''Focus on...'' session: update of randomised trials

019 PRELIMINARY RESULTS OF QUALITY OF LIFE (QOL) ANALYSES FROM THE INTERGROUP PHASE III RANDOMISED TRIAL OF RITUXIMAB VS A WATCH AND WAIT APPROACH IN PATIENTS WITH ADVANCED STAGE, ASYMPTOMATIC, NON-BULKY FOLLICULAR LYMPHOMA (FL).

K. M. Ardeshna[1], W. Qian[2], R. Stephens[3], P. Smith[4], J. Warden[4], L. Lowry[4], N. Braganca[4], L. Stevens[4], C. F. Pocock[5], F. Miall[6], D. Cunningham[7], J. Davies[8], J. Walewski[9], A. Jack[10], K. Bradstock[11], D. C. Linch[12]
[1]Haematology, University College Hospital London, London, United Kingdom, [2]Trials Unit, MRC, London, United Kingdom, [3]Trials Unit, MRC, London, United Kingdom, [4]Cancer Trials Centre, Cancer Research UK & UCL, London, United Kingdom, [5]Haematology, Kent and Cantebury Hospital, Cantebury, United Kingdom, [6]Haematology, Leicester Royal infirmary, Leicester, United Kingdom, [7]Haematology, Royal Marsden Hospital, London, United Kingdom, [8]Haematology, Western General Hospital, Edinburgh, United Kingdom, [9]Haematology, Maria Sklodowska-Curie Memorial Institute , Warsaw, Poland, [10]Haematological Malignancy, Diagnostic Service, Leeds, United Kingdom, [11]Haematology, Westmead Hospital, Sydney, Australia, [12]Haematology, University College London, London, United Kingdom

Introduction: Little is known about the QoL of patients (pts) with advanced stage asymptomatic follicular lymphoma who undergo watchful waiting (WW). This study was designed to compare immediate treatment with rituximab (R) with WW. It was powered for both clinical outcome and QoL.

Materials and Methods: Eligible pts were randomised between WW, R induction (R4) and R induction followed by R maintenance over 2yr (RM). QoL was assessed before randomisation, 1 month after randomisation, then 2 monthly for 2 yr and then 6 monthly for 2 yr. QoL questionnaires used were Functional Assessment of Cancer Therapy (FACT-G) with 4 additional questions (Additional Concerns (AC)) relating to worries about 1) their disease becoming more aggressive, 2) requiring therapy, 3) being unable to support themselves or their family 4) having difficulty planning for the future. The Hospital Anxiety and Depression Scale (HADS), Impact of Event Scale-Revised, Illness Coping Style, Illness Impact Bank, Mental Adjustment to Cancer Scale were also used. The primary aim was to determine if there were alterations in anxiety or depression and functional well-being (WB) at mo 7. Secondary aims were the same at 13, 25 and 37 mo. Here we present a preliminary analysis of the QoL data (FACT-G, HADS and AC) at baseline (M0), at mo7 (M7) and mo13 (M13). Except for HAD subscale, all subscale scores were standardised on a 100 scale with 100 indicating perfect health. P value <0.01 was considered as statistically significant. A change of 5-10 points is regarded as a minimal clinical important difference.

Results: Between Sep04 and May09 463 pts were randomised, of which 456 participated in QoL. Over 80% compliance at M0, M7 and M13 was achieved. Baseline QoL was similar between arms: mean scores were 89, 84, 73, 80 and 53 for physical WB, social/family WB, emotional (EWB), functional WB and AC, respectively; 27% borderline/case anxiety, 9% borderline/case depression. At M7 and M13, EWB and AC were significantly improved in all arms with a mean difference >5 with the biggest improvement in RM group. Anxiety was unchanged in WW and R4 arms but significantly reduced in RM from 29% to 14% by M13 p=0.0005

Conclusions: Emotional WB and additional concerns improved and this was greater in RM compared with WW. There was a significant reduction in anxiety in RM group. Further analyses with all questionnaires used will be presented.

020 IMPROVED SURVIVAL AFTER A MEDIAN FOLLOW-UP OF 6 YEARS FOR IMMUNOCHEMOTHERAPY (R-MCP) VERSUS CHEMOTHERAPY ALONE (MCP) IN ADVANCED FOLLICULAR LYMPHOMA (FL) - UPDATE OF THE OSHO#39 TRIAL

M. Herold[1], G. Maschmeyer[2], V. Lakner[3], G. Dölken[4], G. Ehninger[5], M. Hänel[6], A. Hochhaus[7], R. Rohrberg[8], A. Neubauer[9], L. Fischer[10], H. Al-Ali[11], M. Wußling[12], D. Hähling[13], S. Hahnfeld[14], F. A. Hoffmann[15], C. Kahl[16].
[1]4. Medizinische Klinik, HELIOS Klinikum Erfurt, Erfurt, Germany, [2]Innere Medizin, Klinikum Ernst von Bergmann, Potsdam, Germany, [3]Hämatologie, Onkologische Schwerpunktpraxis, Rostock, Germany, [4]Innere Medizin C, Ernst-Moritz-Arndt Universität, Greifswald, Germany, [5]Medizinische Klinik I, Universitätsklinikum Carl-Gustav-Carus, Dresden, Germany, [6]Klinik für Innere Medizin, Klinikum Chemnitz, Chemnitz, Germany, [7]Innere Medizin II, Friedrich-Schiller-Universität, Jena, Germany, [8]Onkologie, Schwerpunktpraxis, Halle, Germany, [9]Innere Medzin, Universitätsklinikum Marburg, Marburg, Germany, [10]Medizinische Klinik III, Charite Campus Benjamin Franklin, Berlin, Germany, [11]Hämatologie/Onkologie, Universität Leipzig, Leipzig, Germany, [12]Onkologie, Schwerpunktpraxis, Nordhausen, Germany, [13]Innere Medizin, HELIOS Klinikum Schwerin, Schwerin, Germany, [14]Onkologie, Schwerpunktpraxis, Jena, Germany, [15]Onkologie, Schwerpunktpraxis, Leipzig, Germany, [16]Innere Medizin, Städtisches Klinikum, Magdeburg, Germany

Introduction: When we presented our results of R-MCP for advanced FL at the 2005 ICML, this was the first randomized phase III study ever demonstrating an overall survival advantage for immunochemotherapy. Now we are now able to report mature data with a median f/u of 6 years.

Methods: After informed consent previously untreated patients with advanced stage, symptomatic CD 20-positive indolent NHL and mantle cell lymphoma (n=358) were randomized to receive either MCP-chemotherapy (mitoxantrone 8 mg/m^2 d1+2, chlorambucil 3x3 mg/m^2 d 1-5, prednisolone 25 mg/m^2 d 1-5 x 8 q 4 weeks) or MCP + rituximab (375 mg/m^2 d -1) followed by interferon (IFN) maintenance treatment (3 x 4.5 mioIU per week) for responding (CR, PR) patients.

Here we report the 72 months results of the follicular lymphoma patients (grade 1+2), who represented the majority of patients and for whom the sample size was calculated, so this is not a subgroup analysis. Study endpoints included overall and complete response rate (RR + CR), progression free survival (PFS), event free survival (EFS), overall survival (OS) and toxicities.

Results: Concerning toxicities there was no striking difference.

For the FL – ITT population the treatment results are as follows:

	R-MCP (n=105)	MCP (n=96)	p-value
Response rate	92,4%	75%	.0009
Complete response	49,5%	25%	.0004
PFS median	90 mo.	35 mo.	<.0001
PFS 6 years	57%	25%	
EFS median	86 mo.	27 mo.	.0001
EFS 6 years	54%	22%	
OS median	n.r.	108 mo.	.0069
OS 6 years	80%	65%	

Conclusions: Concerning all end points R-MCP remains to be significantly superior to MCP alone: after a median f/u of 6 years we can demonstrate that an improvement in induction treatment results in a highly significant advantage concerning survival parameters: PFS, EFS as well are more than doubled and OS is clinically and statistically superior too. At the 11th ICML 7 year results will be presented and the potential role of IFN maintenance will be discussed.

021 *EIGHT-YEAR FOLLOW-UP* OF THE GELA-GOELAMS FL2000 STUDY COMPARING CHVP-INTERFERON TO CHVP-INTERFERON PLUS RITUXIMAB IN FOLLICULAR LYMPHOMA PATIENTS

E. Bachy[1], R. Houot[2], F. Morschhauser[3], C. Doyen[4], J. F. Rossi[5], C. Haioun[6], P. Brice[7], P. Feugier[8], B. Mahe[9], C. Sebban[10], C. Foussard[11], G. Salles[1]
[1]Hematology, Hospices Civils de Lyon, Lyon, France, [2]Hematology, CHU de Rennes, Rennes, France, [3]Hematology, CHU de Lille, Lille, France, [4]Hematology, Université Catholique de Louvain, Mont-Godinne, Belgium, [5]Hematology, CHU de Montpellier, Montpellier, France, [6]Hematology, Hôpital Henri-Mondor, Paris, France, [7]Hematology, Hôpital Saint Louis, Paris, France, [8]Hematology, CHU de Nancy, Nancy, France, [9]Hematology, CHU de Nantes, Nantes, France, [10]Hematology, Centre Léon Bérard, Lyon, France, [11]Hematology, CHU d'Angers, Angers, France

Introduction: Anti-CD20-containing chemotherapy regimens have become the standard of care for newly diagnosed follicular lymphoma (FL) needing cytotoxic therapy. Four randomized trials have demonstrated a clinical benefit for FL patients (pts) treated with rituximab (R). However, no long-term follow-up (i.e. > 5 years) of these trials has yet been published.

Material and methods: Between May 2000 and May 2002, 358 high-tumor burden FL patients were randomized to receive either CHVP-interferon (183 pts) or R-CHVP-interferon (175 pts) (Salles et al., Blood 2008) and their outcome was updated.

Results: Cut-off date was set at 01/02/2010 (median follow-up was 8.3 years). Nineteen patients (5.3%) were lost for follow-up at that time. Over these additional 3 years, overall survival (OS) and event-free survival (EFS) rates decreased only slightly: 81.8% at 5 years (95% CI, 77.8-85.8) and 74.1% at 8 years (95% CI, 69.5-78.7) for OS and 44.1% (95% CI, 38.9-49.2) and 35.9% (95% CI, 30.8-41.0) respectively for EFS. With longer follow-up, addition of rituximab remained significantly associated with prolonged EFS and suggested a trend towards longer OS. Median EFS was 2.8 years (95% CI, 2.4-3.6) with CHVP-interferon compared to 5.5 years (95% CI, 3.9-8.8) with R-CHVP-interferon (p<0.001) and 8-year actuarial EFS rates were respectively 27.9% (95% CI, 21.1-34.6) and 44.1% (95% CI, 36.7-51.7). OS at 8 years was 69.8% (95% CI,

63.1-76.6) and 78.6% (95% CI, 72.5-84.7) in CHVP-interferon and R-CHVP-interferon groups, respectively (p=0.076). After FLIPI adjustment using a multivariate proportional-hazards Cox regression model, OS appeared significantly superior in the rituximab-containing arm (HR=0.64, 95% CI 0.42-0.96, p=0.033). FLIPI (but not FLIPI2) score was strongly associated with outcome for both EFS (p<0.001) and OS (p<0.001) in univariate analysis, and its prognostic value remained significant after adjusting for treatment arm in multivariate models (p for trend <0.001 both for EFS and OS).

Conclusion: Long-term follow-up of FL patients treated in the FL2000 study confirms the clinical benefit of rituximab, with an advantage in OS.

022 IMPACT OF INDUCTION CHEMOTHERAPY REGIMEN ON RESPONSE, SAFETY AND OUTCOME IN THE PRIMA STUDY

F. Morschhauser[1], J. Seymour[2], P. Feugier[3], F. Offner[4], A. Lopez-Guillermo[5], R. Bouabdallah[6], L. Pedersen[7], P. Brice[8], D. Belada[9], L. Xerri[6], G. Salles[10]
[1]*Hematology, CHU de Lille, Lille, France,* [2]*Hematology, Peter MacCallum Cancer Institute, Melbourne, Australia,* [3]*Hematology, CHU, Nancy, France,* [4]*Hematology, Ghent University, Ghent, Belgium,* [5]*Hematology, Hospital Clinic, Barcelona, Spain,* [6]*Hematology, IPC, Marseille, France,* [7]*Hematology, University Hospital, Odense, Denmark,* [8]*Hematology, Saint-Louis, Paris, France,* [9]*Hematology, University Hospital, Hradec Králové, Czech Republic,* [10]*Hospices Civils de Lyon, Pierre-Benite, France*

Background: The intergroup PRIMA study demonstrated a significant increase of progression free survival (PFS) in follicular lymphoma patients (pts) receiving rituximab maintenance for 2-years after first line immunochemotherapy (Salles et al., Lancet 2011). We examined the impact of induction chemotherapy on efficacy and safety.

Methods: Induction –chosen by each center- consisted in either R-CHOP (885 pts), R-CVP (272 pts) or R-FCM (45 pts). Pre-induction characteristics were well balanced between the different induction regimen. 1018 eligible pts responding to induction therapy were randomized (stratified by regimen and response to induction) to observation or R-maintenance, 375 mg/m^2 i.v. every 8 weeks for 2 years.

Results: At the end of induction therapy, overall response rates (ORR) and complete response (CR) or unconfirmed CR for R-CHOP, R-CVP and R-FCM pts were respectively 92.8/67.2 ; 84,7/53 and 75/61.4 (missing 4.2; 9.7 and 20.5). Serious adverse events occurred in respectively 23%, 22% and 17% of pts, with infections in 6%, 7% and 9% and febrile neutropenia in 2%, 0% and 11%. 3-years PFS for pts randomized in the rituximab maintenance arm or no further treatment, after R-CHOP (n=768), R-CVP (n=222) and R-FCM (n=28) were 78.6 vs. 59.6 (HR 0.51 [0.39–0.65]), 61.6 vs. 50 (HR 0.68 [0.45–1.02] and 78.6 vs. 64.3 (0.54 [0.13–2.24]) respectively. In a Cox regression multivariate analysis adjusted by prognostic factors, a longer PFS was significantly associated with randomization to the rituximab maintenance group (HR 0.55, 0.44–0.68; p<0.0001), an age of 60 years or older (0.68, 0.54–0.86; p=0.0013), female sex (0.76, 0.62–0.94; p=0.013), lower FLIPI score categories (overall p<0.0001), and R-CHOP or R-FCM as induction treatment (0.39, 0.17–0.89; p=0?0029). Overall survival in the rituximab maintenance and observation groups were not significantly different for the 3 induction regimens: 95.6/95.2 (R-CHOP), 93.7/89.9 (R-CVP) and 74.5/100 (R-FCM)

Conclusions: Preliminary results indicate that the R-CHOP had a comparable safety profile compared to R-CVP but was associated with a higher response rate, a better PFS and a more substantial benefit of rituximab maintenance.

023 ALTERNATING COURSES OF 3X CHOP AND 3X DHAP PLUS RITUXIMAB FOLLOWED BY A HIGH DOSE ARA-C CONTAINING MYELOABLATIVE REGIMEN AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IS SUPERIOR TO 6 COURSES OF CHOP PLUS RITUXIMAB FOLLOWED BY MYELOABLATIVE RADIOCHEMOTHERAPY AND ASCT IN MANTLE CELL LYMPHOMA: UPDATE OF RESULTS OF THE MCL YOUNGER TRIAL OF THE EUROPEAN MANTLE CELL LYMPHOMA NETWORK (*MCL NET*)

O. R. Hermine[1], E. Hoster[2], J. Walewski[3], V. Ribrag[4], W. Klapper[5], N. Brousse[1], F. Berger[6], C. Thieblemont[7], A. Bosly[8], B. Coiffier[9], W. Hiddemann[10], M. Unterhalt[2], M. Dreyling[10]
[1]*Hematology, Necker Hospital, Paris, France,* [2]*Statistics, Klinikum der Universität München - Campus Grosshadern Medizinische, Munchen, Germany,* [3]*Hematology, Warsaw University Hospital, Warsaw, Poland,* [4]*Hematology, Institut Gustave Roussy, Villejuif, France,* [5]*Pathology, Kiehl University Hospital, Kiehl, Germany,* [6]*Pathology, Pierre Benite CHU Lyon, Lyon, France,* [7]*Hematology, Hôpital Saint Louis, Paris, France,* [8]*Hematology, Namur University Hospital, Namur, Belgium,* [9]*Hematology, Pierre Benite CHU Lyon, Lyon, France,* [10]*Hematology, Klinikum der Universität München - Campus Grosshadern Medizinische, Munchen, Germany*

To evaluate the potential superiority of a high dose ARA-C containing regimen, the *MCL net* initiated a randomized trial comparing 6 courses of R-CHOP followed by ASCT (12 Gray TBI, 2x60mg/kg EDX) (arm A) versus alternating courses of 3x R-CHOP and 3x R-DHAP followed by ASCT (10 Gray TBI, 4x1,5 g/m2 Ara-C, 140mg/m2 melphalan) (arm B). Pt eligibility criteria included previously untreated MCL stage II-IV, <65 years. TTF was monitored continuously by a sequential procedure. Randomization was stopped as soon as a significant difference was observed. From July 2004 to May 2010, 497 patients were randomized. The 391 pts evaluable for the primary analysis displayed similar characteristics in both arms. ORR was high in both arms (A: 90% vs B: 94%; p=0.19) and CR and CR/CRu were significantly higher in arm B (26% vs 36%; p=0.012 and 40% vs 55%; p=0.0003). The number of pts transplanted was similar in both arms (79% vs 77%) and after transplantation ORR and CR rates were comparable in both arms (97% vs 97% and 62% vs 61%). After a median FU of 27m, pts in arm B experienced a significantly longer TTF (49 m vs NR; p=0.0384, hazard ratio 0.68) due to a lower number of relapses after CR/CRu/PR (23% vs 10%). Rate of ASCT-related deaths in remission was similar in both arms (3% vs 4%). Remission duration after ASCT was superior in Arm B (48m vs NR; p=0.047). OS was similar in both arms 79% vs. 80% survival rates at 3 years (p=0.74). Safety after induction was comparable in both arms except for an increased grade 3/4 hematological and excess of renal (creatinine grade 1/2: 8% vs 38%, grade 3/4: none vs 2%) toxicities in arm B. Toxicities of both conditioning regimen were similar. Induction regimen containing high dose ARA-C followed by ASCT should become the new standard of care of MCL.

024 SURVIVAL IMPACT OF DARBEPOETIN ALFA IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) TREATED WITH IMMUNOCHEMOTHERAPY: THE LNH03-6B GELA STUDY

R. Delarue[1], C. Haioun[2], B. Coiffier[3], L. Fornecker[4], M. Fournier[5], N. Mounier[6], T. Molina[7], S. Bologna[8], C. Fruchart[9], S. Picard[10], H. Tilly[11], A. Bosly[12]
[1]*Hematology, Hopital Necker, Paris, France,* [2]*Hematology, Hopital H. Mondor, Creteil, France,* [3]*Hematology, CH Lyon Sud, Pierre Benite, France,* [4]*Hematology, Hopital Saint Louis, Paris, France,* [5]*Biostatistics, GELARC, Pierre Benite, France,* [6]*Hematology, CHU, Nice, France,* [7]*Pathology, Hotel Dieu, Paris, France,* [8]*Hematology, CHU, Nancy, France,* [9]*Hematology, Centre F. Baclesse, Caen, France,* [10]*Clinical research, GELARC, Pierre Benite, France,* [11]*Hematology, Centre H. Becquerel, Rouen, France,* [12]*Hematology, UCL Mont-Godinne, Yvoir, France*

Background: Use of erythropoiesis-stimulating agents (ESAs) in chemotherapy-induced anemia is a major issue. FDA has recently modified labeling for ESAs to include a black box warning that limited prescription to pts receiving chemotherapy for non-curative intent. The GELA has conducted a randomized phase III study to evaluate survival impact of Darbepoetin alfa (DA) in pts with DLBCL treated by chemotherapy. We report results of the second interim analysis, with a median follow-up of 44 months.

Methods: Pts between 60 and 80 years old with DLBCL and aaIPI≥1 were eligible. They were randomized between two chemotherapy regimens (R-CHOP14 or 21) for 8 cycles and between an investigational arm with DA given to maintain Hb level between 13 and 15 g/dL and a conventional arm with usual management of anemia, including transfusion and ESA. Objective was to evaluate efficacy of DA as measured by PFS, EFS, DFS and OS, and to analyze toxicity.

Results: 602 pts were included and 600 were evaluable; 238 in DA arm and 362 in conventional arm. Median age was 70 years. Pts characteristics were similar in both arms. Median baseline Hb level was 12.3 g/dL. During treatment, median Hb level was 11.6 g/dL in DA arm and 10.8 g/dL in conventional arm. Three-year PFS was 66% in DA arm compared to 58% in conventional arm (HR 0.77; CI95%: 0.59-0.99; p=0.04). This difference was also significant for DFS (HR 0.65; CI95%: 0.45-0.92; p=0.02). Despite a trend, OS was not statistically significantly longer in DA arm (HR 0.81; CI95%: 0.60-1.09; p=0.16). In conventional arm, 40% of pts received ESA. Despite no difference in Hb level, PFS was better when comparing pts who receive ESAs with those who did not (HR: 0.73; CI95%: 0.57-0.94; p=0.01). Number of serious adverse events was similar in both arms. Rate of thrombotic events was higher in DA arm (13%) than in conventional arm (6%). Number of pts who died because of treatment toxicity was similar in both arms.

Conclusions: Prophylactic use of DA was associated with better PFS. This is the first evidence of positive survival impact of DA in pts receiving chemotherapy for malignancy.