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

K. M. Ardesneth1, W. Qian2, R. Stephens1, P. Smith1, J. Warden1, L. Lowry1, N. Braganc1, L. Stevens1, C. F. Poccio2, F. Miall3, D. Cunningham4, J. Davies1, J. Walewski2, A. Jack1, K. Bradstock1, D. C. Linch1

1Haematology, University College Hospital, London, United Kingdom, 2Trials Unit, MRC, London, United Kingdom, 3Trials Unit, MRC, London, United Kingdom, 4Cancer Trials Centre, Cancer Research UK & UCL, London, United Kingdom, 5Haematology, Kent and Canterbury Hospital, Canterbury, United Kingdom, 6Haematology, Leicester Royal infirmary, Leicester, United Kingdom, 7Haematology, Royal Marsden Hospital, London, United Kingdom, 8Haematology, Western General Hospital, Edinburgh, United Kingdom, 9Haematology, Maria Sklodowska-Curie Memorial Institute, Warsaw, Poland, 10Haematological Malignancy, Diagnostic Service, Leeds, United Kingdom, 11Haematology, Westmead Hospital, Sydney, Australia, 12Haematology, University College 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 following randomisation, 1 month after randomisation, then 2 monthly for 2yr and then 6 monthly for 2yr. 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 were also used. The primary aim was to determine if there were alterations in anxiety or depression and functional well-being (WB) at 2mo. Secondary aims were the same at 13, 25 and 37mo. 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 <0.05 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 were powered for both clinical outcome and Qol. Follow-up was over 6yr (M13). Concerning all end points R-MCP remained to be significantly superior to MCP alone: after a median f/u of 6years we can demonstrate that an improvement in EFS and PFS is maintained for responders (CR, PR) patients. PFS median n.r. 108 mo. .0069

**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.

**020 IMPROVED SURVIVAL AFTER A MEDIUM 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. Herold1, G. Maschmeyer2, V. Lakner3, G. Dökin4, E. Ehninger1, M. Hänel1, A. Hochhaus1, R. Rohrbacht, R. Neubauer1, L. Fischer1, H. A. Al-Ali1, M. Wüßling1, D. Häding1, S. Hahnfeld1, F. A. Hoffmann1, K. Kahl1

1Innere Medizin, Städtisches Klinikum, Magdeburg, Germany, 2Onkologie, Schwerpunktpraxis, Leipzig, Germany, 3Innere 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 randomised phase III study ever demonstrating an overall survival advantage for immunochemo therapy. 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 CD20-positive indolent NHL and mantle cell lymphoma (n=358) were randomized to receive either MCP-chemotherapy (mitoxantrone 8 mg/m² d1-2, chlorambucil 3x3 mg/m² d 1-5, prednisolone 25 mg/m² d 1-5 x 4 weeks) or MCP + rituximab (375 mg/m² d-1) followed by interferon (IFN) maintenance treatment (3 x 4.5 mioU per week) for responding (CR, PR) patients.

Here we report the 72 months results of the follicular lymphoma patients (grade I-2), who represented the majority of patients and for whom the sample size was calculated, so this is 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:

<table>
<thead>
<tr>
<th>R-MCP (n=105)</th>
<th>MCP (n=96)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>92.4%</td>
<td>75%</td>
</tr>
<tr>
<td>Complete response</td>
<td>49.5%</td>
<td>25%</td>
</tr>
<tr>
<td>PFS median</td>
<td>90 mo.</td>
<td>55 mo.</td>
</tr>
<tr>
<td>EFS 6 years</td>
<td>57%</td>
<td>25%</td>
</tr>
<tr>
<td>EFS median</td>
<td>86 mo.</td>
<td>27 mo.</td>
</tr>
<tr>
<td>EFS 6 years</td>
<td>54%</td>
<td>22%</td>
</tr>
<tr>
<td>OS median</td>
<td>n.r.</td>
<td>108 mo.</td>
</tr>
<tr>
<td>OS 6 years</td>
<td>80%</td>
<td>65%</td>
</tr>
</tbody>
</table>

**Conclusions:** Concerning 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. Bachy1, R. Houot2, F. Morschhauser3, C. Dreyer1, J. F. Rossi1, C. Haouin4, P. Breard1, P. Feugier5, B. Mähe6, C. Sebban1, G. Salles1

1Hematologie, Hospices Civils de Lyon, Lyon, France, 2Hematology, CHU de Rennes, Rennes, France, 3Hematology, CHU de Lille, Lille, France, 4Hematology, Université catholique de Louvain, Mont-Godinne, Belgium, 5Hematology, CHU de Montpeller, Montpellier, France, 6Hematology, Hospital Henri-Mondor, Paris, France. 7Hematologie, CHU de Nantes, Nantes, France, 8Hematology, Centre Léon Bérard, Lyon, France, 9Hematologie, 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 5.3 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, 28.0-37.5).
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 FLIP1 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). FLIP1 (but not FLIP12) 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


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 regimens. 1018 eligible pts responding to induction therapy were randomized (stratified by regimen and response to induction) to observation or R-maintenance, 357 mg/m2 iv. every 8 weeks for 2 years.

Results: At the end of induction therapy, overall response rate (ORR) and complete response (CR) or unconfirmed CR for R-CHOP, R-CVP and R-FCM pts were respectively 92.6/67.2; 84.7/73 and 75/64.1 (missing 4; 2.9 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 76.8 vs. 63.4 (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 0.68) 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 (48ms 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 hemolymphatic 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 rituximab with 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 IMMUNO-CHEMOTHERAPY: THE LNH03-0B GELA STUDY

R. Delaere1, C. Hainaut2, B. Coiffier1, L. Fornecker3, M. Fournier4, N. Mounier5, T. Molina6, S. Bologna7, C. Frucht8, P. Picard9, H. Tilly10, A. Bosly11

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 aaIPI21 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 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.

Conclusion: 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.