

## **RESPONSE-ADAPTED THERAPY BASED ON INTERIM FDG-PET SCANS IN ADVANCED HODGKIN LYMPHOMA: 1st ANALYSIS OF THE SAFETY OF DE-ESCALATION & EFFICACY OF ESCALATION IN THE INTERNATIONAL RATHL STUDY CRUK/07/033**

Abstract presented at the plenary session of 13-ICML.

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### **Introduction:**

This prospective randomized study was designed to test whether interim FDG PET-CT scanning could assess early chemotherapy response and guide subsequent treatment for patients with advanced classical Hodgkin lymphoma(HL).

### **Methods:**

Adult patients (pts) with newly diagnosed HL (Ann Arbor stages IIB–IV, or IIA with bulk or  $\geq 3$  involved sites) underwent paired baseline and interim PET-CT scans after 2 cycles of ABVD (PET2). Quality control for PET-CT was supervised by national core labs using standard methodologies. Images were centrally reviewed using the 5-point scale as negative (1–3) or positive (4–5). Pts with negative scans were randomized to ABVD or AVD for 4 more cycles. Pts with positive scans proceeded to intensification with either 4 BEACOPP-14 or 3 escalated BEACOPP before a third scan (PET3). Pts with negative PET3 completed a further 2 BEACOPP-14 or 1 eBEACOPP; pts with positive PET3 received off-study salvage regimens. Radiotherapy (RT) was not advised for pts with interim negative scans, irrespective of baseline bulk or residual masses.

### **Results:**

1214 pts were registered; 77 were withdrawn before PET2, mostly for breaching PET quality control standards. Median age was 33 years, with 500 (41%) stage II, 372 (31%) stage III and 342 (28%) stage IV. 445 (37%) pts had international prognostic score (IPS)  $\geq 3$ . PET2 results from 1137 pts were negative in 954 (84%). 952 pts were randomized to continue ABVD or AVD, of whom 17 were ineligible and excluded from analyses. 33 (4%) pts received consolidation RT. With median follow-up of 32 months, PFS at 3 years was the same for ABVD: 85.45% (95% CI: 83.42–89.70) and for AVD: 84.48% (82.47–88.97). There was similarly no difference in 3-year OS: for ABVD, 97.0% (94.5–98.4), and for

AVD, 97.5% (95.1–98.7). Prognostic factors for treatment failure after negative PET2 were initial stage ( $p = 0.01$ ) and IPS ( $p = 0.05$ ), but not bulk, B symptoms or PET2 score (1 vs 2 vs 3). ABVD showed more pulmonary toxicity than AVD, with significant differences between the arms in changes of transfer factor at end of therapy ( $p$

### Conclusions:

This study suggests that interim PET-CT can be used to guide subsequent treatment, despite more treatment failures among PET-negative pts than previously reported in retrospective series. Omission of bleomycin following negative interim PET reduces pulmonary toxicity without loss of efficacy. These encouraging overall results support response-adapted therapy, with selective use of intensive chemotherapy and consolidation RT.

## ADDITION OF THIOTEPA AND RITUXIMAB TO ANTIMETABOLITES SIGNIFICANTLY IMPROVES OUTCOME IN PRIMARY CNS LYMPHOMA: FIRST RANDOMIZATION OF THE IELSG32 TRIAL

Abstract presented at the plenary session of 13-ICML.

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### Introduction:

IELSG #32 is an international randomized phase II trial addressing the tolerability and efficacy of adding rituximab (R) ± thiotepa (TT) to methotrexate (MTX)-cytarabine (ARAC) combination, followed by a 2nd randomization comparing consolidation with whole-brain irradiation (WBRT) or autologous stem cell transplantation (ASCT) in patients (pts) with primary CNS lymphoma (PCNSL) (NCT01011920). Herein, we report results of the first randomization.

### Methods:

HIV-neg pts 18–70 year old and ECOG PS  $\leq 3$  (PS  $\leq 2$  if age 66–70 years) with new histology-proven PCNSL and measurable disease were randomly assigned to receive four courses of MTX 3.5 g/m<sup>2</sup> d1 + ARAC 2 g/m<sup>2</sup> °— 2/d d2–3 (arm A), or MTX-ARAC + R 375 mg/m<sup>2</sup> d-5 and 0 (arm B), or MTX-ARAC-

R + TT 30 mg/m<sup>2</sup> d4 (arm C). ASC were collected after the second course. Response was assessed after the 2nd and 4th courses; pts with responsive disease were further randomized between WBRT and BCNU-TT conditioned/ASCT. Histology and neuroimaging were centrally reviewed. Primary endpoints were CRR (1st random) and 2-year FFS (2nd random). Sample size was estimated on the basis of 2nd random: with P0 65% and P1 85% (one-sided test;  $\alpha$  5%;  $\beta$  95%), 52 patients/arm required.

### Results:

227 pts (median age 58 years; 18–70) were enrolled in 52 centres of 5 countries; 8 pts were excluded due to misdiagnosis, systemic disease or concomitant cancer. No differences in clinical presentation among 3 arms (A 75; B 69; C 75) were observed (Table). 733/876 (84%) planned courses were delivered. G4 haematological toxicity was more common in arm C, but infective complications were similar in the 3 arms. G4 non-haematological toxicities were rare. Chemotherapy was 227 pts (median age 58 years; 18–70) were enrolled in 52 centres of 5 countries; 8 pts were excluded due to misdiagnosis, systemic disease or concomitant cancer. No differences in clinical presentation among 3 arms (A 75; B 69; C 75) were observed (Table). 733/876 (84%) planned courses were delivered. G4 haematological toxicity was more common in arm C, but infective complications were similar in the 3 arms. G4 non-haematological toxicities were rare. Chemotherapy was interrupted due to toxicity in 21 (9%) pts; 13 (6%) pts died of toxicity. ASC were collected in 152/161 (94%) pts.

Arm C was significantly more active, with a CRR of 49% and an ORR of 87%; 118 pts (A 35; B 35; C 48) were referred to 2nd random (59 pts/arm). At a median follow-up of 20 months (7–60), 111 pts remain failure-free (A 25; B 37; C 49), with 2-year FFS of  $34 \pm 6\%$ ,  $52 \pm 6\%$  and  $64 \pm 6\%$  ( $p = 0.0006$ ), respectively. 124 pts are alive (A 31; B 41; C 52), with 2-year OS of  $40 \pm 6\%$ ,  $58 \pm 6\%$  and  $66 \pm 6\%$  ( $p = 0.01$ ), respectively.

The addition of TT and R to MTX-ARAC (MATRIX regimen) is associated with significantly improved response, FFS and OS rates in PCNSL pts. With the exception of greater haematological toxicity, MATRIX was not associated with higher rates of severe complications, allowed preservation of antimetabolites dose intensity and permitted high rates of successful ASC collection.

## **NIVOLUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOID MALIGNANCIES AND CLASSICAL HODGKIN LYMPHOMA: UPDATED RESULTS OF A PHASE 1 STUDY (CA209-039)**

Abstract presented at the plenary session of 13-ICML.

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### **Introduction:**

The PD-1 pathway functions as a checkpoint which limits T-cell mediated tumour immune responses. Nivolumab (NIVO), a fully human IgG4 monoclonal PD-1 blocking antibody, potentiates T-cell activity. Prior results from this study (median follow-up 40 weeks) showed that NIVO was tolerated and achieved an overall response rate of 87% in classical Hodgkin lymphoma (cHL), 40% in follicular B-cell lymphoma (FBL), 36% in diffuse large B-cell lymphoma (DLBCL) and 17% in T-cell non-Hodgkin lymphoma (T-NHL). The stable disease rate in multiple myeloma (MM) was 67%. Herein, we report the updated follow-up and safety profile of this study.

### **Methods:**

Patients (pts) were treated using a dose-escalation design (1 and 3 mg/kg) of NIVO administered every 2 weeks (wks) for 2 years. Responses were assessed using standard criteria. Primary endpoint was safety. The secondary endpoint was efficacy.

### **Results:**

105 pts were enrolled (23 cHL, 31 B-NHL, 23 T-NHL, 27 MM and 1 chronic myelogenous leukaemia). Pts were heavily pretreated with 88%, 78%, 68% and 66% of pts with cHL, T-NHL, B-NHL and MM, respectively, having received  $\geq 3$  prior regimens. Previous ASCT was reported for 75% of pts with cHL, 56% of MM, 13% of B-NHL and 9% of T-NHL. As of 1/8/2015, median duration of follow-up was 62 wks (range: 2 to 106+ wks).

Drug-related adverse events (DrAEs) occurred in 71 (67%) pts. The most common DrAEs occurring in >5% were fatigue (15%), rash (11%), diarrhoea, pneumonitis, pruritus (each 9%), pyrexia (8%), thrombocytopenia, decreased appetite (each 7%), hypocalcaemia, lipase increased, leukopenia, lymphopenia (each 6%) and nausea (5%). Serious DrAE in  $\geq 5\%$  of pts included pneumonitis (5%). Efficacy results shown below.

The rate of stable disease in MM (n = 27) was 63%. Among the 20 responding cHL pts, 10 discontinued NIVO, 6 (1 CR and 5 PR) to undergo SCT, 3 for disease progression and 1 for toxicity (MDS, thrombocytopenia), and 10 (7 PR and 3 CR) continue to respond. Among responding B- and T-NHL pts, 1/4 DLBCL, 3/4 FL and 3/4 T-NHL pts remain in response. In this updated analysis, median duration of response has not been reached in cHL, B-NHL and T-NHL.

#### Conclusions:

Encouraging, durable objective responses were observed in cHL, DLBCL and FL, including CR and PR. NIVO treatment remains safe and tolerable with a safety profile similar to that in solid tumours, and further analysis is warranted in cHL and selected B-NHLs and T-NHLs.