle and continuous daily oral cyclophosphamide 25 mg/m^2. The study was initially designed with 80% power (5% 2-sided alpha level) to detect an increase in 3 yr Event Free Survival (EFS) from 55% to 67%, a Hazard Ratio of 0.67, but was successively amended to allow a detection of a relative reduction in the relapse rate of 50% in the M-arm, with 80% power, testing at the 5% significance level (2-sided). **Results:** 670 pts were entered between 4/2006-12/2016, with 371 confirmed eligible and 186 assigned to the std-arm and 185 to M-arm. Clinical features were well balanced in the two arms and included ERMS 67%, ARMS 33%, age 10+ years 21%; IRS Group III 86%; N1 16%. Most common primary tumor sites were parameningeal (32%) and "other" sites (23%). With median follow up of 5 years in surviving pts, 3 yr EFS and overall survival (OS) in M-arm vs Std-arm were respectively: EFS 78.4% (95% IC -71.5-83.8) vs 72.3% (95% IC -65.0-78.3) (p 0.061) and OS 87.3% (95% IC 81.2-91.6) vs 77.4 (95% IC 70.1-83.1) (p = 0.011). Toxicity in the M-arm was manageable: grade 3/4 febrile neutropenia in 25% of pts, grade 4 neurotoxicity in 1.1%. **Conclusions:** The addition of maintenance after std treatment significantly improves OS in HR RMS patients and support its inclusion in future EpSSG trials. Clinical trial information: 2005-000217-35.

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LATE-BREAKING ABSTRACTS: LBA3

CARMENA: Cytoreductive nephrectomy followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma—Results of a phase III noninferiority trial.

GENITOURINARY (NONPROSTATE) CANCER

Plenary Session
Sunday, 1:00 PM-4:00 PM
Location: Hall B1

First Author: Arnaud Mejean, MD, PhD
Hôpital Européen Georges-Pompidou, Paris Descartes University
Discussant: Daniel J. George, MD
Duke University

Background: Cytoreductive nephrectomy (CN) has been the standard of care in mRCC in the past twenty years, supported by randomized and large retrospective studies. However the efficacy of targeted therapies has challenged this standard. CARMENA was designed to answer the question of whether upfront CN should continue to be performed before sunitinib. **Methods:** CARMENA was a randomized phase III trial. Patients (pts) with synchronous mRCC, amenable to CN, were enrolled after confirmation of clear cell histology on biopsy if PS 0-1, absence of symptomatic brain metastasis, acceptable organ function and eligible for sunitinib therapy. Pts were randomized 1:1 to either CN followed by sunitinib (arm A) or sunitinib alone (arm B), and stratified by MSKCC risk groups. Sunitinib was given at 50 mg/d, 4/6wk with dose adaptation to routine practice. In arm A, sunitinib had to start 4 to 6 wk after surgery. Primary endpoint was overall survival (OS). A total of 576 pts had to be enrolled to demonstrate non inferiority hypothesis (H0: $\lambda E/\lambda C > 1.20$), with 80% power at a 1-sided significance level of 5%. **Results:** 450 pts were included from 9/09 to 9/17, 226 and 224 in arm A and B, respectively. Median age was 62, ECOG-PS was 0 in 56% and 1 in 44%. MSKCC risk groups were intermediate/poor in 55.6/44.4% (arm A) and in 58.5/41.5% (arm B). In arm A, 6.7% did not have CN and 22.5% never received sunitinib. In arm B, 4.9 % never received sunitinib and 17% had secondary nephrectomy. At the time of the analysis, 326 deaths have been observed with a median follow-up of 50.9 mo. OS was not inferior in arm B, overall as well as by MSKCC risk groups (table). No difference in response rate and PFS was observed. Safety of sunitinib was as expected in both arms. **Conclusions:** Sunitinib alone is not inferior to CN followed by sunitinib in synchronous mRCC both in intermediate and poor MSKCC risk groups. CN should not be anymore the standard of care when medical treatment is required. Clinical trial information: NCT00930033.

	Arm A	Arm B	HR [CI95%]
OS Median (mo) [CI95%]	13.9 [12-18]	18.4 [15-23]	0.89 [0.71-1.10]
MSKCC Intermediate	19.0 [12-28]	23.4 [17-32]	0.92 [0.68-1.24]
MSKCC Poor	10.2 [9-14]	13.3 [9-17	0.85 [0.62-1.17]
ORR	35.9%	35.9%	
PFS Median (mo) [CI95%]	7.2 [6.2-8.5]	8.3 [6.2-9.9]	

See full session details p. 20D

LATE-BREAKING ABSTRACTS: LBA4

Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study.

LUNG CANCER—NON–SMALL CELL METASTATIC

Plenary Session
Sunday, 1:00 PM-4:00 PM
Location: Hall B1

First Author: Gilberto Lopes, MD, MBA
Sylvester Comprehensive Cancer Center, University of Miami Health System
Discussant: Leena Gandhi, MD, PhD
NYU Perlmutter Cancer Center

Background: In KEYNOTE-024, pembro significantly improved PFS (primary end point) and OS (secondary end-point) over chemo as first-line therapy for metastatic NSCLC without targetable alterations and PD-L1 TPS ≥50%. In KEYNOTE-042, we compared pembro with chemo at the lower TPS of ≥1%. **Methods:** Eligible patients (pts) were randomized 1:1 to ≤35 cycles of pembro 200 mg Q3W or investigator's choice of ≤6 cycles of paclitaxel + carboplatin or pemetrexed (peme) + carboplatin with optional peme maintenance (nonsquamous only). Randomization was stratified by region (east Asia vs non-east Asia), ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and TPS (≥50% vs 1-49%). Primary end-points were OS in pts with TPS ≥50%, ≥20%, and ≥1%. OS differences were assessed sequentially using the stratified log-rank test. Efficacy boundaries at the prespecified second interim analysis were one-sided P = .0122, .01198, and .01238, respectively. **Results:** 1274 pts were randomized: 637 to each arm. 599 pts (47.0%) had TPS ≥50%, 818 (64.2%) had TPS ≥20%. After 12.8-mo median follow-up, 13.7% were still on pembro and 4.9% were receiving peme maintenance. Pembro significantly improved OS in pts with TPS ≥50% (HR 0.69), TPS ≥20% (HR 0.77), and TPS ≥1% (HR 0.81) (Table). Grade 3-5 drug-related AEs were less frequent with pembro (17.8% vs 41.0%). The external DMC recommended continuing the trial to evaluate PFS (secondary end-point). **Conclusion:** KEYNOTE-042 is the first study with a primary end-point of OS to demonstrate superiority of pembro over platinum-based chemo in pts with previously untreated advanced/metastatic NSCLC without sensitizing *EGFR* or *ALK* alterations and a PD-L1 TPS ≥1%. These data confirm and potentially extend the role of pembro monotherapy as a standard first-line treatment for PD-L1-expressing advanced/metastatic NSCLC. Clinical trial information: NCT02220894.

	PD-L1 TPS					
	≥50%		≥20%		≥1%	
	Pembro N = 299	Chemo N = 300	Pembro N = 413	Chemo N = 405	Pembro N = 637	Chemo N = 637
OS						
HR (95% CI)	0.69 (0.56-0.85)		0.77 (0.64-0.92)		0.81 (0.71-0.93)	
P	.0003		.0020		.0018	
Median (95% CI), mo	20.0 (15.4-24.9)	12.2 (10.4-14.2)	17.7 (15.3-22.1)	13.0 (11.6-15.3)	16.7 (13.9-19.7)	12.1 (11.3-13.3)

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Sessions

Continued from page 1D

MEET THE PROFESSOR SESSION

How Do I Treat Hepatocellular Carcinoma?—Ticketed Session
E253d
Gastrointestinal (Noncolorectal) Cancer

Anthony B. El-Khoueiry, MD
USC Norris Comprehensive Cancer Center
New Trends for Advanced Metastatic Hepatocellular Carcinoma

Graziano Oldani, MD
HepatoPancreato-Biliary Centre, Geneva University Hospitals
When Should I Indicate Surgical Procedures for Hepatocellular Carcinoma?

8:00 AM–11:00 AM

ORAL ABSTRACT SESSION

Breast Cancer—Metastatic
Hall D2

Beverly Moy, MD, FASCO—Co-Chair
Massachusetts General Hospital Cancer Center

Ruth O'Regan, MD—Co-Chair
University of Wisconsin Carbone Cancer Center

8:00 AM
Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC): Results from MONALEESA-3. (Abstract 1000)

Dennis J. Slamon, MD, PhD

8:12 AM
Genetic landscape of resistance to CDK4/6 inhibition in circulating tumor DNA (ctDNA) analysis of the PALOMA3 trial of palbociclib and fulvestrant versus placebo and fulvestrant. (Abstract 1001)

Nicholas C. Turner, MD, PhD

8:24 AM
Abemaciclib for pre/perimenopausal women with HR+, HER2- advanced breast cancer. (Abstract 1002)

Patrick Neven, MD, PhD

Discussion

8:36 AM
Angela DeMichele, MD, MSCE
(Discussion of Abstracts 1000-1002)
Penn Medicine Abramson Cancer Center
Present and Future of CDK Inhibitors

8:48 AM
Panel Question and Answer

9:00 AM
Phase III multicenter, randomized study of utidelone plus capecitabine versus capecitabine alone for heavily pretreated, anthracycline- and taxane-refractory metastatic breast cancer. (Abstract 1003)

Binghe Xu, MD, PhD

9:12 AM
Efficacy of sacituzumab govitecan (anti-Trop-2-SN-38 antibody-drug conjugate) for treatment-refractory hormone-receptor positive (HR+)/HER2- metastatic breast cancer (mBC). (Abstract 1004)

Aditya Bardia, MD, MPH

Discussion

9:24 AM
Virginia G. Kaklamani, MD
(Discussion of Abstracts 1003-1004)
The University of Texas Health Science Center
HER2-Negative Metastatic Breast Cancer: Chemotherapy With a Twist

9:36 AM
Panel Question and Answer

9:48 AM
Everolimus (EVE) + exemestane (EXE) vs EVE alone or capecitabine (CAP) for estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): BOLERO-6, an open-label phase 2 study. (Abstract 1005)

Guy Heinrich Maria Jerusalem, MD, PhD

10:00 AM
Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER. (Abstract LBA1006)

Jose Baselga, MD, PhD, FASCO

10:12 AM
AZD5363 plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial. (Abstract 1007)

Peter Schmid, MD, PhD, FCRP

10:24 AM
Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally advanced/metastatic triple-negative breast cancer (mTNBC). (Abstract 1008)

Rebecca Alexandra Dent, MD

Discussion

10:36 AM
Cynthia X. Ma, MD, PhD
(Discussion of Abstracts 1005-1008)
Washington University School of Medicine in St. Louis
The PI3K-AKT-mTOR Pathway: Are We Making Headway?

10:48 AM
Panel Question and Answer

ORAL ABSTRACT SESSION

Cancer Prevention, Hereditary Genetics, and Epidemiology
S404

Veda N. Giri, MD—Co-Chair
The Sidney Kimmel Cancer Center at Thomas Jefferson University

Noelle K. LoConte, MD—Co-Chair
University of Wisconsin Carbone Cancer Center

8:00 AM
Low-fat dietary pattern and all cancer mortality in the Women's Health Initiative (WHI) randomized trial. (Abstract 1500)

Rowan T. Chlebowski, MD, PhD, FASCO

8:12 AM
Pre- and post-treatment body weight and prognosis in a multiethnic cohort of breast cancer patients. (Abstract 1501)

Lihua Shang, MD

8:24 AM
Cardiorespiratory fitness and incident lung and colon cancer: FIT-Cancer Cohort. (Abstract 1502)

Catherine Handy, MD, MPH

Discussion

8:36 AM
Jennifer A. Ligibel, MD
(Discussion of Abstracts 1500-1502)
Dana-Farber Cancer Institute
The Role of Diet and Fitness in Optimizing Cancer Prevention and Outcomes

8:48 AM
Panel Question and Answer

9:00 AM
Inherited mutations in breast cancer patients with and without multiple primary cancers. (Abstract 1503)

Kara Noelle Maxwell, MD, PhD

9:12 AM
Frequency of actionable cancer predisposing germline mutations in patients with lung cancers. (Abstract 1504)

Semanti Mukherjee, PhD

9:24 AM
Pathogenic somatic mutation (SM) of mismatch repair (MMR) genes and associations with microsatellite instability (MSI), tumor mutational burden (TMB) and SM in other DNA repair pathways in 24,223 tumor genomic profiles. (Abstract 1505)

Joseph Nicholas Bodor, MD, PhD

Discussion

9:36 AM
Mark E. Burkard, MD, PhD
(Discussion of Abstracts 1503-1505)
University of Wisconsin Carbone Cancer Center
Patient Evaluation in an Expanding Genetic World: Multiple Genes, Multiple Cancers, Multiple Molecular Signatures

9:48 AM
Panel Question and Answer

10:00 AM
A breast cancer risk model as a predictor of interval cancer rate and tumor characteristics. (Abstract 1506)

Nickolas Dreher

10:12 AM
Validation of a combined residual risk score for healthy unaffected women presenting to breast cancer (BC) screening centers. (Abstract 1507)

Kathryn Dalton, DO, FACS

10:24 AM
Polygenic risk score for breast cancer in high-risk women. (Abstract 1508)

Mary Helen Black, PhD, MS

Discussion

10:36 AM
Antonis Antoniou, PhD
(Discussion of Abstracts 1506-1508)
University of Cambridge
Controversies in Cancer Risk Modeling: Breast Density and Polygenic Risk Scores

10:48 AM
Panel Question and Answer

ORAL ABSTRACT SESSION

Genitourinary (Nonprostate) Cancer
Arie Crown Theater

Amishi Yogesh Shah, MD—Co-Chair
The University of Texas MD Anderson Cancer Center

Matthew R. Zibelman, MD—Co-Chair
Fox Chase Cancer Center

8:00 AM
Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (accRCC): Results from cohort A of KEYNOTE-427. (Abstract 4500)

David F. McDermott, MD

8:12 AM
A randomized, open label, multicenter phase 2 study, to evaluate the efficacy of sorafenib (So) in patients (pts) with metastatic renal cell carcinoma (mRCC) after a radical resection of the metastases: RESORT trial. (Abstract 4502)

Giuseppe Procopio, MD

8:24 AM
Patient-reported outcomes (PROs) in IMmotion151: Atezolizumab (atezo) + bevacizumab (bev) vs sunitinib (sun) in treatment (tx) naive metastatic renal cell carcinoma (mRCC). (Abstract 4511)

Bernard Escudier, MD

Discussion

8:36 AM
Toni K. Choueiri, MD
(Discussion of Abstracts 4500-4511)
Dana-Farber Cancer Institute
Optimizing Systemic Therapy in Advanced Renal Cell Carcinoma

8:48 AM
Panel Question and Answer

9:00 AM
First results from the primary analysis population of the phase 2 study of erdafitinib (ERDA; JNJ-42756493) in patients (pts) with metastatic or unresectable urothelial carcinoma (mUC) and FGFR alterations (FGFRalt). (Abstract 4503)

Arlene O. Siefker-Radtke, MD

9:12 AM
Updated results from the enfortumab vedotin phase 1 (EV-101) study in patients with metastatic urothelial cancer (mUC). (Abstract 4504)

Jonathan E. Rosenberg, MD

9:24 AM
Cctg BL12: Randomized phase II trial comparing nab-paclitaxel (Nab-P) to paclitaxel (P) in patients (pts) with advanced urothelial cancer progressing on or after a platinum containing regimen (NCT02033993). (Abstract 4505)

Srikala S. Sridhar, MD, FRCPC

Discussion

9:36 AM
Andrea B. Apolo, MD
(Discussion of Abstracts 4503-4505)
Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute at the National Institutes of Health
Nonimmunotherapy Strategies in Advanced Bladder Cancer

9:48 AM
Panel Question and Answer

10:00 AM
A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS). (Abstract 4506)

Thomas Powles, MD

10:12 AM
Preoperative pembrolizumab (pembro) before radical cystectomy (RC) for muscle-invasive urothelial bladder carcinoma (MIUC): Interim clinical and biomarker findings from the phase 2 PURE-01 study. (Abstract 4507)

Andrea Necchi, MD

10:24 AM
Multicenter randomized phase 2 trial of paclitaxel, ifosfamide, and cisplatin (TIP) versus bleomycin, etoposide, and cisplatin (BEP) for first-line treatment of patients (pts) with intermediate- or poor-risk germ cell tumors (GCT). (Abstract 4508)

Darren R. Feldman, MD

Discussion

10:36 AM
Matt D. Galsky, MD
(Discussion of Abstracts 4506-4508)
Icahn School of Medicine at Mount Sinai/Tisch Cancer Institute
Neoadjuvant Immunotherapy in Localized Bladder Cancer: Frontline Management of High-Risk Germ Cell Cancer

10:48 AM
Panel Question and Answer

ORAL ABSTRACT SESSION

Head and Neck Cancer
E451

Charu Aggarwal, MD, MPH—Co-Chair
Abramson Cancer Center

Jessica Ruth Bauman, MD—Co-Chair
Fox Chase Cancer Center

8:00 AM
Results of a randomized phase III study of nimotuzumab in combination with concurrent radiotherapy and cisplatin versus radiotherapy and cisplatin alone, in locally advanced squamous cell carcinoma of the head and neck. (Abstract 6000)

Vijay Maruti Patil, MD, MBBS

8:12 AM
Definitive cetuximab-based (CRT-CX) vs. non-cetuximab based chemoradiation (CRT) in older patients with squamous cell carcinoma of the head and neck (HNSCC): Analysis of the SEER-Medicare linked database. (Abstract 6001)

Dan Paul Zandberg, MD

8:24 AM
Are women with head and neck cancer undertreated? (Abstract LBA6002)

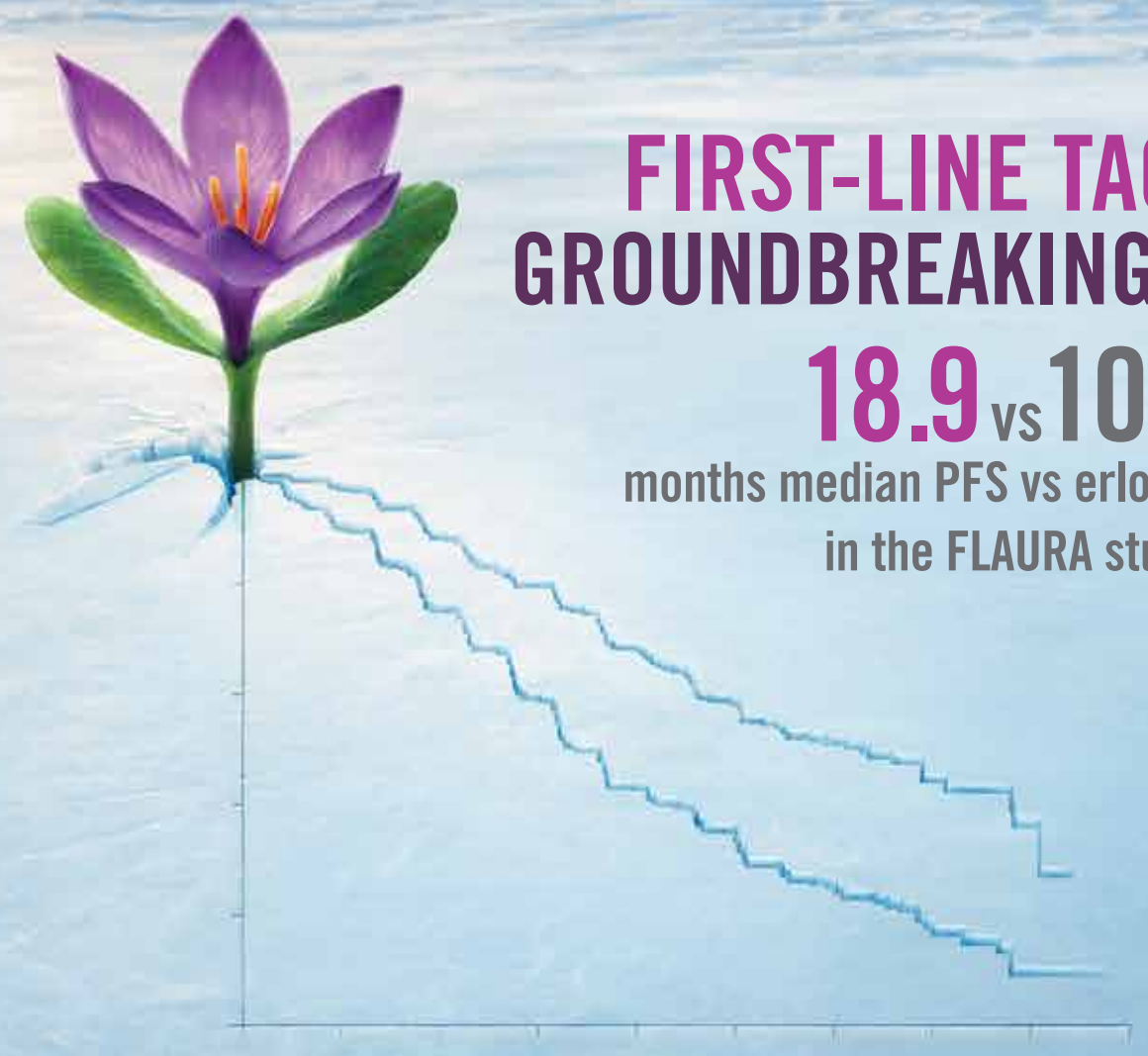
Annie Park, MD

Discussion

8:36 AM
Faye M. Johnson, MD, PhD
(Discussion of Abstracts 6000-LBA6002)
The University of Texas MD Anderson Cancer Center
Redefining Perceptions in Locally Advanced Disease

See Sessions, Page 14D

NEW INDICATION FOR THE TREATMENT OF METASTATIC EGFRm NSCLC



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months median PFS vs erlotinib/gefitinib in the FLAURA study

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TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

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- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

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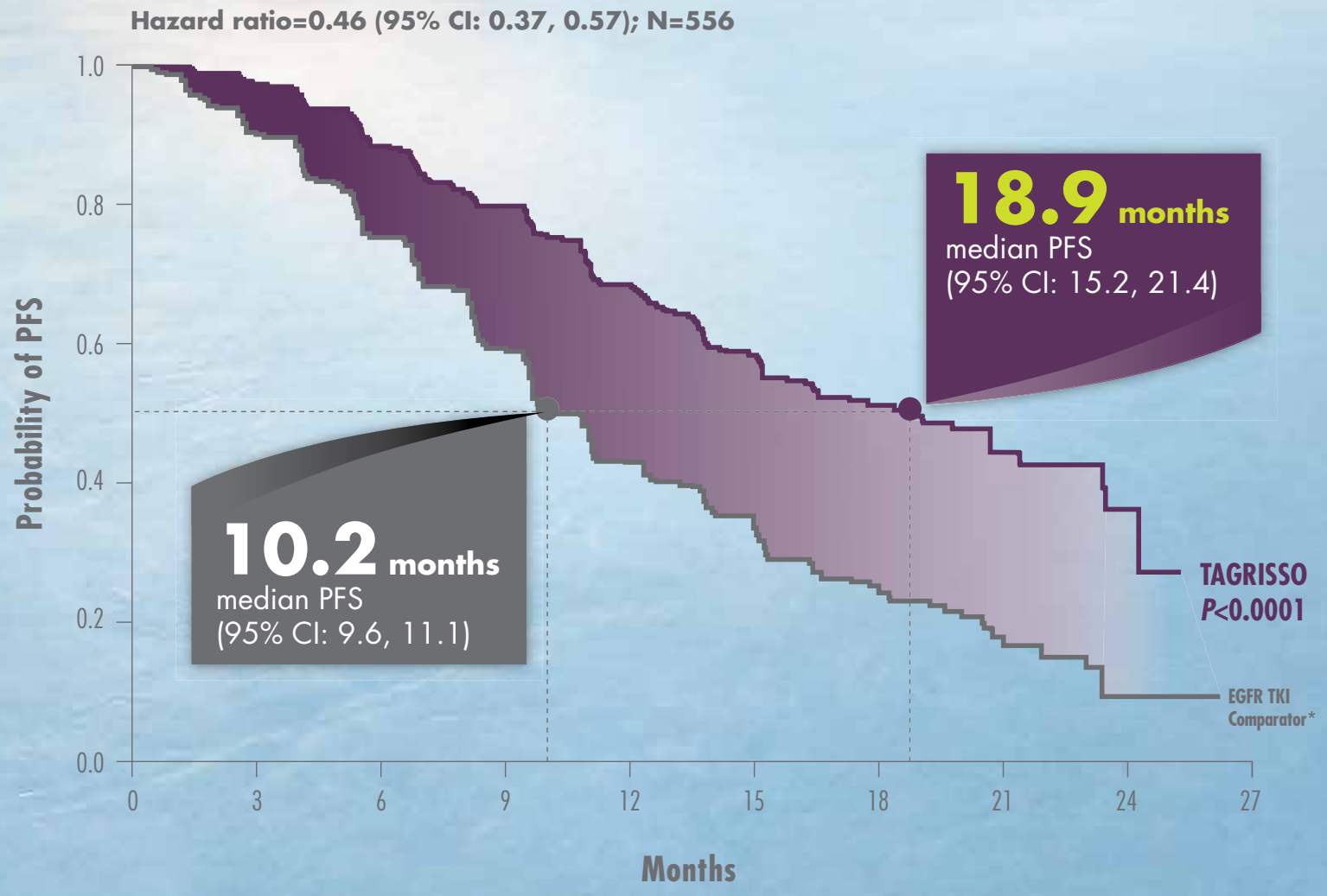

*In the FLAURA study, all US patients in the comparator arm received erlotinib.[2]

SELECT SAFETY INFORMATION

- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO

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Demonstrated unprecedented 18.9 months median PFS vs 10.2 months for EGFR TKI comparator[1]

- Hazard ratio=0.46 (95% CI: 0.37, 0.57), *P*<0.0001

ALL SUBGROUPS

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- Including patients with or without CNS metastases

Osimertinib (TAGRISSO) is an NCCN-recommended first-line therapy option[4]

Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). Crossover was allowed for patients in the EGFR TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v1.1). Secondary endpoints included ORR, DOR, OS, and safety.[1,3]

SELECT SAFETY INFORMATION

- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

Abbreviations: CNS, central nervous system; **DOR**, duration of response; **EGFRm**, epidermal growth factor receptor mutation-positive; **NSCLC**, non–small-cell lung cancer; **ORR**, overall response rate; **OS**, overall survival; **PFS**, progression-free survival; **RECIST**, Response Evaluation Criteria In Solid Tumors; **TKI**, tyrosine kinase inhibitor.

REFERENCES: 1. TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. **2.** Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125 [protocol]. **3.** Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.3.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed March 1, 2018. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. To view the most recent and complete version of the guideline, go online to NCCN.org.

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First-line treatment of metastatic EGFRm NSCLC

Sessions

Continued from page 10D

8:48 AM
Panel Question and Answer

9:00 AM
Treatment deintensification to surgery only for stage I human papillomavirus-associated oropharyngeal cancer. (Abstract 6003)

John David Cramer, MD

9:12 AM
Phase II study: Induction chemotherapy and transoral surgery as definitive treatment (Tx) for locally advanced oropharyngeal squamous cell carcinoma (OPSCC): A novel approach. (Abstract 6004)

Robert S. Siegel, MD

9:24 AM
Survival outcomes by HPV status in non-oropharyngeal head and neck cancers: A propensity score matched analysis of population level data. (Abstract 6005)

Sibo Tian, MD

Discussion

9:36 AM
Sharon Spencer, MD
(Discussion of Abstracts 6003-6005)
University of Alabama at Birmingham
HPV: Will Less Be More?

9:48 AM
Panel Question and Answer

10:00 AM
Results of a randomized, placebo (PBO) controlled, double-blind P2b trial of GC4419 (avisopasem manganese) to reduce duration, incidence and severity and delay onset of severe radiation-related oral mucositis (SOM) in patients (pts) with locally advanced squamous cell cancer of the oral cavity (OC) or oropharynx (OP). (Abstract 6006)

Carryn M. Anderson, MD

10:12 AM
Phase II trial of high-dose melatonin oral gel for the prevention and treatment of oral mucositis in H&N cancer patients undergoing chemoradiation (MUCOMEL). (Abstract 6007)

Alicia Lozano, MD

10:24 AM
Multicenter phase II trial of palbociclib, a selective cyclin dependent kinase (CDK) 4/6 inhibitor, and cetuximab in platinum-resistant HPV unrelated (-) recurrent/metastatic head and neck squamous cell carcinoma (RM HNSCC). (Abstract 6008)

Douglas Adkins, MD

Discussion

10:36 AM
Stuart J. Wong, MD
(Discussion of Abstracts 6006-6008)
Medical College of Wisconsin
Potpourri of Stuff That Matters (Really)

10:48 AM
Panel Question and Answer

ORAL ABSTRACT SESSION
Patient and Survivor Care
S102

Piyush Srivastava, MD—Co-Chair
Kaiser Permanente

Martin R. Stockler, MBBS, MS, FRACP—Co-Chair
NHMRC Clinical Trials Centre, The University of Sydney

8:00 AM
Omega-3 fatty acid use for obese breast cancer patients with aromatase inhibitor-related arthralgia (SWOG S0927). (Abstract 10000)

Sherry Shen, MD

8:12 AM
The effect of acupuncture versus cognitive behavior therapy on insomnia in cancer survivors: A randomized clinical trial. (Abstract 10001)

Jun J. Mao, MD

Discussion

8:24 AM
Gabriel Lopez, MD
(Discussion of Abstracts 10000-10001)
The University of Texas MD Anderson Cancer Center
Integrating Integrative Medicine Into Supportive Care: Are We Ready?

8:36 AM
Panel Question and Answer

8:48 AM
Improving communication with older patients with cancer using geriatric assessment (GA): A University of Rochester NCI Community Oncology Research Program (NCORP) cluster randomized controlled trial (CRCT). (Abstract LBA10003)

Supriya Gupta Mohile, MD, MS

9:00 AM
Symptom burden in hospitalized patients with curable and incurable cancers. (Abstract 10004)

Richard Newcomb, MD

9:12 AM
Randomized trial of a symptom monitoring intervention for hospitalized patients with cancer. (Abstract 10005)

Charn-Xin Fuh

Discussion

9:24 AM
Ethan M. Basch, MD, FASCO
(Discussion of Abstracts LBA10003-10005)
The University of North Carolina at Chapel Hill
Patient-Reported Assessments: Tell Us How You Really Feel

9:36 AM
Panel Question and Answer

9:48 AM
Does timing of palliative care consults impact end-of-life health services utilization in pancreatic cancer patients? (Abstract 10006)

Nizar Bhulani, MD, MPH

10:00 AM
Patient (Pt) and oncologist (MD) discordance in goals of care in end of life (EOL) decision making. (Abstract 10007)

Sara L. Douglas, PhD

10:12 AM
Understanding factors contributing to geographic variations in end-of-life expenditures. (Abstract 10008)

Nancy Lynn Keating, MD, MPH

Discussion

10:24 AM
Shelly S. Lo, MD
(Discussion of Abstracts 10006-10008)
Loyola University Medical Center
The Sooner the Better: Palliative Care and End-of-Life Discussions

10:36 AM
Panel Question and Answer

ORAL ABSTRACT SESSION
Pediatric Oncology II
S504

Jacqueline Casillas, MD—Co-Chair
University of California, Los Angeles

Sogol Mostoufi-Moab, MD, MSCE—Co-Chair
The Children's Hospital of Philadelphia

8:00 AM
Subsequent malignant neoplasms (SMNs) among non-irradiated survivors of childhood cancer treated with chemotherapy in the Childhood Cancer Survivor Study. (Abstract 10509)

Lucie Marie Turcotte, MD

8:12 AM
Risk-adapted therapy for pediatric Hodgkin lymphoma (HL) results in lower risk of late effects: a report from the Childhood Cancer Survivor Study (CCSS). (Abstract 10510)

Kevin C. Oeffinger, MD

8:24 AM
Mortality following breast cancer in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. (Abstract 10511)

Chaya S. Moskowitz, PhD

Discussion

8:36 AM
Patricia A. Ganz, MD, FASCO
(Discussion of Abstracts 10509-10511)
University of California, Los Angeles
Defining the Risks of Secondary Malignancies in Childhood Cancer Survivors

8:48 AM
Panel Question and Answer

9:00 AM
Association of exercise with late mortality in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor study. (Abstract 10512)

Jessica Scott, PhD

9:12 AM
Impact of exercise on psychological burden in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). (Abstract 10513)

Emily S. Tonorezos, MD

9:24 AM
Patient-level predictors of lack of healthcare provider recommendation for human papillomavirus (HPV) vaccination as reported by childhood cancer survivors and their families. (Abstract 10514)

Jocelyn York

Discussion

9:36 AM
Leontien Kremer, MD, PhD
(Discussion of Abstracts 10512-10514)
Emma Children's Hospital and Academic Medical Center
Cancer Prevention Strategies in Childhood Cancer Survivors

9:48 AM
Panel Question and Answer

10:00 AM
Targeted resequencing of pediatric rhabdomyosarcoma: report from the Children's Oncology Group, the Children's Cancer and Leukaemia Group, The Institute of Cancer Research UK, and the National Cancer Institute. (Abstract 10515)

John Frederick Shern, MD

See Sessions, Page 16D

Sessions

Continued from page 15D

10:12 AM
A prospective study of pediatric renal cell carcinoma: A report from the Children's Oncology Group study AREN0321. (Abstract 10516)

James I. Geller, MD

10:24 AM
Hope and benefit-finding among adolescents and young adults with cancer: Results from the PRISM randomized controlled trial. (Abstract 10517)

Abby R. Rosenberg, MD, MS, MA, FAAP

Discussion

10:36 AM
Todd Michael Cooper, DO
(Discussion of Abstracts 10515-10517)
Seattle Children's Cancer and Blood Disorders Center, University of Washington
Innovative Trials in Pediatric Cancer

10:48 AM
Panel Question and Answer

8:00 AM–11:30 AM

POSTER SESSIONS

Hall A

Boards 1-112b
Gastrointestinal (Colorectal) Cancer

Boards 198-333b
Gastrointestinal (Noncolorectal) Cancer

Boards 114-190b
Lung Cancer—Non–Small Cell Local-Regional/Small Cell/Other Thoracic Cancers

Boards 335-433b
Lung Cancer—Non–Small Cell Metastatic

9:45 AM–11:00 AM

EDUCATION SESSION

A New Era in the Management of Melanoma Brain Metastases
S100bc
Melanoma/Skin Cancers; Central Nervous System Tumors; Immunotherapy

Grant A. McArthur, MBBS, PhD, FRACP
Peter MacCallum Cancer Centre and University of Melbourne
Biology of Melanoma Brain Metastases: Incidence, Prognosis, Surveillance, and More

Caroline Robert, MD, PhD
Gustave Roussy Institute
Different Combinations of Systemic Therapy for Melanoma Brain Metastases

Hussein Abdul-Hassan Tawbi, MD, PhD—Chair
The University of Texas MD Anderson Cancer Center
What to Do First in Case of Melanoma Brain Metastases and Simultaneous Extracerebral Disease

Panel Question and Answer

EDUCATION SESSION

ASCO/European CanCer Organization (ECCO) Joint Session: Access and Innovation With Multiplex Genomic Testing
S100a
Global Health

Bruce E. Johnson, MD, FASCO—Co-Chair
Dana-Farber Cancer Institute

Philip Poortmans, MD, PhD—Co-Chair
Institut Curie

Kojo Elenitoba-Johnson, MD
Perelman School of Medicine at the University of Pennsylvania
Utilization of Multiplex Testing in the United States

Matti S. Aapro, MD
Cancer Center, Clinique de Genolier
Utilization of Multiplex Testing in Europe

David R. Spigel, MD
Sarah Cannon Research Institute, Tennessee Oncology
Reimbursement and Payment of Multiplex Testing in the United States

Jan Geissler, MBA
Leukemia Patient Advocates Foundation
European Patient Perspective

Panel Question and Answer

MEET THE PROFESSOR SESSION

Biology and Therapeutic Promise of Exploiting IDH Mutations in Gliomas—Ticketed Session
E253c
Central Nervous System Tumors; Developmental Therapeutics and Translational Research

Daniel P. Cahill, MD, PhD
Massachusetts General Hospital
Update on the Biology of IDH Mutations

Ranjit Bindra, MD
Yale University
Updates in Therapeutic Strategies Toward Exploitation of IDH Mutations

MEET THE PROFESSOR SESSION

How to Bring Geriatric Assessment Into Your Practice—Ticketed Session
E253d
Geriatric Oncology; Care Delivery and Practice Management

Shabbir M.H. Alibhai, MD
University Health Network
How to Bring Geriatric Assessment to Your Practice

9:45 AM–11:15 AM

CLINICAL SCIENCE SYMPOSIUM

Compelling Combinations: Raising the Bar With Immunotherapy
Hall D1

David C. Smith, MD—Chair
University of Michigan

Discussion

9:45 AM
Solange Peters, MD, PhD
Centre Hospitalier Universitaire Vaudois - CHUV
Setting the Stage: Where Are We Now With Immunotherapy?

9:57 AM
Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). (Abstract 104)

Sibylle Loibl, MD, PhD

10:09 AM
Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC). (Abstract 105)

Luis G. Paz-Ares, MD, PhD

10:21 AM
TOPACIO/Keynote-162 (NCT02657889): A phase 1/2 study of niraparib + pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—Results from ROC cohort. (Abstract 106)

Panagiotis A. Konstantinopoulos, MD, PhD

10:33 AM
Epacadostat (E) plus pembrolizumab (P) versus pembrolizumab alone in patients (pts) with unresectable or metastatic melanoma: Results of the phase 3 ECHO-301/KEYNOTE-252 study. (Abstract 108)

Georgina V. Long, MD, PhD, FRACP

Discussion

10:45 AM
Charles G. Drake, MD, PhD
(Discussion of Abstracts 104-106)
Columbia University Herbert Irving Comprehensive Cancer Center
Putting It Together: Have Combinations Come of Age?

10:57 AM
Panel Question and Answer

CLINICAL SCIENCE SYMPOSIUM

Engaging the Immune System in Ovarian Cancer
S406
Gynecologic Cancer

Marcus O. Butler, MD—Co-Chair
Princess Margaret Cancer Centre, University Health Network

Kunle Odunsi, MD—Co-Chair
Roswell Park Comprehensive Cancer Center

9:45 AM
Dendritic cell vaccine (DCVAC) with chemotherapy (ct) in patients (pts) with epithelial ovarian carcinoma (EOC) after primary debulking surgery (PDS): Interim analysis of a phase 2, open-label, randomized, multicenter trial. (Abstract 5509)

Lukas Rob, MD, PhD

9:57 AM
Clinical data from the DeCidE1 trial: Assessing the first combination of DPX-Survivac, low dose cyclophosphamide (CPA), and epacadostat (INCB024360) in subjects with stage IIc-IV recurrent epithelial ovarian cancer. (Abstract 5510)

Oliver Dorigo, MD, PhD

Discussion

10:09 AM
Leisha A. Emens, MD, PhD
(Discussion of Abstracts 5509-5510)
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and Bloomberg-Kimmel Institute for Cancer Immunotherapy
Vaccines: Beyond Prevention

10:21 AM
Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: Interim results from the phase 2 KEYNOTE-100 study. (Abstract 5511)

Ursula A. Matulonis, MD

10:33 AM
Association of high tumor mutation (TMB) with DNA damage repair (DDR) alterations and better prognosis in ovarian cancer. (Abstract 5512)

Wenjuan Tian, MD

Discussion

10:45 AM
Janos Laszlo Tanyi, MD, PhD
(Discussion of Abstracts 5511-5512)
University of Pennsylvania
Immune Therapy in Ovarian Cancer: The Continuing Search for Biomarkers

10:57 AM
Panel Question and Answer

9:45 AM–12:45 PM

ORAL ABSTRACT SESSION

Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia
E450

Christopher Flowers, MD, MS, FASCO—Co-Chair
Emory University, Winship Cancer Institute

Barbara Pro, MD—Co-Chair
Northwestern University Feinberg School of Medicine

9:45 AM
RELEVANCE: Phase III randomized study of lenalidomide plus rituximab (R2) versus chemotherapy plus rituximab, followed by rituximab maintenance, in patients with previously untreated follicular lymphoma. (Abstract 7500)

Nathan Hale Fowler, MD

9:57 AM
Acalabrutinib in patients (pts) with Waldenström macroglobulinemia (WM). (Abstract 7501)

Roger Owen, MD

10:09 AM
Phase 2 CAPTIVATE results of ibrutinib (ibr) plus venetoclax (ven) in first-line chronic lymphocytic leukemia (CLL). (Abstract 7502)

William G. Wierda, MD, PhD

Discussion

10:21 AM
Bruce D. Cheson, MD, FASCO
(Discussion of Abstracts 7500-7502)
Georgetown University Hospital, Lombardi Comprehensive Cancer Center
Toward a Chemotherapy-Free Future in Lymphoid Malignancies

See Sessions, Page 18D

Plenary Session Preview

Continued from page 1D

defined as high risk according to the EpSSG stratification.

"This study aims to improve outcomes for a historically difficult disease to treat," Dr. Partridge said. Douglas S. Hawkins, MD, of Seattle Cancer Care Alliance, will discuss the abstract.

Arnaud Mejean, MD, PhD, of Paris Descartes University, in France, will then present LBA3, "CARMENA: Cytoreductive nephrectomy (CN) followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma (mRCC)—Results of a phase III noninferiority trial." For 2 decades, CN has been standard of care in mRCC—but the efficacy of targeted therapies has challenged this standard as of late. The CARMENA study was designed to determine if upfront CN should continue to be performed before sunitinib therapy. The randomized phase III trial enrolled patients with synchronous mRCC, amenable to CN, with the primary endpoint of overall survival.

"CARMENA is an excellent study that is challenging conventional wisdom and standard of care in the era of improved targeted therapy for patients with mRCC," Dr. Partridge said. "In this case, the big question at hand is whether or not the affected kidney tumor needs to be removed."

Finally, Gilberto de Lima Lopes Jr., MD, MBA, FAMS, of the Sylvester Comprehensive Cancer Center at the University of Miami, will present LBA4, "Pembrolizumab versus platinum-based chemotherapy as first-line therapy for advanced/metastatic non–small cell lung cancer (NSCLC) with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-level, phase III KEYNOTE-042 study." The study looked at progression-free survival as a primary endpoint and overall survival as a secondary endpoint.

"Potentially expanding the substantial role that checkpoint inhibitors play in helping patients with advanced lung cancer is an important therapeutic goal," Dr. Partridge said. "This abstract represents a groundbreaking study testing first-line chemotherapy versus pembrolizumab in patients with 1% or greater PD-L1 positivity." ●

–Caroline Hopkins

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Sessions

Continued from page 16D

10:33 AM
Panel Question and Answer

10:45 AM
Randomized phase III study comparing an early PET driven treatment de-escalation to a not PET-monitored strategy in patients with advanced stages Hodgkin lymphoma: Final analysis of the AHL2011 LYSA study. (Abstract 7503)

Olivier Casasnovas, MD

10:57 AM
Activity and tolerability of the first-in-class anti-CD47 antibody Hu5F9-G4 with rituximab tolerated in relapsed/refractory non-Hodgkin lymphoma: Initial phase 1b/2 results. (Abstract 7504)

Ranjana H. Advani, MD

11:09 AM
Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. (Abstract 7505)

Jeremy S. Abramson, MD

Discussion

11:21 AM
Caron Alyce Jacobson, MD
(Discussion of Abstracts 7503-7505)
Dana-Farber Cancer Institute
CAR T and Other Vehicles for Immunotherapy

11:33 AM
Panel Question and Answer

11:45 AM
Randomized phase 2 trial of polatuzumab vedotin (pola) with bendamustine and rituximab (BR) in relapsed/refractory (r/r) FL and DLBCL. (Abstract 7507)

Laurie Helen Sehn, MD, MPH

11:57 AM
High, durable minimal residual disease negativity (MRD–) with venetoclax + rituximab (VenR) in relapsed/refractory (R/R) CLL: MRD kinetics from phase 3 MURANO study. (Abstract 7508)

Peter Hillmen, MBChB

Discussion

12:09 PM
Alison J. Moskowitz, MD
(Discussion of Abstracts 7507-7508)
Memorial Sloan Kettering Cancer Center
Tailoring Therapy in Lymphoid Malignancies

12:21 PM
Panel Question and Answer

11:30 AM–12:45 PM

POSTER DISCUSSION SESSION

Gastrointestinal (Colorectal) Cancer
Hall D2

Mark Kozloff, MD—Co-Chair
Ingalls Memorial Hospital

Chi Lin, MD, PhD—Co-Chair
University of Nebraska Medical Center

Discussion

11:30 AM
Alberto F. Sobrero, MD
(Discussion of Abstracts 3508-3511)
IRCCS A.O.U. San Martino IST
My Take: Timing of EGFR-Directed Therapy

11:42 AM
Panel Question and Answer

Discussion

11:48 AM
Ryan Bruce Corcoran, MD, PhD
(Discussion of Abstract 3513)
Massachusetts General Hospital
Molecular Subsets: Prognosis and Prediction

12:00 PM
Panel Question and Answer

Discussion

12:06 PM
Neil Howard Segal, MD, PhD
(Discussion of Abstracts 3514-3515)
Memorial Sloan Kettering Cancer Center
Immune Therapy: Why Don't We Have the KEY for VICTORy?

12:18 PM
Panel Question and Answer

Discussion

12:24 PM
Dustin A. Deming, MD
(Discussion of Abstracts 3516-3518)
University of Wisconsin Carbone Cancer Center
Biomarkers and New Approaches in Anorectal Cancer

Posters discussed in this session are on display in the Gastrointestinal (Colorectal) Cancer Poster Session. See the iPlanner for poster titles and presenters.

POSTER DISCUSSION SESSION

Lung Cancer—Non–Small Cell Metastatic
Arie Crown Theater

Joshua Bauml, MD—Co-Chair
University of Pennsylvania

Heather A. Wakelee, MD—Co-Chair
Stanford Cancer Institute

Discussion

11:30 AM
Stephen V. Liu, MD
(Discussion of Abstracts 9012-9014)
Georgetown University Medical Center
Novel Approaches for EGFR-Mutant Non–Small Cell Lung Cancer

11:42 AM
Panel Question and Answer

Discussion

11:48 AM
D. Ross Camidge, MD, PhD
(Discussion of Abstracts 9015-9019)
University of Colorado, Denver
Old Targets Revisited, New Drug Discovery

12:00 PM
Panel Question and Answer

Discussion

12:09 PM
Jhanelle Elaine Gray, MD
(Discussion of Abstracts 9020-9021)
Moffitt Cancer Center
What Immunotherapy Means to Patients

12:21 PM
Panel Question and Answer

Discussion

12:27 PM
Sarah B. Goldberg, MD
(Discussion of Abstracts 9022-9023)
Yale Cancer Center
Optimizing the Use of Immunotherapy

Posters discussed in this session are on display in the Lung Cancer—Non–Small Cell Metastatic Poster Session. See the iPlanner for poster titles and presenters.

EDUCATION SESSION

Controversies in Adjuvant/Neoadjuvant Chemotherapy in Localized Soft Tissue Sarcoma
E451
Sarcoma; Care Delivery and Practice Management; Gynecologic Cancer; Pediatric Oncology

Jonathan C. Trent, MD, PhD
Sylvester Comprehensive Cancer Center
Neoadjuvant/Adjuvant Chemotherapy Should Be Considered Standard in High-Risk Extremity Soft Tissue Sarcoma

Axel Le Cesne, MD
Gustave Roussy Cancer Campus
Neoadjuvant/Adjuvant Chemotherapy Should Be Considered Experimental in High-Risk Extremity Soft Tissue Sarcoma

Elizabeth H. Baldini, MD, MPH—Chair
Dana-Farber Cancer Institute and Brigham and Women's Hospital
Is There a Role for Neoadjuvant Chemoradiation in High-Risk Extremity Soft Tissue Sarcoma?

Panel Question and Answer

EDUCATION SESSION

Filling the Gap: Creating an Outpatient Palliative Care Program in Your Institution
S504
Care Delivery and Practice Management; Global Health; Health Services Research, Clinical Informatics, and Quality of Care; Patient and Survivor Care; Value

Esme Finlay, MD
University of New Mexico Cancer Research and Treatment Center
How to Obtain Buy-in From Stakeholders to Support Outpatient Palliative Care

Michael Rabow, MD
University of California, San Francisco
Understanding the Finances of Outpatient Palliative Care Programs

Mary K. Buss, MD, MPH—Chair
Beth Israel Deaconess Medical Center
Peering Behind the Curtain: Examples of Successful Palliative Care Practices and Why They Work

Panel Question and Answer

EDUCATION SESSION

How Can Genetics Personalize Cancer Survivorship?
S102
Patient and Survivor Care; Cancer Prevention, Hereditary Genetics, and Epidemiology

Lindsay M. Morton, PhD—Chair
National Cancer Institute at the National Institutes of Health
Germline Genomics and the Risk of Developing Treatment-Related Subsequent Neoplasms

Sarah L. Kerns, PhD, MPH
University of Rochester Medical Center
Using Genetic Information for Risk Prediction of Radiotherapy Toxicity

M. Eileen Dolan, PhD
The University of Chicago
Role of Genomics in Precision Management of Chemotherapy-Induced Ototoxicity and Neuropathy

Panel Question and Answer

EDUCATION SESSION

Lynch Syndrome 360
S404
Cancer Prevention, Hereditary Genetics, and Epidemiology; Gastrointestinal (Colorectal) Cancer; Gynecologic Cancer; Immunotherapy

Heather Hampel, MS
The Ohio State University Comprehensive Cancer Center
Identification of Lynch Syndrome: From Universal Testing to Tumor Sequencing in Colorectal and Endometrial Cancer

Luis A. Diaz, MD
Memorial Sloan Kettering Cancer Center
The Treatment of Lynch Syndrome-Associated Advanced Malignancy

Matthew B. Yurgelun, MD—Chair
Dana-Farber Cancer Institute
Lynch Syndrome: Update on Comprehensive Screening and Risk Reduction

Panel Question and Answer

EDUCATION SESSION

Management of Biochemically Recurrent Prostate Cancer: Which Imaging, Which Treatment, and When?
S406
Genitourinary (Prostate) Cancer

Michael J. Morris, MD
Memorial Sloan Kettering Cancer Center
Lifting the Veil on Micrometastatic Disease: Emerging Imaging Strategies in Biochemical Recurrence

Daniel Eidelberg Spratt, MD
University of Michigan
Precision Risk Stratification and Treatment in Biochemical-Recurrent Prostate Cancer

Alicia K. Morgans, MD, MPH—Chair
Vanderbilt University Medical Center
Biochemical Recurrence: Judicious Clinical Management of an Evolving Disease State

Panel Question and Answer

EDUCATION SESSION

Moving From Mutation to Actionability
S100bc
Gynecologic Cancer; Care Delivery and Practice Management; Developmental Therapeutics and Translational Research

Amit M. Oza, MD—Chair
Princess Margaret Cancer Centre, University Health Network
The Role of Targeted Therapy in Gynecologic Cancers

Shannon Neville Westin, MD
The University of Texas MD Anderson Cancer Center
Tumor Sequencing: Who, What, When, and Why to Order Tumor Mutation Analysis

Elise C. Kohn, MD
National Cancer Institute at the National Institutes of Health
Rational Approach to Utilizing Genetic Information

Panel Question and Answer

MEET THE PROFESSOR SESSION

Primary and Acquired Resistance to Checkpoint Inhibitors—Ticketed Session
E253d
Developmental Therapeutics and Translational Research; Immunotherapy; Lung Cancer; Melanoma/Skin Cancers

Charles G. Drake, MD, PhD
Columbia University Herbert Irving Comprehensive Cancer Center
Approach to Primary and Acquired Resistance to Checkpoint Inhibitors: Genitourinary Cancers

Scott N. Gettinger, MD
Yale Cancer Center, Yale New Haven Hospital
Approach to Primary and Acquired Resistance to Checkpoint Inhibitors: Lung Cancer

MEET THE PROFESSOR SESSION

Treatment Strategies for Locoregionally Advanced Nasopharyngeal Cancer: Making Sense of Recent Studies—Ticketed Session
E253c
Head and Neck Cancer; Global Health

Anthony T. C. Chan, MD
State Key Laboratory of Oncology in South China, The Chinese University of Hong Kong
Locoregionally Advanced Nasopharyngeal Cancer: Making Sense of Recent Studies

Sue Sun Yom, MD, PhD
University of California, San Francisco
Locoregionally Advanced Nasopharyngeal Cancer: Making Sense of Recent Studies

11:30 AM–1:00 PM

CLINICAL SCIENCE SYMPOSIUM

Innovative Approaches to Oncology Education
S103
Professional Development

James A. Stewart, MD, FACP, FASCO—Chair
Baystate Medical Center

Discussion

11:30 AM
James A. Stewart, MD, FACP, FASCO
Baystate Medical Center
Introduction

11:35 AM
Addressing the burden of cancer in East Africa through cascaded training and education by local doctors. (Abstract 11000)

Jennifer Eastin

See Sessions, Page 20D

RET alterations can act as primary oncogenic drivers in many cancer types[1]

LOXO ONCOLOGY IS INVESTIGATING A NEW APPROACH TO TREATING *RET*-ALTERED CANCERS

RET=rearranged during transfection.

> VISIT OUR BOOTH AT THE *2018 ASCO ANNUAL MEETING*

RET alterations can result in constitutively active RET signaling that promotes cancer growth[1-3]

LOXO-292, an investigational selective RET inhibitor, is currently in clinical development.

NCT03157128: Phase 1 Study of LOXO-292 in Patients With Advanced Solid Tumors, *RET*-Fusion Lung Cancer, and Medullary Thyroid Cancer*

A phase 1, open-label, first-in-human study designed to evaluate LOXO-292 in patients with advanced solid tumors, including *RET*-fusion non–small cell lung cancer (NSCLC), medullary thyroid cancer (MTC), and other tumors with increased RET activity.

Primary Outcome Measures: Maximum tolerated dose (MTD)/recommended dose for further study

Secondary Outcome Measures:

- Safety
- Pharmacokinetics
- Overall response rate
- Duration of response
- Clinical benefit rate
- Median duration of progression-free survival
- Median overall survival

*Information consistent with ClinicalTrials.gov as of March 7, 2018.

STUDY DESIGN

Advanced solid tumor

↓

Target exposure

↓

Advanced solid tumor with *RET* alteration/increased RET activity

Prior therapy with multikinase inhibitors (MKIs) that inhibit RET allowed

Dose escalation

MTD/recommended dose expansion

Dose expansion

1	2	3	4	5
Advanced *RET*-fusion† NSCLC	**Advanced *RET*-fusion† NSCLC**	**Advanced *RET*-mutant† MTC**	**Advanced *RET*-mutant† MTC**	***RET*-altered solid tumor, including:**
≥ 1 prior MKI that inhibits RET	No prior MKI that inhibits RET	≥ 1 prior MKI that inhibits RET	No prior MKI that inhibits RET	• Disease not measurable • Other *RET* alterations • cfDNA for *RET* alteration • *RET* mutation-negative MTC • Any prior MKI that inhibits RET

†Bona fide *RET* fusion, ATA moderate- and high-risk *RET* mutation.

To enroll, patients must meet eligibility requirements, including:

- Locally advanced or metastatic solid tumor which progressed following standard therapy, or for whom no standard therapy exists
- Age ≥ 12
- Any number of prior MKIs
- ECOG score ≤ 2
- Life expectancy of at least 3 months

For full eligibility requirements, visit ClinicalTrials.gov.

For more information about the RET program or to participate as a trial site, visit **LoxoRETtrials.com** or call **1-855-RET-4-292.**

References: 1. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. *Nat Rev Clin Onc.* 2018;15(3):151-167. **2.** Hofstra RM, Landsvater RM, Ceccherini I, et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. *Nature.* 1994;367(6461):375-376. **3.** Grieco M, Santoro, M, Berlingieri, MT, et al. PTC is a novel rearranged form of the ret proto-oncogene and is frequently detected in vivo in human thyroid papillary carcinomas. *Cell.* 1990;23(60):557-563.

LOXO ONCOLOGY

Sessions

Continued from page 18D

11:47 AM
Bridging the gap in global advanced radiation oncology training: Impact of a web-based open-access interactive three-dimensional contouring atlas on radiation oncology practice in Russia. (Abstract 11001)

Natalia Dengina, MD

11:59 AM
The teaching of multi-disciplinary cancer care: A flipped classroom approach. (Abstract 11002)

Helen Sarah Winter, MBBS

12:11 PM
Professional development improves geriatric focused oncology activities in settings across the nation. (Abstract 11003)

Denice Economou, MSN

Discussion

12:23 PM
Leora Horn, MD
(Discussion of Abstracts 11000-11003)
Vanderbilt University Medical Center
Innovative Approaches, Evaluation, and Outcomes From a Domestic Perspective

Discussion

12:35 PM

Frank Douglas Ferris, MD
OhioHealth
Innovative Approaches, Evaluation, and Outcomes From an International Perspective

12:47 PM
Panel Question and Answer

EDUCATION SESSION

Collecting and Using Real-World Evidence: Supplementing and Perhaps Replacing Clinical Trials (Includes Presentation of Public Service Award)
S100a
Health Services Research, Clinical Informatics, and Quality of Care; Care Delivery and Practice Management; Clinical Trials; Patient and Survivor Care

Monica M. Bertagnolli, MD, FACS, FASCO
Dana-Farber-Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School
Presentation of the 2018 Public Service Award

Gideon Michael Blumenthal, MD
U.S. Food and Drug Administration
Public Service Award Recipient

Lynne Penberthy, MD—Chair
National Cancer Institute at the National Institutes of Health
NCI-SEER Now and Into the Future as a Partner in Real-World Evidence Generation

Katherine Elizabeth Reeder-Hayes, MD, MBA, MS
The University of North Carolina at Chapel Hill
Yin and Yang: Leveraging Clinical Trials and Real-World Data to Inform Evidence-Based Cancer Care

Sean Khozin, MD, MPH
U.S. Food and Drug Administration
FDA's Informed: Real-World Evidence Comes of Age

Jinani Jayasekera, PhD
Lombardi Cancer Center MedStar Georgetown University Hospital
Simulation Modeling of Cancer Clinical Trials: Drawing New Conclusions From Old Trials

Panel Question and Answer

Mid-Day Sessions

1:00 PM–4:00 PM

PLENARY SESSION

Plenary Session Including the Science of Oncology Award and Lecture
Hall B1
Simulcast Location: Hall D1

Bruce E. Johnson, MD, FASCO—Co-Chair
Dana-Farber Cancer Institute

Ann H. Partridge, MD, MPH, FASCO—Co-Chair
Dana-Farber Cancer Institute

1:00 PM
Bruce E. Johnson, MD, FASCO, and Ann H. Partridge, MD, MPH, FASCO
Dana-Farber Cancer Institute
Welcome and Introductions

1:05 PM
Daniel F. Hayes, MD, FACP, FASCO
University of Michigan Comprehensive Cancer Center
Presentation of the 2018 Science of Oncology Award

1:10 PM
Douglas R. Lowy, MD
National Institutes of Health
Preventing HPV-Associated Cancers by Vaccination

1:40 PM
Bruce E. Johnson, MD, FASCO, and Ann H. Partridge, MD, MPH, FASCO
Dana-Farber Cancer Institute
Introduction to Plenary Session

1:45 PM
TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score. (Abstract LBA1)

Joseph A. Sparano, MD

Discussion

2:00 PM
Lisa A. Carey, MD
The University of North Carolina

2:15 PM
Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). (Abstract LBA2)

Gianni Bisogno, MD

Discussion

2:30 PM
Douglas S. Hawkins, MD
Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center

2:45 PM
CARMENA: Cytoreductive nephrectomy followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma—Results of a phase III noninferiority trial. (Abstract LBA3)

Arnaud Mejean, MD, PhD

Discussion

3:00 PM
Daniel J. George, MD
Duke University

3:15 PM
Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. (Abstract LBA4)

Gilberto Lopes, MD, MBA

Discussion

3:30 PM
Leena Gandhi, MD, PhD
NYU Perlmutter Cancer Center

Late-Afternoon Sessions

4:00 PM–4:30 PM

POST-PLENARY SESSION

Post-Plenary Discussion Session I: Breast Cancer
S100a

Elizabeth A. Mittendorf, MD, PhD—Chair
Dana-Farber/Brigham and Women's Cancer Center

Joseph A. Sparano, MD
Montefiore Medical Center
Panelist

Lisa A. Carey, MD
The University of North Carolina at Chapel Hill
Panelist

Eric P. Winer, MD, FASCO
Dana-Farber Cancer Institute
Panelist

4:30 PM–5:00 PM

POST-PLENARY SESSION

Post-Plenary Discussion Session II: Rhabdomyosarcoma
S100bc

Richard Aplenc, MD—Chair
Children's Hospital of Philadelphia

Douglas S. Hawkins, MD
Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center
Panelist

Gianni Bisogno, MD
University Hospital of Padova
Panelist

Robin Lewis Jones, MD, MBBS, MRCP
Royal Marsden Hospital, The Institute of Cancer Research
Panelist

4:45 PM–6:00 PM

POSTER DISCUSSION SESSION

Gastrointestinal (Noncolorectal) Cancer
Hall D2

Vaibhav Sahai, MBBS, MS—Co-Chair
University of Michigan Comprehensive Cancer Center

Sunil Sharma, MD, FACP, MBA—Co-Chair
Translational Genomics Research Institute

Discussion

4:45 PM
Joseph Chao, MD
(Discussion of Abstracts 4009-4011)
City of Hope
Gastroesophageal Cancers: What Can We Learn From Randomized Trials?

4:57 PM
Panel Question and Answer

Discussion

5:03 PM
Daniel Tandel Chang, MD
(Discussion of Abstracts 4012-4013)
Stanford University School of Medicine
Esophageal Cancer: Is More Really More?

5:15 PM
Panel Question and Answer

Discussion

5:21 PM
Rachna T. Shroff, MD
(Discussion of Abstracts 4014-4016)
University of Arizona
Moving Beyond Gemcitabine Therapy in Pancreatic and Biliary Cancers?

5:33 PM
Panel Question and Answer

5:39 PM
Jordan Berlin, MD, FASCO
(Discussion of Abstract(s) 4017-4020)
Vanderbilt University Ingram Cancer Center
Expanding the Treatment Landscape in Hepatocellular Carcinoma

5:51 PM
Panel Question and Answer

Posters discussed in this session are on display in the Gastrointestinal (Noncolorectal) Cancer Poster Session. See the iPlanner for poster titles and presenters.

POSTER DISCUSSION SESSION

Lung Cancer—Non–Small Cell Local-Regional/Small Cell/Other Thoracic Cancers
Arie Crown Theater

David R. Gandara, MD, FASCO—Co-Chair
University of California, Davis

Kristin Ann Higgins, MD—Co-Chair
Winship Cancer Institute of Emory University

Discussion

4:45 PM
Mark G. Kris, MD, FASCO
(Discussion of Abstracts 8508-8510)
Memorial Sloan Kettering Cancer Center
What, When, and How? Juggling Sequence and Agent Choices

4:57 PM
Panel Question and Answer

Discussion

5:03 PM
Alexander V. Louie, MD, PhD, MSc, FRCPC
(Discussion of Abstracts 8511-8513)
London Regional Cancer Program
Rethinking Radiation: Is The Stereo(tactic) Too Loud?

5:15 PM
Panel Question and Answer

Discussion

5:21 PM
Charu Aggarwal, MD, MPH
(Discussion of Abstracts 8514-8516)
Abramson Cancer Center
New Targets: Time To Get Excited?

5:33 PM
Panel Question and Answer

Discussion

5:39 PM
Corey J. Langer, MD
(Discussion of Abstracts 8517-8519)
University of Pennsylvania Perelman School of Medicine
PD-L1, CTLA-4, Cyclin D, Oh My!

Posters discussed in this session are on display in the Lung Cancer—Non–Small Cell Local-Regional/Small Cell/Other Thoracic Cancers Poster Session. See the iPlanner for poster titles and presenters.

EDUCATION SESSION

Common Themes in Uncommon Lymphomas: How Biology and Novel Treatments Are Changing the Landscape
E450
Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia; Central Nervous System Tumors

Francine M. Foss, MD—Chair
Yale Cancer Center
Emerging Role of Novel Therapies in Cutaneous T-Cell Lymphoma

See Sessions, Page 22D

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Sessions

Continued from page 20D

Christian Grommes, MD
Memorial Sloan Kettering Cancer Center
Treatment of Primary Central Nervous System Lymphoma: From Chemotherapy to Small Molecules

Thierry Lamy, MD, PhD
Centre Hospitalier Universitaire Pontchaillou
Latest Advances in the Diagnosis and Treatment of Large Granular Lymphocytic Leukemia

Panel Question and Answer

EDUCATION SESSION
Communicating the Financial Burden of Treatment With Patients
S404
Health Services Research, Clinical Informatics, and Quality of Care; Care Delivery and Practice Management; Disparities; Ethics; Patient and Survivor Care; Value

Ryan David Nipp, MD—Chair
Massachusetts General Hospital
The Clinician's Perspective on Discussing Costs With Patients

Gery Guy, PhD, MPH
Centers for Disease Control and Prevention
Cost in the Era of Targeted Therapies and Immunotherapies for Cancer

Ellen Sonet, MBA, JD
CancerCare
Assisting Patients With the Cost Burden of Cancer Diagnosis and Treatment: Next-Generation Sequencing Testing, Off-Label Medications, and More

Panel Question and Answer

EDUCATION SESSION
Global Myeloma, Health Disparities, and the Cost of Drugs
E451
Hematologic Malignancies—Plasma Cell Dyscrasia; Disparities; Global Health; Value

Timothy Rebbeck, PhD
Harvard T. H. Chan School of Public Health and Dana Farber Cancer Institute
Myeloma Outcomes and Disparities in African Americans

Philippe Moreau, MD—Chair
CHU de Nantes-Hôtel Dieu
Global Approaches in Myeloma: Critical Trials That May Change Practice

S. Vincent Rajkumar, MD
Mayo Clinic
Debate: Value and Cost of Myeloma Therapy—We Cannot Afford It

Rafael Fonseca, MD
Mayo Clinic
Debate: Value and Cost of Myeloma Therapy—We Can Afford It

Panel Question and Answer

EDUCATION SESSION
Innovative Strategies Targeting Subtypes in Metastatic Breast Cancer
Hall B1
Breast Cancer

Matthew P. Goetz, MD
Mayo Clinic
ER+ Metastatic Breast Cancer: Beyond CDK Inhibitors

Stacy L. Moulder, MD, MS—Chair
The University of Texas MD Anderson Cancer Center
Novel Druggable Pathways in Triple-Negative Breast Cancer

Mark D. Pegram, MD
Stanford School of Medicine
Overcoming Resistance in HER2+ Metastatic Breast Cancer

Panel Question and Answer

EDUCATION SESSION
Lifestyle Modifications for Primary and Secondary Cancer Prevention: Diet, Exercise, Sun Safety, and Alcohol Reduction
S102
Cancer Prevention, Hereditary Genetics, and Epidemiology; Breast Cancer; Gastrointestinal (Colorectal) Cancer; Head and Neck Cancer; Patient and Survivor Care

Noelle K. LoConte, MD—Chair
University of Wisconsin Carbone Cancer Center
Alcohol and Cancer: A Review of the ASCO Position Paper

Jeffrey E. Gershenwald, MD
The University of Texas MD Anderson Cancer Center
Malignant Melanoma Prevention: Lifestyle Changes and Legislation

Jennifer A. Ligibel, MD
Dana-Farber Cancer Institute
Diet and Exercise: Role in Primary Cancer Prevention and Cancer Recurrence

Panel Question and Answer

EDUCATION SESSION
Novel Approaches in Bone and Soft Tissue Sarcomas: The Emerging Role of Precision Medicine
S103
Sarcoma; Developmental Therapeutics and Translational Research; Immunotherapy; Pediatric Oncology

Seth Pollack, MD
Fred Hutchinson Cancer Research Center
Is There a Role for Immunotherapy in Sarcomas?

Emanuela Palmerini, MD
Istituto Ortopedico Rizzoli
Precision Medicine in Bone Tumors

Daniela Katz, MD—Chair
Assaf Harofeh Medical Center
Over 50 Subtypes of Soft Tissue Sarcoma: Can We Ever Have a Specific Treatment for Each?

Panel Question and Answer

EDUCATION SESSION
Pediatric Clinical Trials: Economics, Cost, and Value of Investment
S504
Pediatric Oncology; Clinical Trials; Patient and Survivor Care; Value

Sharon M. Castellino, MD, MSc
Children's Healthcare of Atlanta
Proof-of-Paradigm of Cost-Effectiveness Analysis Within a Therapeutic Clinical Trial

Susan K. Parsons, MD—Chair
Tufts Medical Center
Financial Consideration of Novel Therapeutics Within the Setting of Pediatric Oncology

K. Robin Yabroff, PhD
American Cancer Society
Financial Hardship Associated With Cancer Survivorship

Panel Question and Answer

EDUCATION SESSION
Precision Medicine for a Single Patient: What Does It Really Mean and How Do We Do It?
S406
Tumor Biology; Care Delivery and Practice Management; Developmental Therapeutics and Translational Research; Health Services Research, Clinical Informatics, and Quality of Care

Victoria Meucci Villaflor, MD—Chair
Northwestern University
Complexity of Delivering Precision Medicine: Challenges and Opportunities

Matthew Meyerson, MD, PhD
Dana-Farber Cancer Institute
Role of Big Data and Informatics in Precision Medicine

Amy E. McKee, MD
U.S. Food and Drug Administration
Regulatory Science: The Challenges with "SMALL DATA": Small Trials, Off-Label Use, and Single Patient INDs—Are We Doing Enough?

Panel Question and Answer

EDUCATION SESSION
The Winds of Change: Optimizing Immunotherapy, Radiopharmaceuticals, and PARP Inhibition in Prostate Cancer
Hall D1
Genitourinary (Prostate) Cancer; Immunotherapy

Martin Pomper, MD
Johns Hopkins University School of Medicine
Radiopharmaceuticals: Emitting the Right Signals in Prostate Cancer

Carmel Jo Pezaro, MBChB
Monash University
Optimal Integration of PARP Inhibitors for Prostate Cancer: Which Test, Which Patient, and Which Therapy?

Ravi Amrit Madan, MD—Chair
National Cancer Institute at the National Institutes of Health
Immunotherapy in Prostate Cancer: The Path Forward

Panel Question and Answer

MEET THE PROFESSOR SESSION
Addressing Fertility in Young Adult Cancer Survivors— Ticketed Session
E253d
Patient and Survivor Care; Pediatric Oncology

Karine Chung, MD
USC Fertility
Fertility and Pregnancy Outcomes: Current Trends in Preservation and Reproductive Health and Communicating Fertility-Related Information

MEET THE PROFESSOR SESSION
The Peer-Review Process and Writing an Outstanding Manuscript— Ticketed Session
E253c
Professional Development

Stephen A. Cannistra, MD, FASCO
Beth Israel Deaconess Medical Center

5:00 PM–5:30 PM

POST-PLENARY SESSION
Post-Plenary Discussion Session III: Kidney Cancer
S100a

Toni K. Choueiri, MD—Chair
Dana-Farber Cancer Institute

Daniel J. George, MD
Duke University
Panelist

Arnaud Mejean, MD, PhD
Hôpital Européen Georges-Pompidou-Paris Descartes University
Panelist

David Chen, MD
Fox Chase Cancer Center
Panelist

5:30 PM–6:00 PM

POST-PLENARY SESSION
Post-Plenary Discussion Session IV: Lung Cancer
S100bc

Melissa Lynne Johnson, MD—Chair
Sarah Cannon Research Institute

Gilberto Lopes, MD, MBA
Sylvester Comprehensive Cancer Center, University of Miami Health System
Panelist

Leena Gandhi, MD, PhD
NYU Perlmutter Cancer Center
Panelist

Scott Joseph Antonia, MD, PhD
Moffitt Cancer Center
Panelist

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Renal cell carcinoma, urothelial carcinoma, gastric adenocarcinoma, and colorectal adenocarcinoma—relapsed/refractory

PCYC-1128-CA (NCT02599324)

A phase 1b/2 study of ibrutinib combination therapy in selected advanced gastrointestinal and genitourinary tumors.

Key eligibility criteria

- Pathologically confirmed RCC (clear cell), urothelial carcinoma (transitional cell), gastric or gastroesophageal junctional (GEJ) adenocarcinoma, or K-RAS wild-type EGFR expressing CRC
- Renal cell carcinoma: 1-4 previous lines of therapy; ECOG 0-1 (2 may be acceptable)
- Urothelial carcinoma: 1-2 previous lines of therapy; ECOG 0-1
- Gastric or GEJ adenocarcinoma: 1-3 previous lines of therapy; ECOG 0-1
- Colorectal adenocarcinoma: 2-4 previous lines of therapy; ECOG 0-1 (2 may be acceptable)

Study Locations

View location details at clinicaltrials.gov (search: NCT02599324)

Huntsville, AL
La Jolla, CA
Los Angeles, CA
San Francisco, CA
Santa Monica, CA
Norwalk, CT
Washington, DC
Jacksonville, FL
Lafayette, IN
Fairway, KS
Metairie, LA
Boston, MA
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Omaha, NE
Winston-Salem, NC
Portland, OR
Hershey, PA
Philadelphia, PA
Nashville, TN
Galveston, TX
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