CLINICAL STUDY REPORT

PROTOCOL CORAL: 50-03B

RANDOMIZED STUDY OF ICE PLUS RITUXIMAB (R-ICE) VERSUS DHAP PLUS RITUXIMAB (R-DHAP) IN PREVIOUSLY TREATED PATIENTS WITH CD 20 POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA, ELIGIBLE FOR TRANSPLANTATION FOLLOWED BY RANDOMIZED MAINTENANCE TREATMENT WITH RITUXIMAB

Phase III clinical trial

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CONTENTS:

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Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trnery, Andre Bosly, Nicolas Ketterer, Ofer Shipilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, and Norbert Schmitz

See accompanying articles on pages 4191, 4199, and 4207

ABSTRACT

Purpose
Salvage chemotherapy followed by high-dose therapy and autologous stem-cell transplantation (ASCT) is the standard treatment for relapsed diffuse large B-cell lymphoma (DLBCL). Salvage regimens have never been compared; their efficacy in the rituximab era is unknown.

Patients and Methods
Patients with CD20+ DLBCL in first relapse or who were refractory after first-line therapy were randomly assigned to either rituximab, ifosfamide, etoposide, and carboplatin (R-ICE) or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP). Responding patients received high-dose chemotherapy and ASCT.

Results
The median age of the 396 patients enrolled (R-ICE, n = 202; R-DHAP, n = 194) was 55 years. Similar response rates were observed after three cycles of R-ICE (63.5%; 95% CI, 56% to 70%) and R-DHAP (62.8%; 95 CI, 55% to 69%). Factors affecting response rates (P < .001) were refractory disease/relapse less than versus more than 12 months after diagnosis (46% v 88%, respectively), International Prognostic Index (IPI) of more than 1 versus 0 to 1 (52% v 71%, respectively), and prior rituximab treatment versus no prior rituximab (51% v 83%, respectively). There was no significant difference between R-ICE and R-DHAP for 3-year event-free survival (EFS) or overall survival. Three-year EFS was affected by prior rituximab treatment versus no rituximab (21% v 47%, respectively), relapse less than versus more than 12 months after diagnosis (20% v 45%, respectively), and IPI of 2 to 3 versus 0 to 1 (18% v 40%, respectively). In the Cox model, these parameters were significant (P < .001).

Conclusion
In patients who experience relapse more than 12 months after diagnosis, prior rituximab treatment does not affect EFS. Patients with early relapses after rituximab-containing first-line therapy have a poor prognosis, with no difference between the effects of R-ICE and R-DHAP.

INTRODUCTION

During the last decade, the addition of the anti-CD20 monoclonal antibody rituximab to various chemotherapies1-3 has dramatically improved response rates in diffuse large B-cell lymphoma (DLBCL), with complete responses (CRs) in 75% to 80% of patients. The use of rituximab in first-line treatment improved 5-year event-free survival (EFS) from 29% to 47% in the initial study of patients between age 60 and 80 years4 and improved 3-year EFS from 59% to 79% in patients age 18 to 60 years;5 rituximab was also associated with improved overall survival (OS). Before the rituximab era, 5-year OS rate for relapsed DLBCL was 53% after high-dose chemotherapy with autologous stem-cell transplantation (ASCT).6 Various parameters greatly affect the results of ASCT, including chemotherapy sensitivity before ASCT,7 time from diagnosis to relapse of less than 12 months,8 and the presence of prognostic factors at relapse, as defined by the secondary age-adjusted International Prognostic Index (saIPI).9,10 The addition of rituximab to second-line chemotherapy followed by ASCT significantly improved progression-free survival (PFS) in patients not exposed to rituximab as part of their first-line treatment.11 For patients who have experienced relapse, no comparative studies have thus far been performed to our knowledge to evaluate the efficacy of the different salvage regimens.12 Therefore, we compared the effects of two established salvage regimens...
followed by ASCT, attempted to identify the parameters influencing the effectiveness of each regimen, and aimed to establish whether or not the widespread use of rituximab as part of first-line therapy affects the outcome of patients with relapsed DLBCL.6

The present Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study was a collaborative effort by 12 countries worldwide. Patients with refractory or relapsed CD20+ DLBCL were randomly assigned to one of the following two widely used regimens that included rituximab: rituximab, ifosfamide, carboplatin, and etoposide (R-ICE)13 or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP).14 In responding patients, peripheral progenitor cells were collected after chemotherapy and reinfused after a high-dose chemotherapy conditioning regimen. We also investigated the impact of post-transplantation rituximab administration. Here, we report the results of the comparison between these two salvage regimens and the factors affecting outcome.

### Patients and Methods

#### Patients

Eligible patients were age 18 to 65 years and had aggressive CD20+ B-cell non-Hodgkin’s lymphoma, including DLBCL, and had experienced relapse or did not achieve CR with a standard anthracycline-based regimen composed of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Before enrollment, CD20+ aggressive B-cell lymphoma was histologically confirmed in all patients. Patients eligible for inclusion had a performance status of 0 to 1. Exclusion criteria included CNS involvement, a history of HIV infection, post-transplantation lymphoproliferative disorders, and inadequate organ function. Patients were fully evaluated by examinations that included thoracic and abdominal computed tomography scans and bone marrow biopsy. saaIPI factor status was determined by the absence or presence of risk factors, poor performance status, elevated lactate dehydrogenase, and disseminated stage before salvage treatment.9,10 The study was approved by the

### Fig 1.

CONSORT diagram of distribution of patients according to arm resulting from the first random assignment. CRF, case report forms; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin; BEAM, carmustine, etoposide, cytarabine, melphalan; ASCT, autologous stem-cell transplantation.
relevant institutional review boards or ethics committees, and all patients gave written informed consent.

The study was registered under European Union Drug Regulating Authorities Clinical Trials (EudraCT) No. 2004-002103-32 and ClinicalTrials.gov NCT 00137995. Four hundred patients were enrolled between July 2003 and September 2007 for part 1 of the study. On an intent-to-treat basis, 396 patients were randomly assigned (202 patients to the R-ICE arm and 194 patients to the R-DHAP arm), and 388 patients were actually treated (Fig 1). Patient characteristics are listed in Table 1. No significant differences between the two arms were observed. Histology was reviewed by local hematopathologists attached to the participating centers. In addition, an international central review was performed in 289 (73%) of 396 patients. Only 13 patients did not have DLBCL; three patients had grade 3 follicular lymphoma, six patients had grade 2 follicular lymphoma, two patients had T-cell lymphoma, and two patients had Hodgkin’s lymphoma. Only four patients were CD20⁺, and CD20 status was not documented in 13 patients. All of the patients were included in an intent-to-treat analysis and received the protocol arm.

**Study Design and Treatment**

This study was a phase III multicenter randomized trial designed to compare the efficacy of R-ICE and R-DHAP in patients with previously treated DLBCL, followed by ASCT with or without rituximab maintenance therapy (Fig 2). There were two random assignments, the first for salvage therapy and the second for maintenance treatment. The efficacy of the two salvage regimens is the subject of this report.

Patients were stratified according to participating country, prior rituximab treatment, and relapse occurring less than or more than 12 months after diagnosis. Every 3 weeks, patients were given three cycles of chemotherapy, followed by ASCT. In both regimens, rituximab (375 mg/m²) was administered before chemotherapy, and in the first course, additional rituximab was given on day −1. The R-ICE regimen consisted of etoposide (100 mg/m²) on days 1 through 3, ifosfamide (5,000 mg/m²) infused continuously for 24 hours on days 2 and 3 with mesna; and carboplatin (area under the curve = 5; maximum dose, 800 mg) on day 2. The R-DHAP regimen consisted of cisplatin (100 mg/m²) on day 1 via continuous 24-hour infusion, followed on day 2 by cytarabine (2 g/m²) in a 3-hour infusion repeated after 12 hours, and dexamethasone (40 mg/d) for 4 consecutive days. Granulocyte colony-stimulating factor was administered after R-ICE and, depending on site policy, with R-DHAP, but always after the third cycle until the end of leukaphereses. Leukaphereses were performed after the third or second course of salvage therapy to obtain a target of 2,000,000 CD34⁺ hematopoietic stem cells per kilogram for cryopreservation. In case of inadequate peripheral stem-cell collection after the third course, patients were considered to be experiencing treatment failure and withdrawn from the study.

**Assessment of Response and Follow-Up**

Response was assessed by conventional diagnostic methods, including computed tomography scans, after the third chemotherapy course. Bone marrow biopsies were only repeated if abnormal before treatment.

Response was assessed using the International Working Group criteria. CR was defined by the disappearance of all documented disease; unconfirmed CR (CRu) was used when a residual mass was present without evidence of treatment failure and withdrawn from the study.

### Table 1. Baseline Patient Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Demographic or Clinical Characteristic</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>R-ICE (n = 202)</td>
</tr>
<tr>
<td>Median</td>
<td>54</td>
</tr>
<tr>
<td>Range</td>
<td>19-65</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>125</td>
</tr>
<tr>
<td>Female</td>
<td>77</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>81</td>
</tr>
<tr>
<td>III-IV</td>
<td>119</td>
</tr>
<tr>
<td>Extranodal site &gt; 1</td>
<td>55</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>17</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>104</td>
</tr>
<tr>
<td>saaIPI at relapse</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>119</td>
</tr>
<tr>
<td>2-3</td>
<td>75</td>
</tr>
<tr>
<td>Time to relapse after diagnosis, months</td>
<td></td>
</tr>
<tr>
<td>&lt; 12*</td>
<td>112</td>
</tr>
<tr>
<td>≥ 12*</td>
<td>122</td>
</tr>
<tr>
<td>Prior rituximab treatment</td>
<td></td>
</tr>
<tr>
<td>Prior first-line CHOP-like chemotherapy</td>
<td>171</td>
</tr>
<tr>
<td>Intensified CHOP</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; NS, not significant; LDH, lactate dehydrogenase; saaIPI, secondary age-adjusted international prognostic index at relapse; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*Including patients not achieving complete response after first-line treatment.
active disease. Partial response (PR) was defined as a 50% reduction of measurable disease. The mobilization response rate was defined as the objective CR and PR rates associated with the target mobilization of the peripheral stem cells (2,000,000 CD34+ hematopoietic stem cells/kg). Response was evaluated 3 months after transplantation. Follow-up procedures included a physical examination every 3 months for the first year and every 6 months thereafter for 2 years and a complete evaluation at the end of the first year or earlier if necessary.

**ASCT**

Patients who achieved a CR or PR after the third cycle of salvage treatment were given carmustine, etoposide, cytarabine, and melphalan (BEAM) high-dose chemotherapy. The BEAM regimen included carmustine (300 mg/m²) on day −6, etoposide (200 mg/m²), cytarabine (200 mg/m²) on days −5 to −2, and melphalan (140 mg/m²) on day −1. Peripheral-blood stem cells were reinfused on day 0, at least 24 hours after completion of BEAM.

Radiotherapy after transplantation was not allowed and was considered to be an event. Supportive treatments were given according to standard use in each center.

## RESULTS

**Statistical Analysis**

The primary end point was the mobilization-adjusted response rate after three cycles of chemotherapy. A higher favorable response rate was expected for R-ICE than for R-DHAP, with fewer failed stem-cell collections. To detect a difference of 15% in the mobilization-adjusted response rate between R-ICE, for which this rate was 60% (75% response minus 15% mobilization failure), and R-DHAP, with a corresponding rate of 45% (65% response minus 20% mobilization failure) with a power of 82% and a 5% significance level, 400 patients had to be randomly assigned to the two chemotherapy arms. This allowed the second random assignment of 240 patients, with an expected dropout rate of 40% (Appendix, online only).

Administration of an alternative treatment was considered as an event. EFS was defined as the time from the start of treatment to progression, relapse, new treatment, or death (irrespective of cause), whichever event occurred first. DFS was defined as the time from study entry until disease progression or death. OS was defined as the time from the start of treatment to death.

The Kaplan-Meier method was used to estimate EFS, DFS, and OS, and 95% CIs were calculated. Cox regression analysis was used to calculate the hazard ratio between the two arms. All reported P values are two-sided, and P < .05 was considered significant. All analyses were carried out with SAS 9.1.3 software (SAS Institute, Cary, NC).

The study was designed by the Steering Committee of CORAL. The same investigator (C.G.) checked the data for medical coherence, analyzed and interpreted the data, and was the principal writer of this article (Appendix).

### Table 2. Response After Induction Treatment (including death) for All Patients

<table>
<thead>
<tr>
<th>Response</th>
<th>R-ICE (n = 197)</th>
<th>R-DHAP (n = 191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Complete response</td>
<td>48 (24)</td>
<td>53 (28)</td>
</tr>
<tr>
<td>Unconfirmed complete response</td>
<td>24 (12)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Partial response</td>
<td>53 (27)</td>
<td>45 (24)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>23 (12)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>38 (19)</td>
<td>35 (18)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (3)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Premature withdrawal, not evaluated</td>
<td>4 (2)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

**Autologous transplantation**

- **Median CD34+ cells collected, million/kg**: 4.5 (4.9) days/H11021
- **Collection failure < 2,000,000 CD34+ cells**: 20 (10) /H11021
- **Mobilization-adjusted response**: 103 (52.3) /H11021
- **Consolidation with BEAM performed per protocol**: 101 (51) /H11021

**Abbreviations:** 
- R-ICE, rituximab, ifosfamide, carboplatin, and etoposide
- R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin
- BEAM, carmustine, etoposide, cytarabine, and melphalan
- saaIPI, secondary age-adjusted International Prognostic Index

### Table 3. Response Rate and Survival According to Prognostic Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>All patients (n = 398)</th>
<th>R-ICE (n = 197)</th>
<th>R-DHAP (n = 191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response CR/CRu/PR</td>
<td>246/122/38</td>
<td>148/124/51</td>
<td></td>
</tr>
<tr>
<td>Total No. of Patients</td>
<td>398</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Year Event-Free Survival</td>
<td>% 63/31/51/50</td>
<td>% 51/70</td>
<td></td>
</tr>
<tr>
<td>3-Year Overall Survival</td>
<td>% 50/41/66/64</td>
<td>% 70/40</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** 
- CR, complete response
- CRu, unconfirmed complete response
- PR, partial response
- saaIPI, secondary age-adjusted International Prognostic Index
(73%) of 181 evaluable patients had CR or CRu, 24 (13%) had PR, one had stable disease, and 17 (9%) had progressive disease.

Survival
After a median follow-up time of 27 months, the 3-year EFS rate was 31% (95% CI, 26% to 36%) and was not significantly different between the R-ICE and R-DHAP arms (26% and 35%, respectively; \( P = .6 \)). Three-year PFS was 37% (95% CI, 31% to 42%), and again, the R-ICE and R-DHAP arms were not significantly different (31% and 42%, respectively; \( P = .4 \)). Three-year OS (Figs 3A and 3B) was 49% (95% CI, 43% to 55%), with no difference between the R-ICE and R-DHAP arms (47% and 51%, respectively; \( P = .4 \)). For patients who underwent ASCT, 3-year PFS was 53% (Fig 4A). There was no difference between the numbers of patients who achieved CR and PR just before ASCT (Fig 4B).

Three-year EFS, PFS, and OS were affected by prior rituximab treatment, early relapse, and saaIPI (Table 3). In the Cox model, all of these parameters remained significant (\( P < .001 \)) for EFS, PFS, and OS; prior rituximab treatment was significant at a lower level (\( P = .2 \)). The treatment arm was not significant.

When patients were analyzed according to early relapse and prior rituximab treatment, there was no difference in PFS, EFS, or OS for patients with relapse more than 12 months after diagnosis (Figs 3C and 3D). Early relapse and prior rituximab treatment (\( n = 187 \)) defined a population with a poor response rate to the standard treatment; thus, their 3-year PFS was only 23%. However, for responding patients who underwent ASCT (\( n = 68 \)), 3-year PFS was 39%, compared with 14% for patients who did not receive transplantation (\( n = 119; P < .001 \); Appendix Fig A1, online only). At the time of our analysis, 92 deaths (47%) had occurred in the R-ICE arm, and 82 deaths (43%) had occurred in the R-DHAP arm, mainly as a result of lymphoma.

Relapse and Progression
Progression or relapse was experienced by 104 patients in the R-ICE arm and 97 patients in the R-DHAP arm, mostly at the initial site and by half of patients during the treatment period. Various treatments were administered, including radiotherapy and chemotherapy, with or without transplantation (32 autotransplantations and 14 allografts; Appendix Tables A1 to A3, online only). A second CR was experienced by 32 of 176 patients. In all, 48 patients, 24 in each treatment arm, reported an event as a result of a new treatment after progression.

Adverse Events
The median time between salvage cycles was 22 days for both arms for the 230 patients who completed three cycles. Grade 3 to 4 hematologic toxicities were more severe in the R-DHAP arm than the R-ICE arm.
R-ICE arm, and more patients required at least one platelet transfusion during the induction phase (57% in R-DHAP arm v 35% in R-ICE arm). In all, 90 serious adverse events occurred in 58 patients in the R-ICE arm, and 120 serious events occurred in 68 patients in the R-DHAP arm.

In both arms, the most common serious adverse events were infections, with a similar rate of infection as a result of neutropenia (16%) in both arms. Grade 3 to 4 nonhematologic toxicities were more severe in the R-DHAP arm and included grade 4 renal toxicity in 11 patients (Appendix Tables A4 and A5, online only). Patients who underwent BEAM followed by ASCT experienced the usual patterns of hematologic and nonhematologic toxicity, and three toxic deaths occurred.

**DISCUSSION**

In DLBCL, two populations are candidates for salvage treatment followed by high-dose chemotherapy and ASCT—patients who experience a relapse after achieving CR and those who do not achieve CR but are still responding to treatment. From the PARMA data, patients experiencing early relapses less than 12 months after diagnosis have the same poor prognosis as incomplete responders. Such patients constituted 57% of all patients in the present study. Because this study was performed between 2003 and 2007, not all of the patients had access to rituximab as first-line treatment. This fact enabled us to prospectively enroll patients who did and did not have prior rituximab treatment (62% and 36%, respectively).

Because no randomized comparison of any salvage regimens had ever been previously reported, it was not clear which regimen was preferable for treatment of relapsed DLBCL. The R-ICE regimen was chosen because we assumed that rituximab would improve its results, as suggested by the Memorial Sloan-Kettering Cancer Center. Because DHAP has been widely used all over the world and was the salvage regimen of the PARMA study, it was used here as comparator. Both regimens were supplemented with rituximab, which has been shown to improve treatment results of patients with relapsed DLBCL and not previously treated with rituximab.

The present results show a similar response rate of 63% for the two regimens, with a CR rate of only 38%, even after adjustment for mobilization failure. Furthermore, similar prospective mobilization failure rates of 10% were observed after both regimens. Only 50% of patients were able to undergo ASCT. Toxicities were similar, but there were more platelets and renal toxicity in the R-DHAP arm. An important finding was that several independent factors significantly affected response rates after salvage therapy, including saaIPI score, early relapse less than 12 months after diagnosis, and prior rituximab treatment. The same independent factors were found for OS, EFS, and PFS. R-ICE and R-DHAP gave similar results for all conceivable situations, thus demonstrating that it will be difficult to improve therapy without new drugs.

In this study, it was possible to identify a population with late relapse who benefited from the introduction of rituximab into their salvage regimen and exhibited an 80% response rate and a 3-year EFS ranging from 40% to 50%. Here, the standard treatment with ASCT reproduced the PARMA results. However, there was a group of patients with a poor prognosis whose prior rituximab treatment was predictive, in cases of early relapse, of a response rate of 50% and 3-year EFS of only 20%. For these patients, the results of standard therapy should be improved, and new approaches are needed.

At the time of this analysis, there were not enough events (85 of 140 events) to determine the impact of rituximab administered as post-transplantation maintenance therapy. For patients who underwent transplantation, 3-year PFS was 53% (Fig 4).

Our results seem less favorable than those reported in a nonrandomized study with R-ICE and in a study using high-dose rituximab before and after transplantation. In the randomized CORAL study, the three courses of R-ICE were separated by a 3-week interval instead of 2 weeks, which may have helped to lower the CR rate. However, the patients in the present study differed from those in both of the previously cited studies because they had not had previous rituximab treatment and their response was evaluated by functional imaging. We believe, however, that our results are more representative of the general population with relapsed DLBCL than those reported by single institutions with limited numbers of patients and no random assignment. When we looked at the initial prognostic parameters before failure/relapse according to prior rituximab treatment, patients who had received rituximab had more adverse factors, a finding likely to prove representative of the patients we will have to treat in the future.
Consequently, new drugs designed to increase the response rate of salvage regimens and new approaches, including allogeneic transplantation, should be explored. In the era of antibody chemotherapy, novel targeted therapy resulting from better understanding of the biology of DLBCL, including studies of patient tumor specimens, will play a key role in these respects.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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**Expert Testimony:** None

**Other Remuneration:** None

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Data analysis and interpretation: Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Ofer Shpilberg, Norbert Schmitz

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Final approval of manuscript: Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trneny, Andre Bosly, Nicolas Ketterer, Ofer Shpilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, Norbert Schmitz
The Germinal Center/Activated B-Cell Subclassification Has a Prognostic Impact for Response to Salvage Therapy in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Bio-CORAL Study


See accompanying editorial on page 4065

ABSTRACT

Purpose
To evaluate the prognostic value of the cell of origin (COO) in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), prospectively treated by rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) versus rituximab, ifosfamide, carboplatin, and etoposide and followed by intensive therapy plus autologous stem-cell transplantation on the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) trial.

Patients and Methods
Among the 396 patients included on the trial, histologic material was available for a total of 249 patients at diagnosis (n = 189 patients) and/or at relapse (n = 147 patients), which included 87 matched pairs. The patient data were analyzed by immunochemistry for CD10, BCL6, MUM1, FOXP1, and BCL2 expression and by fluorescent in situ hybridization for BCL2, BCL6, and c-MYC breakpoints. The correlation with survival data was performed by using the log-rank test and the Cox model.

Results
Characteristics of immunophenotype and chromosomal abnormalities were statistically highly concordant in the matched biopsies. In univariate analysis, the presence of c-MYC gene rearrangement was the only parameter to be significantly correlated with a worse progression-free survival (PFS; \( P = .02 \)) and a worse overall survival (\( P = .04 \)). When treatment interaction was tested, the germinal center B (GCB)–like DLBCL that was based on the algorithm by Hans was significantly associated with a better PFS in the R-DHAP arm. In multivariate analysis, independent prognostic relevance was found for the GCB/non-GCB the Hans phenotype interaction treatment (\( P = .04 \)), prior rituximab exposure (\( P = .0052 \)), secondary age-adjusted International Prognostic Index (\( P = .039 \)), and FoxP1 expression (\( P = .047 \)). Confirmation was obtained by gene expression profiling in a subset of 39 patients.

Conclusion
COO remains a major and independent factor in relapsed/refractory DLBCL, with a better response to R-DHAP in GCB-like DLBCL. This needs confirmation by a prospective study.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a well-defined entity\(^1\) and the most common form of adult non-Hodgkin’s lymphoma.\(^2\) Complexity and heterogeneity of the disease have been demonstrated over the past 10 years, first by the most recent WHO classification that includes no less than 15 different subentities\(^3\) and second by the gene expression profiling analyses leading to a molecular classification of DLBCL into at least three distinct subtypes: germinal center B (GCB)–cell-like, activated B-cell (ABC)–like, and primary mediastinal B-cell lymphoma (PMBL)\(^4,5\) associated with different oncogenic events\(^6,7\).

The prognosis has been demonstrated to be variable, with a poorer outcome for patients with ABC-like DLBCL than for those with GCB-like DLBCL.
when treated with conventional anthracycline-based chemotherapy (usually cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]). Consequently, surrogates of this molecular classification have been developed for routine usage on the basis of immunohistochemical protein expression or genetic markers detected by fluorescence in situ hybridization (FISH), the most concordant with the microarray results being the algorithms of Cho and Hans. Published algorithms encompass proteins such as CD10, BCL2, MUM1, FOXP1, GCET1, and BCL2. Individually, these proteins have shown to have equivocal prognostic relevance. Expression of the antiapoptotic molecule BCL2 has been associated with a poor clinical outcome, although treatment with rituximab appears to eliminate the unfavorable effect from BCL2 expression. High-level expression of FOXP1 is correlated with the non-GC phenotype and has been reported to be an independent adverse prognostic marker for DLBCL.

In first-line therapy with conventional CHOP or intensive chemotherapy plus autograft, most studies that are based on GCB/ABC subtyping report a better outcome in patients with GCB-like than in patients with ABC-like DLBCL. In patients treated with a combination of rituximab and chemotherapy, the clinical significance of the GCB/ABC subtyping is more controversial. The pivotal study published by Lenz et al showed that cell of origin (COO) was highly predictive in patients treated by rituximab plus CHOP (R-CHOP) as well as in patients treated by CHOP. Other studies found that patients with de novo DLBCL no longer showed differential clinical outcomes in GCB and non-GCB subgroups when treated with R-CHOP. At relapse, no data regarding the clinical significance of GCB/ABC subtyping were available. In this context, the international Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study addressed the question of the best induction treatment in young patients with relapsed/refractory DLBCL between the most widely used regimens, R-ICE (ie, rituximab, ifosfamide, carboplatin, and etoposide) and R-DHAP (ie, rituximab, dexamethasone, high-dose cytarabine, and cisplatin). The study found no difference between R-ICE and R-DHAP.

In this study, we wanted to assess whether tumor biology is a predictive factor for response to R-ICE or R-DHAP in relapse/refractory DLBCL compared with other known clinical prognostic factors.

## PATIENTS AND METHODS

The patients studied for the present biologic analyses were a subset of the 396 patients analyzed in the CORAL study, which was designed to compare the efficacy of R-ICE and R-DHAP followed by high-dose therapy and autologous stem-cell transplantation in patients age 18 to 65 years old who presented with relapsed/refractory CD20(+)

### Morphology, Immunohistochemistry, and COO Algorithms

Histologic material was available in a total of 249 patients at diagnosis (n = 189 patients) and/or at relapse (n = 147 patients). A panel of seven hematopathologists (J.B., P.G., H.U.V., C.S., S.C., P.T., A.J.) conducted a central review to confirm the diagnosis of CD20(+) DLBCL and to evaluate the immunostaining and FISH. Among these 249 patients, eight (3%) presented with a primary mediastinal B-cell lymphoma (PMBL), and 12 (4.8%) presented with a follicular lymphoma (FL) grade 1 to 2 either at diagnosis or at relapse. Immunostaining against CD10, BCL2, IRF4/MUM1, BCL6, and FOXP1 were performed by using 3-µm sections either from full slides or from tissue microarrays containing two or three representative 0.6-mm cores of routinely formalin-fixed paraffin-embedded tissues. LMO2 expression was not evaluated, because its predictive value was not confirmed in our previous work. The tissue quality was evaluated morphologically on hepatoyxin and eosin staining. All evaluable occurrences were given a secondary classification according to the COO algorithms previously published by Hans et al, Muris et al, and Nyman et al.

### FISH Analysis

FISH analysis was performed on tissue microarray or full paraffin-embedded 2- to 3-µm tissue sections by using the breakapart probes for c-MYC(8q24), BCL2(18q21), and BCL6(3q27) (Abbott, Paris, France). Samples were analyzed with an AxioImager.M1 epifluorescence microscope (Carl Zeiss, Hamburg, Germany). Images were captured with a ×63 or ×100 oil objective and were analyzed by using the Isis software (METASystems, Alt-Lusseheim, Germany). The hybridization signal scoring was performed according to Haralambieva et al. with a normal cutoff value of 10%. On the basis of the results of BCL6(3q27) gene rearrangement and expression levels of MUM1 and FOXP1, the occurrences were scored with the immunofISH index, as reported by Copie-Bergman et al.

### Microarray Procedures and Analyses

Fresh-frozen lymphoma samples were obtained retrospectively from 50 patients included on the CORAL trial. None of them presented with an FL or a PMBL. Tumor infiltration was checked on hepatoyxin and eosin–stained frozen sections. Total RNA quantity and initial quality were estimated by a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE), and quality was assessed by electrophoresis (Agilent 2100 Bioanalyzer; Agilent Technologies, Missisauga, Ontario). Overall, 11 samples were not accepted for additional experimentation: three were of insufficient quantity, and eight were of insufficient quality. A total of 44 samples (n = 14 primary biopsies, n = 20 relapse biopsies, and n = 5 matched cases) that corresponded to 39 patients were analyzed. The Agilent Whole Human Genome microarray (G4112F) and a gene voting method were used to determine the COO on the basis of the genes discriminating GCB/ABC signatures that were published initially by Alizadeh et al. Details of the

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Index of Variation Considering Immunophenotypes and Chromosomal Abnormalities Between Primary and Relapse Biopsies in Matched Pairs</th>
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</thead>
<tbody>
<tr>
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<td>BCL2</td>
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<td>Chromosomal breakpoint</td>
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<td>BCL6(3q27)</td>
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<td>GCB/ABC surrogate publication</td>
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<td>Muris et al</td>
<td>73</td>
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<tr>
<td>Nyman et al</td>
<td>67</td>
</tr>
</tbody>
</table>

Abbreviations: ABC, activated B-cell; GCB, germinal center B.
procedures and analyses are in the Data Supplement. Microarray data have been submitted to the Gene Expression Omnibus (GEO; GSE26812).

**Statistical Analysis**

Each biologic parameter obtained at diagnosis and at relapse within the matched pairs were analyzed for variation. The results showed no statistical variation (Wilcoxon paired ranked test; Table 1). This finding allowed us to analyze all data in a similar manner, irrespective of whether they were generated by diagnostic or relapse biopsies. For the survival analyses, all analyses were performed on an intention-to-treat basis. Patient characteristics and complete remission rates were compared by the χ² and Fisher’s exact tests.

Progression-free survival (PFS) was defined as the time from study entry until disease progression or death. Overall survival (OS) was defined as the time from the start of treatment to death. Survival functions were estimated by the Kaplan-Meier method and were compared by the log-rank test. Differences between the results of comparative tests were considered significant at a two-sided P < .05. Because the CORAL trial was not stratified by biologic data, we controlled for the effects of prognostic factors on outcome that resulted from sampling fluctuation in the treatment groups by using multivariate analysis of survival in a Cox model. All statistical analyses were performed with SAS 9.13 (SAS Institute, Cary, NC) and S-Plus 6.2 (MathSoft, Cambridge, MA) software.

<table>
<thead>
<tr>
<th>Table 2. Baseline Characteristics of Patients Enrolled Onto Bio-CORAL and CORAL</th>
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<th>At Time to Relapse</th>
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</tr>
<tr>
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<td>Time to relapse, months</td>
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<tr>
<td>CR/CRU</td>
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<tr>
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<tr>
<td>Transplantation</td>
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</table>

NOTE. Baseline characteristics of the patients in the CORAL study included in the bio-CORAL study.

Abbreviations: CORAL, Collaborative Trial in Relapsed Aggressive Lymphoma; CR, complete response; CRU, complete response undetermined; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PR, partial response; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide.
RESULTS

Patient Characteristics and Outcome

Overall, 249 patients included in the CORAL trial were enrolled onto this study (Table 2). At initial therapy, the median age was 53 years (range, 18 to 65 years), and 40% had a high-intermediate or high age-adjusted International Prognostic Index (aIPI). At relapse and time to CORAL inclusion, the median age was 54 years (range, 19 to 65 years), and 38% had a secondary high-intermediate or high aIPI. At salvage therapy, 123 patients were treated with R-DHAP;126, with R-I CE.

After a median follow-up time of 27 months, the 3-year PFS was 47.5% and was not significantly different between the R-ICE and R-DHAP arms (28.7% v 40.9%, respectively; \( P = .24 \)). Three-year OS was 50.8% (95% CI, 43% to 55%), with no difference between the R-ICE and R-DHAP arms (47.7% v 54%, respectively; \( P = .23 \); data not shown). As initially described in the CORAL study,27 early relapse less than 12 months after the diagnosis, prior rituximab exposure, and secondary aIPI were the individual risk factors for OS and PFS (\( P < .001 \), \( P < .001 \), and \( P < .001 \), respectively). Moreover, initial aIPI and response to initial treatment had a significant impact on outcome (OS and PFS, \( P < .001 \) and \( P < .001 \), respectively; data not shown).

Tumor Biology

Immunohistochemical expression of CD10, BCL6, MUM1/IRF4, BCL2, and FOXP1 in tumor cells were observed in 59%, 60%, 42%, 73%, and 65% of the cells, respectively, when pooled (Table 3). Among the tumor samples displaying interpretable FISH signals, BCL2/18q21, BCL6/3q27, and c-MYC/8q24 gene rearrangements were found in 31%, 18%, and 13% of the samples, respectively. BCL2/18q21 and c-MYC/8q24 rearrangements were strongly associated with the GCB category according to the Hans classifier (\( P = .0007 \) and \( P = .0001 \), respectively). BCL6/3q27 rearrangement was not correlated to any Hans category. On the basis of the algorithm by Hans,14 49% of the patients were classified as GCB, and 51% were classified as non-GCB. On the basis of the algorithm by Muris,15 72% were classified as group 1, and 28% were classified as group 2. On the basis of the algorithm by Nyman,24 73% were classified as ABC, and 27% were classified as others.

Biologic Prognostic Factors

By univariate analysis, c-MYC/8q24 gene rearrangement was the only parameter to be significantly correlated with a worse PFS (\( P = .02 \)) and a worse OS (\( P = .04 \); Table 3). To investigate the impact of different treatment arms on some biomarkers, we studied clinical outcome according to the treatment arms in each biomarker subgroup. PFS was significantly different when we studied BCL6 protein expression, BCL2/18q21 gene rearrangement, GCB/non-GCB classification on the basis of the Hans algorithm, and ABC phenotype on the basis of the algorithm by Nyman, in the R-ICE arm and R-DHAP arms. Interaction between GCB/non-GCB Hans classification and the R-ICE treatment versus R-DHAP treatment was significant (\( P < .035 \)). Patients with GCB DLBCL according to the algorithm by Hans, who were treated with R-DHAP, had a better PFS than patients with non-GCB DLBCL (3-year PFS rate and standard deviation, 52% ± 7% v 32% ± 7%, respectively; \( P = .01 \); Fig 1A). Patients treated with R-ICE had a poor PFS without significant difference between the GCB and non-GCB Hans phenotypes (3-year PFS rate and standard deviation, 31% ± 7% v 27% ± 7%, respectively; \( P = .81 \); Fig 1B). Similar results were observed for OS (Figs IC and ID). Analysis realized after removing PMBL and transformed FL occurrences resulted in unchanged results neither in PFS (non-GC v GC, 34% v 72%; 2-year PFS for R-DHAP, \( P = .04 \); 41% v 51% for R-ICE; \( P = .60 \)), nor in OS (non-GC v GC, 51% v 83%; 2-year OS for R-DHAP, \( P = .11 \); 57% v 62% for R-ICE; \( P = .65 \)).

Multivariate analysis showed an independent prognostic impact of the following parameters on PFS: GCB/non-GCB Hans phenotype interaction with treatment (\( P = .04 \)), prior rituximab exposure (\( P = .0052 \)), secondary aIPI (\( P = .039 \)), and FoxP1 expression (\( P = .047 \)). This analysis confirmed that R-DHAP was significantly more beneficial than R-ICE in patients presenting with GCB DLBCL as classified by Hans et al,14 irrespective of clinical variables, such as aIPI.

Gene Expression Profiling

Gene expression–based COO predictor. A diagnostic predictor was built on the basis of the gene expression signatures published by Alizadeh et al.3 From this report,3 we obtained a reference of 325 IMAGE clones.31 We could obtain references to 185 genes by using MADgene,32 and 140 did not have any annotation. Among them, 85 genes (258 probes) were listed in the Agilent Whole Human Genome microarrays (G4112F). From this set, we selected the genes, discriminating the samples into two classes, one overexpressing GCB genes and another overexpressing ABC genes. This selection resulted in a list of 48 genes.

Sample classification with the gene expression–based COO predictor. The prediction of GCB and ABC classes for each sample is shown in Appendix Figure A1 (online only). Considering the gene expression classification by Alizadeh et al,3 51% of the cases were predicted as GCB occurrences, and 49% were predicted as ABC occurrences, with an identical prediction within the matched pairs. Two samples could not be predicted. Concordance between the algorithm by Hans and gene expression profiling results was calculated at 75% of the occurrences (\( n = 28 \) of 37). Two patients were classified as GCB by the Hans algorithm who were showing ABC gene expression profiling. Six patients were classified as non-GCB by the Hans algorithm who were showing GCB gene expression profiling.

Prognostic impact. Survival analysis demonstrated that GCB-like DLBCLs have a better PFS and OS than ABC-like DLBCLs, with 3-year OS rates of 74% for GCB and 40% for ABC and with 3-year PFS rates at 70% for GCB and 28% for ABC. When subgrouping the patients according to their gene expression profiling groups and according to the type of treatment with R-DHAP or R-ICE (\( n = 10, 16, 12, \) and 8, respectively), patients with GCB-like DLBCL treated with R-DHAP had a better outcome than patients with GCB-like DLBCL treated with R-ICE (Figs 2A to 2D). The 3-year PFS was 100% for GCB-like DLBCL treated with R-DHAP, whereas the 3-year PFS for GCB DLBCL treated with R-ICE was 27% (\( P = .01 \)). Patients with ABC-like DLBCL had an unfavorable course irrespective of the treatment, R-ICE or R-DHAP, with 3-year PFS rates of 60% and 30%, respectively.
DISCUSSION

In this study, we biologically analyzed a population of patients younger than 65 years who had DLBCL at first relapse or progression after one line of chemotherapy that was based on anthracycline and who were enrolled on the international, multicenter, CORAL trial.\(^2^7\) Selected patients were representative of the whole population, with similar clinical characteristics and identical clinical prognostic parameters, including aIPI, early relapse, prior rituximab exposure and secondary aIPI. We confirmed that patients who had relapsed/refractory DLBCL could be profiled on the basis of the COO entities, and we demonstrated that patients with GCB-like DLBCL have an improved outcome when treated with R-DHAP compared with R-ICE in the context of a randomized trial.

Biomarkers were analyzed to help us understand the biologic basis for the outcomes of these patients with relapsed/refractory DLBCL. We did not find any individual immunohistochemical or FISH markers sufficiently powerful to predict survival independently from the aIPI, except FOXP1. FOXP1 expression was significantly associated with a poorer PFS and OS but had a marginal prognostic

### Table 3. Immunohistochemical Staining Results, Cell of Origin Classification, Chromosomal Break Points, and Their Association With OS and PFS by Univariate Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diagnosis</th>
<th>Relapse</th>
<th>Pooled Occurrences</th>
<th>OS</th>
<th>PFS</th>
<th>CR</th>
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Abbreviations: ABC, activated B-cell; CR, complete response; FISH, fluorescent in situ hybridization; GC, germinal cell; GCB, germinal center B; OS, overall survival; PFS, progression-free survival.

\(^1^3\)Double-hit lymphomas were observed in 20 occurrences with the combination BCL2+/MYC+, BCL6+/MYC+, BCL2+/BCL6+ in 12, four, and four occurrences, respectively. BCL2+/BCL6+/MYC+ triple-hit lymphomas were observed in four occurrences.
value in our series (PFS, \(P = .02\); OS, \(P = .03\)). Several other biomarkers (BCL6, BCL2 expression, and c-MYC breakpoint) had a statistical significance in PFS or in OS in the separated subgroups as defined by the group of primary biopsies or the group of relapse biopsies. However, none of these abnormalities, except for the c-MYC breakpoint, were associated with a poorer outcome when the analysis was conducted for the whole group of patients. Additionally, none of the algorithms significantly predicted survival. These results may be due to the interaction between biomarkers and clinical characteristics and/or treatment. Interactions between several biologic markers, such as BCL6 expression, BCL2 breakpoint, Hans algorithm, and treatment were found to be significant, indicating that treatment efficacy depended on the pattern of these risk factors.

Thirty-one percent of the occurrences interpretable by FISH harbored \(t(14;18)\). This chromosomal abnormality was significantly associated with a GCB phenotype on the basis of the Hans algorithm. We cannot exclude that, in our retrospective series, these occurrences of GCB-DLBCL with \(t(14;18)\) correspond to transformed FL, which can not be distinguish morphologically—including by histology, immunohistochemistry, and gene expression profiling—from de novo GCB DLBCL.

Importantly, in studying matched cases, we observed similar phenotype and genotype between primary and relapse biopsies, suggesting that tumor biology of DLBCL is present at time of diagnosis with all characteristics and is stable over the evolution. Therapeutic implications of this observation are important because of the possible use of targeted therapies.

Our results demonstrated that COO is one of the main predictive factors for the response to treatment in patients with relapsed/refractory DLBCL treated by a nonanthracycline-based immunochecmotherapy. This finding has already been suggested in first-line therapy.\(^{20,33,34}\) However, this finding remains controversial, and others authors have not reported any differences.\(^{35}\) This controversy may be explained by these differences: retrospective analyses gather different population of patients, different treatment protocols (R-CHOP, DA-EPOCH with sequential rituximab or concurrent rituximab) can be used, and there was a relatively short follow-up period.\(^{36}\) One important issue is also the accuracy of immunohistochemical determination of tumor phenotype. Validation with gene expression profiling is an important control. These limitations have been well reported by the Lunenbourg Lymphoma Biomarker Consortium study.\(^{37,38}\) In this study, even if the series of patients analyzed by gene expression profiling was small, we could confirm by gene expression profiling a survival benefit under R-DHAP treatment in patients who had GCB-like DLBCL compared with patients who had ABC-like DLBCL.

![Fig 1.](image-url) (A, B) Progression-free survival (PFS) and (C, D) overall survival (OS) according to the (A, C) rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) versus (B, D) rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) treatment arms (ie, Collaborative Trial in Relapsed Aggressive Lymphoma [CORAL] first-line therapy.\(^{20,33,34}\) However, this finding remains controversial, and others authors have not reported any differences.\(^{35}\) This controversy may be explained by these differences: retrospective analyses gather different population of patients, different treatment protocols (R-CHOP, DA-EPOCH with sequential rituximab or concurrent rituximab) can be used, and there was a relatively short follow-up period.\(^{36}\) One important issue is also the accuracy of immunohistochemical determination of tumor phenotype. Validation with gene expression profiling is an important control. These limitations have been well reported by the Lunenbourg Lymphoma Biomarker Consortium study.\(^{37,38}\) In this study, even if the series of patients analyzed by gene expression profiling was small, we could confirm by gene expression profiling a survival benefit under R-DHAP treatment in patients who had GCB-like DLBCL compared with patients who had ABC-like DLBCL.
However, the present findings were retrospectively observed and should be cautiously considered as hypothesis generating. Definitive observation of the survival benefit under R-DHAP treatment in patients with GCB-like DLBCL have to be performed by prospective randomized trials that are based on a COO stratification.

Understanding the relationship of tumor biology to outcome is important for the identification of molecular targets and for improvement of therapy. The hypothesis as proposed by Wilson et al.\textsuperscript{20} for a different result of DA-EPOCH with a better efficacy in GCB-like DLBCL than in ABC-like DLBCL was due to a prolonged exposure of agents, particularly topoisomerase II inhibitors.\textsuperscript{20} Our results did not support this hypothesis, as the best results were obtained with cytarabine in GCB-like DLBCL and not with etoposide. However, drug combinations and regimen schedules were also different, and this could be of importance. The BCL6 oncogenic transcriptional repressor is required for the development of germinal center centroblasts and directly represses TP53.\textsuperscript{39} One can hypothesize that cytarabine might modulate BCL6 expression through epigenetic mechanisms to allow the release of TP53. Dexamethasone known for inducing apoptosis in leukemia cells, via mechanisms that are yet unknown, might also act differently in function of the COO. In contrast, the poor outcome of ABC-like DLBCL, might relate to the constitutive activation of the nuclear factor kappa \( \beta \) pathway.\textsuperscript{7,40,41} Inhibition of nuclear factor kappa \( \beta \) and blockade of its ability to inhibit apoptosis in ABC cell lines is toxic, and recent clinical evidence suggests that the ABC-like DLBCL can be preferentially targeted (over the GCB-like DLBCL) by strategies that block I kappa \( \beta \) degradation.\textsuperscript{6,7,34,40}

In conclusion, COO remains a major factor in patients who experienced disease relapse and who have a better response to R-DHAP salvage chemotherapy in GCB-like DLBCL. Treatment of the ABC subtype is still unsatisfactory, with a classical multidrug regimen. Our study highlights the pivotal role of tumor biology in the rational design of targeted therapies in DLBCL and the importance of well-designed prospective studies.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about

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**Fig 2.** Progression-free survival (FFS; A, B) and overall survival (OS; C, D) according to the treatment and germinal center B (GCB)/activated B-cell (ABC) status as classified by the gene predictor on the basis of gene signatures published by Alizadeh et al.\textsuperscript{3} Blue lines indicate patients with a GCB profile (n = 19; 51%). Gold lines indicate patients with an ABC profile (n = 18; 49%). Patients with GCB-like diffuse large B-cell lymphoma (DLBCL) treated with rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) had a significant better (A) FFS and (C) OS than patients with ABC-like DLBCL treated with R-DHAP. Patients treated with (B, D) rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) had poor survival regardless of the molecular subtype.
Thieblemont et al

Provision of study materials or patients: Catherine Thieblemont, Andreas Rosenwald, Andrew Jack, Christer Sundstrom, Sergio Cogliatti, Philippe Trouougoboff, Ludmila Boudova, Loic Ysebaert, Dominique Bron, Norbert Schmitz, Philippe Gaulard, Christian Gisselbrecht


Manuscript writing: All authors

Final approval of manuscript: All authors

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Rituximab Maintenance Therapy After Autologous Stem-Cell Transplantation in Patients With Relapsed CD20\(^+\) Diffuse Large B-Cell Lymphoma: Final Analysis of the Collaborative Trial in Relapsed Aggressive Lymphoma


ABSTRACT

Purpose
The standard treatment for relapsed diffuse large B-cell lymphoma (DLBCL) is salvage chemotherapy followed by high-dose therapy and autologous stem-cell transplantation (ASCT). The impact of maintenance rituximab after ASCT is not known.

Patients and Methods
In total, 477 patients with CD20\(^+\) DLBCL who were in their first relapse or refractory to initial therapy were randomly assigned to one of two salvage regimens. After three cycles of salvage chemotherapy, the responding patients received high-dose chemotherapy followed by ASCT. Then, 242 patients were randomly assigned to either rituximab every 2 months for 1 year or observation.

Results
After ASCT, 122 patients received rituximab, and 120 patients were observed only. The median follow-up time was 44 months. The 4-year event-free survival (EFS) rates after ASCT were 52% and 53% for the rituximab and observation groups, respectively (\(P = .7\)). Treatment with rituximab was associated with a 15% attributable risk of serious adverse events after day 100, with more deaths (six deaths v three deaths in the observation arm). Several factors affected EFS after ASCT (\(P < .05\)), including relapsed disease within 12 months (EFS: 46% v 56% for relapsed disease after 12 months), secondary age-adjusted International Prognostic Index (saaIPI) more than 1 (EFS: 37% v 61% for saaIPI < 1), and prior treatment with rituximab (EFS: 47% v 59% for no prior rituximab). A significant difference in EFS between women (63%) and men (46%) was also observed in the rituximab group. In the Cox model for maintenance, the saaIPI was a significant prognostic factor (\(P < .001\)), as was male sex (\(P = .01\)).

Conclusion
In relapsed DLBCL, we observed no difference between the control group and the rituximab maintenance group and do not recommend rituximab after ASCT.

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INTRODUCTION

The addition of the anti-CD20 monoclonal antibody rituximab to various chemotherapies\(^1-3\) has dramatically improved the response rates in diffuse large B-cell lymphoma (DLBCL) and has resulted in complete responses (CRs) in 75% to 80% of patients. The use of rituximab in first-line treatment improves the overall survival (OS), the 5-year event-free survival (EFS) from 29% to 47% in older patients (60 to 80 years),\(^4\) and the 3-year EFS from 59% to 79% in younger patients (18 to 60 years).\(^5\) However, patients with a poor International Prognostic Index (IPi) require more effective treatment options because they have an unsatisfactory CR rate and a high relapse rate.\(^6,7\) In patients who do not achieve a CR or who experience relapse but remain sensitive to salvage chemotherapy, the therapy should be consolidated with high-dose therapy (HDT) and autologous stem-cell transplantation (ASCT).\(^8\) Even in
the rituximab era,\textsuperscript{9} only 10\% of these patients obtain long-term disease-free survival with salvage chemotherapy alone.\textsuperscript{10} The addition of rituximab to second-line chemotherapy followed by ASCT significantly improves progression-free survival (PFS) in patients who do not receive rituximab in their first-line treatment.\textsuperscript{11}

Maintenance treatment has been used successfully in relapsed follicular lymphoma.\textsuperscript{12} Furthermore, maintenance treatment after ASCT showed some encouraging results in refractory DLBCL,\textsuperscript{13,14} but a randomized study in first-line treatment revealed no significant survival advantage.\textsuperscript{15}

The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study was organized among 12 countries. In this study, patients with refractory or relapsed CD20\textsuperscript{−} DLBCL were randomly assigned to either rituximab, ifosfamide, carboplatin, and etoposide (R-ICE)\textsuperscript{16} or rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP).\textsuperscript{17} Patients who responded to the chemotherapy were submitted to HDT and ASCT. The initial results\textsuperscript{18} revealed no significant difference in outcome between the two regimens. However, several factors did affect survival, including early relapse (< 12 months), the IPI at relapse, and prior exposure to rituximab. The results of the post-transplantation part of the trial, comparing rituximab treatment every 2 months for 1 year with observation alone, and the factors that influenced patient outcome are reported herein.

### PATIENTS AND METHODS

This study was a phase III, multicenter, randomized trial that compared the efficacy of R-ICE and R-DHAP in patients with previously treated DLBCL followed by ASCT with or without rituximab maintenance therapy. There were two separate random assignments for salvage therapy and maintenance therapy after transplantation.\textsuperscript{18} The present report focuses on the primary end point for the maintenance phase.

Patients were stratified according to participating country, prior rituximab treatment, and relapse within 12 months of diagnosis. The primary end point was EFS, and the secondary end points included response rate, PFS, OS, and toxicities. To detect a 15\% change in the 2-year EFS after ASCT in the maintenance therapy arm (65\%) versus no maintenance therapy (50\%) and to provide an 80\% power at the overall 5\% (two-sided) significance level, power analyses revealed that 240 patients who underwent ASCT were required for a 1:1 random assignment into two treatment groups over 3 years and that they should be observed for a minimum of 2 years. The expected number of events during a 3-year period was 140 events. This sample size takes drop-out rates as a result of the salvage treatment and transplantation procedure into account. Initially, we expected a 40\% drop-out rate, but this estimate was adjusted to 50\% after the first interim analysis of 200 patients. As suggested by the data monitoring committee in May 2007, the initial sample size was amended from 400 to 480 participants to maintain the planned power with 240 patients (Data Supplement).

This study was designed by the steering committee of CORAL and approved by the relevant institutional review boards or ethics committees. All patients gave written informed consent. The study is registered under EUDRACT No. 2004-002103-32 and ClinicalTrials.gov NCT00137995.

### Patients

In brief, the CORAL study included patients 18 to 65 years old with aggressive CD20\textsuperscript{+} B-cell lymphoma, including DLBCL with relapse or patients who did not achieve CR using a standard anthracycline-based (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen. All patients underwent histologic confirmation of CD20\textsuperscript{+} aggressive B-cell lymphoma before enrollment. Eligible patients had a WHO performance status of 0 to 1. Exclusion criteria included CNS involvement, history of HIV infection, post-transplantation lymphoproliferative disorder, and inadequate organ function. Patients were fully evaluated, including computed tomography (CT) scanning of the thorax and abdomen and bone marrow biopsy. The secondary age-adjusted IPI (saaIPI) was determined according to the absence or presence of risk factors, poor performance status, elevated lactate dehydrogenase, and disseminated stage before salvage treatment.\textsuperscript{19,20} Patient enrollment occurred between July 2003 and June 2008, and the last patient was randomly assigned in the maintenance phase of the study in October 2008. In total, 481 patients were randomly assigned to the R-ICE arm (n = 243) or the R-DHAP arm (n = 234; Fig 1). A total of 255 patients who achieved CR (n = 142), partial response (PR; n = 92), or stable disease (n = 7) after the third cycle of salvage treatment received consolidation with ASCT, and 242 patients received maintenance rituximab (n = 122) or observation (n = 120; Fig 1).

Characteristics at the second random assignment are listed in Table 1. Patient characteristics at entry for all patients are provided in the Data Supplement. No significant differences between the two arms were observed. Histologic materials were reviewed by local hematopathologists in the participating centers. An international central review was performed in 69\% of the patients, and 18 patients were not reviewed as having DLBCL (two patients had follicular lymphoma grade 3, five patients had follicular lymphoma grade 2, two patients had T-cell lymphoma, two patients had Hodgkin lymphoma, and seven patients remained unclassified).

### Treatment

Details of the treatment and monitoring have been published previously.\textsuperscript{18} Briefly, only chemotherapy-sensitive patients (CR, unconfirmed CR [CRu], or PR) after three cycles of R-ICE\textsuperscript{16} or R-DHAP\textsuperscript{17} received a consolidation with high-dose chemotherapy (carmustine, etoposide, cytarabine, and melphalan [BEAM]) followed by ASCT. These patients were randomly assigned to groups with or without rituximab maintenance therapy (375 mg/m\textsuperscript{2} every 8 weeks for 1 year) on day 28 after ASCT (Fig 2).

Radiotherapy after transplantation was not performed, and it was considered as an event. Supportive treatments were administered according to the standard use in each center.

### Assessment of Response and Follow-Up

Response was assessed using conventional diagnostic methods, including CT scanning after the third chemotherapy course. Positron emission tomography scans were not mandatory, and bone marrow biopsies were repeated only if the samples were observed to be abnormal before treatment.

Response was assessed using the International Working Group criteria.\textsuperscript{21} CR was defined as the disappearance of all documented disease, and CRu was used in cases of residual mass. PR included a 50\% reduction in measurable disease. Follow-up procedures included a physical examination every 3 months for the first year with a complete evaluation at the end or at an earlier time point if clinically indicated. Follow-up procedures were performed every 6 months for 2 years thereafter, and thoracic and abdominal CT scans were performed annually.

### Statistical Analysis

Analyses were first performed following the intent-to-treat principle. EFS was defined as the time from treatment initiation to progression, relapse, new treatment, or death by any cause, whichever occurred first. It was considered an event if patients received alternative treatment outside of the protocol. PFS was defined as the time from study entry until disease progression or death by any cause. OS was defined as the time from treatment initiation to death by any cause.

Survival functions were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses
were performed using a Cox proportional hazards model. Differences between the results of comparative tests were considered significant if the two-sided $P < .05$. All statistical analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, NC).

**RESULTS**

**Response to Treatment**

The overall response rate (CR + CRu + PR) after salvage chemotherapy and before transplantation was 63% in the R-ICE group and 64% in R-DHAP group, with 142 patients (58%) experiencing CR or CRu and 92 patients (38%) exhibiting PR before ASCT. For patients with prior exposure to rituximab and progression within 12 months of diagnosis, the overall response rate was 46% (Data Supplement).

A total of 245 patients received BEAM and ASCT, and 242 evaluable patients were randomly assigned to either the treatment group (Fig 2, Table 1) with rituximab or the observation-only group. In the treatment group, 78 patients (67%) received all six cycles; new progression of the disease was the primary reason for patients not completing the full treatment. At the end of the maintenance therapy, the CR rates were 57% and 50% for the rituximab and observation groups, respectively, including all deaths.

**Survival**

After a median follow-up of 44 months for the 469 patients who were enrolled, no difference was detected between the treatment and control arms of the study. The 4-year OS was 43% (95% CI, 36% to 50%) for the R-ICE arm and 34% (95% CI, 36% to 50%) in the R-DHAP arm ($P = .2$; Appendix Figs A1A and A1B, online only).

Considering only patients who received ASCT and were randomly assigned to the maintenance arm after ASCT, the 4-year EFS was 52% (95% CI, 42% to 61%) in the rituximab group and 53% (95% CI, 44% to 62%) in the observation group ($P = .7$; Fig 3A). We observed no difference in the PFS ($P = .8$) or OS between the rituximab group and the observation group (Table 2). We also observed no significant difference between the patients who achieved CR or PR before ASCT (Table 2, Fig 3B).

The 4-year EFS, PFS, and OS after ASCT were affected by a number of factors, including prior treatment with rituximab, early relapse, and saaIPI (Table 2, Figs 3C and 3D). However, the Cox model revealed that only an saaIPI of 2 to 3 remained significant ($P < .001$) for the EFS, PFS, and OS. Men performed significantly poorer than women (Table 2), a finding that was related to the superior survival of women in the rituximab group (Figs 4A to 4C). Additional subset analyses are included in the Data Supplement. In the multivariate analyses of PFS, male sex ($P = .01$) and saaIPI ($P < .001$) remained significant prognostic factors. Treatment arm, early relapse, prior rituximab exposure, and PR were no longer significant factors (Data Supplement). However, in a subset analysis based on sex that compared the rituximab and observation groups, the 3-year EFS was 43% (95% CI, 31% to 54%) in men and 69% (95% CI, 53% to 81%) in women ($P = .1$; Data Supplement).

**Relapse and Progression**

The first progression or relapse was observed in 47 and 46 patients in the rituximab and observation groups, respectively, among 469 patients who were enrolled in the study. The 4-year DFS was 52% (95% CI, 42% to 61%) in the rituximab group and 53% (95% CI, 44% to 62%) in the observation group ($P = .7$; Appendix Figs A1A and A1B, online only).

A total of 245 patients received BEAM and ASCT, and 242 evaluable patients were randomly assigned to either the treatment group (Fig 2, Table 1) with rituximab or the observation-only group. In the treatment group, 78 patients (67%) received all six cycles; new progression of the disease was the primary reason for patients not completing the full treatment. At the end of the maintenance therapy, the CR rates were 57% and 50% for the rituximab and observation groups, respectively, including all deaths.

**Survival**

After a median follow-up of 44 months for the 469 patients who were enrolled, no difference was detected between the treatment and control arms of the study. The 4-year OS was 43% (95% CI, 36% to 50%) for the R-ICE arm and 34% (95% CI, 36% to 50%) in the R-DHAP arm ($P = .2$; Appendix Figs A1A and A1B, online only).

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during the follow-up period. Although this occurrence was at the initial site, half included a new site of involvement. These patients underwent various additional treatments, including radiotherapy (25%) and chemotherapy (76%) with transplantation (14 allografts; Data Supplement). A second CR was observed in 21 patients and a PR in 13 patients.

The majority of deaths were a result of lymphoma. Forty-three deaths occurred in the rituximab group, and 17 of these deaths occurred within 1 year after the transplantation. Thirty-eight deaths occurred in the observation group, and 19 occurred within 1 year after ASCT.

### Adverse Events

The treatment was well tolerated, and the reported events were separated into those that occurred before day 100 after ASCT and those that occurred after day 100. A total of 87 adverse events (AEs) were reported in 54 patients (47%) within 100 days in the rituximab group, whereas 75 AEs were reported in 50 patients (42%) in the observation group. A total of 75 AEs were reported in 35 patients (30%) in the rituximab group more than 100 days after ASCT, whereas 24 AEs were observed in 20 patients (17%) in the observation group. The majority of the AEs were infections; 45 episodes of infection were reported in the rituximab group, and 13 episodes were reported in the observation group. Grade 3 or greater delayed neutropenia after day 100, excluding values after additional treatment, was reported in 11 patients (9%) in the rituximab group and in seven patients (6%) in the observation group.

Forty-three serious AEs (SAEs) were reported in the rituximab group, and 22 SAEs were reported in the observation group. After day 100, 23 SAEs were reported in the rituximab arm, and only five were reported in the observation group. Fatal outcomes were observed in six patients in the rituximab group and three patients in the observation group; four deaths resulted from secondary cancers (two in the rituximab group and two in the observation group), one death resulted from varicella and one death resulted from myocarditis several months after the end of the treatment, and three deaths resulted from infections and pneumonia.

### DISCUSSION

The present results demonstrate a similar response rate of 63% for the two initial chemotherapy regimens over a 4-year follow-up, but only 37% of the patients attained CR. In addition, only 51% of patients were able to undergo ASCT. We did not observe a difference in the

---

**Table 1. Baseline Demographic and Clinical Characteristics of the Patients Randomly Assigned for Maintenance (Intent to Treat)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rituximab (n = 122)</th>
<th>Observation (n = 120)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>54</td>
<td>54</td>
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</tr>
<tr>
<td>Range</td>
<td>19-65</td>
<td>19-65</td>
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<tr>
<td>&lt; 40</td>
<td>17</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46</td>
<td>37</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Median</td>
<td>25.8</td>
<td>26.7</td>
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<td>Range</td>
<td>17.3-36.8</td>
<td>18.3-45.2</td>
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</tr>
<tr>
<td>&gt; 30</td>
<td>21</td>
<td>28</td>
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<td>Ann Arbor stage</td>
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<tr>
<td>I-II</td>
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<td>III-IV</td>
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<td>Extranal site &gt; 1</td>
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<tr>
<td>Elevated LDH</td>
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<tr>
<td>Response after salvage</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>therapy</td>
<td>CR + CRu</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td>PR</td>
<td>47</td>
<td>45</td>
<td></td>
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<tr>
<td>Stable disease</td>
<td>2</td>
<td>5</td>
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<tr>
<td>saaIPI at relapse</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0-1</td>
<td>84</td>
<td>81</td>
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<tr>
<td>2-3</td>
<td>36</td>
<td>36</td>
<td>NS</td>
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<tr>
<td>Time to relapse, months</td>
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<tr>
<td>&lt; 12*</td>
<td>33</td>
<td>41</td>
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<tr>
<td>≥ 12</td>
<td>89</td>
<td>76</td>
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<tr>
<td>Prior rituximab treatment</td>
<td>63</td>
<td>62</td>
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<tr>
<td>Prior CHOP-like first-line</td>
<td>102</td>
<td>100</td>
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<td>chemotherapy</td>
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<tr>
<td>Salvage regimen</td>
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<tr>
<td>R-ICE</td>
<td>60</td>
<td>56</td>
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</tr>
<tr>
<td>R-DHAP</td>
<td>62</td>
<td>64</td>
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</tr>
</tbody>
</table>

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; CRu, uncertain complete response; LDH, lactate dehydrogenase; NS, not significant; PR, partial response; R-DHAP, rituximab, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; SD, stable disease.

*Including patients not achieving CR in first-line treatment.
survival rates between the two treatment regimens after ASCT. In the multivariate analysis for maintenance, the hazard ratio for R-ICE was 1.47 (95% CI, 0.98 to 2.2; $P = 0.06$). This trend of an improved outcome for R-DHAP (Appendix Fig A1) may reflect the observed preference for the germinal center B subtype for this regimen in the subset analysis.22

The objective of the second part of this study was to test the hypothesis that rituximab treatment after transplantation would reduce the relapse rate in these patients. Although patients who received HDT with BEAM and ASCT were randomly assigned to either rituximab or the observation group, no difference was observed between these two groups (Fig 3). However, the toxicity was increased by 15% in reported SAEs in the rituximab arm after day 100 after ASCT, with an excess of deaths by infections that was most likely related to immunodeficiency. Only 10% of patients in the rituximab-treated group experienced delayed neutropenia, which was not significantly different from patients in the observation arm. Maintenance rituximab therapy after ASCT has been evaluated over different durations and treatment strategies, but it has been primarily examined in the context of short treatment courses administered soon after transplantation.13-15 The increase in toxicity that was observed after this treatment raises concerns about prolonging immunodeficiency after ASCT and leads us to propose only 1 year of treatment, rather than the 2 years of treatment recommended in cases of follicular lymphoma.

This first randomized study does not support the promising results that had been described in two phase II studies after ASCT.13,14 These results are consistent with our randomized study of high-risk DLBCL where 269 patients were randomly assigned to either an observation-only control group or a treatment group who received 4 weekly injections of rituximab after transplantation,15 which found that rituximab treatment lacked efficacy. These results are also consistent with those of the Intergroup study,3 which reported that maintenance therapy had no impact on patients who had previously been exposed to rituximab. The duration of the maintenance therapy does not explain these results because 50% of the relapses after ASCT occurred during the maintenance period. Rituximab alone has limited activity in DLBCL, and its role is mostly related to chemotherapy sensitization of the lymphoma by different mechanisms that are not completely understood.23

The previously described factors that affected the outcome of patients who received transplantation were also identified in our univariate analysis (Table 2). The saaIPI score was the only significant variable that was associated with male sex in the multivariate analyses.
Male sex is an adverse prognostic factor in follicular lymphomas and DLBCL in the rituximab era.\textsuperscript{24,25} One striking observation in the present study was the significant survival difference between women and men who received rituximab maintenance therapy. This disparity cannot be explained by the underlying sex-related mortality hazard (ie, the natural 5- to 10-year survival advantage of women over men in the general population) because no such sex difference was observed in the observation arm. A higher rituximab clearance in males, which results in lower rituximab exposure, has been reported previously.\textsuperscript{24} These results are similar to the findings of Ng et al\textsuperscript{26} in a population approach examining the outcome of rituximab in patients with rheumatoid arthritis. These investigators also observed a 39% greater clearance of rituximab in men than in women. In our study, the impact of rituximab was obscured in overweight postmenopausal women who presented higher testosterone levels as a result of hyperinsulinism.\textsuperscript{27} Therefore, we hypothesize that the lower survival impact of rituximab that we observed in males may be a result of hormone-related pharmacokinetic variations. Thus, the impact of an increased dose of rituximab on survival requires further investigation using randomized studies.

<table>
<thead>
<tr>
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<tr>
<td>Patients</td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td>Arm</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Observation</td>
</tr>
<tr>
<td>R-ICE</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Observation</td>
</tr>
<tr>
<td>R-DHAP</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Observation</td>
</tr>
<tr>
<td>Prior rituximab</td>
</tr>
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<td>No</td>
</tr>
<tr>
<td>Treatment failure, months</td>
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<tr>
<td>≥12</td>
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<td>Sex</td>
</tr>
<tr>
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</tr>
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<td>Rituximab arm</td>
</tr>
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<td>Female</td>
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<tr>
<td>Female</td>
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Abbreviations: CR, complete response; CRu, unconfirmed complete response; EFS, event-free survival; OS, overall survival; PFS, progression-free survival; PR, partial response; R-DHAP, rituximab dexamethasone, cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; saaIPI, secondary age-adjusted International Prognostic Index.

Our data are surprising because no other drugs were involved after ASCT. The role of rituximab in DLBCL requires further analysis, as does the role of sex, in large randomized studies with or without rituximab maintenance. In summary, rituximab maintenance therapy does not prevent relapse after ASCT and was associated with higher toxicity. Therefore,
this treatment is not recommended in relapsed DLBCL. The initial prognostic parameters still apply for patients who receive transplantation. The patient population in this study is representative of patients who will require innovative approaches to treatment in the future. Consequently, new drugs that are designed to increase the response rate of salvage regimens and novel approaches, including allogeneic transplantation, should be explored. An improved understanding of the biology of DLBCL derived at least in part from studies of patient tumor specimens will play a key role in the development of novel targeted therapies for this disease.

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix


Overall Survival (proportion)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
</tr>
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<tr>
<td>Overall Survival (proportion)</td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

P = .2672

Arm A/R-ICE

Arm B/R-DHAP

No. of Patients: 239

Event: 71% (170)

Censored: 29% (69)

Median Survival (95% CI): 6.51 (4.99 to 9.92)

No. of Patients: 230

Event: 67% (153)

Censored: 33% (77)

Median Survival (95% CI): 7.49 (5.82 to 12.71)

P = .338

Arm A/R-ICE

Arm B/R-DHAP

No. of Patients: 239

Event: 52% (125)

Censored: 48% (114)

Median Survival (95% CI): 34.53 (23.85 to 51.42)

No. of Patients: 230

Event: 49% (112)

Censored: 51% (118)

Median Survival (95% CI): 58.97 (23.23 to NA)

Fig A1. (A) Event-free survival (EFS) according to treatment arm from induction treatment. (B) Overall survival (OS) according to treatment arm (induction intent to treat). NA, not available; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide.
PROTOCOL CORAL: 50-03B / STATISTICAL REPORT:
ANALYSIS OF INDUCTION PART

RANDOMIZED STUDY OF ICE PLUS RITUXIMAB (R-ICE) versus DHAP PLUS RITUXIMAB
(R-DHAP) IN PREVIOUSLY TREATED PATIENTS WITH CD 20 POSITIVE DIFFUSE LARGE B-
CELL LYMPHOMA, ELIGIBLE FOR TRANSPLANTATION FOLLOWED BY RANDOMIZED
MAINTENANCE TREATMENT WITH RITUXIMAB

Phase III clinical trial

SPONSOR:

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LIST OF ABBREVIATIONS

AE  Adverse Event
CRF  Case Report Form
FAS  Full Analysis Set
ITT  Intent-to-Treat
Max  Maximum
Min  Minimum
Q1  First quartile
Q3  Third quartile
SAE  Serious Adverse Event
Std  Standard deviation
vs  versus
95% CI  95% Confidence Interval
1. INVESTIGATIONAL PLAN

1.1. Overall study design
This study is a multicenter, phase III open-label, randomized trial evaluating the efficacy of R-ICE compared to R-DHAP in patients aged from 18 to 65 years with previously treated diffuse large B-cell lymphoma, followed by high-dose chemotherapy +/- rituximab maintenance therapy. There will be two phases in the study and patients will undergo two randomizations according to induction phase or maintenance phase.

1.2. Study objectives

1.2.1. Primary objective
Part I (induction chemotherapy): Overall response rate (CR and PR) after 2 and/or 3 cycles of ICE+Rituximab in comparison to DHAP+rituximab, adjusted to successful mobilization of stem cells in patients aged from 18 to 65 years with previously treated diffuse large B-cell lymphoma CD20.
Part II (Maintenance vs. observation): Event free survival (EFS) at 2 years after autotransplant with or without maintenance therapy with rituximab. Events are defined as death from any cause, relapse for complete responders and unconfirmed complete responders (CRu), progression during or after treatment for partial responders, and institution of new antilymphoma therapy. The absence of transplantation procedure will be not considered as an event for the intent to treat analysis.

1.2.2. Secondary objectives
– Eligibility for transplant, (independent from whether transplantation was done or not) transplantation done or not.
– Safety toxicities.
– Event-Free Survival, Progression-Free Survival and Overall Survival for the whole randomized population, for patients submitted to ASCT.
– Progression-Free Survival and Overall Survival for patients randomized in maintenance.

2. STATISTICAL METHODOLOGY

2.1. Statistical methods
Statistical analysis was planned and performed as it follows:

Descriptive statistics
Quantitative variables were summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles were presented when considered relevant.
Qualitative variables were described in terms of frequencies of each response category and frequencies converted into percentages of the number of patients or adverse events examined depending on the statistical unit under investigation.
Censored data were presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% CIs. The median time to event was calculated (if reached) with 95% CIs. Estimates of the treatment effect were expressed as hazard ratios based on the Cox regression with 95% confidence interval.
Statistical inference

Statistical tests were two-sided and performed using a 5% level of significance. 95% confidence intervals were also presented when considered relevant. Survival endpoints were analyzed using the log rank test (unstratified) and Cox model for corresponding hazard ratio and p-value of treatment effect and multivariate models.

The number and proportion of responders and non responders in each treatment group, together with the two-sided 95% Pearson-Clopper CI were presented, as well as the difference between proportion, the two-sided 95% asymptotic confidence interval and p-value of chi-square test.

All statistical analyses were carried out with SAS 9.1.3 software (SAS Institute, Cary, NC).

2.2. Determination of sample size

Part I induction:

The primary end point is mobilization adjusted response rate after 3 cycles of chemotherapy and it is expected to detect a difference in mobilization adjusted response rate of 15% between R-ICE 60% (75% response rate and 15% mobilization failure) and R-DHAP 45% (65% response rate and 20% mobilization failure) with a 82% power at 5% significance level. 400 patients should be randomized between the two chemotherapy arms. Initially 400 patients are to be randomised 1:1 to either R-ICE or R-DHAP.

It was expected that 40% of these patients will either not achieve Complete Response or Partial Response or drop-out before ASCT. Immediately prior to ASCT it was expected that there will be 240 patients (400 x 60%) available for second randomisation (1:1) into the maintenance or mabthera arms. First safety analysis on 100 patients (reviewed by DSMC on 14th November 2005) and first interim analysis on 200 patients (18th April 2007) showed that the drop-out rate is 50%.

Then, in order to keep the planned power with 240 patients for the maintenance or mabthera arms, we increase the initial sample size from 400 to 480 (240 each)

Part II maintenance:

The primary endpoint of event free survival (EFS) was used to assess sample size. If we wish to detect after transplantation a change in the 2 year event-free of 15% in favor of the MabThera arm 65 % versus no maintenance 50 %, 240 patients transplanted, randomized 1:1 between the two treatment groups recruited over 3 years and followed for a minimum of two years, will provide 80% power at the overall 5% (2-sided) significance level to detect the expected difference.

2.3. Interim analysis

An interim analysis of the two parts, response rate and EFS efficacy parameter was planned after 200 patients, necessitating an adjustment of the nominal significance (α-level) for the final analysis to maintain the overall global significance level. The O’Brien-Fleming adjustment will be used to partition the α-level with α=0.003 at the first interim for response and α=0.05 at the final analysis.

An interim analysis of the primary efficacy parameter was planned after the inclusion of 200 patients leading to 100 patients randomized to the maintenance treatment. It necessitates an adjustment of the nominal significance (α-level) for the final analysis to maintain the overall global significance level. The O’Brien-Fleming adjustment will be used to partition the α-level with α=8.10^{-5} (40 events) at the first interim and α=0.05 at the final analysis. The expected number of events during the five years is 140 to 145.
3. STUDY PATIENTS

3.1. Disposition of patients

The whole set of 481 patients was first randomized from July 24, 2003 to June 30, 2008 (approximately five years of enrollment). 245 patients were then randomized in the 2nd part of the study from October 21, 2003 to October 21, 2008.

Nevertheless, CRFs for 4 patients could not be recovered.

<table>
<thead>
<tr>
<th>Listing 3.1-1 Patients with CRF not recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm of treatment=ARM A / R-ICE</strong></td>
</tr>
<tr>
<td>Randomization Number</td>
</tr>
<tr>
<td>----------------------</td>
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<tr>
<td>5003620201405</td>
</tr>
<tr>
<td>5003631201412</td>
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<tr>
<td><strong>N = 3</strong></td>
</tr>
</tbody>
</table>

<p>| Arm of treatment=ARM B / R-DHAP               |</p>
<table>
<thead>
<tr>
<th>Randomization Number</th>
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<th>Initials of family name</th>
<th>Initials of first name</th>
<th>Date of Birth</th>
<th>First Randomization Date</th>
<th>Date of 2nd randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003613301404</td>
<td>Australie - Nouvelle-Zélande</td>
<td>KEL</td>
<td>ER</td>
<td>30/01/1946</td>
<td>14/11/2006</td>
<td>08/02/2007</td>
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<td><strong>N = 1</strong></td>
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<td></td>
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</tr>
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</table>

Thus, 477 patients, 243 from R-ICE arm and 234 from R-DHAP arm, are evaluable for induction part, and 242 patients, 122 from the rituximab arm and 120 from the observation arm, are evaluable for maintenance part of the study.

This report deals with analysis of the induction part of the study.

The following flowcharts describe the disposition of patients during the whole study.
Figure 3.1-1 Disposition of patients according to arm of 1st randomization

Randomized patients
N = 481

CRF not recovered
N = 4

Evaluable patients
N = 477

R-ICE
N = 243

No study treatment received
N = 4
(one death, 3 protocol violations)

Received study treatment
N = 239

Withdrawn during induction
N = 34
(14 after C1, 20 after C2)
(20 for induction treatment failure, 7 for treatment toxicity, 3 for death, 2 for voluntary withdrawal, one other reason, one unknown)

Completed induction phase
N = 205
(one pt with only 2 cycles)

Received BEAM+ASCT
N = 123

Withdrawn during consolidation
N = 7
(2 deaths, 5 other reasons)

Randomized in maintenance
N = 116
(60 rituximab, 56 observation)

R-DHAP
N = 234

No study treatment received
N = 4
(one death, one protocol violation, 2 patient voluntary withdrawals)

Received study treatment
N = 230

Withdrawn during induction
N = 34
(14 after C1, 19 after C2)
(24 for induction treatment failure, 4 for treatment toxicity, 5 for death, one other reason)

Completed induction phase
N = 196

Received BEAM+ASCT
N = 132

Withdrawn during consolidation
N = 6
(one death, 5 other reasons)

Randomized in maintenance
N = 126
(62 rituximab, 64 observation)
Figure 3.1-2 Disposition of patients according to arm of 2\textsuperscript{nd} randomization

Randomized in maintenance  
$N = 245$

Evaluable patients  
$N = 242$

Rituximab  
$N = 122$  
(60 with R-ICE, 62 with R-DHAP)

Observation  
$N = 120$  
(56 with R-ICE, 64 with R-DHAP)

No maintenance visit  
$N = 3$  
(one transplantation failure, one voluntary withdrawal, one missing withdrawal)

Completed maintenance phase  
(6 injections)  
$N = 78$

Completed maintenance phase  
(6 visits)  
$N = 30$

Received study treatment  
(i.e. at least one injection)  
$N = 116$

Received study treatment  
(i.e. at least one visit)  
$N = 119$

No study treatment received  
$N = 6$  
(2 voluntary withdrawals, one lost to FU after ASCT, one missing withdrawal, 2 not treated with rituximab but maintenance visits)

Switched from rituximab arm  
$N = 2$
3.2. Patients recruitment

32 patients (7%) did not respect at least one criterion of inclusion/non inclusion: 19 patients (8%) in R-ICE arm and 13 patients (6%) in R-DHAP arm.

<table>
<thead>
<tr>
<th>Table 3.2-1 Criteria exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm of treatment</td>
</tr>
<tr>
<td></td>
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<tr>
<td>At least one criteria exception</td>
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</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

The following tables details inclusion and non inclusion criteria.

**Inclusion criteria**

1- Patient with histologically proven, CD20+ diffuse large B cell lymphoma in 1st relapse after CR, less than PR or partial response to first line treatment
2- Aged from 18 to 65 years inclusive
3- Eligible for transplant
4- Previously treated with chemotherapy regimen containing anthracyclin with or without rituximab
5- ECOG performance status ≤ 2
6- With a minimum life expectancy of 3 months
7- Signed informed consent form prior to randomization

The following table presents the number and the percentage of patients respecting or not the inclusion criteria:

<table>
<thead>
<tr>
<th>Table 3.2-2 Inclusion criteria</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Inclusion Criteria 5</td>
</tr>
<tr>
<td>Inclusion Criteria 6</td>
</tr>
<tr>
<td>Inclusion Criteria 7</td>
</tr>
</tbody>
</table>

**Exclusion criteria**

1- Burkitt, mantle cell, T-cell lymphoma
2- CD20-negative NHL
3- HIV or HBV disease
4- Central nervous system or meningeal involvement by lymphoma
5- Not previously treated with anthracycline containing regimens
6- Prior transplantation
7- Contraindication to any drug contained in the chemotherapy regimens
8- Any serious active disease or co-morbid medical condition (according to the investigator’s decision)
9- Poor renal function (creatinin level > 150 µmol/l), poor hepatic function (total bilirubin level > 30 mmol/l, transaminases > 2.5 maximum normal level) unless these abnormalities are related to the lymphoma
10. Poor bone marrow reserve as defined by neutrophils < 1.5 G/l or platelets < 100 G/l, unless related to bone marrow infiltration
11. Any history of cancer during the last 5 years, with the exception of non-melanoma skin tumors or stage 0 (in situ) cervical carcinoma
12. Treatment with any investigational drug within 30 days before planned first cycle of chemotherapy and during the study
13. Pregnant woman
14. Adult patient unable to give informed consent because of intellectual impairment

The following table presents the number and the percentage of patients respecting or not the non inclusion criteria:

**Table 3.2-3 Exclusion criteria**

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<th>CRITERIA</th>
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**Listing 3.2-1 Criteria not fulfilled**

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</table>

N = 42
3.3. Protocol deviations

3.3.1. Protocol violations

Protocol violations in course of the study were described in blind-review document.

3.3.2. Withdrawals

318 premature withdrawals (67%) were observed during this trial: 8 before treatment period, 214 during induction period, 13 during consolidation period and for patients randomized in the second part of the study, 83 in maintenance period.

166 patients (68%) were withdrawn in R-ICE arm versus 152 patients (65%) in R-DHAP arm.

Table 3.3-1 Withdrawals from study

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>PREMATURE WITHDRAWAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>77</td>
<td>32</td>
<td>82</td>
</tr>
<tr>
<td>Yes</td>
<td>166</td>
<td>68</td>
<td>152</td>
</tr>
<tr>
<td>Total</td>
<td>243</td>
<td>100</td>
<td>234</td>
</tr>
</tbody>
</table>

Table 3.3-2 Period of withdrawal from study

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Treatment period at withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEFORE TREATMENT</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>INDUCTION PHASE</td>
<td>116</td>
<td>70</td>
<td>98</td>
</tr>
<tr>
<td>CONSOLIDATION PHASE</td>
<td>7</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>FOLLOW UP PERIOD</td>
<td>39</td>
<td>23</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td>166</td>
<td>100</td>
<td>152</td>
</tr>
</tbody>
</table>

Table 3.3-3 Reason of withdrawal from study

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Reason for premature withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INDUCTION TREATMENT FAILURE</td>
<td>94</td>
<td>57</td>
<td>73</td>
</tr>
<tr>
<td>TRANSPLANTATION FAILURE</td>
<td>11</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>TREATMENT TOXICITY</td>
<td>8</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>MAJOR PROTOCOL VIOLATION</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PATIENT VOLONTARY WITHDRAWAL</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>DEATH</td>
<td>9</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>OTHER</td>
<td>35</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Missing</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>166</td>
<td>100</td>
<td>152</td>
</tr>
</tbody>
</table>
The main reasons for premature withdrawal were treatment failure (53%) and other reason (24%). 8 patients (5% of withdrawals) were withdrawn due to treatment toxicity in R-ICE arm versus 12 patients (8%) in R-DHAP arm.

All patients withdrawn prematurely from trial are listed in section §6.1.

4. EFFICACY EVALUATION

4.1. Eligible patients for analysis

Five populations of patients were identified:

- **Induction full analysis set** (following the intent-to-treat principle) refers to all randomized patients regardless they have received study treatment or not: 477 patients analyzed according the therapy they were randomized to receive (243 in R-ICE arm and 234 in R-DHAP arm).

- **Induction Intent-To-Treat (ITT) population** refers to patients receiving at least one injection of study treatment, regardless the quantity injected: 469 patients analyzed according the therapy they were randomized to receive (239 in R-ICE arm and 230 in R-DHAP arm).

- **Induction safety population** refers to patients receiving at least one injection of study treatment: 469 patients analyzed according the therapy they actually received (239 in R-ICE arm and 230 in R-DHAP arm).

- **Maintenance Intent-To-Treat (ITT) population** refers to all patients formally randomized in the 2nd part of the study: 242 patients analyzed according the therapy they were randomized to receive (122 in rituximab arm and 120 in observation arm).

- **Maintenance safety population** refers to all patients formally randomized in the 2nd part of the study and have received at least one dose of rituximab or have only been observed, and have at least one maintenance follow-up assessment: 235 patients analyzed according the therapy they actually received, i.e. patient will be included in rituximab arm if he/she had received at least one dose of rituximab during any maintenance visit otherwise, he/she will be included in observation arm (thus, 116 in rituximab arm and 119 in observation arm).

Since all patients received randomized induction treatment, induction ITT and safety populations are equivalent.

The following tables summarize the repartition of patients per population and lists present excluded patients.
Table 4.1-1 Eligible patients for analysis per efficacy populations

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Arm of 2nd randomization</th>
<th>All</th>
<th>Arm of 2nd randomization</th>
<th>All</th>
<th>Arm of 2nd randomization</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
<td>NOT APPLICABLE</td>
<td>All</td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Induction full analysis population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60</td>
<td>13</td>
<td>56</td>
<td>12</td>
<td>127</td>
<td>27</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Induction ITT population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60</td>
<td>25</td>
<td>56</td>
<td>23</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>127</td>
<td>54</td>
</tr>
<tr>
<td>Maintenance ITT population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60</td>
<td>13</td>
<td>56</td>
<td>12</td>
<td>127</td>
<td>27</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>127</td>
<td>54</td>
</tr>
<tr>
<td>TOTAL</td>
<td>60</td>
<td>13</td>
<td>56</td>
<td>12</td>
<td>127</td>
<td>27</td>
</tr>
</tbody>
</table>
### Table 4.1-2 Eligible patients for analysis per safety populations

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>Actual arm of maintenance</th>
<th>Actual arm of maintenance</th>
<th>Actual arm of maintenance</th>
<th>Actual arm of maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>N</td>
<td>%</td>
<td>ARM A / R-ICE</td>
<td>N</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>59</td>
<td>13</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>56</td>
<td>12</td>
<td>56</td>
<td>12</td>
</tr>
<tr>
<td>NOT APPLICABLE</td>
<td>124</td>
<td>26</td>
<td>124</td>
<td>26</td>
</tr>
<tr>
<td>All</td>
<td>239</td>
<td>51</td>
<td>239</td>
<td>51</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>N</td>
<td>%</td>
<td>ARM B / R-DHAP</td>
<td>N</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>57</td>
<td>12</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>63</td>
<td>13</td>
<td>63</td>
<td>13</td>
</tr>
<tr>
<td>NOT APPLICABLE</td>
<td>110</td>
<td>23</td>
<td>110</td>
<td>23</td>
</tr>
<tr>
<td>All</td>
<td>230</td>
<td>49</td>
<td>230</td>
<td>49</td>
</tr>
<tr>
<td>NOT APPLICABLE</td>
<td>234</td>
<td>50</td>
<td>234</td>
<td>50</td>
</tr>
<tr>
<td>All</td>
<td>469</td>
<td>100</td>
<td>469</td>
<td>100</td>
</tr>
</tbody>
</table>

### Listing 4.1-1 Patients excluded from MITT/safety populations

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>First Randomization Date</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>50030101041606</td>
<td>ARM A / R-ICE</td>
<td>03/12/2003</td>
<td>05/12/2003</td>
<td>BEFORE TREATMENT</td>
<td>MAJOR PROTOCOL VIOLATION</td>
<td></td>
</tr>
<tr>
<td>5003603201627</td>
<td>ARM A / R-ICE</td>
<td>28/03/2007</td>
<td>03/04/2007</td>
<td>BEFORE TREATMENT</td>
<td>DEATH</td>
<td></td>
</tr>
<tr>
<td>5003609201013</td>
<td>ARM A / R-ICE</td>
<td>14/03/2005</td>
<td>14/03/2005</td>
<td>BEFORE TREATMENT</td>
<td>OTHER</td>
<td>MEET NOT INCLUSION CRITERIAS</td>
</tr>
<tr>
<td>5003614301614</td>
<td>ARM A / R-ICE</td>
<td>16/06/2005</td>
<td>17/06/2005</td>
<td>BEFORE TREATMENT</td>
<td>MAJOR PROTOCOL VIOLATION</td>
<td></td>
</tr>
<tr>
<td>50031010171620</td>
<td>ARM B / R-DHAP</td>
<td>29/10/2004</td>
<td>29/10/2004</td>
<td>BEFORE TREATMENT</td>
<td>PATIENT VOLONTARY WITHDRAWAL</td>
<td></td>
</tr>
<tr>
<td>5003601601004</td>
<td>ARM B / R-DHAP</td>
<td>02/11/2007</td>
<td>04/11/2007</td>
<td>BEFORE TREATMENT</td>
<td>PATIENT VOLONTARY WITHDRAWAL</td>
<td></td>
</tr>
<tr>
<td>5003603201005</td>
<td>ARM B / R-DHAP</td>
<td>08/10/2004</td>
<td>12/10/2004</td>
<td>BEFORE TREATMENT</td>
<td>MAJOR PROTOCOL VIOLATION</td>
<td></td>
</tr>
<tr>
<td>5003603201027</td>
<td>ARM B / R-DHAP</td>
<td>26/01/2006</td>
<td>26/01/2006</td>
<td>BEFORE TREATMENT</td>
<td>DEATH</td>
<td></td>
</tr>
</tbody>
</table>

N = 8
### Listing 4.1-2 Patients excluded from maintenance safety population

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Arm of 2nd randomization</th>
<th>Date of 2nd randomization</th>
<th>Date of withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003601301015</td>
<td>RITUXIMAB</td>
<td>08/02/2008</td>
<td>18/03/2008</td>
<td>FOLLOW UP PERIOD</td>
<td>PATIENT VOLONTARY WITHDRAWAL</td>
</tr>
<tr>
<td>5003604901602</td>
<td>RITUXIMAB</td>
<td>02/05/2005</td>
<td>28/06/2005</td>
<td>FOLLOW UP PERIOD</td>
<td>OTHER</td>
</tr>
<tr>
<td>5003608301605</td>
<td>RITUXIMAB</td>
<td>25/08/2004</td>
<td>13/09/2004</td>
<td>FOLLOW UP PERIOD</td>
<td>PATIENT VOLONTARY WITHDRAWAL</td>
</tr>
<tr>
<td>5003617201613</td>
<td>RITUXIMAB</td>
<td>22/09/2005</td>
<td>-</td>
<td>-</td>
<td>LOST TO FOLLOW-UP AFTER BMT</td>
</tr>
<tr>
<td>5003101601610</td>
<td>OBSERVATION</td>
<td>17/05/2004</td>
<td>11/08/2004</td>
<td>FOLLOW UP PERIOD</td>
<td>TRANSPLANTATION FAILURE</td>
</tr>
<tr>
<td>5003102361203</td>
<td>OBSERVATION</td>
<td>19/02/2004</td>
<td>13/03/2004</td>
<td>FOLLOW UP PERIOD</td>
<td>PATIENT VOLONTARY WITHDRAWAL</td>
</tr>
<tr>
<td>5003631201619</td>
<td>OBSERVATION</td>
<td>14/06/2006</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

N = 7

### Listing 4.1-3 Patients with actual arm for maintenance treatment different from randomized

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Arm of 2nd randomization</th>
<th>Actual arm of maintenance</th>
<th>Date of 2nd randomization</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003617201021</td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
<td>14/02/2006</td>
<td>17/03/2006</td>
<td>FOLLOW UP PERIOD</td>
<td>OTHER</td>
<td>PATIENT STATUS : DUE TO HEP C INFECTION AFTER APHERESIS AND BAD CONDITION WE DECIDED TO STOP RITUXIMAB THERAPY / EXAMINATION ABNORMAL DUE TO LYMPHOMA ; NO B-SYMPTOMS / LDH = 344 U/L (&lt; 250 U/L)</td>
</tr>
</tbody>
</table>

N = 2
4.2. Baseline data

4.2.1. Demography

Table 4.2-1 Demography (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>243</td>
<td>234</td>
<td>477</td>
</tr>
<tr>
<td>Mean</td>
<td>50.7</td>
<td>52.3</td>
<td>51.5</td>
</tr>
<tr>
<td>Std</td>
<td>11.10</td>
<td>10.48</td>
<td>10.82</td>
</tr>
<tr>
<td>Median</td>
<td>54.0</td>
<td>55.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Min</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Max</td>
<td>65</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>N</td>
<td>243</td>
<td>233</td>
<td>476</td>
</tr>
<tr>
<td>Mean</td>
<td>79.4</td>
<td>77.8</td>
<td>78.6</td>
</tr>
<tr>
<td>Std</td>
<td>17.38</td>
<td>16.30</td>
<td>16.87</td>
</tr>
<tr>
<td>Median</td>
<td>77.0</td>
<td>76.0</td>
<td>76.0</td>
</tr>
<tr>
<td>Min</td>
<td>47</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Max</td>
<td>176</td>
<td>137</td>
<td>176</td>
</tr>
<tr>
<td>N</td>
<td>243</td>
<td>233</td>
<td>476</td>
</tr>
<tr>
<td>Mean</td>
<td>172.4</td>
<td>172.5</td>
<td>172.5</td>
</tr>
<tr>
<td>Std</td>
<td>9.47</td>
<td>9.21</td>
<td>9.33</td>
</tr>
<tr>
<td>Median</td>
<td>173.0</td>
<td>173.0</td>
<td>173.0</td>
</tr>
<tr>
<td>Min</td>
<td>147</td>
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<td>Max</td>
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<td>198</td>
<td>198</td>
</tr>
<tr>
<td>N</td>
<td>243</td>
<td>232</td>
<td>475</td>
</tr>
<tr>
<td>Mean</td>
<td>1.914</td>
<td>1.891</td>
<td>1.903</td>
</tr>
<tr>
<td>Std</td>
<td>0.2192</td>
<td>0.2074</td>
<td>0.2136</td>
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<tr>
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<td>1.900</td>
<td>1.900</td>
<td>1.900</td>
</tr>
<tr>
<td>Min</td>
<td>1.46</td>
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<td>1.40</td>
</tr>
<tr>
<td>Max</td>
<td>2.79</td>
<td>2.45</td>
<td>2.79</td>
</tr>
</tbody>
</table>

The median age at 1st randomization was 54 years old (range from 19 to 65).

Table 4.2-2 Age by category and sex ratio (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>156</td>
<td>147</td>
<td>303</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>FEMALE</td>
<td>87</td>
<td>87</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>41</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>&gt;=40 years</td>
<td>202</td>
<td>202</td>
<td>404</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>243</td>
<td>234</td>
<td>477</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
4.2.2. Initial diagnosis

Table 4.2-3 Time between initial diagnosis and 1st randomization (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>241</td>
<td>233</td>
<td>474</td>
</tr>
<tr>
<td>Mean</td>
<td>27.1</td>
<td>30.8</td>
<td>28.9</td>
</tr>
<tr>
<td>Std</td>
<td>32.34</td>
<td>40.72</td>
<td>36.70</td>
</tr>
<tr>
<td>Median</td>
<td>14.1</td>
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<td>1</td>
</tr>
<tr>
<td>Max</td>
<td>180</td>
<td>238</td>
<td>238</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from initial diagnosis to 1st randomization (months)</th>
</tr>
</thead>
<tbody>
<tr>
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Table 4.2-4 Time between initial diagnosis and 1st randomization by category (FAS)

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<table>
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<th>Time from initial diagnostic biopsy to 1st randomization</th>
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Table 4.2-5 Characteristics at initial diagnosis (FAS)

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<td>1</td>
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### Table 4.2-6 International Prognostic Index and individual factors at initial diagnosis (FAS)

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<td>%</td>
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Table 4.2-6 International Prognostic Index and individual factors at initial diagnosis (FAS)

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</tr>
<tr>
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<td>%</td>
<td>N</td>
<td>%</td>
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<td>%</td>
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<td>%</td>
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Table 4.2-7 p-values of Chi-2 test for individual factors of IPI at initial diagnosis (FAS)

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<td>B Symptoms at diagnosis (No Vs Yes)</td>
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Table 4.2-8 Anatomopathological report at initial diagnosis - review (FAS)

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<th>ARM B / R-DHAP</th>
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<td></td>
<td>N</td>
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<td>N</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B</td>
<td>65</td>
<td>46</td>
<td>63</td>
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<tr>
<td>Lymphome diffus à grandes cellules B (centroblastique)</td>
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<td>18</td>
<td>13</td>
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<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire</td>
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<td>6</td>
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<tr>
<td>Lymphome diffus à grandes cellules B (immunoblastique)</td>
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<td>Lymphome à grandes cellules B thymique</td>
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<td>4</td>
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<tr>
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<td>3</td>
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<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale</td>
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<td>Lymphome folliculaire grade 2</td>
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<tr>
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Final anatomo-pathological review was done for 264 patients (55%). Considering local diagnosis (only reported for non Gela patients) if review was not done, histology is available for 358 patients (75%).
<table>
<thead>
<tr>
<th>Histology (review if available, otherwise local) at initial diagnosis</th>
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<th>ARM B / R-DHAP</th>
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<td>Lymphome diffus à grandes cellules B (centroblastique)</td>
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<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire</td>
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<td>Lymphome diffus à grandes cellules B (B riche en T / histiocytes)</td>
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<tr>
<td>Lymphome à grandes cellules B non classable pour raisons techniques</td>
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</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à &quot;petites cellules&quot; sans précision</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>lymphome B agressif non classable</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lymphome B non classable pour raisons techniques</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome à grandes cellules non classable</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (anaplasique)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B plasmoblastique</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome T périphérique (sans spécificité)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome T angio-immunoblastique</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome T angio-immunoblastique avec progression cytologique B</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire probable</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome folliculaire et diffus</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Zone grise entre Hodgkin / lymphoprolifération EBV</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 B</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 1-2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 A</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>186</td>
<td>100</td>
<td>172</td>
</tr>
</tbody>
</table>
### 4.2.3. Initial treatment

**Table 4.2-10 Time between initial treatment and 1\(^{st}\) randomization (FAS)**

<table>
<thead>
<tr>
<th>Time from initial treatment to 1st randomization (months)</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean 240</td>
<td>228</td>
<td>468</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Std 25.9</td>
<td>30.0</td>
<td>27.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median 31.54</td>
<td>40.83</td>
<td>36.38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min 13.4</td>
<td>13.1</td>
<td>13.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max 179</td>
<td>238</td>
<td>238</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.2-11 Characteristics of initial treatment (FAS)**

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>CHOP - LIKE</td>
<td>203 84</td>
<td>203 87</td>
<td>406 85</td>
<td></td>
</tr>
<tr>
<td>ACVB - LIKE</td>
<td>32 13</td>
<td>27 12</td>
<td>59 12</td>
<td></td>
</tr>
<tr>
<td>OTHER</td>
<td>7 3</td>
<td>4 2</td>
<td>11 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 0</td>
<td>0 0</td>
<td>1 0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>155 64</td>
<td>151 65</td>
<td>306 64</td>
<td></td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>1 0</td>
<td>1 0</td>
<td>2 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>87 36</td>
<td>82 35</td>
<td>169 35</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>LOCAL</td>
<td>63 26</td>
<td>51 22</td>
<td>114 24</td>
<td></td>
</tr>
<tr>
<td>OTHER</td>
<td>2 1</td>
<td>1 0</td>
<td>3 1</td>
<td></td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>2 1</td>
<td>7 3</td>
<td>9 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>176 72</td>
<td>175 75</td>
<td>351 74</td>
<td></td>
</tr>
</tbody>
</table>

| TOTAL        | 243 100          | 234 100 | 477 100 |

Overall 406 patients (85\%) received CHOP-like chemotherapy as initial treatment and 306 patients (64\%) received rituximab.

For patient 5003612501021, immunotherapy was missing, nevertheless as it was declared at randomization that patient previously received rituximab, he/she will be considered with prior rituximab for exploratory analyses.

Details of other chemotherapy regimens and doses of radiotherapy are listed in section §6.2.
Table 4.2-12 Response at 1\textsuperscript{st} line (FAS)

<table>
<thead>
<tr>
<th>Response after first line</th>
<th>Arm of treatment</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>COMPLETE RESPONSE</td>
<td>129</td>
<td>53</td>
</tr>
<tr>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>PARTIAL RESPONSE</td>
<td>44</td>
<td>18</td>
</tr>
<tr>
<td>STABLE DISEASE</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>PROGRESSIVE DISEASE</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>NOT EVALUATED</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>242</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4.2-13 p-value of Chi-2 test for response after 1\textsuperscript{st} line (FAS)

<table>
<thead>
<tr>
<th>Variable/Treatment</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response after first line (CR/CRu vs other)</td>
<td>0.3968</td>
</tr>
</tbody>
</table>

4.2.4. Progression/relapse diagnosis

Table 4.2-14 Time intervals with progression/relapse diagnosis (FAS)

<table>
<thead>
<tr>
<th>Time from 1st treatment to relapse diagnostic biopsy (months)</th>
<th>Arm of treatment</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>187</td>
<td>29.6</td>
</tr>
<tr>
<td></td>
<td>174</td>
<td>36.2</td>
</tr>
<tr>
<td></td>
<td>361</td>
<td>32.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from relapse diagnostic biopsy to 1st randomization (months)</th>
<th>Arm of treatment</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>189</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>179</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>368</td>
<td>0.7</td>
</tr>
</tbody>
</table>
The following tables present the number and percentage of patients for baseline clinical assessments:

### Table 4.2-15 Characteristics at relapse (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Performance Status at relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>105</td>
<td>43</td>
<td>113</td>
</tr>
<tr>
<td>1</td>
<td>109</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Ann Arbor stage at relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAGE 1</td>
<td>40</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>STAGE 2</td>
<td>53</td>
<td>22</td>
<td>57</td>
</tr>
<tr>
<td>STAGE 3</td>
<td>45</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>STAGE 4</td>
<td>104</td>
<td>43</td>
<td>110</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>242</td>
<td>100</td>
<td>232</td>
</tr>
<tr>
<td><strong>B symptoms at relapse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>178</td>
<td>74</td>
<td>176</td>
</tr>
<tr>
<td>Yes</td>
<td>63</td>
<td>26</td>
<td>53</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>241</td>
<td>100</td>
<td>229</td>
</tr>
</tbody>
</table>

### Table 4.2-16 Number of extra nodal sites at relapse (FAS)

<table>
<thead>
<tr>
<th>Total of extra-nodal sites at relapse</th>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>242</td>
<td>232</td>
<td>474</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.1</td>
<td>1.3</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>1.31</td>
<td>1.37</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

The median number of extra nodal sites was 1 in both arms.
The details of nodal and extra-nodal involvement are listed in section §6.3.
### Table 4.2-17 International Prognostic Index and individual factors at relapse (FAS)

<table>
<thead>
<tr>
<th>Performance Status at relapse</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>&lt;2</td>
<td>214</td>
<td>88</td>
<td>203</td>
</tr>
<tr>
<td>&gt;=2</td>
<td>28</td>
<td>12</td>
<td>29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ann Arbor stage at relapse</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>I-II</td>
<td>93</td>
<td>38</td>
<td>89</td>
</tr>
<tr>
<td>III-IV</td>
<td>149</td>
<td>62</td>
<td>143</td>
</tr>
<tr>
<td>TOTAL</td>
<td>242</td>
<td>100</td>
<td>232</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LDH at relapse</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=Normal</td>
<td>111</td>
<td>47</td>
<td>112</td>
</tr>
<tr>
<td>&gt;Normal</td>
<td>126</td>
<td>53</td>
<td>117</td>
</tr>
<tr>
<td>TOTAL</td>
<td>237</td>
<td>100</td>
<td>229</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age-adjusted IPI at relapse</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>47</td>
<td>20</td>
<td>52</td>
</tr>
<tr>
<td>1</td>
<td>95</td>
<td>40</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>34</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Subtotal 0-1</td>
<td>142</td>
<td>60</td>
<td>139</td>
</tr>
<tr>
<td>Subtotal 2-3</td>
<td>93</td>
<td>40</td>
<td>88</td>
</tr>
<tr>
<td>TOTAL</td>
<td>235</td>
<td>100</td>
<td>227</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nb of extra-nodal sites at relapse</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=1</td>
<td>175</td>
<td>72</td>
<td>154</td>
</tr>
<tr>
<td>&gt;1</td>
<td>67</td>
<td>28</td>
<td>78</td>
</tr>
<tr>
<td>TOTAL</td>
<td>242</td>
<td>100</td>
<td>232</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPI at relapse</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35</td>
<td>15</td>
<td>46</td>
</tr>
<tr>
<td>1</td>
<td>72</td>
<td>31</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>29</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Subtotal 0-2</td>
<td>4</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Subtotal 3-5</td>
<td>174</td>
<td>74</td>
<td>156</td>
</tr>
<tr>
<td>TOTAL</td>
<td>60</td>
<td>26</td>
<td>71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ann Arbor stage at relapse</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>234</td>
<td>100</td>
<td>227</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 4.2-18 p-values of Chi-2 test for individual factors of IPI at progression/relapse diagnosis (FAS)

<table>
<thead>
<tr>
<th>Variable/Treatment</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Status at baseline (&lt;2 Vs &gt;=2)</td>
<td>0.7557</td>
</tr>
<tr>
<td>Ann Arbor stage at baseline (I-II Vs III-IV)</td>
<td>0.9879</td>
</tr>
<tr>
<td>LDH at baseline (=&lt; 1 N Vs &gt; 1 N)</td>
<td>0.6543</td>
</tr>
<tr>
<td>Age adjusted IPI at baseline (0-1 Vs 2-3)</td>
<td>0.8588</td>
</tr>
<tr>
<td>Total of extra nodal site at baseline (&lt;=1 Vs &gt;1)</td>
<td>0.1610</td>
</tr>
<tr>
<td>B Symptoms at baseline (No Vs Yes)</td>
<td>0.4513</td>
</tr>
<tr>
<td>IPI at baseline (0-2 Vs 3-5)</td>
<td>0.1798</td>
</tr>
</tbody>
</table>

Table 4.2-19 Other characteristics at relapse (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>beta 2 microglobulin (mg/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>127</td>
<td>78</td>
<td>124</td>
</tr>
<tr>
<td>&gt;=3</td>
<td>35</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>162</td>
<td>100</td>
<td>158</td>
</tr>
<tr>
<td>Albumin baseline (G/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=35</td>
<td>35</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>&gt;35</td>
<td>171</td>
<td>83</td>
<td>170</td>
</tr>
<tr>
<td>Total</td>
<td>206</td>
<td>100</td>
<td>210</td>
</tr>
</tbody>
</table>

Table 4.2-20 Bone marrow biopsy at relapse (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Bone marrow Biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not involved</td>
<td>196</td>
<td>81</td>
<td>180</td>
</tr>
<tr>
<td>Involved</td>
<td>21</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Unspecified</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Not Done</td>
<td>23</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>TOTAL</td>
<td>243</td>
<td>100</td>
<td>233</td>
</tr>
<tr>
<td>If BM involved, type of cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LARGE CELLS</td>
<td>14</td>
<td>67</td>
<td>13</td>
</tr>
<tr>
<td>SMALL CELLS</td>
<td>5</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>2</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>21</td>
<td>100</td>
<td>22</td>
</tr>
</tbody>
</table>

Overall, 43 patients (9%) presented an involved bone marrow biopsy at baseline, mainly with large cells (63%).
Table 4.2-21 PET scan at relapse (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET Scan at relapse</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>85</td>
<td>35</td>
<td>84</td>
</tr>
<tr>
<td>NOT DONE</td>
<td>152</td>
<td>63</td>
<td>145</td>
</tr>
<tr>
<td>Total</td>
<td>240</td>
<td>100</td>
<td>231</td>
</tr>
</tbody>
</table>

PET scan at relapse is available for 174 patients (37%).

Table 4.2-22 Number of sites used for response evaluation at relapse diagnosis (FAS)

<table>
<thead>
<tr>
<th>Number of sites used for evaluation of response per patient</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>243</td>
<td>234</td>
<td>477</td>
</tr>
<tr>
<td>Mean</td>
<td>2.5</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Std</td>
<td>1.54</td>
<td>1.43</td>
<td>1.49</td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Sum</td>
<td>611</td>
<td>540</td>
<td>1151</td>
</tr>
</tbody>
</table>

The median number of sites used for response evaluation was 2 (range: 1 to 6). The lesions' codification is presented in section §6.3.
<table>
<thead>
<tr>
<th>Histology (review) at relapse</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B</td>
<td>51</td>
<td>41</td>
<td>62</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (centroblastique)</td>
<td>29</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B thymique</td>
<td>8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (immunoblastique)</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Lymphome B non classable pour raisons techniques</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B non classable pour raisons techniques</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome agressif non classable</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Insuffisance de matériel</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire et diffus</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (B riche en T / histiocytes)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (anaplasique)</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 B</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 A</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B plasmoblastique</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire T périphérique (sans spécificité)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome folliculaire en transformation possible (en L. à grandes cellules B)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à &quot;petites cellules&quot; sans précision</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome B à &quot;petites cellules&quot; non classable pour raisons techniques</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome à grandes cellules non classable</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lymphome folliculaire non gradable</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Zone grise entre Hodgkin / lymphoprolifération EBV</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>125</td>
<td>100</td>
<td>127</td>
</tr>
</tbody>
</table>

Final anatomo-pathological review was done for 252 patients (53%).
Considering local diagnosis (only reported for non Gela patients) if review was not done, histology is available for 315 patients (66%).
### Table 4.2-24 Anatomopathological report at relapse – review or if missing, local (MITT)

<table>
<thead>
<tr>
<th>Texte Complet</th>
<th>Arm of treatment</th>
<th>Arm of treatment</th>
<th>Arm of treatment</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B</td>
<td>78 50</td>
<td>90 57</td>
<td>168 53</td>
<td></td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (centroblastique)</td>
<td>29 18</td>
<td>27 17</td>
<td>56 18</td>
<td></td>
</tr>
<tr>
<td>Lymphome à grandes cellules B thymique</td>
<td>9 6</td>
<td>4 3</td>
<td>13 4</td>
<td></td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (immunoblastique)</td>
<td>5 3</td>
<td>6 4</td>
<td>11 3</td>
<td></td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire</td>
<td>4 3</td>
<td>4 3</td>
<td>8 3</td>
<td></td>
</tr>
<tr>
<td>Lymphome B non classable pour raisons techniques</td>
<td>2 1</td>
<td>5 3</td>
<td>7 2</td>
<td></td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale</td>
<td>4 3</td>
<td>1 1</td>
<td>5 2</td>
<td></td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (B riche en T / histiocytes)</td>
<td>2 1</td>
<td>3 2</td>
<td>5 2</td>
<td></td>
</tr>
<tr>
<td>Lymphome à grandes cellules B non classable pour raisons techniques</td>
<td>3 2</td>
<td>1 1</td>
<td>4 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome B agressif non classable</td>
<td>1 1</td>
<td>3 2</td>
<td>4 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome folliculaire grade 2</td>
<td>1 1</td>
<td>3 2</td>
<td>4 1</td>
<td></td>
</tr>
<tr>
<td>Insuffisance de matériel</td>
<td>3 2</td>
<td>1 1</td>
<td>4 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome folliculaire et diffus</td>
<td>1 1</td>
<td>2 1</td>
<td>3 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome à grandes cellules non classable</td>
<td>3 2</td>
<td>0 0</td>
<td>3 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (anaplastique)</td>
<td>2 1</td>
<td>1 1</td>
<td>3 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 B</td>
<td>1 1</td>
<td>1 1</td>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 A</td>
<td>1 1</td>
<td>1 1</td>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome folliculaire grade 1</td>
<td>2 1</td>
<td>0 0</td>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome à grandes cellules B plasmoblastique</td>
<td>1 1</td>
<td>1 1</td>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>Lymphome T périphérique (sans spécificité)</td>
<td>1 1</td>
<td>0 0</td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td>Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)</td>
<td>1 1</td>
<td>0 0</td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td>Lymphome folliculaire en transformation possible (en L. à grandes cellules B)</td>
<td>1 1</td>
<td>0 0</td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à &quot;petites cellules&quot; sans précision</td>
<td>0 0</td>
<td>1 1</td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td>Lymphome B à &quot;petites cellules&quot; non classable pour raisons techniques</td>
<td>0 0</td>
<td>1 1</td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td>Lymphome folliculaire non gradable</td>
<td>0 0</td>
<td>1 1</td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td>Zone grise entre Hodgkin / lymphoprolifération EBV</td>
<td>1 1</td>
<td>0 0</td>
<td>1 0</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>157 100</strong></td>
<td><strong>158 100</strong></td>
<td><strong>315 100</strong></td>
<td></td>
</tr>
</tbody>
</table>
4.2.5. Medical history

343 patients (72%) presented with medical relevant history and 266 patients (56%) presented at least one persisting disease at baseline.

Table 4.2-25 Medical history (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Medical relevant history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>178</td>
<td>73</td>
<td>165</td>
</tr>
<tr>
<td>No</td>
<td>65</td>
<td>27</td>
<td>69</td>
</tr>
<tr>
<td>At least one persisting disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>132</td>
<td>54</td>
<td>134</td>
</tr>
<tr>
<td>No</td>
<td>111</td>
<td>46</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>243</td>
<td>100</td>
<td>234</td>
</tr>
</tbody>
</table>

4.2.6. Concomitant treatments

294 patients (62%) presented at least one concomitant treatment at inclusion and 106 patients (22%) presented at least one prescription due to lymphoma.

Table 4.2-26 Concomitant treatments (FAS)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Concomitant treatment at randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>146</td>
<td>60</td>
<td>148</td>
</tr>
<tr>
<td>No</td>
<td>97</td>
<td>40</td>
<td>86</td>
</tr>
<tr>
<td>At least one due to symptoms related to lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>21</td>
<td>56</td>
</tr>
<tr>
<td>No</td>
<td>193</td>
<td>79</td>
<td>178</td>
</tr>
<tr>
<td>Total</td>
<td>243</td>
<td>100</td>
<td>234</td>
</tr>
</tbody>
</table>
### 4.3. Evaluation after induction treatment

**Table 4.3-1 Induction – Bone marrow biopsy (induction ITT)**

<table>
<thead>
<tr>
<th>Bone marrow biopsy after induction</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL negative</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>10</td>
<td>27</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>NHL positive</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Not Done</td>
<td>199</td>
<td>88</td>
<td>188</td>
<td>86</td>
<td>387</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>226</td>
<td>100</td>
<td>218</td>
<td>100</td>
<td>444</td>
</tr>
</tbody>
</table>

**Table 4.3-2 Induction – PET scan (induction ITT)**

<table>
<thead>
<tr>
<th>PET scan after induction</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>16</td>
<td>37</td>
<td>17</td>
<td>72</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>38</td>
<td>17</td>
<td>42</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>NOT DONE</td>
<td>149</td>
<td>67</td>
<td>135</td>
<td>63</td>
<td>284</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>222</td>
<td>100</td>
<td>214</td>
<td>100</td>
<td>436</td>
</tr>
</tbody>
</table>

**Table 4.3-3 Induction - Number of sites used for response evaluation (induction ITT)**

<table>
<thead>
<tr>
<th>Number of sites used for evaluation of response per patient</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>230</td>
<td>221</td>
<td>451</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.5</td>
<td>2.4</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>1.53</td>
<td>1.45</td>
<td>1.49</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td>575</td>
<td>525</td>
<td>1100</td>
<td></td>
</tr>
</tbody>
</table>

On the 451 patients with reported sites, the median number of sites used for response evaluation was 2 (range: 1 to 6).

The lesions’ codifications are presented in section §6.4.
4.4. Follow-up

Stopping date was set to June 1, 2010 since last event occurred on this date. 90% of patients had a date of last contact after September 1, 2009.

**Table 4.4-1 Stopping date (induction ITT)**

<table>
<thead>
<tr>
<th>Date of last contact earlier than 01/06/2010 (stopping date)</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>140</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>Date of last contact earlier than 01/09/2009</td>
<td>No</td>
<td>209</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>230</td>
<td></td>
</tr>
</tbody>
</table>

The list of the 52 patients with a date of contact earlier than September 1, 2009 is presented in section §6.5.

**Table 4.4-2 Follow-up duration (induction ITT)**

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>Arm of treatment</th>
<th>N</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months)</td>
<td>ALL</td>
<td>469</td>
<td>45</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>45</td>
<td>0</td>
<td>77</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>45</td>
<td>0</td>
<td>79</td>
</tr>
</tbody>
</table>

With date of last contact censored at the stopping date, the median duration of follow-up for the induction ITT population (calculated from date of 1st randomization) is 45 months (range from 0 to 77 months).
4.5. Efficacy results

4.5.1. Primary criterion

The primary criterion for the 1st randomization part of the study is the mobilization adjusted response rate, i.e overall response rate (ORR) (Complete Response CR/CRu and Partial Response PR) adjusted with successful mobilization at the end of 2 and/or 3 cycles of induction chemotherapy treatment before high-dose chemotherapy and autologous transplantation.

Thus, response rate after induction treatment needs to be first described.

24 patients (13 in R-ICE arm and 11 in R-DHAP arm) presented with no response (not evaluated or missing) at the end of induction. Out of them, 10 were because of death (5 in both arms) and 2 in R-ICE arm due to patient voluntary withdrawal. The list of these patients is shown in section §6.6.1.

Including deaths in response evaluation only for patients with no response, the results are the following ones:

Table 4.5-1 Primary criterion – Response after induction treatment (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Response after complete induction (including deaths for not evaluated patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>57</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
</tr>
</tbody>
</table>

Table 4.5-2 Primary criterion – Overall Response rate after induction treatment (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu/PR)</th>
<th>OR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>153</td>
<td>64.0</td>
<td>57.6</td>
<td>70.1</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>148</td>
<td>64.3</td>
<td>57.8</td>
<td>70.5</td>
</tr>
</tbody>
</table>

Table 4.5-3 Primary criterion – Difference between OR rates after induction treatment (induction ITT)

<table>
<thead>
<tr>
<th>Difference between OR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE vs R-DHAP</td>
<td>-0.3</td>
<td>-9.0</td>
<td>8.3</td>
</tr>
</tbody>
</table>
### Table 4.5-4 Primary criterion – Complete Response rate after induction treatment (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu)</th>
<th>CR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>88</td>
<td>36.8</td>
<td>30.7</td>
<td>43.3</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>85</td>
<td>37.0</td>
<td>30.7</td>
<td>43.5</td>
</tr>
</tbody>
</table>

### Table 4.5-5 Primary criterion – Difference between CR rates after induction treatment (induction ITT)

<table>
<thead>
<tr>
<th></th>
<th>Difference between CR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE vs R-DHAP</td>
<td>-0.1</td>
<td>-8.9</td>
<td>8.6</td>
<td>0.9756</td>
</tr>
</tbody>
</table>

Considering deaths during induction phase even if patients had a response after induction treatment, 8 additional patients died:

- 2 patients in R-ICE arm: 1 received one cycle and was then in progressive disease and one was in CRu after complete induction but died of concurrent illness.
- 6 patients in R-DHAP arm: 5 were in progressive disease (4 received one cycle and one received 3 cycles) and one was in stable disease after complete induction but died of toxicity of study treatment.

The list of the 18 patients who died during treatment phase (7 in R-ICE arm and 11 in R-DHAP arm) is shown in section §6.6.1. Including these deaths, the results are the following ones:

### Table 4.5-6 Primary criterion – Response after induction treatment including deaths for all patients (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nb patients</td>
<td>Nb %</td>
<td>Nb patients</td>
<td>Nb %</td>
<td>Nb patients</td>
<td>Nb %</td>
<td></td>
</tr>
<tr>
<td>COMPLETE RESPONSE</td>
<td>57 24</td>
<td>60 26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>30 13</td>
<td>25 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARTIAL RESPONSE</td>
<td>65 27</td>
<td>63 27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STABLE DISEASE</td>
<td>26 11</td>
<td>26 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROGRESSIVE DISEASE</td>
<td>46 19</td>
<td>39 17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEATH</td>
<td>7 3</td>
<td>11 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOT EVALUATED</td>
<td>5 2</td>
<td>4 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3 1</td>
<td>2 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>239 100</td>
<td>230 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4.5-7 Primary criterion – Overall Response rate after induction treatment including deaths for all patients (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu/PR)</th>
<th>OR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>152</td>
<td>63.6</td>
<td>57.2</td>
<td>69.7</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>148</td>
<td>64.3</td>
<td>57.8</td>
<td>70.5</td>
</tr>
</tbody>
</table>
Table 4.5-8 Primary criterion – Difference between OR after induction treatment including deaths for all patients (induction ITT)

<table>
<thead>
<tr>
<th></th>
<th>Difference between OR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE vs R-DHAP</td>
<td>-0.7</td>
<td>-9.4</td>
<td>7.9</td>
<td>0.8658</td>
</tr>
</tbody>
</table>

Table 4.5-9 Primary criterion – Complete Response rate after induction treatment including deaths for all patients (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu)</th>
<th>CR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>87</td>
<td>36.4</td>
<td>30.3</td>
<td>42.8</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>85</td>
<td>37.0</td>
<td>30.7</td>
<td>43.5</td>
</tr>
</tbody>
</table>

Table 4.5-10 Primary criterion – Difference between CR rates after induction treatment including deaths for all patients (induction ITT)

<table>
<thead>
<tr>
<th></th>
<th>Difference between CR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE vs R-DHAP</td>
<td>-0.6</td>
<td>-9.3</td>
<td>8.2</td>
<td>0.9008</td>
</tr>
</tbody>
</table>

To evaluate mobilization adjusted response rate, collection failure needs to be described.

Table 4.5-11 Primary criterion – Collection failure (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>159</td>
<td>65</td>
<td>167</td>
<td>71</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>37</td>
<td>15</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>243</td>
<td>100</td>
<td>234</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4.5-12 Primary criterion – Reason of collection failure (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>29</td>
<td>78</td>
<td>20</td>
<td>83</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>6</td>
<td>16</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100</td>
<td>24</td>
<td>100</td>
</tr>
</tbody>
</table>

List of other reason of collection failure are described in section §6.6.1, 5 were due to no collection according to protocol rules since previous one available.
Table 4.5-13 Primary criterion – Overall Response Rate adjusted with successful mobilization (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Collection failure</th>
<th>CR/CRu/PR</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>123</td>
<td>51</td>
<td>130</td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No</td>
<td>36</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Missing</td>
<td>39</td>
<td>16</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
<td>230</td>
</tr>
</tbody>
</table>

Table 4.5-14 Primary criterion – Mobilization Adjusted Response Rate (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Nb patients</th>
<th>Nb responders with successful mobilization</th>
<th>MARR (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>123</td>
<td>51.5</td>
<td>42.0</td>
<td>55.1</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>130</td>
<td>56.5</td>
<td>37.0</td>
<td>50.2</td>
</tr>
</tbody>
</table>

Table 4.5-15 Primary criterion – Difference between Mobilization Adjusted Response Rates (induction ITT)

<table>
<thead>
<tr>
<th>Difference between MARR (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE vs R-DHAP</td>
<td>-5.1</td>
<td>-14.1</td>
<td>4.0</td>
</tr>
</tbody>
</table>

The mobilization adjusted response rate is 51.5% in R-ICE arm vs 56.5% in R-DHAP arm (p=0.27).

If mobilization adjusted response rate is calculated for patients in complete response (CR/CRu) and no collection failure, results are shown in section §6.6.1.
### 4.5.2. Secondary criteria

#### 4.5.2.1. Mobilization

#### Table 4.5-16 Mobilization – Collected cells (induction ITT)

<table>
<thead>
<tr>
<th>Collection failure</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>157</td>
<td>166</td>
</tr>
<tr>
<td>Mean</td>
<td>9.490</td>
<td>16.542</td>
</tr>
<tr>
<td>Std</td>
<td>40.2192</td>
<td>69.8178</td>
</tr>
<tr>
<td>Median</td>
<td>5.300</td>
<td>5.230</td>
</tr>
<tr>
<td>Min</td>
<td>1.14</td>
<td>1.20</td>
</tr>
<tr>
<td>Max</td>
<td>507.15</td>
<td>629.00</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Mean</td>
<td>1.486</td>
<td>2.647</td>
</tr>
<tr>
<td>Std</td>
<td>3.4004</td>
<td>3.3759</td>
</tr>
<tr>
<td>Median</td>
<td>0.520</td>
<td>0.900</td>
</tr>
<tr>
<td>Min</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Max</td>
<td>15.09</td>
<td>9.42</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>176</td>
<td>179</td>
</tr>
<tr>
<td>Mean</td>
<td>8.626</td>
<td>15.533</td>
</tr>
<tr>
<td>Std</td>
<td>38.0704</td>
<td>67.3229</td>
</tr>
<tr>
<td>Median</td>
<td>4.865</td>
<td>5.100</td>
</tr>
<tr>
<td>Min</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Max</td>
<td>507.15</td>
<td>629.00</td>
</tr>
</tbody>
</table>

#### Table 4.5-17 Mobilization – Number of collections (induction ITT)

<table>
<thead>
<tr>
<th>Collection failure</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>158</td>
<td>167</td>
</tr>
<tr>
<td>Mean</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Std</td>
<td>1.02</td>
<td>0.78</td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Min</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Max</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Mean</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Std</td>
<td>1.71</td>
<td>1.01</td>
</tr>
<tr>
<td>Median</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>
### Table 4.5-18 Mobilization – Source of stem cells (induction ITT)

<table>
<thead>
<tr>
<th>Source of Stem Cells</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Peripheral source</td>
<td>184</td>
<td>97</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral source + Bone marrow</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>190</td>
<td>100</td>
</tr>
</tbody>
</table>

### 4.5.2.2. Consolidation treatment: BEAM+ASCT

All patients who received BEAM regimen underwent autologous stem cell transplantation. Thus, 123 patients (51%) in R-ICE arm and 132 patients (57%) in R-DHAP arm received ASCT.

### Table 4.5-19 Consolidation – Patients with BEAM and ASCT (induction ITT)

<table>
<thead>
<tr>
<th></th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Consolidation treatment (BEAM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>123</td>
<td>51</td>
</tr>
<tr>
<td>No</td>
<td>116</td>
<td>49</td>
</tr>
<tr>
<td>Transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>123</td>
<td>51</td>
</tr>
<tr>
<td>No</td>
<td>116</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

14 patients who where eligible to transplantation (responders and no collection failure) did not receive ASCT (7 in both arms).

On the other hand, 9 patients who where not eligible to transplantation received ASCT: 7 were in stable disease after induction (1 in R-ICE arm and 6 in R-DHAP arm) and 2 (one in both arms) had a missing response. 8 of them was then randomized in maintenance part.

These patients are described in section §6.6.2.

3 patients received also ASCT with collected CD34+ cells less than $2.10^6$/kg (2 in R-ICE arm and one in RDHAP arm).
## Table 4.5-20 Consolidation – Time intervals with collection and transplantation (induction ITT)

<table>
<thead>
<tr>
<th>Time from C3 to 1st collection date (days)</th>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>177</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.6</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>41.15</td>
<td>86.02</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13.0</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>-413</td>
<td>-966</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>122</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from 1st collection date to 1st administration of BEAM (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Std</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Min</td>
</tr>
<tr>
<td>Max</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from 1st collection date to transplantation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Std</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Min</td>
</tr>
<tr>
<td>Max</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from 1st administration of BEAM to transplantation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Std</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Min</td>
</tr>
<tr>
<td>Max</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from transplantation to 2nd randomization date (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Std</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Min</td>
</tr>
<tr>
<td>Max</td>
</tr>
</tbody>
</table>
### Table 4.5-21 Consolidation – Period of collection (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Period of collection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Before C1</strong></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>C1-C2</strong></td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><strong>C2-C3</strong></td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td><strong>After C3</strong></td>
<td>134</td>
<td>76</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>177</td>
<td>100</td>
</tr>
</tbody>
</table>

#### 4.5.2.3. Event-Free Survival

According to the definition of events, 323 patients (69%) presented with an event: 67 (14%) with a new treatment out of progression, 226 (48%) with progression/relapse and 30 (6%) with death without progression.

### Table 4.5-22 Secondary criteria – Events for survival analysis (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No event</strong></td>
<td>69</td>
<td>29</td>
</tr>
<tr>
<td><strong>New treatment out of progression</strong></td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td><strong>Progression/relapse</strong></td>
<td>119</td>
<td>50</td>
</tr>
<tr>
<td><strong>Death without progression</strong></td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

170 patients in the R-ICE arm and 153 patients in the R-DHAP arm presented with an event (respectively 71% and 67%): 36 and 31 (respectively 15% and 13%) with a new treatment out of progression, 119 and 107 (respectively 50% and 47%) with progression/relapse, and 15 and 15 (respectively 6% and 7%) with death without progression.

Event-Free survival is measured from date of 1st randomization to date of 1st event.
Figure 4.5-1 Secondary criteria – Event-Free Survival (induction ITT)

![Graph showing survival probability over time with survival rate data points.]

Table 4.5-23 Secondary criteria – Duration of Event-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>EFS (months)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>469</td>
<td>7</td>
<td>6</td>
<td>10</td>
<td>0</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.5-24 Secondary criteria – Kaplan-Meier estimates for Event-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>41.9</td>
<td>37.4</td>
<td>46.4</td>
<td>190</td>
</tr>
<tr>
<td>24</td>
<td>35.5</td>
<td>31.1</td>
<td>39.9</td>
<td>150</td>
</tr>
<tr>
<td>36</td>
<td>30.5</td>
<td>26.2</td>
<td>34.8</td>
<td>102</td>
</tr>
<tr>
<td>48</td>
<td>30.2</td>
<td>25.9</td>
<td>34.5</td>
<td>67</td>
</tr>
<tr>
<td>60</td>
<td>29.7</td>
<td>25.4</td>
<td>34.1</td>
<td>33</td>
</tr>
<tr>
<td>72</td>
<td>24.4</td>
<td>19.0</td>
<td>30.1</td>
<td>8</td>
</tr>
</tbody>
</table>
Figure 4.5-2 Secondary criteria – Event-Free Survival according to treatment arm (induction ITT)

![Event-Free Survival graph](image)

Logrank p=0.2672

Table 4.5-25 Secondary criteria – Duration of Event-Free Survival according to treatment arm (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>12</td>
<td>39.8</td>
<td>33.4</td>
<td>46.0</td>
<td>91</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>24</td>
<td>33.5</td>
<td>27.5</td>
<td>39.6</td>
<td>70</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>36</td>
<td>26.2</td>
<td>20.5</td>
<td>32.2</td>
<td>43</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>48</td>
<td>26.2</td>
<td>20.5</td>
<td>32.2</td>
<td>23</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>60</td>
<td>26.2</td>
<td>20.5</td>
<td>32.2</td>
<td>11</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>72</td>
<td>20.9</td>
<td>13.4</td>
<td>29.5</td>
<td>1</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>12</td>
<td>44.1</td>
<td>37.6</td>
<td>50.4</td>
<td>99</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>24</td>
<td>37.4</td>
<td>31.1</td>
<td>43.7</td>
<td>80</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>36</td>
<td>34.8</td>
<td>28.6</td>
<td>41.0</td>
<td>59</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>48</td>
<td>34.2</td>
<td>28.0</td>
<td>40.5</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 4.5-26 Secondary criteria – Kaplan-Meier estimates for Event-Free Survival according to treatment arm (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>12</td>
<td>71% (170)</td>
<td>29% (69)</td>
<td>6.51 ( 4.99 - 9.92)</td>
<td></td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>24</td>
<td>67% (153)</td>
<td>33% (77)</td>
<td>7.49 ( 5.82 - 12.71)</td>
<td></td>
</tr>
</tbody>
</table>

No. of Subjects | Event | Censored |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>71%</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>67%</td>
</tr>
</tbody>
</table>

Table 4.5-24 Secondary criteria – Event-Free Survival according to treatment arm (induction ITT)
Table 4.5-27 Secondary criteria – Hazard ratio of R-ICE arm for Event-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE</td>
<td>0.2687</td>
<td>1.131</td>
<td>0.909, 1.408</td>
</tr>
</tbody>
</table>

4.5.2.4. Progression-Free Survival

Progression-Free survival is measured from date of randomization to date of progression/relapse or death from any cause.

115 events in the R-ICE arm and 103 events in the R-DHAP arm were taken into account for Progression-Free Survival.

Table 4.5-28 Secondary criteria – Duration of Progression-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>PFS (months)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>469</td>
<td>13</td>
<td>10</td>
<td>21</td>
<td>0</td>
<td>79</td>
</tr>
</tbody>
</table>
Table 4.5-29 Secondary criteria – Kaplan-Meier estimates for Progression-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>51.7</td>
<td>47.0</td>
<td>56.1</td>
<td>233</td>
</tr>
<tr>
<td>24</td>
<td>43.4</td>
<td>38.8</td>
<td>47.9</td>
<td>181</td>
</tr>
<tr>
<td>36</td>
<td>37.7</td>
<td>33.1</td>
<td>42.2</td>
<td>123</td>
</tr>
<tr>
<td>48</td>
<td>37.4</td>
<td>32.8</td>
<td>41.9</td>
<td>79</td>
</tr>
<tr>
<td>60</td>
<td>35.7</td>
<td>31.0</td>
<td>40.4</td>
<td>38</td>
</tr>
<tr>
<td>72</td>
<td>30.2</td>
<td>24.3</td>
<td>36.3</td>
<td>9</td>
</tr>
</tbody>
</table>

Figure 4.5-4 Secondary criteria – Progression-Free Survival according to treatment arm (induction ITT)

Table 4.5-30 Secondary criteria – Duration of Progression-Free Survival according to treatment arm (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>N</th>
<th>Median</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>13</td>
<td>9</td>
<td>23</td>
<td>0</td>
<td>77</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>14</td>
<td>10</td>
<td>24</td>
<td>0</td>
<td>79</td>
</tr>
</tbody>
</table>
Table 4.5-31 Secondary criteria – Kaplan-Meier estimates for Progression-Free Survival according to treatment arm (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>12</td>
<td>50.9</td>
<td>44.3</td>
<td>57.2</td>
<td>116</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>24</td>
<td>42.9</td>
<td>36.4</td>
<td>49.2</td>
<td>89</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>36</td>
<td>34.2</td>
<td>27.9</td>
<td>40.6</td>
<td>54</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>48</td>
<td>34.2</td>
<td>27.9</td>
<td>40.6</td>
<td>31</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>60</td>
<td>31.5</td>
<td>24.8</td>
<td>38.5</td>
<td>15</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>72</td>
<td>27.0</td>
<td>19.1</td>
<td>35.5</td>
<td>2</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>12</td>
<td>52.3</td>
<td>45.7</td>
<td>58.6</td>
<td>117</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>24</td>
<td>43.8</td>
<td>37.3</td>
<td>50.2</td>
<td>92</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>36</td>
<td>41.2</td>
<td>34.6</td>
<td>47.5</td>
<td>69</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>48</td>
<td>40.6</td>
<td>34.0</td>
<td>47.0</td>
<td>48</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>60</td>
<td>39.6</td>
<td>33.0</td>
<td>46.1</td>
<td>23</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>72</td>
<td>33.4</td>
<td>25.0</td>
<td>42.1</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 4.5-32 Secondary criteria – Hazard ratio of R-ICE arm for Progression-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE</td>
<td>0.4109</td>
<td>1.102</td>
<td>0.875 1.387</td>
</tr>
</tbody>
</table>

4.5.2.5. Overall Survival

Overall survival is measured from date of randomization to date of death from any cause.

125 deaths in the R-ICE arm and 112 deaths in the R-DHAP arm were taken into account for Overall Survival.
Figure 4.5-5 Secondary criteria – Overall Survival (induction ITT)

Table 4.5-33 Secondary criteria – Duration of Overall Survival (induction ITT)

<table>
<thead>
<tr>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months)</td>
<td>469</td>
<td>37</td>
<td>27</td>
<td>61</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4.5-34 Secondary criteria – Kaplan-Meier estimates for Overall Survival (induction ITT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>70.1</td>
<td>65.6</td>
<td>74.0</td>
<td>315</td>
</tr>
<tr>
<td>24</td>
<td>56.1</td>
<td>51.4</td>
<td>60.5</td>
<td>228</td>
</tr>
<tr>
<td>36</td>
<td>50.2</td>
<td>45.4</td>
<td>54.8</td>
<td>162</td>
</tr>
<tr>
<td>48</td>
<td>47.5</td>
<td>42.5</td>
<td>52.3</td>
<td>100</td>
</tr>
<tr>
<td>60</td>
<td>44.9</td>
<td>39.5</td>
<td>50.1</td>
<td>48</td>
</tr>
<tr>
<td>72</td>
<td>38.3</td>
<td>31.6</td>
<td>45.0</td>
<td>11</td>
</tr>
</tbody>
</table>
Table 4.5-35 Secondary criteria – Duration of Overall Survival according to treatment arm (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>12</td>
<td>68.7</td>
<td>62.2</td>
<td>74.2</td>
<td>155</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>24</td>
<td>56.1</td>
<td>49.3</td>
<td>62.2</td>
<td>114</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>36</td>
<td>48.9</td>
<td>42.0</td>
<td>55.4</td>
<td>79</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>48</td>
<td>43.4</td>
<td>36.2</td>
<td>50.4</td>
<td>43</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>60</td>
<td>40.9</td>
<td>33.4</td>
<td>48.3</td>
<td>20</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>72</td>
<td>34.0</td>
<td>24.6</td>
<td>43.6</td>
<td>4</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>12</td>
<td>71.4</td>
<td>65.1</td>
<td>76.9</td>
<td>160</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>24</td>
<td>56.1</td>
<td>49.4</td>
<td>62.3</td>
<td>114</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>36</td>
<td>51.6</td>
<td>44.7</td>
<td>58.0</td>
<td>83</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>48</td>
<td>51.6</td>
<td>44.7</td>
<td>58.0</td>
<td>57</td>
</tr>
</tbody>
</table>
### Table 4.5-37 Secondary criteria – Hazard ratio of R-ICE arm for Overall Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE</td>
<td>0.3389</td>
<td>1.133</td>
<td>0.878 1.462</td>
</tr>
</tbody>
</table>

#### 4.5.2.6. Event-Free Survival of patients submitted to ASCT

Event-Free Survival of patients submitted to ASCT is measured from date of transplantation.

![Graph showing Event-Free Survival](image)

**Table 4.5-38 Secondary criteria – Duration of Event-Free Survival (patients with ASCT)**

<table>
<thead>
<tr>
<th>EFS (months)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (months)</td>
<td>255</td>
<td>57</td>
<td>26</td>
<td>-</td>
<td>0</td>
<td>76</td>
</tr>
</tbody>
</table>
Table 4.5-39 Secondary criteria – Kaplan-Meier estimates for Event-Free Survival (patients with ASCT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>66.5</td>
<td>60.3</td>
<td>72.0</td>
<td>165</td>
</tr>
<tr>
<td>24</td>
<td>58.1</td>
<td>51.7</td>
<td>64.0</td>
<td>124</td>
</tr>
<tr>
<td>36</td>
<td>52.0</td>
<td>45.5</td>
<td>58.2</td>
<td>90</td>
</tr>
<tr>
<td>48</td>
<td>52.0</td>
<td>45.5</td>
<td>58.2</td>
<td>55</td>
</tr>
<tr>
<td>60</td>
<td>46.1</td>
<td>38.0</td>
<td>53.9</td>
<td>25</td>
</tr>
<tr>
<td>72</td>
<td>43.8</td>
<td>35.0</td>
<td>52.4</td>
<td>6</td>
</tr>
</tbody>
</table>

Figure 4.5-8 Secondary criteria – Event-Free Survival according to treatment arm (patients with ASCT)

Table 4.5-40 Secondary criteria – Duration of Event-Free Survival according to treatment arm (patients with ASCT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>123</td>
<td>52%</td>
<td>48%</td>
<td>27.66 (21.06 NA )</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>132</td>
<td>43%</td>
<td>57%</td>
<td>31.77 ( NA )</td>
</tr>
</tbody>
</table>

Table 4.5-40 Secondary criteria – Duration of Event-Free Survival according to treatment arm (patients with ASCT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>N</th>
<th>Median</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (months)</td>
<td>123</td>
<td>28</td>
<td>21</td>
<td>-</td>
<td>0</td>
<td>74</td>
</tr>
<tr>
<td>EFS (months)</td>
<td>132</td>
<td>-</td>
<td>32</td>
<td>-</td>
<td>0</td>
<td>76</td>
</tr>
</tbody>
</table>
### Table 4.5-41 Secondary criteria – Kaplan-Meier estimates for Event-Free Survival according to treatment arm (patients with ASCT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>12</td>
<td>64.5</td>
<td>55.3</td>
<td>72.3</td>
<td>77</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>24</td>
<td>55.5</td>
<td>46.1</td>
<td>63.9</td>
<td>59</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>36</td>
<td>46.4</td>
<td>36.9</td>
<td>55.3</td>
<td>37</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>48</td>
<td>46.4</td>
<td>36.9</td>
<td>55.3</td>
<td>19</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>60</td>
<td>42.2</td>
<td>30.5</td>
<td>53.3</td>
<td>10</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>72</td>
<td>36.1</td>
<td>21.9</td>
<td>50.6</td>
<td>1</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>12</td>
<td>68.4</td>
<td>59.7</td>
<td>75.7</td>
<td>88</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>24</td>
<td>60.4</td>
<td>51.4</td>
<td>68.3</td>
<td>65</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>36</td>
<td>57.4</td>
<td>48.2</td>
<td>65.5</td>
<td>53</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>48</td>
<td>57.4</td>
<td>48.2</td>
<td>65.5</td>
<td>36</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>60</td>
<td>50.3</td>
<td>39.1</td>
<td>60.6</td>
<td>15</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>72</td>
<td>50.3</td>
<td>39.1</td>
<td>60.6</td>
<td>5</td>
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</table>

### Table 4.5-42 Secondary criteria – Hazard ratio of R-ICE arm for Event-Free Survival (patients with ASCT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE</td>
<td>0.1612</td>
<td>1.291</td>
<td>0.903 1.846</td>
</tr>
</tbody>
</table>
4.5.2.7. Progression-Free Survival of patients submitted to ASCT

Progression-Free Survival for patients submitted to ASCT is measured from date of transplantation to date of progression/relapse or death from any cause.

Table 4.5-43 Secondary criteria – Duration of Progression-Free Survival (patients with ASCT)

<table>
<thead>
<tr>
<th>PFS (months)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>255</td>
<td>59</td>
<td>32</td>
<td>-</td>
<td>0</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 4.5-44 Secondary criteria – Kaplan-Meier estimates for Progression-Free Survival (patients with ASCT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>69.3</td>
<td>63.2</td>
<td>74.6</td>
<td>172</td>
</tr>
<tr>
<td>24</td>
<td>60.9</td>
<td>54.5</td>
<td>66.6</td>
<td>128</td>
</tr>
<tr>
<td>36</td>
<td>54.7</td>
<td>48.1</td>
<td>60.9</td>
<td>92</td>
</tr>
<tr>
<td>48</td>
<td>54.7</td>
<td>48.1</td>
<td>60.9</td>
<td>56</td>
</tr>
<tr>
<td>60</td>
<td>48.7</td>
<td>40.4</td>
<td>56.5</td>
<td>26</td>
</tr>
<tr>
<td>72</td>
<td>46.4</td>
<td>37.3</td>
<td>54.9</td>
<td>6</td>
</tr>
</tbody>
</table>
Figure 4.5-10 Secondary criteria – Progression-Free Survival according to treatment arm (patients with ASCT)

Table 4.5-45 Secondary criteria – Duration of Progression-Free Survival according to treatment arm (patients with ASCT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>ARM A / R-ICE</td>
<td>123</td>
<td>32</td>
<td>23</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ARM B / R-DHAP</td>
<td>132</td>
<td>-</td>
<td>57</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4.5-46 Secondary criteria – Kaplan-Meier estimates for Progression-Free Survival according to treatment arm (patients with ASCT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>12</td>
<td>66.1</td>
<td>57.0</td>
<td>73.8</td>
<td>79</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>24</td>
<td>57.2</td>
<td>47.7</td>
<td>65.5</td>
<td>61</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>36</td>
<td>48.1</td>
<td>38.6</td>
<td>57.0</td>
<td>38</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>48</td>
<td>48.1</td>
<td>38.6</td>
<td>57.0</td>
<td>20</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>60</td>
<td>44.1</td>
<td>32.6</td>
<td>55.0</td>
<td>11</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>72</td>
<td>38.6</td>
<td>24.6</td>
<td>52.3</td>
<td>1</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>12</td>
<td>72.3</td>
<td>63.7</td>
<td>79.1</td>
<td>93</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>24</td>
<td>64.2</td>
<td>55.2</td>
<td>71.8</td>
<td>67</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>36</td>
<td>61.1</td>
<td>51.6</td>
<td>69.1</td>
<td>54</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>48</td>
<td>61.1</td>
<td>51.8</td>
<td>69.1</td>
<td>36</td>
</tr>
<tr>
<td>Arm of treatment</td>
<td>Time Point (months)</td>
<td>PFS (%)</td>
<td>95% CI Lower</td>
<td>95% CI Upper</td>
<td>Patients at risk</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------</td>
<td>---------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>60</td>
<td>53.6</td>
<td>41.8</td>
<td>64.0</td>
<td>15</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>72</td>
<td>53.6</td>
<td>41.8</td>
<td>64.0</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 4.5-47 Secondary criteria – Hazard ratio of R-ICE arm for Progression-Free Survival (patients with ASCT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE</td>
<td>0.0850</td>
<td>1.383</td>
<td>0.956 2.000</td>
</tr>
</tbody>
</table>

4.5.2.8. Overall Survival of patients submitted to ASCT

Overall survival for patients submitted to ASCT is measured from date of transplantation to date of death from any cause.

Figure 4.5-11 Secondary criteria – Overall Survival (patients with ASCT)

Table 4.5-48 Secondary criteria – Duration of Overall Survival (patients with ASCT)

<table>
<thead>
<tr>
<th>OS (months)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months)</td>
<td>255</td>
<td>-</td>
<td>58</td>
<td>-</td>
<td>0</td>
<td>76</td>
</tr>
</tbody>
</table>
Table 4.5-49 Secondary criteria – Kaplan-Meier estimates for Overall Survival (patients with ASCT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
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<tbody>
<tr>
<td>12</td>
<td>84.5</td>
<td>79.3</td>
<td>88.4</td>
<td>210</td>
</tr>
<tr>
<td>24</td>
<td>74.9</td>
<td>68.9</td>
<td>79.8</td>
<td>157</td>
</tr>
<tr>
<td>36</td>
<td>67.6</td>
<td>61.0</td>
<td>73.3</td>
<td>112</td>
</tr>
<tr>
<td>48</td>
<td>64.2</td>
<td>57.3</td>
<td>70.3</td>
<td>68</td>
</tr>
<tr>
<td>60</td>
<td>55.2</td>
<td>45.9</td>
<td>63.5</td>
<td>30</td>
</tr>
<tr>
<td>72</td>
<td>52.1</td>
<td>41.5</td>
<td>61.7</td>
<td>6</td>
</tr>
</tbody>
</table>

Figure 4.5-12 Secondary criteria – Overall Survival according to treatment arm (patients with ASCT)

Table 4.5-50 Secondary criteria – Duration of Overall Survival according to treatment arm (patients with ASCT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months) ARM A / R-ICE</td>
<td>123</td>
<td>59</td>
<td>39</td>
<td>-</td>
<td>0</td>
<td>74</td>
</tr>
<tr>
<td>OS (months) ARM B / R-DHAP</td>
<td>132</td>
<td>-</td>
<td>58</td>
<td>-</td>
<td>0</td>
<td>76</td>
</tr>
</tbody>
</table>
Table 4.5-51 Secondary criteria – Kaplan-Meier estimates for Overall Survival according to treatment arm (patients with ASCT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>12</td>
<td>81.0</td>
<td>72.8</td>
<td>87.0</td>
<td>97</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>24</td>
<td>71.4</td>
<td>62.3</td>
<td>78.6</td>
<td>77</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>36</td>
<td>63.1</td>
<td>53.3</td>
<td>71.3</td>
<td>51</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>48</td>
<td>56.4</td>
<td>46.0</td>
<td>65.5</td>
<td>27</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>60</td>
<td>48.8</td>
<td>35.5</td>
<td>60.9</td>
<td>13</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>72</td>
<td>41.9</td>
<td>25.1</td>
<td>57.7</td>
<td>1</td>
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<tr>
<td>ARM B / R-DHAP</td>
<td>12</td>
<td>87.7</td>
<td>80.7</td>
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<td>113</td>
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<tr>
<td>ARM B / R-DHAP</td>
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<td>78.1</td>
<td>69.9</td>
<td>84.4</td>
<td>80</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>36</td>
<td>71.9</td>
<td>62.8</td>
<td>79.2</td>
<td>61</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>48</td>
<td>71.9</td>
<td>62.8</td>
<td>79.2</td>
<td>41</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>60</td>
<td>61.5</td>
<td>48.5</td>
<td>72.2</td>
<td>17</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>72</td>
<td>61.5</td>
<td>48.5</td>
<td>72.2</td>
<td>5</td>
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</tbody>
</table>

Table 4.5-52 Secondary criteria – Hazard ratio of R-ICE arm for Overall Survival (patients with ASCT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE</td>
<td>0.0625</td>
<td>1.494</td>
<td>0.979</td>
</tr>
</tbody>
</table>
4.5.3. **Exploratory analyses**

The prognostic impact of the two stratifications factors (prior treatment with rituximab and failure from diagnosis) is analysed on the induction ITT population.

**Table 4.5-53 Exploratory analyses – Stratification factors (induction ITT)**

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Failure from diagnosis</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>12 months</td>
<td>94</td>
<td>39</td>
<td>193</td>
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<tr>
<td></td>
<td>Yes</td>
<td>145</td>
<td>61</td>
<td>276</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>239</td>
<td>100</td>
<td>469</td>
</tr>
</tbody>
</table>

**Table 4.5-54 Exploratory analyses – p-values of Chi-2 test for stratification factors (induction ITT)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Rituximab according to arm</td>
<td>0.9842</td>
</tr>
<tr>
<td>Failure from diagnosis according to arm</td>
<td>0.4140</td>
</tr>
<tr>
<td>Failure from diagnosis according to prior rituximab</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
4.5.3.1. According to prior rituximab

Table 4.5-55 Exploratory analyses – Characteristics at initial diagnosis according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Performance Status at diagnosis</th>
<th>Prior treatment with Rituximab</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>&lt;2</td>
<td>126</td>
<td>89</td>
<td>237</td>
<td>83</td>
</tr>
<tr>
<td>&gt;=2</td>
<td>15</td>
<td>11</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>TOTAL</td>
<td>141</td>
<td>100</td>
<td>285</td>
<td>100</td>
</tr>
<tr>
<td>Ann Arbor Stage at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>97</td>
<td>60</td>
<td>99</td>
<td>33</td>
</tr>
<tr>
<td>III-IV</td>
<td>65</td>
<td>40</td>
<td>202</td>
<td>67</td>
</tr>
<tr>
<td>TOTAL</td>
<td>162</td>
<td>100</td>
<td>301</td>
<td>100</td>
</tr>
<tr>
<td>LDH at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 1 N</td>
<td>87</td>
<td>63</td>
<td>99</td>
<td>36</td>
</tr>
<tr>
<td>&gt; 1 N</td>
<td>52</td>
<td>37</td>
<td>177</td>
<td>64</td>
</tr>
<tr>
<td>TOTAL</td>
<td>139</td>
<td>100</td>
<td>276</td>
<td>100</td>
</tr>
<tr>
<td>Age adjusted IPI at initial diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>54</td>
<td>43</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>30</td>
<td>111</td>
<td>42</td>
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<td>25</td>
<td>20</td>
<td>89</td>
<td>34</td>
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<tr>
<td>3</td>
<td>8</td>
<td>6</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>Subtotal 0-1</td>
<td>92</td>
<td>74</td>
<td>141</td>
<td>54</td>
</tr>
<tr>
<td>Subtotal 2-3</td>
<td>33</td>
<td>26</td>
<td>122</td>
<td>46</td>
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<tr>
<td>TOTAL</td>
<td>125</td>
<td>100</td>
<td>263</td>
<td>100</td>
</tr>
<tr>
<td>Nb of extra nodal sites at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;=1</td>
<td>142</td>
<td>89</td>
<td>197</td>
<td>67</td>
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<tr>
<td>&gt;1</td>
<td>18</td>
<td>11</td>
<td>99</td>
<td>33</td>
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<tr>
<td>TOTAL</td>
<td>160</td>
<td>100</td>
<td>296</td>
<td>100</td>
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<tr>
<td>IPI at initial diagnosis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
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<td>2</td>
</tr>
<tr>
<td>Subtotal 0-2</td>
<td>110</td>
<td>88</td>
<td>176</td>
<td>67</td>
</tr>
<tr>
<td>Subtotal 3-5</td>
<td>15</td>
<td>12</td>
<td>86</td>
<td>33</td>
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<tr>
<td>TOTAL</td>
<td>125</td>
<td>100</td>
<td>262</td>
<td>100</td>
</tr>
<tr>
<td>B Symptom at diagnosis</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
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<td>153</td>
<td>52</td>
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</table>
## Prior treatment with Rituximab

<table>
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<tr>
<th>Prior treatment with Rituximab</th>
<th>No</th>
<th>%</th>
<th>Yes</th>
<th>%</th>
<th>All</th>
<th>%</th>
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<tbody>
<tr>
<td>Yes</td>
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<td>29</td>
<td>144</td>
<td>48</td>
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<td>100</td>
<td>297</td>
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<td>453</td>
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</table>

### Table 4.5-56 Exploratory analyses – p-value of Chi-2 test for characteristics at initial diagnosis according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Status at diagnosis (&lt;2 Vs ≥2)</td>
<td>0.0896</td>
</tr>
<tr>
<td>Ann Arbor Stage at diagnosis (I-II Vs III-IV)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDH at diagnosis (=&lt; N Vs &gt; 1 N)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age adjusted IPI at diagnosis (0-1 Vs 2-3)</td>
<td>0.0002</td>
</tr>
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<td>Nb of extra nodal sites at diagnosis (≤1 Vs &gt;1)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IPI at diagnosis (0-2 Vs 3-5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>B Symptoms at diagnosis (No Vs Yes)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
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### Table 4.5-57 Exploratory analyses – Characteristics at progression/relapse diagnosis according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>No</th>
<th>%</th>
<th>Yes</th>
<th>%</th>
<th>All</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
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<td>14</td>
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<td>17</td>
<td>73</td>
<td>16</td>
</tr>
<tr>
<td>&gt;=40 years</td>
<td>144</td>
<td>86</td>
<td>252</td>
<td>83</td>
<td>396</td>
<td>84</td>
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<tr>
<td>Total</td>
<td>167</td>
<td>100</td>
<td>302</td>
<td>100</td>
<td>469</td>
<td>100</td>
</tr>
<tr>
<td>Performance Status at relapse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>155</td>
<td>93</td>
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<td>86</td>
<td>412</td>
<td>88</td>
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<tr>
<td>&gt;=2</td>
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<td>7</td>
<td>43</td>
<td>14</td>
<td>54</td>
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</tr>
<tr>
<td>TOTAL</td>
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<td>100</td>
<td>300</td>
<td>100</td>
<td>466</td>
<td>100</td>
</tr>
<tr>
<td>Ann Arbor stage at relapse</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>I-II</td>
<td>69</td>
<td>42</td>
<td>110</td>
<td>37</td>
<td>179</td>
<td>38</td>
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<tr>
<td>III-IV</td>
<td>97</td>
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<td>190</td>
<td>63</td>
<td>287</td>
<td>62</td>
</tr>
<tr>
<td>TOTAL</td>
<td>166</td>
<td>100</td>
<td>300</td>
<td>100</td>
<td>466</td>
<td>100</td>
</tr>
<tr>
<td>LDH relapse</td>
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<td></td>
<td></td>
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<td>≤Normal</td>
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<td>51</td>
<td>137</td>
<td>46</td>
<td>220</td>
<td>48</td>
</tr>
<tr>
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<td>49</td>
<td>158</td>
<td>54</td>
<td>239</td>
<td>52</td>
</tr>
<tr>
<td>TOTAL</td>
<td>164</td>
<td>100</td>
<td>295</td>
<td>100</td>
<td>459</td>
<td>100</td>
</tr>
<tr>
<td>Age-adjusted IPI at relapse</td>
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<td>34</td>
<td>21</td>
<td>63</td>
<td>22</td>
<td>97</td>
<td>21</td>
</tr>
<tr>
<td>1</td>
<td>78</td>
<td>48</td>
<td>103</td>
<td>35</td>
<td>181</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>28</td>
<td>99</td>
<td>34</td>
<td>144</td>
<td>32</td>
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</table>
### Table 4.5-58 Exploratory analyses: p-value of Chi-2 test for characteristics at progression/relapse diagnosis according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;40y vs &gt;=40y)</td>
<td>0.4259</td>
</tr>
<tr>
<td>Performance Status at baseline (&lt;2 Vs &gt;=2)</td>
<td>0.0128</td>
</tr>
<tr>
<td>Ann Arbor stage at baseline (I-II Vs III-IV)</td>
<td>0.2977</td>
</tr>
<tr>
<td>LDH at baseline (=&lt; 1 N Vs &gt; 1 N)</td>
<td>0.3916</td>
</tr>
<tr>
<td>Age adjusted IPI at baseline (0-1 Vs 2-3)</td>
<td>0.0128</td>
</tr>
<tr>
<td>Nb of extra nodal sites at baseline (=&lt;1 Vs &gt;1)</td>
<td>0.0520</td>
</tr>
<tr>
<td>B Symptoms at baseline (No Vs Yes)</td>
<td>0.2655</td>
</tr>
<tr>
<td>IPI at baseline (0-2 Vs 3-5)</td>
<td>0.0060</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Subtotal 0-1</td>
<td>112</td>
<td>69</td>
<td>166</td>
</tr>
<tr>
<td>Subtotal 2-3</td>
<td>51</td>
<td>31</td>
<td>126</td>
</tr>
<tr>
<td>TOTAL</td>
<td>163</td>
<td>100</td>
<td>292</td>
</tr>
<tr>
<td>Nb of extra nodal sites at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=1</td>
<td>125</td>
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<td>200</td>
</tr>
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<td>&gt;1</td>
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<td>25</td>
<td>100</td>
</tr>
<tr>
<td>TOTAL</td>
<td>166</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>IPI at relapse</td>
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<td>0</td>
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<td>4</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1</td>
<td>7</td>
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<tr>
<td>Subtotal 0-2</td>
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<td>80</td>
<td>197</td>
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<td>Subtotal 3-5</td>
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<td>20</td>
<td>94</td>
</tr>
<tr>
<td>TOTAL</td>
<td>163</td>
<td>100</td>
<td>291</td>
</tr>
<tr>
<td>B symptoms at relapse</td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>130</td>
<td>79</td>
<td>221</td>
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<td>Yes</td>
<td>35</td>
<td>21</td>
<td>77</td>
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<tr>
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<td>165</td>
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<td>298</td>
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</table>
Table 4.5-59 Exploratory analyses – Overall response rate according to prior rituximab (induction ITT)

<table>
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<tr>
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<th>No</th>
<th>%</th>
<th>Yes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response after complete induction</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRu/PR</td>
<td>137</td>
<td>82</td>
<td>164</td>
<td>54</td>
</tr>
<tr>
<td>Other</td>
<td>30</td>
<td>18</td>
<td>138</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>167</td>
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<td>302</td>
<td>100</td>
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</tbody>
</table>

Table 4.5-60 Exploratory analyses – Complete response rate according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
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<th>No</th>
<th>%</th>
<th>Yes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response after complete induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRu</td>
<td>84</td>
<td>50</td>
<td>89</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>83</td>
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<td>213</td>
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</tr>
<tr>
<td>Total</td>
<td>167</td>
<td>100</td>
<td>302</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4.5-61 Exploratory analyses – Mobilization adjusted response rate according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
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<th>No</th>
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<th>Yes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobilization adjusted overall response rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>44</td>
<td>26</td>
<td>172</td>
<td>57</td>
</tr>
<tr>
<td>Yes</td>
<td>123</td>
<td>74</td>
<td>130</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>167</td>
<td>100</td>
<td>302</td>
<td>100</td>
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</table>

Table 4.5-62 Exploratory analyses – Univariate analysis for response rates according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Prior rituximab: No</th>
<th>p-value (Wald Chi-2)</th>
<th>Odds ratio estimates</th>
<th>95% Wald confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to induction CR/CRu/PR</td>
<td>&lt;.0001</td>
<td>3.843</td>
<td>2.437</td>
</tr>
<tr>
<td>Response to induction CR/CRu</td>
<td>&lt;.0001</td>
<td>2.422</td>
<td>1.637</td>
</tr>
<tr>
<td>Mobilization adjusted response rate</td>
<td>&lt;.0001</td>
<td>0.270</td>
<td>0.179</td>
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Figure 4.5-13 Exploratory analyses – Event-Free Survival according to prior rituximab (induction ITT)

![Graph showing event-free survival probability over time for patients with and without prior rituximab treatment. The graph includes Kaplan-Meier estimates for survival with log-rank p-value of 0.0001.]

**Table 4.5-63 Exploratory analyses – Duration of Event-Free Survival according to prior rituximab (induction ITT)**

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>167</td>
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<td>23</td>
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<td>79</td>
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<td>3</td>
<td>6</td>
<td>0</td>
<td>78</td>
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</tbody>
</table>

**Table 4.5-64 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to prior rituximab (induction ITT)**

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>12</td>
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<td>54.7</td>
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<td>23.5</td>
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<td>28.4</td>
<td>63</td>
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<td>16.4</td>
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<td>16.4</td>
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Table 4.5-65 Exploratory analyses – Hazard ratio of prior rituximab for Event-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>&lt;.0001</td>
<td>0.439</td>
<td>0.343 0.561</td>
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Figure 4.5-14 Exploratory analyses – Progression-Free Survival according to prior rituximab (induction ITT)

Table 4.5-66 Exploratory analyses – Duration of Progression-Free Survival according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
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<tr>
<td>No</td>
<td>167</td>
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<td>1</td>
<td>79</td>
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Table 4.5-67 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to prior rituximab (induction ITT)

<table>
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<tr>
<th>Prior treatment with Rituximab</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
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<tr>
<td>No</td>
<td>12</td>
<td>75.1</td>
<td>67.7</td>
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<td>Prior treatment with Rituximab</td>
<td>Time Point (years)</td>
<td>Survival (%)</td>
<td>95% CI Lower</td>
<td>95% CI Upper</td>
<td>Patients at risk</td>
</tr>
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<td>-------------------</td>
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<td>--------------</td>
<td>--------------</td>
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<td>28.9</td>
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<td>34.3</td>
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<td>23.7</td>
<td>34.3</td>
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<td>33.4</td>
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**Table 4.5-68 Exploratory analyses – Hazard ratio of prior rituximab for Progression-Free Survival (induction ITT)**

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<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>&lt;.0001</td>
<td>0.455</td>
<td>0.351 0.589</td>
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**Figure 4.5-15 Exploratory analyses – Overall Survival according to prior rituximab (induction ITT)**

**Table 4.5-69 Exploratory analyses – Duration of Overall Survival according to prior rituximab (induction ITT)**

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>167</td>
<td>62</td>
<td>54</td>
<td>-</td>
<td>2</td>
<td>79</td>
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<td>14</td>
<td>27</td>
<td>0</td>
<td>78</td>
</tr>
</tbody>
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### Table 4.5-70 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
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<td>80.3</td>
<td>90.9</td>
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<td>67.2</td>
<td>80.7</td>
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<td>74.1</td>
<td>83</td>
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<td>69.4</td>
<td>62</td>
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<td>64.9</td>
<td>30</td>
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<td>56.9</td>
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<td>55.0</td>
<td>66.2</td>
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<td>45.7</td>
<td>39.9</td>
<td>51.4</td>
<td>114</td>
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<td>40.6</td>
<td>34.8</td>
<td>46.4</td>
<td>79</td>
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<tr>
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<td>48</td>
<td>39.8</td>
<td>33.8</td>
<td>45.7</td>
<td>38</td>
</tr>
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<td>60</td>
<td>39.8</td>
<td>33.8</td>
<td>45.7</td>
<td>18</td>
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<tr>
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<td>27.6</td>
<td>44.8</td>
<td>3</td>
</tr>
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### Table 4.5-71 Exploratory analyses – Hazard ratio of prior rituximab for Overall Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>&lt;.0001</td>
<td>0.485</td>
<td>0.364 0.646</td>
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#### 4.5.3.2. According to failure from diagnosis

### Table 4.5-72 Exploratory analyses – Characteristics at initial diagnosis according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th></th>
<th>Failure from diagnosis</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 12 months</td>
<td>&gt;= 12 months</td>
</tr>
<tr>
<td>Performance Status at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>211</td>
<td>152</td>
</tr>
<tr>
<td>&gt;=2</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td>TOTAL</td>
<td>258</td>
<td>168</td>
</tr>
<tr>
<td>Ann Arbor Stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>III-IV</td>
<td>178</td>
<td>89</td>
</tr>
<tr>
<td>TOTAL</td>
<td>275</td>
<td>188</td>
</tr>
<tr>
<td>LDH at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 1 N</td>
<td>79</td>
<td>107</td>
</tr>
<tr>
<td>&gt; 1 N</td>
<td>171</td>
<td>58</td>
</tr>
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<td>165</td>
</tr>
<tr>
<td>Age adjusted IPI at initial diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td>1</td>
<td>87</td>
<td>62</td>
</tr>
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<td>2</td>
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### Table 4.5-73 Exploratory analyses – p-value of Chi-2 test for characteristics at initial diagnosis according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Status at diagnosis (&lt;2 Vs &gt;=2)</td>
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</tr>
<tr>
<td>Ann Arbor Stage at diagnosis (I-II Vs III-IV)</td>
<td>0.0002</td>
</tr>
<tr>
<td>LDH at diagnosis (=&lt; 1 N Vs &gt; 1 N)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age adjusted IPI at diagnosis (0-1 Vs 2-3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Nb of extra nodal sites at diagnosis (&lt;=1 Vs &gt;1)</td>
<td>0.1030</td>
</tr>
<tr>
<td>IPI at diagnosis (0-2 Vs 3-5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>B Symptoms at diagnosis (No Vs Yes)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
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<th>&gt;= 12 months</th>
<th>All</th>
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</thead>
<tbody>
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<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
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<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Subtotal 0-1</td>
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<td>49</td>
<td>117</td>
</tr>
<tr>
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<td>35</td>
</tr>
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<td>TOTAL</td>
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<td>100</td>
<td>152</td>
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<table>
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<th>Nb of extra nodal sites at diagnosis</th>
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<th>&gt;1</th>
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<td>271</td>
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<tr>
<td>%</td>
<td>72</td>
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<td>1</td>
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<td>117</td>
<td>100</td>
<td>70</td>
<td>27</td>
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<th>TOTAL</th>
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Table 4.5-73 Exploratory analyses – p-value of Chi-2 test for characteristics at initial diagnosis according to failure from diagnosis (induction ITT)
### Table 4.5-74 Exploratory analyses – Characteristics at progression/relapse diagnosis according to failure from diagnosis (induction ITT)

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<th>&gt;= 12 months</th>
<th>All</th>
</tr>
</thead>
<tbody>
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<td>N</td>
<td>%</td>
<td>N</td>
</tr>
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<td>177</td>
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<td>100</td>
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</tr>
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<td>Performance Status at relapse</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>180</td>
</tr>
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<td>15</td>
<td>12</td>
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<td>100</td>
<td>192</td>
</tr>
<tr>
<td>Ann Arbor stage at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>106</td>
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<td>73</td>
</tr>
<tr>
<td>III-IV</td>
<td>169</td>
<td>61</td>
<td>118</td>
</tr>
<tr>
<td>TOTAL</td>
<td>275</td>
<td>100</td>
<td>191</td>
</tr>
<tr>
<td>LDH at relapse</td>
<td></td>
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</tr>
<tr>
<td>&lt;=Normal</td>
<td>114</td>
<td>42</td>
<td>106</td>
</tr>
<tr>
<td>&gt;Normal</td>
<td>155</td>
<td>58</td>
<td>84</td>
</tr>
<tr>
<td>TOTAL</td>
<td>269</td>
<td>100</td>
<td>190</td>
</tr>
<tr>
<td>Age-adjusted IPI at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>53</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
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<td>97</td>
<td>36</td>
<td>84</td>
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<td>90</td>
<td>34</td>
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</tr>
<tr>
<td>3</td>
<td>27</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Subtotal 0-1</td>
<td>150</td>
<td>56</td>
<td>128</td>
</tr>
<tr>
<td>Subtotal 2-3</td>
<td>117</td>
<td>44</td>
<td>60</td>
</tr>
<tr>
<td>TOTAL</td>
<td>267</td>
<td>100</td>
<td>188</td>
</tr>
<tr>
<td>Nb of extra nodal sites at relapse</td>
<td></td>
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</tr>
<tr>
<td>&lt;=1</td>
<td>187</td>
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<tr>
<td>&gt;1</td>
<td>87</td>
<td>32</td>
<td>54</td>
</tr>
<tr>
<td>TOTAL</td>
<td>274</td>
<td>100</td>
<td>192</td>
</tr>
<tr>
<td>IPI at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41</td>
<td>15</td>
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<tr>
<td>2</td>
<td>71</td>
<td>27</td>
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<tr>
<td>Subtotal 0-2</td>
<td>184</td>
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<td>143</td>
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<td>Subtotal 3-5</td>
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<td>31</td>
<td>45</td>
</tr>
<tr>
<td>TOTAL</td>
<td>266</td>
<td>100</td>
<td>188</td>
</tr>
<tr>
<td>Parameter</td>
<td>Failure from diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>&lt; 12 months</td>
<td>&gt;= 12 months</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>B symptoms at relapse</td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>201</td>
<td>74%</td>
<td>150</td>
</tr>
<tr>
<td>Yes</td>
<td>71</td>
<td>26%</td>
<td>41</td>
</tr>
<tr>
<td>TOTAL</td>
<td>272</td>
<td>100%</td>
<td>191</td>
</tr>
</tbody>
</table>

Table 4.5-75 Exploratory analyses – p-value of Chi-2 test for characteristics at progression/relapse diagnosis according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;40y vs &gt;=40y)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Performance Status at baseline (&lt;2 Vs &gt;=2)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Ann Arbor stage at baseline (I-II Vs III-IV)</td>
<td>0.9433</td>
</tr>
<tr>
<td>LDH at baseline (=&lt; 1 N Vs &gt; 1 N)</td>
<td>0.0046</td>
</tr>
<tr>
<td>Age adjusted IPI at baseline (0-1 Vs 2-3)</td>
<td>0.0103</td>
</tr>
<tr>
<td>Nb of extra nodal sites at baseline (&lt;=1 Vs &gt;1)</td>
<td>0.4015</td>
</tr>
<tr>
<td>B Symptoms at baseline (No Vs Yes)</td>
<td>0.2514</td>
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<tr>
<td>IPI at baseline (0-2 Vs 3-5)</td>
<td>0.1071</td>
</tr>
</tbody>
</table>

Table 4.5-76 Exploratory analyses – Overall response rate according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Response after complete induction</th>
<th>Failure from diagnosis</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 12 months</td>
<td>&gt;= 12 months</td>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRu/PR</td>
<td>135</td>
<td>49%</td>
<td>166</td>
<td>86%</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>141</td>
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<td>27</td>
<td>14%</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>276</td>
<td>100%</td>
<td>193</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

Table 4.5-77 Exploratory analyses – Complete response rate according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Response after complete induction</th>
<th>Failure from diagnosis</th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 12 months</td>
<td>&gt;= 12 months</td>
<td>All</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRu</td>
<td>66</td>
<td>24%</td>
<td>107</td>
<td>55%</td>
<td></td>
<td></td>
<td></td>
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<td>Other</td>
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<td>86</td>
<td>45%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>276</td>
<td>100%</td>
<td>193</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Table 4.5-78 Exploratory analyses – Mobilization adjusted response rate according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis (Randomization)</th>
<th>&lt; 12 months</th>
<th>&gt;= 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Mobilization adjusted overall response rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>163</td>
<td>59</td>
</tr>
<tr>
<td>Yes</td>
<td>113</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>276</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4.5-79 Exploratory analyses – Univariate analysis for response rates according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis &lt; 12 months</th>
<th>p-value (Wald Chi-2)</th>
<th>Odds ratio estimates</th>
<th>95% Wald confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to induction CR/CRu/PR</td>
<td>&lt;.0001</td>
<td>0.156</td>
<td>0.097 0.249</td>
</tr>
<tr>
<td>Response to induction CR/CRu</td>
<td>&lt;.0001</td>
<td>0.253</td>
<td>0.170 0.375</td>
</tr>
<tr>
<td>Mobilization adjusted response rate</td>
<td>&lt;.0001</td>
<td>3.810</td>
<td>2.562 5.666</td>
</tr>
</tbody>
</table>

Figure 4.5-16 Exploratory analyses – Event-Free Survival according to failure from diagnosis (induction ITT)
### Table 4.5-80 Exploratory analyses – Duration of Event-Free Survival according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>276</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>193</td>
<td>28</td>
<td>21</td>
<td>61</td>
<td>1</td>
<td>79</td>
</tr>
</tbody>
</table>

### Table 4.5-81 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>12</td>
<td>26.1</td>
<td>21.0</td>
<td>31.4</td>
<td>68</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>24</td>
<td>21.8</td>
<td>17.1</td>
<td>27.0</td>
<td>54</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>36</td>
<td>19.5</td>
<td>14.9</td>
<td>24.5</td>
<td>39</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>48</td>
<td>19.5</td>
<td>14.9</td>
<td>24.5</td>
<td>30</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>60</td>
<td>19.5</td>
<td>14.9</td>
<td>24.5</td>
<td>15</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>72</td>
<td>16.4</td>
<td>11.1</td>
<td>22.5</td>
<td>3</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>12</td>
<td>64.3</td>
<td>57.1</td>
<td>70.7</td>
<td>122</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>24</td>
<td>54.7</td>
<td>47.3</td>
<td>61.5</td>
<td>96</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>36</td>
<td>46.0</td>
<td>38.5</td>
<td>53.1</td>
<td>63</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>48</td>
<td>45.2</td>
<td>37.8</td>
<td>52.4</td>
<td>37</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>60</td>
<td>43.9</td>
<td>36.2</td>
<td>51.3</td>
<td>18</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>72</td>
<td>35.6</td>
<td>25.3</td>
<td>46.0</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 4.5-82 Exploratory analyses – Hazard ratio of failure from diagnosis for Event-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>2.450</td>
<td>1.936</td>
</tr>
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</table>
Figure 4.5-17 Exploratory analyses – Progression-Free Survival according to failure from diagnosis (induction ITT)

![Progression-Free Survival Graph](image)

Logrank p<0.0001

Table 4.5-83 Exploratory analyses – Duration of Progression-Free Survival according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>276</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>193</td>
<td>51</td>
<td>29</td>
<td>66</td>
<td>1</td>
<td>79</td>
</tr>
</tbody>
</table>

Table 4.5-84 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>12</td>
<td>35.6</td>
<td>29.9</td>
<td>41.3</td>
<td>92</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>24</td>
<td>29.8</td>
<td>24.4</td>
<td>35.3</td>
<td>72</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>36</td>
<td>27.3</td>
<td>22.0</td>
<td>32.8</td>
<td>52</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>48</td>
<td>27.3</td>
<td>22.0</td>
<td>32.8</td>
<td>38</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>60</td>
<td>27.3</td>
<td>22.0</td>
<td>32.8</td>
<td>19</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>72</td>
<td>24.0</td>
<td>17.8</td>
<td>30.7</td>
<td>4</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>12</td>
<td>74.3</td>
<td>67.5</td>
<td>79.9</td>
<td>141</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>24</td>
<td>62.5</td>
<td>55.2</td>
<td>69.0</td>
<td>109</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>36</td>
<td>52.3</td>
<td>44.7</td>
<td>59.4</td>
<td>71</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>48</td>
<td>51.6</td>
<td>43.9</td>
<td>58.7</td>
<td>41</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>60</td>
<td>47.1</td>
<td>38.6</td>
<td>55.2</td>
<td>19</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>72</td>
<td>38.5</td>
<td>27.4</td>
<td>49.6</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 4.5-85 Exploratory analyses – Hazard ratio of failure from diagnosis for Progression-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>2.319</td>
<td>1.810 2.970</td>
</tr>
</tbody>
</table>

Figure 4.5-18 Exploratory analyses – Overall Survival according to failure from diagnosis (induction ITT)

Table 4.5-86 Exploratory analyses – Duration of Overall Survival according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>276</td>
<td>14</td>
<td>12</td>
<td>22</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>193</td>
<td>62</td>
<td>59</td>
<td>-</td>
<td>1</td>
<td>79</td>
</tr>
</tbody>
</table>
Table 4.5-87 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>12</td>
<td>55.7</td>
<td>49.5</td>
<td>61.5</td>
<td>144</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>24</td>
<td>42.1</td>
<td>36.0</td>
<td>48.0</td>
<td>100</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>36</td>
<td>37.6</td>
<td>31.6</td>
<td>43.6</td>
<td>71</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>48</td>
<td>36.2</td>
<td>30.1</td>
<td>42.3</td>
<td>47</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>60</td>
<td>36.2</td>
<td>30.1</td>
<td>42.3</td>
<td>24</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>72</td>
<td>32.0</td>
<td>24.3</td>
<td>39.9</td>
<td>4</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>12</td>
<td>90.0</td>
<td>84.8</td>
<td>93.5</td>
<td>171</td>
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<tr>
<td>&gt;= 12 months</td>
<td>24</td>
<td>75.6</td>
<td>68.7</td>
<td>81.1</td>
<td>128</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>36</td>
<td>67.6</td>
<td>60.1</td>
<td>74.0</td>
<td>91</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>48</td>
<td>63.3</td>
<td>55.3</td>
<td>70.3</td>
<td>53</td>
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<tr>
<td>&gt;= 12 months</td>
<td>60</td>
<td>56.8</td>
<td>47.1</td>
<td>65.4</td>
<td>24</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>72</td>
<td>46.6</td>
<td>34.4</td>
<td>57.8</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 4.5-88 Exploratory analyses – Hazard ratio of failure from diagnosis for Overall Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>2.391</td>
<td>1.808</td>
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</tbody>
</table>
4.5.3.3. According to prior rituximab and failure from diagnosis

Table 4.5-89 Exploratory analyses – Overall response rate according to prior rituximab and failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>No Failure from diagnosis</th>
<th>Yes Failure from diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 12 months</td>
<td>&gt;= 12 months</td>
</tr>
<tr>
<td>Response after complete induction</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>CR/CRu/PR</td>
<td>28</td>
<td>64</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4.5-90 Exploratory analyses – Complete response rate according to prior rituximab and failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>No Failure from diagnosis</th>
<th>Yes Failure from diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 12 months</td>
<td>&gt;= 12 months</td>
</tr>
<tr>
<td>Response after complete induction</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>Other</td>
<td>30</td>
<td>68</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>100</td>
</tr>
</tbody>
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Table 4.5-91 Exploratory analyses – Mobilization adjusted response rate according to prior rituximab and failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>No Failure from diagnosis</th>
<th>Yes Failure from diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 12 months</td>
<td>&gt;= 12 months</td>
</tr>
<tr>
<td>Mobilization adjusted overall response rate</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>41</td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>59</td>
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<tr>
<td>Total</td>
<td>44</td>
<td>100</td>
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</tbody>
</table>
Figure 4.5-19 Exploratory analyses – Event-Free Survival according to prior rituximab by failure from diagnosis
(induction ITT)

Failure from diagnosis <= 12 months

Logrank p=0.0023

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>44</td>
<td>59% (26)</td>
<td>41% (18) 5.19 ( 3.76 NA )</td>
</tr>
<tr>
<td>Prior rituximab: Yes</td>
<td>232</td>
<td>83% (192)</td>
<td>17% (40) 3.36 ( 3.06 4.14 )</td>
</tr>
</tbody>
</table>

Failure from diagnosis => 12 months

Logrank p=0.0518

<table>
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<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>123</td>
<td>51% (63)</td>
<td>49% (60) 36.17 ( 25.56 65.54 )</td>
</tr>
<tr>
<td>Prior rituximab: Yes</td>
<td>70</td>
<td>60% (42)</td>
<td>40% (28) 15.41 ( 8.21 NA )</td>
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</table>
Figure 4.5-20 Exploratory analyses – Event-Free Survival according to failure from diagnosis by prior rituximab (induction ITT)

Prior treatment with Rituximab=Yes

Prior treatment with Rituximab=No
Table 4.5-92 Exploratory analyses – Duration of Event-Free Survival according to prior rituximab and failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Failure from diagnosis (Randomization)</th>
<th>( N )</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (months)</td>
<td>No</td>
<td>&lt; 12 months</td>
<td>44</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>EFS (months)</td>
<td>No</td>
<td>&gt;= 12 months</td>
<td>123</td>
<td>36</td>
<td>26</td>
<td>66</td>
<td>79</td>
</tr>
<tr>
<td>EFS (months)</td>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>232</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>EFS (months)</td>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>70</td>
<td>15</td>
<td>8</td>
<td>-</td>
<td>66</td>
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</table>

Table 4.5-93 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to prior rituximab and failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Failure from diagnosis</th>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>12</td>
<td>48.6</td>
<td>33.0</td>
<td>62.6</td>
<td>19</td>
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<tr>
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<td>&lt; 12 months</td>
<td>24</td>
<td>43.5</td>
<td>28.3</td>
<td>57.7</td>
<td>17</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>36</td>
<td>40.8</td>
<td>25.9</td>
<td>55.2</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
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<td>40.8</td>
<td>25.9</td>
<td>55.2</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>60</td>
<td>40.8</td>
<td>25.9</td>
<td>55.2</td>
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<td>&lt; 12 months</td>
<td>72</td>
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<td>21.1</td>
<td>51.6</td>
<td>2</td>
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<td>52.7</td>
<td>70.0</td>
<td>70</td>
</tr>
<tr>
<td>No</td>
<td>&gt;= 12 months</td>
<td>36</td>
<td>50.2</td>
<td>40.6</td>
<td>59.0</td>
<td>44</td>
</tr>
<tr>
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<td>&gt;= 12 months</td>
<td>48</td>
<td>49.1</td>
<td>39.5</td>
<td>58.0</td>
<td>31</td>
</tr>
<tr>
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<td>&gt;= 12 months</td>
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<td>47.2</td>
<td>37.4</td>
<td>56.5</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>&gt;= 12 months</td>
<td>72</td>
<td>37.2</td>
<td>24.8</td>
<td>49.6</td>
<td>5</td>
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<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
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<td>21.9</td>
<td>16.7</td>
<td>27.5</td>
<td>49</td>
</tr>
<tr>
<td>Yes</td>
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<td>17.8</td>
<td>13.2</td>
<td>23.1</td>
<td>37</td>
</tr>
<tr>
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<td>&lt; 12 months</td>
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<td>15.5</td>
<td>11.0</td>
<td>20.7</td>
<td>24</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>48</td>
<td>15.5</td>
<td>11.0</td>
<td>20.7</td>
<td>15</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>60</td>
<td>15.5</td>
<td>11.0</td>
<td>20.7</td>
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<td>&lt; 12 months</td>
<td>72</td>
<td>12.4</td>
<td>6.7</td>
<td>19.9</td>
<td>1</td>
</tr>
<tr>
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<td>&gt;= 12 months</td>
<td>12</td>
<td>52.2</td>
<td>39.9</td>
<td>63.2</td>
<td>36</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>24</td>
<td>42.0</td>
<td>30.2</td>
<td>53.2</td>
<td>26</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>36</td>
<td>38.6</td>
<td>27.1</td>
<td>50.0</td>
<td>19</td>
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<tr>
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<td>&gt;= 12 months</td>
<td>48</td>
<td>38.6</td>
<td>27.1</td>
<td>50.0</td>
<td>6</td>
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<tr>
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<td>&gt;= 12 months</td>
<td>60</td>
<td>38.6</td>
<td>27.1</td>
<td>50.0</td>
<td>3</td>
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<tr>
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<td>&gt;= 12 months</td>
<td>72</td>
<td>38.6</td>
<td>27.1</td>
<td>50.0</td>
<td>0</td>
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</tbody>
</table>
Figure 4.5-21 Exploratory analyses – Progression-Free Survival according to prior rituximab by failure from diagnosis (induction ITT)

**Prior treatment with Rituximab=Yes**

![Graph showing Progression-Free Survival for patients with prior rituximab treatment](image1)

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from diagnosis &lt;12 months</td>
<td>232</td>
<td>75% (173)</td>
<td>25% (59)</td>
</tr>
<tr>
<td>Failure from diagnosis ≥12 months</td>
<td>70</td>
<td>53% (37)</td>
<td>47% (33)</td>
</tr>
</tbody>
</table>

**Prior treatment with Rituximab=No**

![Graph showing Progression-Free Survival for patients without prior rituximab treatment](image2)

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from diagnosis &lt;12 months</td>
<td>44</td>
<td>52% (23)</td>
<td>48% (21)</td>
</tr>
<tr>
<td>Failure from diagnosis ≥12 months</td>
<td>123</td>
<td>46% (57)</td>
<td>54% (66)</td>
</tr>
</tbody>
</table>
Figure 4.5-22 Exploratory analyses – Progression-Free Survival according to failure from diagnosis by prior rituximab (induction ITT)

Failure from diagnosis =< 12 months

Logrank p=0.0029

No. of Subjects Event Censored Median Survival (95% CL)
Prior rituximab: No 44 52% (23) 48% (21) 34.69 ( 6.54 NA )
Prior rituximab: Yes 232 75% (173) 25% (59) 4.67 ( 3.84 6.11 )

Failure from diagnosis = >= 12 months

Logrank p=0.1064

No. of Subjects Event Censored Median Survival (95% CL)
Prior rituximab: No 123 46% (57) 54% (66) 60.68 ( 30.88 NA )
Prior rituximab: Yes 70 53% (37) 47% (33) 28.52 ( 15.54 NA )
Table 4.5-94 Exploratory analyses – Duration of Progression-Free Survival according to prior rituximab and failure from diagnosis (induction ITT)

<table>
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<tr>
<th>Prior treatment with Rituximab</th>
<th>Failure from diagnosis (Randomization)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months)</td>
<td>No</td>
<td>44</td>
<td>35</td>
<td>7</td>
<td>-</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>123</td>
<td>61</td>
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<td>79</td>
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<td>232</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td></td>
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<td>70</td>
<td>29</td>
<td>16</td>
<td>-</td>
<td>1</td>
<td>66</td>
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</table>

Table 4.5-95 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to prior rituximab and failure from diagnosis (induction ITT)

<table>
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<tr>
<th>Prior treatment with Rituximab</th>
<th>Failure from diagnosis</th>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>12</td>
<td>62.8</td>
<td>46.6</td>
<td>75.3</td>
<td>25</td>
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<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>24</td>
<td>50.2</td>
<td>34.3</td>
<td>64.2</td>
<td>20</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>36</td>
<td>47.4</td>
<td>31.7</td>
<td>61.7</td>
<td>17</td>
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<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>48</td>
<td>47.4</td>
<td>31.7</td>
<td>61.7</td>
<td>17</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>60</td>
<td>47.4</td>
<td>31.7</td>
<td>61.7</td>
<td>10</td>
</tr>
<tr>
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<td>42.7</td>
<td>26.3</td>
<td>58.1</td>
<td>2</td>
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<tr>
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<td>77</td>
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<tr>
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<td>55.4</td>
<td>45.7</td>
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<td>48</td>
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<td>54.3</td>
<td>44.5</td>
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<td>34</td>
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<tr>
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<td>&gt;= 12 months</td>
<td>60</td>
<td>50.2</td>
<td>39.6</td>
<td>59.9</td>
<td>16</td>
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<tr>
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<td>40.0</td>
<td>26.7</td>
<td>52.8</td>
<td>5</td>
</tr>
<tr>
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<td>67</td>
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<td>25.9</td>
<td>20.4</td>
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<td>52</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>36</td>
<td>23.5</td>
<td>18.0</td>
<td>29.3</td>
<td>35</td>
</tr>
<tr>
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<td>&lt; 12 months</td>
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<td>23.5</td>
<td>18.0</td>
<td>29.3</td>
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<td>&lt; 12 months</td>
<td>72</td>
<td>20.5</td>
<td>13.7</td>
<td>28.2</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
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<td>34.5</td>
<td>58.2</td>
<td>23</td>
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<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
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<td>46.8</td>
<td>34.5</td>
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<td>7</td>
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<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>60</td>
<td>40.2</td>
<td>24.4</td>
<td>55.4</td>
<td>3</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>72</td>
<td>40.2</td>
<td>24.4</td>
<td>55.4</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 4.5-23 Exploratory analyses – Overall Survival according to prior rituximab by failure from diagnosis (induction ITT)

**Failure from diagnosis =< 12 months**

![Graph showing survival probability over OS (months) for patients with and without prior rituximab, divided by failure from diagnosis.](image)

<table>
<thead>
<tr>
<th>Prior rituximab: No</th>
<th>Prior rituximab: Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>44</td>
</tr>
<tr>
<td>Event</td>
<td>52% (23)</td>
</tr>
<tr>
<td>Censored</td>
<td>48% (21)</td>
</tr>
<tr>
<td>Median Survival (95% CL)</td>
<td>34.69 (14.49 NA)</td>
</tr>
</tbody>
</table>

*Logrank p = 0.0812*

**Failure from diagnosis = >= 12 months**

![Graph showing survival probability over OS (months) for patients with and without prior rituximab, divided by failure from diagnosis.](image)

<table>
<thead>
<tr>
<th>Prior rituximab: No</th>
<th>Prior rituximab: Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>123</td>
</tr>
<tr>
<td>Event</td>
<td>35% (43)</td>
</tr>
<tr>
<td>Censored</td>
<td>65% (80)</td>
</tr>
<tr>
<td>Median Survival (95% CL)</td>
<td>64.89 (56.97 NA)</td>
</tr>
</tbody>
</table>

*Logrank p = 0.0762*
Figure 4.5-24 Exploratory analyses – Overall Survival according to failure from diagnosis by prior rituximab (induction ITT)

Prior treatment with Rituximab=Yes

Prior treatment with Rituximab=No
### Table 4.5-96 Exploratory analyses – Duration of Overall Survival according to prior rituximab and failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Failure from diagnosis (Randomization)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months)</td>
<td>No &lt; 12 months</td>
<td>44</td>
<td>35</td>
<td>14</td>
<td>-</td>
<td>3</td>
<td>74</td>
</tr>
<tr>
<td>OS (months)</td>
<td>No &gt;= 12 months</td>
<td>123</td>
<td>65</td>
<td>59</td>
<td>-</td>
<td>2</td>
<td>79</td>
</tr>
<tr>
<td>OS (months)</td>
<td>Yes &lt; 12 months</td>
<td>232</td>
<td>13</td>
<td>11</td>
<td>17</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>OS (months)</td>
<td>Yes &gt;= 12 months</td>
<td>70</td>
<td>-</td>
<td>28</td>
<td>-</td>
<td>1</td>
<td>73</td>
</tr>
</tbody>
</table>

### Table 4.5-97 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to prior rituximab and failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Failure from diagnosis</th>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>12</td>
<td>69.2</td>
<td>52.9</td>
<td>80.8</td>
<td>28</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>24</td>
<td>54.3</td>
<td>38.1</td>
<td>68.0</td>
<td>22</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>36</td>
<td>49.0</td>
<td>33.1</td>
<td>63.2</td>
<td>18</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>48</td>
<td>46.3</td>
<td>30.5</td>
<td>60.7</td>
<td>17</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>60</td>
<td>46.3</td>
<td>30.5</td>
<td>60.7</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>&lt; 12 months</td>
<td>72</td>
<td>41.7</td>
<td>25.4</td>
<td>57.2</td>
<td>7</td>
</tr>
<tr>
<td>No</td>
<td>&gt;= 12 months</td>
<td>12</td>
<td>92.6</td>
<td>86.3</td>
<td>96.1</td>
<td>112</td>
</tr>
<tr>
<td>No</td>
<td>&gt;= 12 months</td>
<td>24</td>
<td>81.6</td>
<td>73.5</td>
<td>87.5</td>
<td>92</td>
</tr>
<tr>
<td>No</td>
<td>&gt;= 12 months</td>
<td>36</td>
<td>73.6</td>
<td>64.3</td>
<td>80.8</td>
<td>65</td>
</tr>
<tr>
<td>No</td>
<td>&gt;= 12 months</td>
<td>48</td>
<td>67.5</td>
<td>57.4</td>
<td>75.6</td>
<td>45</td>
</tr>
<tr>
<td>No</td>
<td>&gt;= 12 months</td>
<td>60</td>
<td>59.0</td>
<td>46.9</td>
<td>69.3</td>
<td>20</td>
</tr>
<tr>
<td>No</td>
<td>&gt;= 12 months</td>
<td>72</td>
<td>46.8</td>
<td>32.5</td>
<td>59.9</td>
<td>6</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>12</td>
<td>53.2</td>
<td>46.4</td>
<td>59.5</td>
<td>116</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>24</td>
<td>39.8</td>
<td>33.3</td>
<td>46.2</td>
<td>78</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>36</td>
<td>35.5</td>
<td>29.1</td>
<td>42.0</td>
<td>53</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>48</td>
<td>34.5</td>
<td>27.9</td>
<td>41.1</td>
<td>30</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>60</td>
<td>34.5</td>
<td>27.9</td>
<td>41.1</td>
<td>14</td>
</tr>
<tr>
<td>Yes</td>
<td>&lt; 12 months</td>
<td>72</td>
<td>30.7</td>
<td>21.8</td>
<td>40.0</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>12</td>
<td>85.5</td>
<td>74.8</td>
<td>91.9</td>
<td>59</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>24</td>
<td>65.0</td>
<td>52.4</td>
<td>75.0</td>
<td>36</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>36</td>
<td>57.2</td>
<td>44.0</td>
<td>68.4</td>
<td>26</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>48</td>
<td>57.2</td>
<td>44.0</td>
<td>68.4</td>
<td>8</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>60</td>
<td>57.2</td>
<td>44.0</td>
<td>68.4</td>
<td>4</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;= 12 months</td>
<td>72</td>
<td>57.2</td>
<td>44.0</td>
<td>68.4</td>
<td>1</td>
</tr>
</tbody>
</table>
4.5.3.4. **According to age-adjusted IPI**

**Table 4.5-98 Exploratory analyses – Overall response rate according to age adjusted IPI (induction ITT)**

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>&lt;2</th>
<th>%</th>
<th>&gt;=2</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response after complete induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRu/PR</td>
<td>198</td>
<td>71</td>
<td>95</td>
<td>54</td>
</tr>
<tr>
<td>Other</td>
<td>80</td>
<td>29</td>
<td>82</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>278</td>
<td>100</td>
<td>177</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 4.5-99 Exploratory analyses – Complete response rate according to age adjusted IPI (induction ITT)**

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>&lt;2</th>
<th>%</th>
<th>&gt;=2</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response after complete induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRu</td>
<td>119</td>
<td>43</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>159</td>
<td>57</td>
<td>125</td>
<td>71</td>
</tr>
<tr>
<td>Total</td>
<td>278</td>
<td>100</td>
<td>177</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 4.5-100 Exploratory analyses – Mobilization adjusted response rate according to age adjusted IPI (induction ITT)**

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>&lt;2</th>
<th>%</th>
<th>&gt;=2</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobilization adjusted overall response rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>108</td>
<td>39</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>Yes</td>
<td>170</td>
<td>61</td>
<td>77</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td>278</td>
<td>100</td>
<td>177</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 4.5-101 Exploratory analyses – Univariate analysis for response rates according to age adjusted IPI (induction ITT)

<table>
<thead>
<tr>
<th>Age adjusted IPI 0-1</th>
<th>p-value (Wald Chi-2)</th>
<th>Odds ratio estimates</th>
<th>95% Wald confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to induction CR/CRu/PR</td>
<td>0.0002</td>
<td>2.136</td>
<td>1.442</td>
</tr>
<tr>
<td>Response to induction CR/CRu</td>
<td>0.0041</td>
<td>1.799</td>
<td>1.204</td>
</tr>
<tr>
<td>Mobilization adjusted response rate</td>
<td>0.0003</td>
<td>0.489</td>
<td>0.334</td>
</tr>
</tbody>
</table>

Figure 4.5-25 Exploratory analyses – Event-Free Survival according to age adjusted IPI (induction ITT)

Table 4.5-102 Exploratory analyses – Duration of Event-Free Survival according to age adjusted IPI (induction ITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>278</td>
<td>13</td>
<td>9</td>
<td>24</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>2-3</td>
<td>177</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>74</td>
</tr>
</tbody>
</table>
Table 4.5-103 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to age adjusted IPI (induction ITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>12</td>
<td>51.8</td>
<td>45.7</td>
<td>57.5</td>
<td>140</td>
</tr>
<tr>
<td>0-1</td>
<td>24</td>
<td>44.7</td>
<td>38.7</td>
<td>50.5</td>
<td>112</td>
</tr>
<tr>
<td>0-1</td>
<td>36</td>
<td>39.9</td>
<td>33.9</td>
<td>45.7</td>
<td>78</td>
</tr>
<tr>
<td>0-1</td>
<td>48</td>
<td>39.4</td>
<td>33.4</td>
<td>45.3</td>
<td>51</td>
</tr>
<tr>
<td>0-1</td>
<td>60</td>
<td>39.4</td>
<td>33.4</td>
<td>45.3</td>
<td>24</td>
</tr>
<tr>
<td>0-1</td>
<td>72</td>
<td>31.7</td>
<td>23.6</td>
<td>40.1</td>
<td>7</td>
</tr>
<tr>
<td>2-3</td>
<td>12</td>
<td>28.4</td>
<td>21.9</td>
<td>35.2</td>
<td>48</td>
</tr>
<tr>
<td>2-3</td>
<td>24</td>
<td>22.4</td>
<td>16.5</td>
<td>28.9</td>
<td>37</td>
</tr>
<tr>
<td>2-3</td>
<td>36</td>
<td>17.7</td>
<td>12.3</td>
<td>23.9</td>
<td>24</td>
</tr>
<tr>
<td>2-3</td>
<td>48</td>
<td>17.7</td>
<td>12.3</td>
<td>23.9</td>
<td>16</td>
</tr>
<tr>
<td>2-3</td>
<td>60</td>
<td>16.4</td>
<td>10.9</td>
<td>22.8</td>
<td>9</td>
</tr>
<tr>
<td>2-3</td>
<td>72</td>
<td>14.3</td>
<td>8.6</td>
<td>21.4</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.5-104 Exploratory analyses – Hazard ratio of age adjusted IPI for Event-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>&lt;.0001</td>
<td>0.538</td>
<td>0.430 0.673</td>
</tr>
</tbody>
</table>

Figure 4.5-26 Exploratory analyses – Progression-Free Survival according to age adjusted IPI (induction ITT)
Table 4.5-105 Exploratory analyses – Duration of Progression-Free Survival according to age adjusted IPI (induction ITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>278</td>
<td>29</td>
<td>16</td>
<td>62</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>2-3</td>
<td>177</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 4.5-106 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to age adjusted IPI (induction ITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>12</td>
<td>61.6</td>
<td>55.6</td>
<td>67.1</td>
<td>166</td>
</tr>
<tr>
<td>0-1</td>
<td>24</td>
<td>52.7</td>
<td>46.5</td>
<td>58.4</td>
<td>131</td>
</tr>
<tr>
<td>0-1</td>
<td>36</td>
<td>47.3</td>
<td>41.1</td>
<td>53.2</td>
<td>92</td>
</tr>
<tr>
<td>0-1</td>
<td>48</td>
<td>46.7</td>
<td>40.6</td>
<td>52.7</td>
<td>59</td>
</tr>
<tr>
<td>0-1</td>
<td>60</td>
<td>44.8</td>
<td>38.3</td>
<td>51.1</td>
<td>27</td>
</tr>
<tr>
<td>0-1</td>
<td>72</td>
<td>37.0</td>
<td>28.3</td>
<td>45.8</td>
<td>8</td>
</tr>
<tr>
<td>2-3</td>
<td>12</td>
<td>38.1</td>
<td>30.9</td>
<td>45.2</td>
<td>64</td>
</tr>
<tr>
<td>2-3</td>
<td>24</td>
<td>30.2</td>
<td>23.5</td>
<td>37.2</td>
<td>48</td>
</tr>
<tr>
<td>2-3</td>
<td>36</td>
<td>24.5</td>
<td>18.1</td>
<td>31.3</td>
<td>30</td>
</tr>
<tr>
<td>2-3</td>
<td>48</td>
<td>24.5</td>
<td>18.1</td>
<td>31.3</td>
<td>19</td>
</tr>
<tr>
<td>2-3</td>
<td>60</td>
<td>22.9</td>
<td>16.4</td>
<td>30.1</td>
<td>10</td>
</tr>
<tr>
<td>2-3</td>
<td>72</td>
<td>20.4</td>
<td>13.3</td>
<td>28.5</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.5-107 Exploratory analyses – Hazard ratio of age adjusted IPI for Progression-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>&lt;.0001</td>
<td>0.532</td>
<td>0.420</td>
</tr>
</tbody>
</table>
Figure 4.5-27 Exploratory analyses – Overall Survival according to age adjusted IPI (induction ITT)

![Survival Probability](image)

Logrank p<0.0001

**Table 4.5-108 Exploratory analyses – Duration of Overall Survival according to age adjusted IPI (induction ITT)**

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>278</td>
<td>66</td>
<td>61</td>
<td>-</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>2-3</td>
<td>177</td>
<td>14</td>
<td>11</td>
<td>22</td>
<td>0</td>
<td>74</td>
</tr>
</tbody>
</table>

**Table 4.5-109 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to age adjusted IPI (induction ITT)**

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>12</td>
<td>80.9</td>
<td>75.7</td>
<td>85.1</td>
<td>219</td>
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<tr>
<td>0-1</td>
<td>24</td>
<td>66.7</td>
<td>60.7</td>
<td>72.0</td>
<td>163</td>
</tr>
<tr>
<td>0-1</td>
<td>36</td>
<td>61.6</td>
<td>55.4</td>
<td>67.3</td>
<td>121</td>
</tr>
<tr>
<td>0-1</td>
<td>48</td>
<td>58.6</td>
<td>52.1</td>
<td>64.5</td>
<td>75</td>
</tr>
<tr>
<td>0-1</td>
<td>60</td>
<td>56.6</td>
<td>49.8</td>
<td>62.9</td>
<td>35</td>
</tr>
<tr>
<td>0-1</td>
<td>72</td>
<td>49.3</td>
<td>40.2</td>
<td>57.9</td>
<td>10</td>
</tr>
<tr>
<td>2-3</td>
<td>12</td>
<td>55.2</td>
<td>47.5</td>
<td>62.3</td>
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<td>2-3</td>
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<td>33.5</td>
<td>48.4</td>
<td>62</td>
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<td>26.7</td>
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<td>2-3</td>
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<td>31.7</td>
<td>24.2</td>
<td>39.4</td>
<td>24</td>
</tr>
<tr>
<td>Age-adjusted IPI</td>
<td>Time Point (years)</td>
<td>Survival (%)</td>
<td>95% CI Lower</td>
<td>95% CI Upper</td>
<td>Patients at risk</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>2-3</td>
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<td>20.0</td>
<td>36.5</td>
<td>12</td>
</tr>
<tr>
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<td>12.7</td>
<td>32.6</td>
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Table 4.5-110 Exploratory analyses – Hazard ratio of age adjusted IPI for Overall Survival (induction ITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>&lt;.0001</td>
<td>0.438</td>
<td>0.337</td>
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</tbody>
</table>

4.5.3.5. Multivariate models

Table 4.5-111 Exploratory analyses – Multivariate logistic model for overall response rate (induction ITT)

<table>
<thead>
<tr>
<th>Response to induction CR/CRu/PR</th>
<th>p-value (Wald Chi-2)</th>
<th>Odds ratio estimates</th>
<th>95% Wald confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.0386</td>
<td>1.744</td>
<td>1.030</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>0.204</td>
<td>0.121</td>
</tr>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>0.0036</td>
<td>1.886</td>
<td>1.231</td>
</tr>
<tr>
<td>Treatment arm: R-ICE</td>
<td>0.9242</td>
<td>0.980</td>
<td>0.642</td>
</tr>
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</table>

Table 4.5-112 Exploratory analyses – Multivariate logistic model for complete response rate (induction ITT)

<table>
<thead>
<tr>
<th>Response to induction CR/CRu</th>
<th>p-value (Wald Chi-2)</th>
<th>Odds ratio estimates</th>
<th>95% Wald confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.3718</td>
<td>1.236</td>
<td>0.776</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>0.298</td>
<td>0.189</td>
</tr>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>0.0325</td>
<td>1.585</td>
<td>1.039</td>
</tr>
<tr>
<td>Treatment arm: R-ICE</td>
<td>0.8947</td>
<td>1.028</td>
<td>0.687</td>
</tr>
</tbody>
</table>

Table 4.5-113 Exploratory analyses – Multivariate logistic model for mobilization adjusted response rate (induction ITT)

<table>
<thead>
<tr>
<th>Mobilization adjusted response rate</th>
<th>p-value (Wald Chi-2)</th>
<th>Odds ratio estimates</th>
<th>95% Wald confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.0012</td>
<td>0.459</td>
<td>0.287</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>2.506</td>
<td>1.595</td>
</tr>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>0.0042</td>
<td>0.553</td>
<td>0.369</td>
</tr>
<tr>
<td>Treatment arm: R-ICE</td>
<td>0.2848</td>
<td>1.242</td>
<td>0.835</td>
</tr>
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</table>

Table 4.5-114 Exploratory analyses – Multivariate Cox model for Event-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th>Event-Free Survival</th>
<th>p-value</th>
<th>Hazard ratio</th>
<th>95% Hazard ratio confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.0011</td>
<td>0.627</td>
<td>0.475</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>1.911</td>
<td>1.465</td>
</tr>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>&lt;.0001</td>
<td>1.633</td>
<td>1.303</td>
</tr>
<tr>
<td>Treatment arm: R-ICE</td>
<td>0.3020</td>
<td>1.125</td>
<td>0.900</td>
</tr>
</tbody>
</table>
### Table 4.5-115 Exploratory analyses – Multivariate Cox model for Progression-Free Survival (induction ITT)

<table>
<thead>
<tr>
<th></th>
<th>p-value</th>
<th>Hazard ratio</th>
<th>95% Hazard ratio confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.0046</td>
<td>0.656</td>
<td>0.490 0.878</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>1.873</td>
<td>1.415 2.479</td>
</tr>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>&lt;.0001</td>
<td>1.677</td>
<td>1.322 2.128</td>
</tr>
<tr>
<td>Treatment arm: R-ICE</td>
<td>0.3554</td>
<td>1.117</td>
<td>0.883 1.414</td>
</tr>
</tbody>
</table>

### Table 4.5-116 Exploratory analyses – Multivariate Cox model for Overall Survival (induction ITT)

<table>
<thead>
<tr>
<th></th>
<th>p-value</th>
<th>Hazard ratio</th>
<th>95% Hazard ratio confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.0765</td>
<td>0.746</td>
<td>0.539 1.032</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>&lt;.0001</td>
<td>2.011</td>
<td>1.461 2.768</td>
</tr>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>&lt;.0001</td>
<td>2.153</td>
<td>1.656 2.799</td>
</tr>
<tr>
<td>Treatment arm: R-ICE</td>
<td>0.2504</td>
<td>1.165</td>
<td>0.898 1.513</td>
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</table>

#### 4.5.3.6. According to response to induction (CR/CRu vs PR)

**Figure 4.5-28 Exploratory analyses – Event-Free Survival according to response to induction (induction ITT)**

![Graph showing Event-Free Survival](image)
Table 4.5-117 Exploratory analyses – Duration of Event-Free Survival according to response to induction (induction ITT)

<table>
<thead>
<tr>
<th>Response after complete induction (including deaths for all patients)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (months) CR/CRu</td>
<td>172</td>
<td>61</td>
<td>25</td>
<td>-</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>EFS (months) PR</td>
<td>128</td>
<td>13</td>
<td>9</td>
<td>29</td>
<td>2</td>
<td>79</td>
</tr>
</tbody>
</table>

Table 4.5-118 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to response to induction (induction ITT)

<table>
<thead>
<tr>
<th>Response after complete induction (including deaths for all patients)</th>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>12</td>
<td>69.5</td>
<td>61.9</td>
<td>75.8</td>
<td>117</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>24</td>
<td>59.9</td>
<td>52.1</td>
<td>66.8</td>
<td>96</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>36</td>
<td>52.4</td>
<td>44.4</td>
<td>59.7</td>
<td>70</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>48</td>
<td>51.6</td>
<td>43.7</td>
<td>59.0</td>
<td>45</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>60</td>
<td>50.4</td>
<td>42.3</td>
<td>58.0</td>
<td>22</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>72</td>
<td>42.5</td>
<td>31.6</td>
<td>52.9</td>
<td>4</td>
</tr>
<tr>
<td>PR</td>
<td>12</td>
<td>50.6</td>
<td>41.5</td>
<td>58.9</td>
<td>63</td>
</tr>
<tr>
<td>PR</td>
<td>24</td>
<td>44.0</td>
<td>35.2</td>
<td>52.5</td>
<td>51</td>
</tr>
<tr>
<td>PR</td>
<td>36</td>
<td>36.1</td>
<td>27.4</td>
<td>44.8</td>
<td>31</td>
</tr>
<tr>
<td>PR</td>
<td>48</td>
<td>36.1</td>
<td>27.4</td>
<td>44.8</td>
<td>22</td>
</tr>
<tr>
<td>PR</td>
<td>60</td>
<td>36.1</td>
<td>27.4</td>
<td>44.8</td>
<td>11</td>
</tr>
<tr>
<td>PR</td>
<td>72</td>
<td>28.1</td>
<td>16.8</td>
<td>40.5</td>
<td>4</td>
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</table>
Figure 4.5-29 Exploratory analyses – Progression-Free Survival according to response to induction (induction ITT)

![Survival Probability Graph]

Table 4.5-119 Exploratory analyses – Duration of Progression-Free Survival according to response to induction (induction ITT)

<table>
<thead>
<tr>
<th>Response after complete induction (including deaths for all patients)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (months) CR/CRu</td>
<td>172</td>
<td>61</td>
<td>34</td>
<td>-</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>PFS (months) PR</td>
<td>128</td>
<td>35</td>
<td>21</td>
<td>-</td>
<td>2</td>
<td>79</td>
</tr>
</tbody>
</table>

Table 4.5-120 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to response to induction (induction ITT)

<table>
<thead>
<tr>
<th>Response after complete induction (including deaths for all patients)</th>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>12</td>
<td>75.9</td>
<td>68.7</td>
<td>81.6</td>
<td>128</td>
</tr>
<tr>
<td>CR/CRu</td>
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<td>57.5</td>
<td>71.8</td>
<td>105</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>36</td>
<td>56.3</td>
<td>48.3</td>
<td>63.6</td>
<td>77</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>48</td>
<td>55.6</td>
<td>47.6</td>
<td>62.9</td>
<td>47</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>60</td>
<td>53.1</td>
<td>44.7</td>
<td>60.8</td>
<td>23</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>72</td>
<td>45.2</td>
<td>34.1</td>
<td>55.6</td>
<td>4</td>
</tr>
<tr>
<td>PR</td>
<td>12</td>
<td>64.7</td>
<td>55.6</td>
<td>72.4</td>
<td>79</td>
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</tbody>
</table>
Table 4.5-121 Exploratory analyses – Duration of Overall Survival according to response to induction (induction ITT)

<table>
<thead>
<tr>
<th>Response after complete induction (including deaths for all patients)</th>
<th>N</th>
<th>Median</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months) CR/CRu</td>
<td>172</td>
<td>-</td>
<td>61</td>
<td>-</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>OS (months) PR</td>
<td>128</td>
<td>62</td>
<td>35</td>
<td>-</td>
<td>2</td>
<td>79</td>
</tr>
</tbody>
</table>
Table 4.5-122 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to response to induction (induction ITT)

<table>
<thead>
<tr>
<th>Response after complete induction (including deaths for all patients)</th>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>12</td>
<td>90.6</td>
<td>85.1</td>
<td>94.1</td>
<td>153</td>
</tr>
<tr>
<td>CR/CRu</td>
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<td>69.8</td>
<td>82.5</td>
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<td>CR/CRu</td>
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<td>69.3</td>
<td>61.5</td>
<td>75.8</td>
<td>96</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>48</td>
<td>65.1</td>
<td>56.9</td>
<td>72.1</td>
<td>58</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>60</td>
<td>60.5</td>
<td>51.1</td>
<td>68.7</td>
<td>27</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>72</td>
<td>50.3</td>
<td>37.9</td>
<td>61.4</td>
<td>5</td>
</tr>
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<td>76.0</td>
<td>89.2</td>
<td>102</td>
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<tr>
<td>PR</td>
<td>24</td>
<td>68.0</td>
<td>58.9</td>
<td>75.5</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>36</td>
<td>58.0</td>
<td>48.1</td>
<td>66.7</td>
<td>45</td>
</tr>
<tr>
<td>PR</td>
<td>48</td>
<td>56.3</td>
<td>46.2</td>
<td>65.3</td>
<td>32</td>
</tr>
<tr>
<td>PR</td>
<td>60</td>
<td>53.7</td>
<td>42.6</td>
<td>63.5</td>
<td>14</td>
</tr>
<tr>
<td>PR</td>
<td>72</td>
<td>49.8</td>
<td>37.2</td>
<td>61.2</td>
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</tbody>
</table>
4.5.3.7. According to PET after induction

Figure 4.5-31 Exploratory analyses – Event-Free Survival according to PET after induction (induction ITT)

Table 4.5-123 Exploratory analyses – Duration of Event-Free Survival according to PET after induction (induction ITT)

<table>
<thead>
<tr>
<th>Pet scan after induction</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (months)</td>
<td>PET -</td>
<td>72</td>
<td>31</td>
<td>15</td>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td>EFS (months)</td>
<td>PET +</td>
<td>80</td>
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<td>3</td>
<td>1</td>
<td>75</td>
</tr>
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</table>

Table 4.5-124 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to PET after induction (induction ITT)

<table>
<thead>
<tr>
<th>Pet scan after induction</th>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET -</td>
<td>12</td>
<td>69.4</td>
<td>57.4</td>
<td>78.7</td>
<td>49</td>
</tr>
<tr>
<td>PET -</td>
<td>24</td>
<td>58.0</td>
<td>45.7</td>
<td>68.5</td>
<td>40</td>
</tr>
<tr>
<td>PET -</td>
<td>36</td>
<td>46.3</td>
<td>34.0</td>
<td>57.7</td>
<td>25</td>
</tr>
<tr>
<td>PET -</td>
<td>48</td>
<td>46.3</td>
<td>34.0</td>
<td>57.7</td>
<td>11</td>
</tr>
<tr>
<td>PET -</td>
<td>60</td>
<td>46.3</td>
<td>34.0</td>
<td>57.7</td>
<td>5</td>
</tr>
<tr>
<td>PET -</td>
<td>72</td>
<td>46.3</td>
<td>34.0</td>
<td>57.7</td>
<td>0</td>
</tr>
<tr>
<td>PET +</td>
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<td>23.2</td>
<td>14.4</td>
<td>33.2</td>
<td>17</td>
</tr>
<tr>
<td>PET +</td>
<td>24</td>
<td>23.2</td>
<td>14.4</td>
<td>33.2</td>
<td>15</td>
</tr>
<tr>
<td>PET +</td>
<td>36</td>
<td>18.1</td>
<td>10.2</td>
<td>27.9</td>
<td>9</td>
</tr>
</tbody>
</table>
# Table 4.5-125 Exploratory analyses – Duration of Progression-Free Survival according to PET after induction (induction ITT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET - 12</td>
<td>76.4</td>
<td>64.8</td>
<td>84.6</td>
<td>54</td>
</tr>
<tr>
<td>PET - 24</td>
<td>63.5</td>
<td>51.2</td>
<td>73.5</td>
<td>44</td>
</tr>
<tr>
<td>PET - 36</td>
<td>52.0</td>
<td>39.5</td>
<td>63.2</td>
<td>29</td>
</tr>
<tr>
<td>PET - 48</td>
<td>52.0</td>
<td>39.5</td>
<td>63.2</td>
<td>13</td>
</tr>
</tbody>
</table>

# Table 4.5-126 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to PET after induction (induction ITT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET - 12</td>
<td>76.4</td>
<td>64.8</td>
<td>84.6</td>
<td>54</td>
</tr>
<tr>
<td>PET - 24</td>
<td>63.5</td>
<td>51.2</td>
<td>73.5</td>
<td>44</td>
</tr>
<tr>
<td>PET - 36</td>
<td>52.0</td>
<td>39.5</td>
<td>63.2</td>
<td>29</td>
</tr>
<tr>
<td>PET - 48</td>
<td>52.0</td>
<td>39.5</td>
<td>63.2</td>
<td>13</td>
</tr>
<tr>
<td>Pet scan after induction</td>
<td>Time Point (months)</td>
<td>PFS (%)</td>
<td>95% CI Lower</td>
<td>95% CI Upper</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------</td>
<td>---------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>PET -</td>
<td>60</td>
<td>47.3</td>
<td>32.9</td>
<td>60.5</td>
</tr>
<tr>
<td>PET -</td>
<td>72</td>
<td>47.3</td>
<td>32.9</td>
<td>60.5</td>
</tr>
<tr>
<td>PET +</td>
<td>12</td>
<td>38.9</td>
<td>28.0</td>
<td>49.7</td>
</tr>
<tr>
<td>PET +</td>
<td>24</td>
<td>36.1</td>
<td>25.4</td>
<td>46.9</td>
</tr>
<tr>
<td>PET +</td>
<td>36</td>
<td>30.5</td>
<td>20.1</td>
<td>41.5</td>
</tr>
<tr>
<td>PET +</td>
<td>48</td>
<td>30.5</td>
<td>20.1</td>
<td>41.5</td>
</tr>
<tr>
<td>PET +</td>
<td>60</td>
<td>30.5</td>
<td>20.1</td>
<td>41.5</td>
</tr>
<tr>
<td>PET +</td>
<td>72</td>
<td>30.5</td>
<td>20.1</td>
<td>41.5</td>
</tr>
</tbody>
</table>

Figure 4.5-33 Exploratory analyses – Overall Survival according to PET after induction (induction ITT)

![Graph showing survival probability over time for PET + and PET - groups](image)

Logrank p=0.0383

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET +</td>
<td>80</td>
<td>48% (36)</td>
<td>53% (42)</td>
</tr>
<tr>
<td>PET -</td>
<td>72</td>
<td>40% (29)</td>
<td>60% (43)</td>
</tr>
</tbody>
</table>

Table 4.5-127 Exploratory analyses – Duration of Overall Survival according to PET after induction (induction ITT)

<table>
<thead>
<tr>
<th>Pet scan after induction</th>
<th>N</th>
<th>Median</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months)</td>
<td>PET -</td>
<td>72</td>
<td>61</td>
<td>41</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>OS (months)</td>
<td>PET +</td>
<td>80</td>
<td>48</td>
<td>13</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 4.5-128 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to PET after induction (induction ITT)

<table>
<thead>
<tr>
<th>Pet scan after induction</th>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET -</td>
<td>12</td>
<td>88.9</td>
<td>79.0</td>
<td>94.3</td>
<td>63</td>
</tr>
<tr>
<td>PET -</td>
<td>24</td>
<td>71.8</td>
<td>59.7</td>
<td>80.8</td>
<td>50</td>
</tr>
<tr>
<td>PET -</td>
<td>36</td>
<td>65.2</td>
<td>52.6</td>
<td>75.2</td>
<td>38</td>
</tr>
<tr>
<td>PET -</td>
<td>48</td>
<td>59.0</td>
<td>45.7</td>
<td>70.1</td>
<td>19</td>
</tr>
<tr>
<td>PET -</td>
<td>60</td>
<td>52.4</td>
<td>35.2</td>
<td>67.1</td>
<td>8</td>
</tr>
<tr>
<td>PET -</td>
<td>72</td>
<td>45.9</td>
<td>26.9</td>
<td>63.0</td>
<td>1</td>
</tr>
<tr>
<td>PET +</td>
<td>12</td>
<td>61.6</td>
<td>49.6</td>
<td>71.5</td>
<td>46</td>
</tr>
<tr>
<td>PET +</td>
<td>24</td>
<td>50.8</td>
<td>39.0</td>
<td>61.4</td>
<td>33</td>
</tr>
<tr>
<td>PET +</td>
<td>36</td>
<td>50.8</td>
<td>39.0</td>
<td>61.4</td>
<td>23</td>
</tr>
<tr>
<td>PET +</td>
<td>48</td>
<td>47.4</td>
<td>34.7</td>
<td>59.1</td>
<td>14</td>
</tr>
<tr>
<td>PET +</td>
<td>60</td>
<td>47.4</td>
<td>34.7</td>
<td>59.1</td>
<td>7</td>
</tr>
<tr>
<td>PET +</td>
<td>72</td>
<td>47.4</td>
<td>34.7</td>
<td>59.1</td>
<td>2</td>
</tr>
</tbody>
</table>
4.5.4. Non study or new treatment out of progression

36 patients (15%) in R-ICE arm and 31 patients (13%) in R-DHAP arm presented a new treatment out of progression (corresponding to the 67 events due to change of therapy for Event-Free survival of induction ITT population).

Table 4.5-129 Patients with non study or new treatment out of progression (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>New treatment out of progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>203</td>
<td>85</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4.5-130 Type of non study or new treatment out of progression (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>58</td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>42</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>29</td>
<td>81</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>75</td>
</tr>
<tr>
<td>Transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>Other treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>94</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100</td>
</tr>
</tbody>
</table>

Details of treatment are listed in section §6.6.3.
4.5.5. Progression/relapse

132 patients (55%) in R-ICE arm and 117 patients (51%) in R-DHAP arm presented a first progression/relapse.

Table 4.5-131 Patients with progression/relapse (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Progression/relapse n°1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>132</td>
<td>117</td>
</tr>
<tr>
<td>No</td>
<td>107</td>
<td>113</td>
</tr>
<tr>
<td>Progression/relapse n°2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>No</td>
<td>218</td>
<td>208</td>
</tr>
<tr>
<td>Progression/relapse n°3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>No</td>
<td>231</td>
<td>222</td>
</tr>
<tr>
<td>Progression/relapse n°4</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>237</td>
<td>228</td>
</tr>
<tr>
<td>Progression/relapse n°5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>237</td>
<td>229</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>230</td>
</tr>
</tbody>
</table>

Table 4.5-132 Progression/relapse n°1 – Period (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Period of Progression / Relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TREATMENT PERIOD</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>FOLLOW UP PERIOD</td>
<td>66</td>
<td>54</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>117</td>
</tr>
</tbody>
</table>

Table 4.5-133 Progression/relapse n°1 – Involvement (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Initial involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>No</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>New involvement</td>
<td>Arm of treatment</td>
<td>Arm of treatment</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Not Done</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>64</td>
<td>48</td>
</tr>
<tr>
<td>No</td>
<td>67</td>
<td>51</td>
</tr>
<tr>
<td>Nodal involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>95</td>
<td>72</td>
</tr>
<tr>
<td>No</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>Extra-nodal involvement</td>
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<tr>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>77</td>
<td>58</td>
</tr>
<tr>
<td>No</td>
<td>54</td>
<td>41</td>
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<tr>
<td>Total</td>
<td>132</td>
<td>100</td>
</tr>
</tbody>
</table>

Details of extra-nodal involvement are listed in section §6.6.4.

Table 4.5-134 Progression/relapse n°1 – Individual factors of IPI (induction ITT)

<p>| Arm of treatment |
|------------------|------------------|------------------|
| ARM A / R-ICE    | ARM B / R-DHAP   |</p>
<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH &gt; Upper Limit</td>
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<tr>
<td>Missing</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Not Done</td>
<td>10</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Yes</td>
<td>71</td>
<td>54</td>
<td>80</td>
</tr>
<tr>
<td>No</td>
<td>49</td>
<td>37</td>
<td>30</td>
</tr>
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<td>Stage III - IV</td>
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<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Not Done</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>81</td>
<td>61</td>
<td>77</td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>PS &gt;= 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Not Done</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>30</td>
<td>38</td>
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<tr>
<td>No</td>
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<td>64</td>
<td>72</td>
</tr>
<tr>
<td>Extra-nodal sites &gt;= 2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Not Done</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>No</td>
<td>93</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>100</td>
<td>117</td>
</tr>
</tbody>
</table>
### Table 4.5-135 Progression/relapse n°1 – Progression/relapse treatment (induction ITT)

<table>
<thead>
<tr>
<th>Progression / Relapse treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>124</td>
<td>94</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>132</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 4.5-136 Progression/relapse n°1 – Type of progression/relapse treatment (induction ITT)

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Done</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>97</td>
<td>78</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Done</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>No</td>
<td>81</td>
<td>65</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Done</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>No</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>Transplantation</td>
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<td></td>
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<tr>
<td>Not Done</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Yes</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>No</td>
<td>91</td>
<td>73</td>
</tr>
<tr>
<td>Other treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Done</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>109</td>
<td>88</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>100</td>
</tr>
</tbody>
</table>

Details of treatment are listed in section §6.6.4.
Table 4.5-137 Progression/relapse n°1 – Response after additional treatments (induction ITT)

<table>
<thead>
<tr>
<th>Response after new treatment</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>COMPLETE RESPONSE</td>
<td>16</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>7</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>PARTIAL RESPONSE</td>
<td>17</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>STABLE DISEASE</td>
<td>4</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>PROGRESSIVE DISEASE</td>
<td>67</td>
<td>54</td>
<td>47</td>
</tr>
<tr>
<td>NOT EVALUATED</td>
<td>12</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>100</td>
<td>102</td>
</tr>
</tbody>
</table>

All information about progression/relapse n°2 are shown in section §6.6.4.
5. SAFETY EVALUATION

5.1. Extent of exposure to trial medication

The number of induction treatment cycles received by each patient is summarized in the following table; in this summary, patients were considered to have received a cycle if they were given at least one study drug.

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>239</td>
<td>100</td>
</tr>
<tr>
<td>Cycle 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>225</td>
<td>94</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Cycle 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>204</td>
<td>85</td>
</tr>
<tr>
<td>No</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

204 patients (85%) in R-ICE arm received the complete treatment and 196 patients (85%) in the R-DHAP arm. One patient in R-ICE arm received only 2 cycles but then received consolidation.

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between cycles 1 and 2 (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>225</td>
<td>214</td>
</tr>
<tr>
<td>Mean</td>
<td>22.7</td>
<td>22.7</td>
</tr>
<tr>
<td>Std</td>
<td>4.48</td>
<td>3.49</td>
</tr>
<tr>
<td>Median</td>
<td>21.0</td>
<td>21.5</td>
</tr>
<tr>
<td>Min</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Max</td>
<td>53</td>
<td>39</td>
</tr>
<tr>
<td>Time between cycles 2 and 3 (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>204</td>
<td>195</td>
</tr>
<tr>
<td>Mean</td>
<td>23.2</td>
<td>23.0</td>
</tr>
<tr>
<td>Std</td>
<td>4.28</td>
<td>3.72</td>
</tr>
<tr>
<td>Median</td>
<td>22.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Min</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Max</td>
<td>55</td>
<td>52</td>
</tr>
</tbody>
</table>
### Table 5.1-3 Induction - Percentage of planned dose received by cycle for rituximab (induction safety population)

<table>
<thead>
<tr>
<th>Rituximab</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual arm of induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>239</td>
<td>228</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>95.0</td>
<td>94.6</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>15.29</td>
<td>15.83</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>37</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>113</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>225</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>98.7</td>
<td>98.4</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>7.87</td>
<td>8.00</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
<td>99.9</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>117</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>204</td>
<td>193</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>98.7</td>
<td>99.0</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>8.06</td>
<td>4.09</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
<td>99.9</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>117</td>
<td>116</td>
<td></td>
</tr>
</tbody>
</table>

Some patients did not receive rituximab as planned:

- At 1st cycle, injection at day -2 was not administrated for 12 patients in R-ICE arm and 8 patients in R-DHAP arm. Injection at day 1 was not administrated for 9 patients in R-ICE arm and 12 patients in R-DHAP arm.
- Overall one patient in R-DHAP arm never received rituximab due to allergy.
### Table 5.1-4 Induction - Percentage of planned dose received by cycle for ICE regimen (induction safety population)

<table>
<thead>
<tr>
<th>Dose received (% of planned dose)</th>
<th>Actual arm of induction ARM A / R-ICE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etoposide</strong></td>
<td></td>
</tr>
<tr>
<td>Cycle 1</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>239</td>
</tr>
<tr>
<td>Mean</td>
<td>98.0</td>
</tr>
<tr>
<td>Std</td>
<td>9.21</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>110</td>
</tr>
<tr>
<td>Cycle 2</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>225</td>
</tr>
<tr>
<td>Mean</td>
<td>97.9</td>
</tr>
<tr>
<td>Std</td>
<td>7.79</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>33</td>
</tr>
<tr>
<td>Max</td>
<td>111</td>
</tr>
<tr>
<td>Cycle 3</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>204</td>
</tr>
<tr>
<td>Mean</td>
<td>97.5</td>
</tr>
<tr>
<td>Std</td>
<td>8.48</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>33</td>
</tr>
<tr>
<td>Max</td>
<td>111</td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
<td></td>
</tr>
<tr>
<td>Cycle 1</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>238</td>
</tr>
<tr>
<td>Mean</td>
<td>99.0</td>
</tr>
<tr>
<td>Std</td>
<td>16.76</td>
</tr>
<tr>
<td>Median</td>
<td>99.0</td>
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<tr>
<td>Min</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>149</td>
</tr>
<tr>
<td>Cycle 2</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>224</td>
</tr>
<tr>
<td>Mean</td>
<td>99.9</td>
</tr>
<tr>
<td>Std</td>
<td>18.85</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>172</td>
</tr>
<tr>
<td>Cycle 3</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>203</td>
</tr>
<tr>
<td>Mean</td>
<td>98.7</td>
</tr>
<tr>
<td>Std</td>
<td>15.64</td>
</tr>
<tr>
<td>Median</td>
<td>99.5</td>
</tr>
<tr>
<td>Min</td>
<td>47</td>
</tr>
<tr>
<td>Max</td>
<td>150</td>
</tr>
</tbody>
</table>
Some patients did not receive at least one drug of ICE regimen:

- Patient 5003621301014 only received injection at day -2 for rituximab and was withdrawn for treatment toxicity.
- One patient did not receive carboplatine at 2\textsuperscript{nd} cycle (permanent stop but anyway withdrawn before C3 for progressive disease).
- One patient did not receive ifosfamide at 2\textsuperscript{nd} and 3\textsuperscript{rd} cycles due to CNS toxicity.
Table 5.1-5 Induction - Percentage of planned dose received by cycle for DHAP regimen (induction safety population)

<table>
<thead>
<tr>
<th>Dose received (% of planned dose)</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dexamethasone</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cycle 1</strong></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>229</td>
</tr>
<tr>
<td>Mean</td>
<td>106.2</td>
</tr>
<tr>
<td>Std</td>
<td>43.02</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>75</td>
</tr>
<tr>
<td>Max</td>
<td>700</td>
</tr>
<tr>
<td><strong>Cycle 2</strong></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>213</td>
</tr>
<tr>
<td>Mean</td>
<td>103.3</td>
</tr>
<tr>
<td>Std</td>
<td>18.65</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>25</td>
</tr>
<tr>
<td>Max</td>
<td>200</td>
</tr>
<tr>
<td><strong>Cycle 3</strong></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>196</td>
</tr>
<tr>
<td>Mean</td>
<td>103.1</td>
</tr>
<tr>
<td>Std</td>
<td>17.62</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>50</td>
</tr>
<tr>
<td>Max</td>
<td>200</td>
</tr>
<tr>
<td><strong>Cisplatine</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cycle 1</strong></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>228</td>
</tr>
<tr>
<td>Mean</td>
<td>97.8</td>
</tr>
<tr>
<td>Std</td>
<td>7.49</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>28</td>
</tr>
<tr>
<td>Max</td>
<td>106</td>
</tr>
<tr>
<td><strong>Cycle 2</strong></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>212</td>
</tr>
<tr>
<td>Mean</td>
<td>95.0</td>
</tr>
<tr>
<td>Std</td>
<td>15.54</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>110</td>
</tr>
<tr>
<td><strong>Cycle 3</strong></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>194</td>
</tr>
<tr>
<td>Mean</td>
<td>91.0</td>
</tr>
<tr>
<td>Std</td>
<td>27.03</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>253</td>
</tr>
</tbody>
</table>
Dose received (% of planned dose) | Actual arm of induction
---|---
Cycle 1 | ARM B / R-DHAP
N | 228
Mean | 96.1
Std | 12.78
Median | 100.0
Min | 13
Max | 114
Cycle 2 | N | 211
Mean | 95.9
Std | 12.09
Median | 100.0
Min | 24
Max | 106
Cycle 3 | N | 194
Mean | 96.1
Std | 11.44
Median | 100.0
Min | 45
Max | 108

Some patients did not receive cisplatine of DHAP regimen due to renal toxicity:
- 4 patients did not receive cisplatine at 2nd and 3rd cycles.
- 7 additional patients did not receive cisplatine at 3rd cycle.

Same results are described in terms of frequency in section §6.7.1.

The following table summarizes the administration of growth factors during induction phase:

Table 5.1-6 Induction – Growth factors (induction safety population)

<table>
<thead>
<tr>
<th>G-CSF</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Cycle 1</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>Yes</td>
<td>194</td>
<td>81</td>
</tr>
<tr>
<td>Not Done</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
<tr>
<td>No</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Yes</td>
<td>197</td>
<td>82</td>
</tr>
<tr>
<td>Not Done</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Missing</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>
### G-CSF

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>No</td>
<td>9</td>
</tr>
<tr>
<td>Yes</td>
<td>192</td>
<td>80</td>
</tr>
<tr>
<td>Not Done</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

The number of days of G-CSF administration is described in section §6.7.1.

**Table 5.1-7 Consolidation - Percentage of planned dose received for BEAM (induction safety population)**

<table>
<thead>
<tr>
<th>Dose received (% of planned dose)</th>
<th>Actual arm of induction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
</tr>
<tr>
<td>BCNU</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>122</td>
</tr>
<tr>
<td>Mean</td>
<td>98.5</td>
</tr>
<tr>
<td>Std</td>
<td>8.47</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>69</td>
</tr>
<tr>
<td>Max</td>
<td>167</td>
</tr>
<tr>
<td>Etoposide</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>122</td>
</tr>
<tr>
<td>Mean</td>
<td>99.1</td>
</tr>
<tr>
<td>Std</td>
<td>21.81</td>
</tr>
<tr>
<td>Median</td>
<td>100.0</td>
</tr>
<tr>
<td>Min</td>
<td>25</td>
</tr>
<tr>
<td>Max</td>
<td>203</td>
</tr>
<tr>
<td>Cytarabine</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>122</td>
</tr>
<tr>
<td>Mean</td>
<td>88.9</td>
</tr>
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<td>Std</td>
<td>20.88</td>
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<td>98.2</td>
</tr>
<tr>
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<tr>
<td>Max</td>
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<tr>
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<td>N</td>
<td>122</td>
</tr>
<tr>
<td>Mean</td>
<td>97.9</td>
</tr>
<tr>
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</tr>
<tr>
<td>Min</td>
<td>50</td>
</tr>
<tr>
<td>Max</td>
<td>108</td>
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</table>

Same results are described in terms of frequency in section §6.7.1.
Table 5.1-8 Consolidation – Administration of growth factors (induction safety population)

<table>
<thead>
<tr>
<th>G-CSF</th>
<th>Actual arm of induction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>No</td>
<td>35</td>
</tr>
<tr>
<td>Yes</td>
<td>86</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
</tr>
</tbody>
</table>

Table 5.1-9 Consolidation – Type of growth factors (induction safety population)

<table>
<thead>
<tr>
<th>G-CSF</th>
<th>Actual arm of induction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>G-CSF</td>
<td>83</td>
</tr>
<tr>
<td>OTHER</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
</tr>
</tbody>
</table>

Other types of growth factors are listed in section §6.7.1.
5.2. Adverse events

All adverse events occurring were graded with CTCAE v3.0.

5.2.1. Overview of toxicity profile

The toxicity profile during the whole induction treatment phase is summarized by the worst grade reported per patient in the following tables:

**Table 5.2-1 Incidence of toxicities by worst grade per patient during induction phase (induction safety population)**

<table>
<thead>
<tr>
<th>Grade affection</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual arm of induction</td>
<td>Actual arm of induction</td>
</tr>
<tr>
<td></td>
<td>Grade</td>
<td>N</td>
</tr>
<tr>
<td>All tox.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>allergic</td>
<td>Grade allergy</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>8</td>
<td>92</td>
</tr>
<tr>
<td>auditory</td>
<td>Grade auditory</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>blood</td>
<td>Grade blood</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>cardiovascular</td>
<td>Grade cardiovascular</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>7</td>
<td>92</td>
</tr>
<tr>
<td>coagulation</td>
<td>Grade coagulation</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>skin</td>
<td>Grade skin</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>15</td>
<td>84</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>Grade gastrointestinal</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td>hepatic</td>
<td>Grade hepatic</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>infection with febrile neutropenia</td>
<td>Grade infection with febrile neutropenia</td>
<td>N</td>
</tr>
<tr>
<td>%</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Grade infection without febrile neutropenia</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Grade</td>
<td>Grade</td>
<td>Grade</td>
</tr>
<tr>
<td>All Tox.</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>35</td>
<td>203</td>
</tr>
<tr>
<td>%</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>Grade metabolic</td>
<td>N</td>
<td>39</td>
</tr>
<tr>
<td>%</td>
<td>16</td>
<td>83</td>
</tr>
<tr>
<td>Grade neurology</td>
<td>N</td>
<td>32</td>
</tr>
<tr>
<td>%</td>
<td>13</td>
<td>86</td>
</tr>
<tr>
<td>Grade pulmonary</td>
<td>N</td>
<td>22</td>
</tr>
<tr>
<td>%</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>Grade renal</td>
<td>N</td>
<td>15</td>
</tr>
<tr>
<td>%</td>
<td>6</td>
<td>93</td>
</tr>
<tr>
<td>Other toxicity</td>
<td>N</td>
<td>81</td>
</tr>
<tr>
<td>%</td>
<td>34</td>
<td>64</td>
</tr>
</tbody>
</table>

NE = Not Evaluated
The toxicity profile is also summarized by grade and cycle for each designation in section §6.7.2. In this summary, the denominator is the number of patients who received treatment at each cycle.

Other toxicities are listed in section §6.7.2.

**Table 5.2-2 Patients with RBC and platelets transfusions during induction (induction safety population)**

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>At least one RBC transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>119</td>
<td>50</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Missing</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>At least one platelets transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>92</td>
<td>38</td>
</tr>
<tr>
<td>No</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
<td>Missing</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

A higher proportion of patients in the R-DHAP arm presented with at least one platelets transfusion during induction phase (58% vs 38% in R-ICE arm).
### Table 5.2-3 Incidence of toxicities during consolidation phase (induction safety population)

<table>
<thead>
<tr>
<th>Grade Infection</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Tox.</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>90</td>
<td>32</td>
</tr>
<tr>
<td>%</td>
<td>73</td>
<td>26</td>
</tr>
<tr>
<td>Grade Neurologic</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>All Tox.</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>2</td>
<td>120</td>
</tr>
<tr>
<td>%</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>Grade Mucositis</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>All Tox.</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>81</td>
<td>41</td>
</tr>
<tr>
<td>%</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>Grade Hepatic</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>All Tox.</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>102</td>
</tr>
<tr>
<td>%</td>
<td>16</td>
<td>83</td>
</tr>
<tr>
<td>Grade Gastrointestinal</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>All Tox.</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>73</td>
<td>49</td>
</tr>
<tr>
<td>%</td>
<td>59</td>
<td>40</td>
</tr>
<tr>
<td>Grade Renal</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>All Tox.</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>9</td>
<td>113</td>
</tr>
<tr>
<td>%</td>
<td>7</td>
<td>92</td>
</tr>
<tr>
<td>Grade Cardiovascular</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>All Tox.</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>16</td>
<td>106</td>
</tr>
<tr>
<td>%</td>
<td>13</td>
<td>86</td>
</tr>
<tr>
<td>Other toxicity</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>All Tox.</td>
<td>0</td>
</tr>
<tr>
<td>N</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>%</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

Other toxicities during consolidation are listed in section §6.7.2.

NE = Not Evaluated
### Table 5.2-4 Patients with RBC and platelets transfusions during consolidation (induction safety population)

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>At least one RBC transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>Yes</td>
<td>94</td>
<td>76</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>At least one platelets transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Yes</td>
<td>115</td>
<td>93</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 5.2-5 Time intervals for hematological recovery after transplant (induction safety population)

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Neutrophils &gt; 1 Giga/l (days after transplant)</td>
<td></td>
<td>117</td>
</tr>
<tr>
<td>Neutrophils &gt; 0.5 Giga/l (days after transplant)</td>
<td></td>
<td>116</td>
</tr>
<tr>
<td>Platelets &gt; 20 Giga/l (days after transplant)</td>
<td>N</td>
<td>119</td>
</tr>
</tbody>
</table>
5.2.2. Description of adverse events

2 AEs were reported for patients who did not receive any study treatment. There are described in section §6.7.3.

On induction safety population, a total of 347 AEs in R-ICE arm and 552 in the R-DHAP arm were reported during the whole study (induction, consolidation and maintenance phases), concerning respectively 154 patients (64%) and 172 patients (75%).

In both arms, the most common System Organ Class was infections and infestations (respectively 135 and 166 AEs in R-ICE and RDHAP arm, 39% and 30% of AEs), then blood and lymphatic system disorders (64 and 116 AEs, 18% and 21% of AEs).

8 AEs (2 in R-ICE arm and 6 in R-DHAP arm) occurred before administration of first induction cycle. The list of these AEs is shown in section §6.7.3.

### Table 5.2-6 Patients with at least one AE (induction safety population)

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Patient with at least one AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>154</td>
<td>64</td>
</tr>
<tr>
<td>No</td>
<td>85</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

The following table summarizes the incidence of AEs by System Organ Class and Preferred Term, ordered by frequency.

### Table 5.2-7 Summary of adverse events by frequency of SOC and PT (induction safety population)

<table>
<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Total number of AEs</td>
<td>347</td>
<td>100</td>
</tr>
</tbody>
</table>
## System Organ Class

### INFECTIONS AND INFESTATIONS

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>135</td>
<td>166</td>
</tr>
<tr>
<td><strong>Actual arm of induction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td><strong>%</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td><em>INFECTION</em></td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td><em>NEUTROPENIC INFECTION</em></td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td><em>NEUTROPENIC SEPSIS</em></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><em>HERPES ZOSTER</em></td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td><em>PNEUMONIA</em></td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td><em>CENTRAL LINE INFECTION</em></td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td><em>LOWER RESPIRATORY TRACT INFECTION</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>SEPSIS</em></td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td><em>SEPTIC SHOCK</em></td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td><em>BRONCHITIS</em></td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td><em>STAPHYLOCOCCAL SEPSIS</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>CATHETER RELATED INFECTION</em></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><em>STAPHYLOCOCCAL INFECTION</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>ORAL HERPES</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>URINARY TRACT INFECTION</em></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><em>FOLLICULITIS</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>BRONCHOPNEUMONIA</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>BACTERIAL SEPSIS</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>* UPPER RESPIRATORY TRACT INFECTION*</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>ESCHERICHIA SEPSIS</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>SINUSITIS</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>RESPIRATORY TRACT INFECTION</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>ESCHERICHIA URINARY TRACT INFECTION</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>CYTOMEGALOVIRUS INFECTION</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>CLOSTRIDUM DIFFICILE COLITIS</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>CATHETER SEPSIS</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>CANDIDIASIS</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>PSEUDOMONAS INFECTION</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>BRONCHOPULMONARY ASPERGILLOSIS</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>ESCHERICHIA INFECTION</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>ENTEROBACTER SEPSIS</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>NASOPHARYNGITIS</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>CLOSTRIDIAL INFECTION</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>KLEBSIELLA INFECTION</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>INFLUENZA</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>HERPES VIRUS INFECTION</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>HAEMOPHILUS INFECTION</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>DIARRHOEA INFECTION</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>* PSEUDOMONAL SEPSIS*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>CELLULITIS</em></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Condition</td>
<td>ARM A / R-ICE</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------</td>
<td>---</td>
</tr>
<tr>
<td>CYSTITIS</td>
<td>0  0</td>
<td></td>
</tr>
<tr>
<td>BRONCHITIS PNEUMOCOCCAL</td>
<td>1  0</td>
<td></td>
</tr>
<tr>
<td>PERTUSSIS</td>
<td>1  0</td>
<td></td>
</tr>
<tr>
<td>GASTROENTERITIS</td>
<td>0  0</td>
<td></td>
</tr>
<tr>
<td>HERPES SIMPLEX</td>
<td>0  0</td>
<td></td>
</tr>
<tr>
<td>ASPERGILLOSIS</td>
<td>1  0</td>
<td></td>
</tr>
<tr>
<td>PNEUMONIA PNEUMOCOCCAL</td>
<td>0  0</td>
<td></td>
</tr>
<tr>
<td>FUNGAL OESOPHAGITIS</td>
<td>0  0</td>
<td></td>
</tr>
<tr>
<td>STREPTOCOCCAL SEPSIS</td>
<td>1  0</td>
<td></td>
</tr>
<tr>
<td>VARICELLA</td>
<td>0  0</td>
<td></td>
</tr>
<tr>
<td>MENINGITIS</td>
<td>1  0</td>
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4 other malignancies in R-ICE arm and 7 in R-DHAP arm were reported (corresponding to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps)).
The following table shows the different characteristics of adverse events:

**Table 5.2-8 Characteristics of adverse events (induction safety population)**

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Table 5.2-9 Action taken with study drugs due to AEs (induction safety population)

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5.2.3. Corrective treatments

Among patients with at least one AE, 131 patients (85%) received a corrective treatment in R-ICE arm versus 141 patients (82%) in R-DHAP arm.

Table 5.2-10 Patients with corrective treatment for AE (induction safety population)

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<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Patients with corrective treatment</td>
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<td></td>
</tr>
<tr>
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<td>31</td>
</tr>
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<tr>
<td>Total</td>
<td>154</td>
<td>172</td>
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</tbody>
</table>

285 AEs in R-ICE arm (82%) were associated with a corrective treatment versus 469 AEs (85%) in R-DHAP arm.

Table 5.2-11 Corrective treatments for AE (induction safety population)

<table>
<thead>
<tr>
<th>Actual arm of treatment</th>
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<tr>
<td></td>
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<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
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<td>N</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>AEs with corrective treatment</td>
<td></td>
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<tr>
<td>Yes</td>
<td>285</td>
<td>469</td>
</tr>
<tr>
<td>No</td>
<td>62</td>
<td>83</td>
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<tr>
<td>Total</td>
<td>347</td>
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</table>
5.3. Deaths and other serious adverse events

5.3.1. Serious adverse events

5.3.1.1. Description of serious adverse events

2 SAEs were reported for patients who did not receive any study treatment. There are described in section §6.7.4.

On induction safety population, a total of 106 SAEs in R-ICE arm and 151 in the R-DHAP arm were reported during the whole study (induction, consolidation and maintenance phases), concerning respectively 66 patients (28%) and 84 patients (37%).

In both arms, the most common System Organ Class was infections and infestations (respectively 46 and 55 SAEs in R-ICE and R-DHAP arm, 43% and 36% of SAEs), then gastrointestinal disorders (10 and 19 SAEs, 9% and 13% of SAEs) and blood and lymphatic system disorders (11 and 16 SAEs, 10% and 11% of SAEs).

5 SAEs were declared to Pharmacovigilance department concerning 2 patients not evaluable due to CRF not recovered. They are listed in section §6.7.4.

All serious adverse events are listed in section §6.7.4.

<table>
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<tr>
<th>Table 5.3-1 Patients with SAE (induction safety population)</th>
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</tr>
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</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>Patient with at least one SAE</td>
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<tr>
<th>Table 5.3-2 Summary of serious adverse events by frequency of SOC and PT (induction safety population)</th>
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<tbody>
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<tr>
<td>%</td>
</tr>
<tr>
<td>Total number of SAEs</td>
</tr>
<tr>
<td>106</td>
</tr>
<tr>
<td>100</td>
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<tr>
<td>151</td>
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<td>System Organ Class</td>
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<td></td>
</tr>
<tr>
<td><strong>Total number of SAEs</strong></td>
</tr>
<tr>
<td><strong>Preferred Term</strong></td>
</tr>
<tr>
<td>NEUTROPENIC SEPSIS</td>
</tr>
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<td>PNEUMONIA</td>
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<td>LOWER RESPIRATORY TRACT INFECTION</td>
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<td>Preferred Term</td>
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<td>Preferred Term</td>
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<td><strong>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</strong></td>
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<tr>
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</tbody>
</table>

4 other malignancies in R-ICE arm and 3 in R-DHAP arm were reported as serious (corresponding to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps)).
The following table shows the different characteristics of adverse events reported as serious:

### Table 5.3-3 Category of SAEs (induction safety population)

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<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
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<td>%</td>
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<tr>
<td>Resulting of death</td>
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<td>Total</td>
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### Table 5.3-4 Characteristics of SAEs (induction safety population)

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<th>ARM B / R-DHAP</th>
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</thead>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Non hematological toxicity grade</td>
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<td>MILD</td>
<td>3</td>
<td>3</td>
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## Table 5.3-5 Action taken with study drugs due to SAE (induction safety population)

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<td>ARM B / R-DHAP</td>
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<td>0</td>
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<tr>
<td>DOSE REGIMEN ADAPTATION</td>
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<td>13</td>
</tr>
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<td>Total</td>
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<td>100</td>
</tr>
<tr>
<td></td>
<td>ARM B / R-DHAP</td>
<td>38</td>
<td>100</td>
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</tbody>
</table>
5.3.1.2. Corrective treatments

Among patients with at least one SAE, 55 patients (83%) received a corrective treatment in R-ICE arm versus 75 patients (89%) in R-DHAP arm.

Table 5.3-6 Patients with corrective treatment for SAE (induction safety population)

<table>
<thead>
<tr>
<th>Actual arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Patients with corrective treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Yes</td>
<td>55</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>100</td>
</tr>
</tbody>
</table>

88 SAEs in R-ICE arm (82%) were associated with a corrective treatment versus 136 SAEs (90%) in R-DHAP arm.

Table 5.3-7 Corrective treatments for SAE (induction safety population)

<table>
<thead>
<tr>
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<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>AEs with corrective treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88</td>
<td>83</td>
</tr>
<tr>
<td>No</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>100</td>
</tr>
</tbody>
</table>
5.3.2. Deaths

4 deaths were reported for patients who did not receive any study treatment. There are described in section §6.7.5.

On induction safety population, 126 deaths (53% of patients) in R-ICE arm and 112 deaths (49%) in R-DHAP arm occurred at time of analysis, mainly due to lymphoma (respectively 78% and 72% of deaths).

Table 5.3-8 Summary of deaths (induction safety population)

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<thead>
<tr>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>126</td>
<td>112</td>
</tr>
<tr>
<td>No</td>
<td>113</td>
<td>118</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>230</td>
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</tbody>
</table>

Table 5.3-9 Cause of death (induction safety population)

<table>
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<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Reason for death</td>
<td></td>
<td></td>
</tr>
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<td>81</td>
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<td>9</td>
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<td>CONCURRENT ILLNESS</td>
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<td>2</td>
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<td>OTHER CANCER</td>
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<td>3</td>
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<td>15</td>
</tr>
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<td>2</td>
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<tr>
<td>Total</td>
<td>126</td>
<td>112</td>
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</table>

See details of deaths in the following list:
### Listing 5.3-1 Deaths (induction safety population)

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<th>Randomization Number</th>
<th>Actual arm of induction</th>
<th>First Randomization Date</th>
<th>Actual arm of maintenance</th>
<th>Date of 2nd randomization</th>
<th>Transplantation date</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Date of death</th>
<th>Reason for death</th>
<th>Specify reason of death</th>
<th>Response at death</th>
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<td>22/10/2004</td>
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<td>04/02/2004</td>
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<td>Actual arm of maintenance</td>
<td>Date of 2nd randomization</td>
<td>Transplantation date</td>
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<td>Response at death</td>
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<td>Sex</td>
<td>Age (years)</td>
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<td>Reason for death</td>
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<td>Response at death</td>
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<td>MALE</td>
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<td>49</td>
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<td>FEMALE</td>
<td>19</td>
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<td>5003619301016</td>
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<td>Actual arm of maintenance</td>
<td>Date of 2nd randomization</td>
<td>Transplantation date</td>
<td>Sex</td>
<td>Age (years)</td>
<td>Date of death</td>
<td>Reason for death</td>
<td>Specify reason of death</td>
<td>Response at death</td>
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<td>------------------</td>
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<td>ARM B / R-DHAP</td>
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<td>-</td>
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<td>24/11/2005</td>
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<td>SEPSIS</td>
<td>PARTIAL RESPONSE</td>
</tr>
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<td>-</td>
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<td>58</td>
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</tr>
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<td>PROGRESSIVE DISEASE</td>
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<td>RITUXIMAB</td>
<td>09/03/2007</td>
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<td>-</td>
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<td>-</td>
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N = 238
### 5.4. Clinical laboratory evaluation

The following tables show statistics summary of parameters registered only at baseline.

**Table 5.4-1 Summary of laboratory tests at relapse diagnosis (induction safety population)**

<table>
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<tr>
<th>Parameter</th>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
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<td></td>
</tr>
<tr>
<td>N</td>
<td>226</td>
<td>224</td>
<td></td>
</tr>
<tr>
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<td>1.102</td>
<td></td>
</tr>
<tr>
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<td>0.7269</td>
<td></td>
</tr>
<tr>
<td>Median</td>
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<td>0.967</td>
<td></td>
</tr>
<tr>
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<td>0.01</td>
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</tr>
<tr>
<td>Max</td>
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<td>4.61</td>
<td></td>
</tr>
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<td>Lymphoma cells (G/L)</td>
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</tr>
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</tr>
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<td>0</td>
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</tr>
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<td>1</td>
<td></td>
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</tr>
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<td>Max</td>
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<td></td>
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<tr>
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</tr>
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<td>beta 2 microglobulin (mg/l)</td>
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<tr>
<td>Aaline phosphatase (UI/L)</td>
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<td>126.0</td>
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<tr>
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<td>-------------------------</td>
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<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
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<td>Total bilirubin (µmol/l)</td>
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<td>Max</td>
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<td>174</td>
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<td>Creatinin (µmol/l)</td>
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<td>Calcium (mmol/l)</td>
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<td>227</td>
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<td>126</td>
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Table 5.4-2 Serum electrophoresis values at relapse diagnosis (induction safety population)

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<th>Total protein (G/L)</th>
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<table>
<thead>
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<th>Albumin (G/L)</th>
<th>Actual arm of induction</th>
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</thead>
<tbody>
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<td></td>
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<table>
<thead>
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<th>Monoclonal component value (G/L)</th>
<th>Actual arm of induction</th>
</tr>
</thead>
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<td></td>
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</tr>
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<td>N</td>
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</tr>
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<td>Std</td>
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<td>1.0</td>
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<tr>
<td>Max</td>
<td>16</td>
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</table>

For each parameter registered at different time over the course of the study, the mean, standard deviation, median, range and changes from baseline are described in section §6.7.6.

5.5. Vitals signs, physical finding and other observations related to safety

Vital signs are described in section §6.7.7.
For clinical examination, a frequency table summarizes the results at each visit.
6. TABLES, LISTINGS AND FIGURES NOT INCLUDED IN THE REPORT

6.1. Withdrawals
**Listing 6.1-1 Withdrawals (FAS)**

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<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>First Randomization Date</th>
<th>Arm of 2nd randomization</th>
<th>Date of 2nd randomization</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
<th>Response at withdrawal</th>
<th>Transplantation date</th>
<th>Nb of cycles received</th>
<th>Nb of maintenance visits</th>
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</thead>
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<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
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<td>ABOUT 2 MONTHS FOLLOWING TRANSPLANT, THE PATIENT UNDERWENT PET-CT EVALUATION. ALTHOUGH THERE WAS NO MAJOR ANATOMICAL CHANGE IN CT, THE MEDIASTINAL NODES WERE FDG AVID WITH SIGNIFICANT UPTAKE DUE TO PET-CT RESULTS, THE TREATING PHYSICIAN SUSPECTED THAT *</td>
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<td>Reason for premature withdrawal</td>
<td>Other reason for premature withdrawal</td>
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<td>Transplantation date</td>
<td>Nb of cycles received</td>
<td>Nb of maintenance visits</td>
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<td>OTHER</td>
<td>ACTIVE HEPATITIS C INFECTION AFTER APERESIS, BAD CONDITION AFTER TRANSPLANTATION / DECISION NOT TO TREAT PATIENT WITH RITUXIMAB FURTHER AS RANDOMIZED IN STUDY</td>
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<td>Transplantation date</td>
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<td>Nb of maintenance visits</td>
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<td>Date of 2nd randomization</td>
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<td>Reason for premature withdrawal</td>
<td>Other reason for premature withdrawal</td>
<td>Response at withdrawal</td>
<td>Transplantation date</td>
<td>Nb of cycles received</td>
<td>Nb of maintenance visits</td>
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N = 318
### 6.2. Initial treatment

#### Listing 6.2-1 Initial treatment - Patients with other chemotherapy (FAS)

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N = 11

#### Listing 6.2-2 Initial treatment – Doses of radiotherapy (FAS)

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### 6.3. Progression/relapse diagnosis

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**Listing 6.3-2 Other extra-nodal involvement localizations (FAS)**

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### Table 6.3-3 Codification of sites used for response evaluation, sorted by most frequent (FAS)

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<td>Caeum</td>
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<tr>
<td>Duodenum</td>
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<td>0%</td>
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</tr>
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<td>Ileon</td>
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### 6.4. Evaluation after complete induction treatment

**Table 6.4-1 Codification of sites used for response evaluation, sorted by most frequent (induction ITT)**

<table>
<thead>
<tr>
<th>Lesion Codification</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Urinary Tract</td>
<td>2</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>2</td>
</tr>
<tr>
<td>Ascites</td>
<td>1</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
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<tr>
<td>Pericardium</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>0%</td>
<td>1</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>1</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>607</td>
<td>100%</td>
<td>537</td>
<td>100%</td>
<td>1144</td>
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</table>

**Table 6.4-1 Codification of sites used for response evaluation, sorted by most frequent (induction ITT)**

<table>
<thead>
<tr>
<th>Lesion Codification</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Para-aortic / Portal</td>
<td>95</td>
<td>17%</td>
<td>74</td>
<td>14%</td>
<td>169</td>
</tr>
<tr>
<td>Mediastinal / Paratracheal</td>
<td>82</td>
<td>14%</td>
<td>59</td>
<td>11%</td>
<td>141</td>
</tr>
<tr>
<td>Celiac / Mesenteric</td>
<td>57</td>
<td>10%</td>
<td>55</td>
<td>10%</td>
<td>112</td>
</tr>
<tr>
<td>Cervical / Post_cervical / Upper cervical / Pre_auricular : Left</td>
<td>42</td>
<td>7%</td>
<td>32</td>
<td>6%</td>
<td>74</td>
</tr>
<tr>
<td>Cervical / Post_cervical / Upper cervical / Pre_auricular : Right</td>
<td>27</td>
<td>5%</td>
<td>34</td>
<td>6%</td>
<td>61</td>
</tr>
<tr>
<td>Axillary : Left</td>
<td>33</td>
<td>6%</td>
<td>21</td>
<td>4%</td>
<td>54</td>
</tr>
<tr>
<td>External iliac / Iliac : Left</td>
<td>20</td>
<td>3%</td>
<td>20</td>
<td>4%</td>
<td>40</td>
</tr>
<tr>
<td>Inguinal / Femoral / Retrocrural : Left</td>
<td>21</td>
<td>4%</td>
<td>19</td>
<td>4%</td>
<td>40</td>
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<tr>
<td>Axillary : Right</td>
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<td>19</td>
<td>4%</td>
<td>38</td>
</tr>
<tr>
<td>Inguinal / Femoral / Retrocrural : Right</td>
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<td>3%</td>
<td>35</td>
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<tr>
<td>Spleen</td>
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<td>21</td>
<td>4%</td>
<td>33</td>
</tr>
<tr>
<td>External iliac / Iliac : Right</td>
<td>20</td>
<td>3%</td>
<td>9</td>
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<td>29</td>
</tr>
<tr>
<td>Liver</td>
<td>13</td>
<td>2%</td>
<td>16</td>
<td>3%</td>
<td>29</td>
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<td>2%</td>
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<tr>
<td>Skin</td>
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<td>14</td>
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<td>21</td>
</tr>
<tr>
<td>Pulmonary hilar</td>
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<td>8</td>
<td>2%</td>
<td>15</td>
</tr>
<tr>
<td>Tonsil / Waldeyer's ring</td>
<td>10</td>
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<td>3</td>
<td>1%</td>
<td>13</td>
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<tr>
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<td>1%</td>
<td>8</td>
<td>2%</td>
<td>13</td>
</tr>
<tr>
<td>Infracavicular / Supraclavicular : Left</td>
<td>9</td>
<td>2%</td>
<td>3</td>
<td>1%</td>
<td>12</td>
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<tr>
<td>Infracavicular / Supraclavicular : Right</td>
<td>6</td>
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<td>6</td>
<td>1%</td>
<td>12</td>
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<tr>
<td>Epitrochlear Right or Left / Other</td>
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<td>1%</td>
<td>11</td>
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<tr>
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<td>1%</td>
<td>4</td>
<td>1%</td>
<td>9</td>
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<tr>
<td>Adrenal</td>
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<td>3</td>
<td>1%</td>
<td>9</td>
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<tr>
<td>Stomach</td>
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<td>Other extra-nodal involvement</td>
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<tr>
<td>Splenic hilar</td>
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<tr>
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### 6.5. Follow-up

#### Listing 6.5- Patients with date of last contact earlier than September 1, 2009 (MITT)

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<td>5003102341045</td>
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<td>09/06/2009</td>
</tr>
<tr>
<td>5003102491616</td>
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<td>15/01/2008</td>
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<td>ARM A / R-ICE</td>
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<td>16/02/2007</td>
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<td>17/06/2009</td>
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<td>15/07/2009</td>
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<td>Date of last contact</td>
</tr>
<tr>
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<td>------------------</td>
<td>----------------------</td>
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N = 52
### 6.6. Efficacy results

#### 6.6.1. Primary criterion

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<th>Randomization Number</th>
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<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
<th>Response at withdrawal</th>
<th>Date of death</th>
<th>Response at death</th>
<th>Nb of cycles received</th>
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<td>Response after complete induction</td>
<td>Date of withdrawal</td>
<td>Treatment period at withdrawal</td>
<td>Reason for premature withdrawal</td>
<td>Other reason for premature withdrawal</td>
<td>Response at withdrawal</td>
<td>Date of death</td>
<td>Response at death</td>
<td>Nb of cycles received</td>
</tr>
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<td>------------------</td>
<td>---------------------</td>
</tr>
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<td>5003101071607</td>
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<td>NOT EVALUATED</td>
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<td>INDUCTION PHASE</td>
<td>TREATMENT TOXICITY</td>
<td></td>
<td>NOT EVALUATED</td>
<td>04/06/2009</td>
<td>PROGRESSIVE DISEASE</td>
<td>1</td>
</tr>
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<td>5003603801013</td>
<td>ARM B / R-DHAP</td>
<td>NOT EVALUATED</td>
<td>15/02/2007</td>
<td>INDUCTION PHASE</td>
<td>TREATMENT TOXICITY</td>
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<td>NOT EVALUATED</td>
<td>24/04/2007</td>
<td>PARTIAL RESPONSE</td>
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</tr>
<tr>
<td>5003604701012</td>
<td>ARM B / R-DHAP</td>
<td>-</td>
<td>04/05/2007</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
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<td>NOT EVALUATED</td>
<td>04/05/2007</td>
<td>NOT EVALUATED</td>
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</tr>
<tr>
<td>5003607301622</td>
<td>ARM B / R-DHAP</td>
<td>-</td>
<td>26/01/2007</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
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<td>NOT EVALUATED</td>
<td>26/01/2007</td>
<td>NOT EVALUATED</td>
<td>2</td>
</tr>
<tr>
<td>5003610701403</td>
<td>ARM B / R-DHAP</td>
<td>-</td>
<td>06/10/2008</td>
<td>FOLLOW UP PERIOD</td>
<td>OTHER</td>
<td>RECURRENT IN FU-PHASE 6 MONTHS AFTER TRANSPLANT</td>
<td>NOT EVALUATED</td>
<td>04/05/2007</td>
<td>PROGRESSIVE DISEASE</td>
<td>3</td>
</tr>
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<td>5003615501007</td>
<td>ARM B / R-DHAP</td>
<td>NOT EVALUATED</td>
<td>23/02/2007</td>
<td>INDUCTION PHASE</td>
<td>OTHER</td>
<td>CVA</td>
<td>NOT EVALUATED</td>
<td>25/05/2007</td>
<td>PROGRESSIVE DISEASE</td>
<td>1</td>
</tr>
<tr>
<td>5003616201413</td>
<td>ARM B / R-DHAP</td>
<td>-</td>
<td>03/06/2008</td>
<td>INDUCTION PHASE</td>
<td>TREATMENT TOXICITY</td>
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<td>NOT EVALUATED</td>
<td>20/08/2008</td>
<td>NOT EVALUATED</td>
<td>1</td>
</tr>
<tr>
<td>5003617201616</td>
<td>ARM B / R-DHAP</td>
<td>NOT EVALUATED</td>
<td>14/10/2005</td>
<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
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<td>NOT EVALUATED</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>5003619501010</td>
<td>ARM B / R-DHAP</td>
<td>NOT EVALUATED</td>
<td>06/04/2007</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td></td>
<td>NOT EVALUATED</td>
<td>06/04/2007</td>
<td>NOT EVALUATED</td>
<td>2</td>
</tr>
<tr>
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<td>ARM B / R-DHAP</td>
<td>NOT EVALUATED</td>
<td>26/07/2007</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td></td>
<td>DEATH WITHOUT PROGRESSION</td>
<td>26/07/2007</td>
<td>NOT EVALUATED</td>
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N = 24
Table 6.6-1 Primary criterion – Overall response rate by arm according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Response after complete induction</td>
<td>CR/CRu/PR</td>
<td>66</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Yes</td>
<td>CR/CRu/PR</td>
<td>87</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>239</td>
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</tr>
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</table>

Table 6.6-2 Primary criterion – Overall response rate by arm according to failure from diagnosis (induction ITT)

<table>
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<tr>
<th>Failure from diagnosis</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Response after complete induction</td>
<td>CR/CRu/PR</td>
<td>71</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>CR/CRu/PR</td>
<td>82</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 6.6-3 Primary criterion – Overall response rate by arm according to country (induction ITT)

<table>
<thead>
<tr>
<th>Country</th>
<th>Arm of treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Gela</td>
<td>CR/CRu/PR</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>77</td>
<td>100</td>
</tr>
<tr>
<td>Germany</td>
<td>CR/CRu/PR</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>24</td>
<td>45</td>
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<td>53</td>
<td>100</td>
</tr>
<tr>
<td>Australia</td>
<td>CR/CRu/PR</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>158</td>
<td>100</td>
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## Table 6.6-4 Primary criterion – Overall response rate by arm according age adjusted IPI (induction ITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>Response after complete induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>CR/CRu/PR</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>98</td>
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<tr>
<td></td>
<td>Other</td>
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<td>Total</td>
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<td>100</td>
</tr>
<tr>
<td>&gt;=2</td>
<td>CR/CRu/PR</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>232</td>
<td>100</td>
</tr>
</tbody>
</table>

## Table 6.6-5 Primary criterion – Complete response rate by arm according to prior rituximab (induction ITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Response after complete induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>CR/CRu</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41</td>
<td>48</td>
</tr>
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<td></td>
<td>Other</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>Yes</td>
<td>CR/CRu</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>107</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>

## Table 6.6-6 Primary criterion – Complete response rate by arm according to failure from diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>Response after complete induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>CR/CRu</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>110</td>
<td>76</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>CR/CRu</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53</td>
<td>56</td>
</tr>
<tr>
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<td>Other</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>239</td>
<td>100</td>
</tr>
</tbody>
</table>
**Table 6.6-7 Primary criterion – Complete response rate by arm according to country (induction ITT)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Response after complete induction</th>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR/CRu</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Gela</td>
<td></td>
<td>32</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>45</td>
<td>58</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>77</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td>15</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Other</td>
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<td>72</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
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<td>54</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td>11</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>17</td>
<td>61</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>28</td>
<td>100</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>158</td>
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<td>160</td>
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**Table 6.6-8 Primary criterion – Complete response rate by arm according to age adjusted IPI (induction ITT)**

<table>
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<tr>
<th>Age-adjusted IPI</th>
<th>Response after complete induction</th>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>CR/CRu</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
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<td></td>
<td>60</td>
<td>43</td>
<td>59</td>
</tr>
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<td></td>
<td>Other</td>
<td>81</td>
<td>57</td>
<td>78</td>
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<td>141</td>
<td>100</td>
<td>137</td>
</tr>
<tr>
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<td>CR/CRu</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>64</td>
<td>70</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>91</td>
<td>100</td>
<td>86</td>
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<td>Total</td>
<td>232</td>
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<td>223</td>
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</table>
## Listing 6.6-2 Induction - Patients who died during treatment phase (induction ITT)

<table>
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<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>First Randomization Date</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Date of death</th>
<th>Reason for death</th>
<th>Response at death</th>
<th>Response after complete induction (raw data from CRF)</th>
<th>Nb of cycles received</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003101071002</td>
<td>ARM B / R-DHAP</td>
<td>16/10/2003</td>
<td>21/11/2003</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>21/11/2003</td>
<td>TOXICITY OF STUDY TREATMENT</td>
<td>NOT EVALUATED</td>
<td>NOT EVALUATED</td>
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</tr>
<tr>
<td>5003101131030</td>
<td>ARM A / R-ICE</td>
<td>16/06/2005</td>
<td>16/08/2005</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>16/08/2005</td>
<td>TOXICITY OF STUDY TREATMENT</td>
<td>NOT EVALUATED</td>
<td>NOT EVALUATED</td>
<td>2</td>
</tr>
<tr>
<td>5003101281017</td>
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<td>18/11/2004</td>
<td>10/12/2004</td>
<td>INDUCTION PHASE</td>
<td>TREATMENT TOXICITY</td>
<td>12/01/2005</td>
<td>LYMPHOMA</td>
<td>PROGRESSIVE DISEASE</td>
<td>PROGRESSIVE DISEASE</td>
<td>1</td>
</tr>
<tr>
<td>5003101601404</td>
<td>ARM A / R-ICE</td>
<td>04/07/2005</td>
<td>21/08/2005</td>
<td>INDUCTION PHASE</td>
<td>TREATMENT TOXICITY</td>
<td>05/09/2005</td>
<td>TOXICITY OF STUDY TREATMENT</td>
<td>NOT EVALUATED</td>
<td>NOT EVALUATED</td>
<td>2</td>
</tr>
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<td>ARM B / R-DHAP</td>
<td>11/03/2004</td>
<td>03/05/2004</td>
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<td>INDUCTION TREATMENT FAILURE</td>
<td>13/05/2004</td>
<td>TOXICITY OF STUDY TREATMENT</td>
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<td>STABLE DISEASE</td>
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</tr>
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<td>ARM A / R-ICE</td>
<td>12/08/2005</td>
<td>01/09/2005</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>01/09/2005</td>
<td>TOXICITY OF STUDY TREATMENT</td>
<td>NOT EVALUATED</td>
<td>NOT EVALUATED</td>
<td>1</td>
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<tr>
<td>5003603901001</td>
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<td>06/10/2004</td>
<td>14/11/2004</td>
<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
<td>19/11/2004</td>
<td>LYMPHOMA</td>
<td>PROGRESSIVE DISEASE</td>
<td>PROGRESSIVE DISEASE</td>
<td>1</td>
</tr>
<tr>
<td>5003604701012</td>
<td>ARM B / R-DHAP</td>
<td>19/04/2007</td>
<td>04/05/2007</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>04/05/2007</td>
<td>TOXICITY OF STUDY TREATMENT</td>
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<td>-</td>
<td>1</td>
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<td>20/06/2004</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>20/06/2004</td>
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<td>UNCONFIRMED COMPLETE RESPONSE</td>
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</tr>
<tr>
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<td>ARM B / R-DHAP</td>
<td>20/04/2007</td>
<td>21/07/2007</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>21/07/2007</td>
<td>OTHER REASON</td>
<td>PROGRESSIVE DISEASE</td>
<td>PROGRESSIVE DISEASE</td>
<td>3</td>
</tr>
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<td>5003617501006</td>
<td>ARM B / R-DHAP</td>
<td>01/12/2006</td>
<td>12/01/2007</td>
<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
<td>04/02/2007</td>
<td>LYMPHOMA</td>
<td>PROGRESSIVE DISEASE</td>
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<td>07/01/2008</td>
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<td>INDUCTION TREATMENT FAILURE</td>
<td>24/01/2008</td>
<td>LYMPHOMA</td>
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<td>ARM B / R-DHAP</td>
<td>14/02/2007</td>
<td>06/04/2007</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>06/04/2007</td>
<td>TOXICITY OF STUDY TREATMENT</td>
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<td>NOT EVALUATED</td>
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<td>First Randomization Date</td>
<td>Date of withdrawal</td>
<td>Treatment period at withdrawal</td>
<td>Reason for premature withdrawal</td>
<td>Date of death</td>
<td>Reason for death</td>
<td>Response at death</td>
<td>Response after complete induction (raw data from CRF)</td>
<td>Nb of cycles received</td>
</tr>
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<td>-----------------------------------------------------</td>
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</tr>
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<td>05/07/2007</td>
<td>26/07/2007</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>26/07/2007</td>
<td>LYMPHOMA</td>
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<td>25/12/2004</td>
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<td>TREATMENT TOXICITY</td>
<td>29/12/2004</td>
<td>LYMPHOMA</td>
<td>PROGRESSIVE DISEASE</td>
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N = 18
### Table 6.6-9 Primary criterion – Overall response rate (including all deaths) by arm according to prior rituximab
(induction ITT)

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<th>Prior treatment with Rituximab</th>
<th>Arm of treatment</th>
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<th>%</th>
<th>N</th>
<th>%</th>
</tr>
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<tbody>
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<td>ARM A / R-ICE</td>
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<td>71</td>
<td>87</td>
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<tr>
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<td>20</td>
<td>24</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>87</td>
<td>56</td>
<td>77</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>CR/CRu/PR</td>
<td>67</td>
<td>44</td>
<td>71</td>
<td>48</td>
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<tr>
<td>Total</td>
<td>ARM A / R-ICE</td>
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<td>Total</td>
<td>ARM B / R-DHAP</td>
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<td></td>
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</table>

### Table 6.6-10 Primary criterion – Overall response rate (including all deaths) by arm according to failure from
diagnosis (induction ITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>Arm of treatment</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>ARM A / R-ICE</td>
<td>71</td>
<td>49</td>
<td>64</td>
<td>49</td>
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<tr>
<td></td>
<td>ARM B / R-DHAP</td>
<td>74</td>
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<td>67</td>
<td>51</td>
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<td>CR/CRu/PR</td>
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<td>86</td>
<td>84</td>
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<td>Other</td>
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<td>14</td>
<td>15</td>
<td>15</td>
</tr>
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<td>Total</td>
<td>ARM A / R-ICE</td>
<td>239</td>
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<td>230</td>
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<td>Total</td>
<td>ARM B / R-DHAP</td>
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### Table 6.6-11 Primary criterion – Overall response rate (including all deaths) by arm according country
(induction ITT)

<table>
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<th>Country</th>
<th>Arm of treatment</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gela</td>
<td>ARM A / R-ICE</td>
<td>50</td>
<td>65</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>ARM B / R-DHAP</td>
<td>27</td>
<td>35</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>CR/CRu/PR</td>
<td>77</td>
<td>100</td>
<td>77</td>
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<tr>
<td>Germany</td>
<td>ARM A / R-ICE</td>
<td>29</td>
<td>55</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>ARM B / R-DHAP</td>
<td>24</td>
<td>45</td>
<td>24</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>CR/CRu/PR</td>
<td>53</td>
<td>100</td>
<td>54</td>
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<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>ARM A / R-ICE</td>
<td>17</td>
<td>61</td>
<td>24</td>
<td>83</td>
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<td></td>
<td>ARM B / R-DHAP</td>
<td>11</td>
<td>39</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>CR/CRu/PR</td>
<td>28</td>
<td>100</td>
<td>29</td>
<td>100</td>
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<td>Other</td>
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<td></td>
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</tr>
<tr>
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<td>100</td>
<td>160</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>ARM B / R-DHAP</td>
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Table 6.6-12 Primary criterion – Overall response rate (including all deaths) by arm according to age adjusted IPI (induction ITT)

<table>
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<tr>
<th>Age-adjusted IPI</th>
<th>Response after complete induction (including deaths for all patients)</th>
<th>ARM A / R-ICE</th>
<th>%</th>
<th>ARM B / R-DHAP</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>CR/CRu/PR</td>
<td>98</td>
<td>70</td>
<td>100</td>
<td>73</td>
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<tr>
<td></td>
<td>Other</td>
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<td>30</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>141</td>
<td>100</td>
<td>137</td>
<td>100</td>
</tr>
<tr>
<td>&gt;=2</td>
<td>CR/CRu/PR</td>
<td>49</td>
<td>54</td>
<td>45</td>
<td>52</td>
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<td></td>
<td>Total</td>
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<td>100</td>
<td>223</td>
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Table 6.6-13 Primary criterion – Complete response rate (including all deaths) by arm according to prior rituximab (induction ITT)

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<tr>
<th>Prior treatment with Rituximab</th>
<th>Response after complete induction (including deaths for all patients)</th>
<th>ARM A / R-ICE</th>
<th>%</th>
<th>ARM B / R-DHAP</th>
<th>%</th>
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</thead>
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<td>CR/CRu/PR</td>
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<td>106</td>
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Table 6.6-14 Primary criterion – Complete response rate (including all deaths) by arm according to failure from diagnosis (induction ITT)

<table>
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<th>Failure from diagnosis</th>
<th>Response after complete induction (including deaths for all patients)</th>
<th>ARM A / R-ICE</th>
<th>%</th>
<th>ARM B / R-DHAP</th>
<th>%</th>
</tr>
</thead>
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<td>&lt; 12 months</td>
<td>CR/CRu/PR</td>
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<td>24</td>
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<td>76</td>
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<td>55</td>
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<td>55</td>
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<td></td>
<td>Other</td>
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<td></td>
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<td>230</td>
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### Table 6.6-15 Primary criterion – Complete response rate (including all deaths) by arm according to country (induction ITT)

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<th>Response after complete induction (including deaths for all patients)</th>
<th>Arm of treatment</th>
<th>Arm of treatment</th>
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</thead>
<tbody>
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<td></td>
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<td>ARM B / R-DHAP</td>
</tr>
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<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
</tr>
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</tr>
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<td>CR/CRu</td>
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<td>42</td>
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<td>Other</td>
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<td>11</td>
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### Table 6.6-16 Primary criterion – Complete response rate (including all deaths) by arm according to age adjusted IPI (induction ITT)

<table>
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<th>Age-adjusted IPI</th>
<th>Response after complete induction (including deaths for all patients)</th>
<th>Arm of treatment</th>
<th>Arm of treatment</th>
</tr>
</thead>
<tbody>
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<td>ARM B / R-DHAP</td>
</tr>
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<td>%</td>
<td>%</td>
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<td>25</td>
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<td>223</td>
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### Table 6.6-3 Primary criterion – Other cause of collection failure (induction ITT)

<table>
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<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Response after complete induction (raw data from CRF)</th>
<th>first collection date</th>
<th>Collected Cells</th>
<th>Collection failure</th>
<th>Specify other cause for collection failure</th>
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<tbody>
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<td>STABLE DISEASE</td>
<td>ND</td>
<td>-</td>
<td>Yes</td>
<td>NO COLLECTION DURING THE STUDY AS COLLECTION HAD BEEN DONE BEFORE</td>
</tr>
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<td>COMPLETE RESPONSE</td>
<td>06/04/2008</td>
<td>3.08</td>
<td>Yes</td>
<td>CELL VIABILITY ISSUE</td>
</tr>
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<td>5003101541415</td>
<td>ARM B / R-DHAP</td>
<td>PARTIAL RESPONSE</td>
<td>21/06/2005</td>
<td>5.1</td>
<td>Yes</td>
<td>NO COLLECTION DURING THE STUDY : ALREADY HARVESTED IN MAY 2005 (5.1 10^6 CD34/KG) ENOUGH CELLS</td>
</tr>
<tr>
<td>5003102541052</td>
<td>ARM A / R-ICE</td>
<td>COMPLETE RESPONSE</td>
<td>09/01/2006</td>
<td>15.09</td>
<td>Yes</td>
<td>COLLECTION DONE BEFORE INCLUSION</td>
</tr>
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<td>PARTIAL RESPONSE</td>
<td>ND</td>
<td>-</td>
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<td>COLLECTION ALREADY ON 23/08/2005</td>
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<tr>
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<td>ARM B / R-DHAP</td>
<td>PARTIAL RESPONSE</td>
<td>05/06/2006</td>
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<td>Yes</td>
<td>WEST NILE VIRUS DISCOVERED DURING COLLECTION</td>
</tr>
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<td>COMPLETE RESPONSE</td>
<td>31/12/2004</td>
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<td>Yes</td>
<td>ADVERSE REACTION, PATIENT EXPIRED</td>
</tr>
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<td>COMPLETE RESPONSE</td>
<td>19/11/2003</td>
<td>9.42</td>
<td>Yes</td>
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<td>PARTIAL RESPONSE</td>
<td>15/02/2008</td>
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<td>INCORRECT DOSE OF G-CSF PRESCRIBED</td>
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<tr>
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<td>ARM A / R-ICE</td>
<td>PARTIAL RESPONSE</td>
<td>10/01/2006</td>
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N = 10

### Table 6.6-17 Complete response rate adjusted with successful mobilization (induction ITT)

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<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
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<td>75</td>
<td>33</td>
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### Table 6.6-18 Mobilization Adjusted Complete Response Rate (induction ITT)

<table>
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<tr>
<th>Arm of treatment</th>
<th>Nb patients</th>
<th>Nb responders with successful mobilization</th>
<th>MARR (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
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<tr>
<td>ARM A / R-ICE</td>
<td>239</td>
<td>163</td>
<td>68.2</td>
<td>61.9</td>
<td>74.1</td>
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<tr>
<td>ARM B / R-DHAP</td>
<td>230</td>
<td>155</td>
<td>67.4</td>
<td>60.9</td>
<td>73.4</td>
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### Table 6.6-19 Difference between Mobilization Adjusted Complete Response Rates (induction ITT)

<table>
<thead>
<tr>
<th>Difference between MARR (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE vs R-DHAP</td>
<td>0.8</td>
<td>-7.6</td>
<td>9.3</td>
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### 6.6.2. Secondary criteria

#### Listing 6.6-4 Consolidation – Responder patients presenting with no collection failure but no BEAM or ASCT (induction ITT)

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Response after complete induction</th>
<th>Collection failure</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
<th>Response at withdrawal</th>
<th>Nb of cycles received</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003101071020</td>
<td>ARM A / R-ICE</td>
<td>PARTIAL RESPONSE</td>
<td>No</td>
<td>20/07/2005</td>
<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
<td>PROGRESSIVE DISEASE</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>5003101071414</td>
<td>ARM B / R-DHAP</td>
<td>COMPLETE RESPONSE</td>
<td>No</td>
<td>16/02/2007</td>
<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
<td>COMPLETE RESPONSE</td>
<td></td>
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<tr>
<td>50031011141406</td>
<td>ARM A / R-ICE</td>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>No</td>
<td>20/12/2005</td>
<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
<td>PROGRESSIVE DISEASE</td>
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<tr>
<td>50031011161028</td>
<td>ARM B / R-DHAP</td>
<td>COMPLETE RESPONSE</td>
<td>No</td>
<td>22/08/2005</td>
<td>INDUCTION PHASE</td>
<td>TREATMENT TOXICITY</td>
<td>COMPLETE RESPONSE</td>
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<td>5003101431204</td>
<td>ARM B / R-DHAP</td>
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<td>No</td>
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<td>INDUCTION PHASE</td>
<td>TREATMENT TOXICITY</td>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
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<td>5003102321024</td>
<td>ARM A / R-ICE</td>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>No</td>
<td>17/08/2005</td>
<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
<td>PROGRESSIVE DISEASE</td>
<td></td>
<td>3</td>
</tr>
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<td>5003601801603</td>
<td>ARM B / R-DHAP</td>
<td>PARTIAL RESPONSE</td>
<td>No</td>
<td>09/03/2005</td>
<td>INDUCTION PHASE</td>
<td>TREATMENT TOXICITY</td>
<td>PARTIAL RESPONSE</td>
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<td>3</td>
</tr>
<tr>
<td>5003604301607</td>
<td>ARM B / R-DHAP</td>
<td>PARTIAL RESPONSE</td>
<td>No</td>
<td>27/10/2004</td>
<td>INDUCTION PHASE</td>
<td>PATIENT VOLUNTARY WITHDRAWAL</td>
<td>PARTIAL RESPONSE</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>5003605301601</td>
<td>ARM A / R-ICE</td>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>No</td>
<td>20/06/2004</td>
<td>INDUCTION PHASE</td>
<td>DEATH</td>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td></td>
<td>3</td>
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<tr>
<td>5003605701404</td>
<td>ARM B / R-DHAP</td>
<td>COMPLETE RESPONSE</td>
<td>No</td>
<td>04/04/2008</td>
<td>INDUCTION PHASE</td>
<td>INDUCTION TREATMENT FAILURE</td>
<td>PROGRESSIVE DISEASE</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>5003609301608</td>
<td>ARM A / R-ICE</td>
<td>PARTIAL RESPONSE</td>
<td>No</td>
<td>25/01/2005</td>
<td>INDUCTION PHASE</td>
<td>OTHER</td>
<td>INVESTIGATOR’S DECISION (REQUIRES 4TH CYCLE OF INDUCTION)</td>
<td>PARTIAL RESPONSE</td>
<td>3</td>
</tr>
<tr>
<td>5003612501016</td>
<td>ARM B / R-DHAP</td>
<td>PARTIAL RESPONSE</td>
<td>No</td>
<td>12/09/2007</td>
<td>INDUCTION PHASE</td>
<td>OTHER</td>
<td>RESPONSE NOT ENOUGH, THERE IS STILL BULKY DISEASE</td>
<td>PARTIAL RESPONSE</td>
<td>3</td>
</tr>
<tr>
<td>5003617501606</td>
<td>ARM A / R-ICE</td>
<td>PARTIAL RESPONSE</td>
<td>No</td>
<td>15/02/2008</td>
<td>INDUCTION PHASE</td>
<td>OTHER</td>
<td>TRANSPLANT CENTRE WOULD NOT TRANSPLANT PATIENT AS PATIENT WAS PET POSITIVE</td>
<td>PARTIAL RESPONSE</td>
<td>3</td>
</tr>
<tr>
<td>5003628201624</td>
<td>ARM A / R-ICE</td>
<td>COMPLETE RESPONSE</td>
<td>No</td>
<td>06/03/2007</td>
<td>INDUCTION PHASE</td>
<td>PATIENT VOLUNTARY WITHDRAWAL</td>
<td>COMPLETE RESPONSE</td>
<td></td>
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N = 14
**Listing 6.6-5 Consolidation – Non responder patients presenting with ASCT (induction ITT)**

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<tr>
<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Response after complete induction</th>
<th>BEAM - date of first administration</th>
<th>Transplantation date</th>
<th>Date of 2nd randomization</th>
<th>Nb of cycles received</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003605701601</td>
<td>ARM A / R-ICE</td>
<td>STABLE DISEASE</td>
<td>03/06/2005</td>
<td>09/06/2005</td>
<td>25/05/2005</td>
<td>3</td>
</tr>
<tr>
<td>5003621501603</td>
<td>ARM A / R-ICE</td>
<td>.</td>
<td>01/08/2007</td>
<td>08/08/2007</td>
<td>.</td>
<td>3</td>
</tr>
<tr>
<td>5003604701002</td>
<td>ARM B / R-DHAP</td>
<td>STABLE DISEASE</td>
<td>10/05/2005</td>
<td>17/05/2005</td>
<td>19/05/2005</td>
<td>3</td>
</tr>
<tr>
<td>5003608701008</td>
<td>ARM B / R-DHAP</td>
<td>STABLE DISEASE</td>
<td>24/04/2006</td>
<td>01/05/2006</td>
<td>19/05/2006</td>
<td>3</td>
</tr>
<tr>
<td>5003608701603</td>
<td>ARM B / R-DHAP</td>
<td>STABLE DISEASE</td>
<td>15/05/2008</td>
<td>21/05/2008</td>
<td>28/05/2008</td>
<td>3</td>
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<tr>
<td>5003610701403</td>
<td>ARM B / R-DHAP</td>
<td>.</td>
<td>03/03/2008</td>
<td>03/03/2008</td>
<td>28/03/2008</td>
<td>3</td>
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<td>5003621501412</td>
<td>ARM B / R-DHAP</td>
<td>STABLE DISEASE</td>
<td>08/10/2008</td>
<td>14/10/2008</td>
<td>01/10/2008</td>
<td>3</td>
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**N = 9**

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**6.6.3. Non study or new treatment out of progression**

**Listing 6.6-6 New treatment out of progression - Chemotherapy (induction ITT)**

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Chemotherapy</th>
<th>Date of chemotherapy</th>
<th>Specify chemotherapy</th>
<th>Nb of cycles of chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003101021014</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>30/11/2004</td>
<td>ENDOXAN (1 CYCLE) + ICE (1 CYCLE ON 14122004)</td>
<td>2</td>
</tr>
<tr>
<td>5003101031007</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>20/04/2004</td>
<td>DHAX</td>
<td>4</td>
</tr>
<tr>
<td>5003101051068</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>02/10/2007</td>
<td>DHAP + 1 ETOPOSIDE IFOSFAMIDE</td>
<td>2</td>
</tr>
<tr>
<td>50031010515603</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>11/02/2004</td>
<td>R-ICE</td>
<td>3</td>
</tr>
<tr>
<td>5003101071647</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>03/07/2008</td>
<td>ICE</td>
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<tr>
<td>50031011141065</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>27/07/2007</td>
<td>DHAOX (OXALOPLATINE, CYTARABINE, DEXAMETHASONE)</td>
<td>2</td>
</tr>
<tr>
<td>5003101331077</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>26/06/2008</td>
<td>DHAP</td>
<td>2</td>
</tr>
<tr>
<td>5003101481403</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>07/12/2005</td>
<td>R-CHOP</td>
<td>1</td>
</tr>
<tr>
<td>5003601601002</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>13/03/2007</td>
<td>EPOCH</td>
<td>2</td>
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<tr>
<td>5003603201406</td>
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<td>Yes</td>
<td>-</td>
<td>DEXA-BEAM</td>
<td>-</td>
</tr>
<tr>
<td>5003603801406</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>12/08/2008</td>
<td>R-GFOX</td>
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<tr>
<td>5003609301608</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>05/02/2005</td>
<td>ICE</td>
<td>1</td>
</tr>
<tr>
<td>5003612501012</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>06/11/2007</td>
<td>VINBLASTINE, METHOTREXATE, BLEOMYCIN, LOMUSTINE, CHLORAMBUCIL</td>
<td>3</td>
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<tr>
<td>5003615501201</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>04/12/2006</td>
<td>GDCVP</td>
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<tr>
<td>5003617201042</td>
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<td>Yes</td>
<td>22/03/2007</td>
<td>R-DHAP</td>
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<tr>
<td>5003617501606</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>02/03/2008</td>
<td>MINI BEAM</td>
<td>1</td>
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<tr>
<td>5003621201023</td>
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<td>Yes</td>
<td>13/02/2006</td>
<td>DEXA-BEAM</td>
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</tr>
<tr>
<td>5003621301014</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>21/11/2007</td>
<td>ICE</td>
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<tr>
<td>5003622201210</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>29/03/2006</td>
<td>R-DHAP</td>
<td>2</td>
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<tr>
<td>5003632201054</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>08/07/2008</td>
<td>RITUXIMAB</td>
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<tr>
<td>5003635201051</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>-</td>
<td>2 X R-DHAP + 2 X R-GEM OX</td>
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<tr>
<td>5003101031006</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>28/03/2004</td>
<td>MIV</td>
<td>2</td>
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<tr>
<td>5003101031411</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>11/12/2006</td>
<td>DHAP N°4</td>
<td>1</td>
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<tr>
<td>5003101051503</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>03/07/2007</td>
<td>R-DHAP</td>
<td>3</td>
</tr>
<tr>
<td>5003101220170</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>01/01/2008</td>
<td>DHAP</td>
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</tr>
<tr>
<td>5003101391613</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>10/07/2004</td>
<td>2 COPADEM + 3 VAD (16/04/2005)</td>
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### Randomization Number

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<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Chemotherapy</th>
<th>Date of chemotherapy</th>
<th>Specify chemotherapy</th>
<th>Nb of cycles of chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>50033101431204</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>19/03/2004</td>
<td>R-ICE (FROM 19 TO 21/03/2004)</td>
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<td>5003602801016</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>04/10/2007</td>
<td>R-GIFOX</td>
<td>1</td>
</tr>
<tr>
<td>5003603001013</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>15/02/2007</td>
<td>R-ICE</td>
<td>1</td>
</tr>
<tr>
<td>5003605201603</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>-</td>
<td>DHAP</td>
<td>3</td>
</tr>
<tr>
<td>5003610201008</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>20/01/2005</td>
<td>IMMUNO-CHEMOTHERAPY (B-ALL PROTOCOL) VINCRI STINE, MTX, CYCLOPHOSPHAMIDE, DOXORUBICINE, DEXAMETHASONE</td>
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</tr>
<tr>
<td>5003610201112</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>-</td>
<td>RITUXIMAB, VINCIR STINE, METHOTREXATE, IFOSFAMIDE, CYTARABIN, ETOPOSIDE (GMALL-B-ALL-PROTOCOL)</td>
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</table>

| N = 38 |

### Radiotherapy (induction ITT)

Listing 6.6-7 New treatment out of progression - Radiotherapy (induction ITT)

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Radiotherapy</th>
<th>Date of radiotherapy</th>
<th>Site of radiotherapy</th>
<th>Dose of radiotherapy (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003603001201</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>16/08/2004</td>
<td>RIGHT ADRENAL GLAND</td>
<td>30</td>
</tr>
<tr>
<td>5003617201048</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>11/10/2007</td>
<td>MEDIASTINUM</td>
<td>46</td>
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<tr>
<td>5003628201009</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>05/08/2005</td>
<td>ABDOMINAL RESIDUAL MASS</td>
<td>-</td>
</tr>
<tr>
<td>50036101391207</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>19/06/2006</td>
<td>LEFT NASAL FOSSA</td>
<td>40</td>
</tr>
<tr>
<td>5003601301613</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>12/11/2004</td>
<td>COELIOMESENTERIC</td>
<td>40</td>
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<tr>
<td>5003604162053</td>
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<td>Yes</td>
<td>22/01/2007</td>
<td>MEDIASTINUM</td>
<td>40</td>
</tr>
<tr>
<td>5003601401001</td>
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<td>Yes</td>
<td>02/05/2004</td>
<td>LEFT PART OF ABDOMEN</td>
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<tr>
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<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>07/07/2006</td>
<td>PARATRACHEAL REGION</td>
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<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>24/03/2005</td>
<td>NECK</td>
<td>40</td>
</tr>
<tr>
<td>5003604901007</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>05/10/2008</td>
<td>MEDIASTINUM</td>
<td>40</td>
</tr>
<tr>
<td>5003617201049</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>14/11/2007</td>
<td>ABDOMINAL LN</td>
<td>36</td>
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<tr>
<td>5003619501009</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>20/07/2007</td>
<td>RIGHT PERINEPHRIC MASS : PET POSITIVE 17/APR/2007</td>
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</tr>
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<td>5003622201037</td>
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<td>Yes</td>
<td>-</td>
<td>RESIDUAL FINDINGS IN SMALL PELVIS</td>
<td>36</td>
</tr>
<tr>
<td>5003623501408</td>
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<td>Yes</td>
<td>02/06/2008</td>
<td>LEFT GROIN</td>
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| N = 18 |
### Listing 6.6-8 New treatment out of progression - Immunotherapy (induction ITT)

<table>
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<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Immunotherapy</th>
<th>Date of immunotherapy</th>
<th>Specify immunotherapy</th>
</tr>
</thead>
<tbody>
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<td>5003101021014</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>14/12/2004</td>
<td>RITUXIMAB WITH ICE</td>
</tr>
<tr>
<td>5003101051068</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>02/10/2007</td>
<td>RITUXIMAB ON 02/10/2007 AND 25/10/2007 AND 05/12/2007</td>
</tr>
<tr>
<td>5003101071647</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>03/07/2008</td>
<td>RITUXIMAB</td>
</tr>
<tr>
<td>5003101311077</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>26/06/2008</td>
<td>RITUXIMAB</td>
</tr>
<tr>
<td>5003609301608</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>05/02/2005</td>
<td>RITUXIMAB</td>
</tr>
<tr>
<td>5003617201042</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>24/04/2007</td>
<td>RITUXIMAB</td>
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### Listing 6.6-9 New treatment out of progression - Transplant (induction ITT)

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### Listing 6.6-10 New treatment out of progression - Other therapy (induction ITT)

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6.6.4. Progression/relapse

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Table 6.6-21 Progression/relapse n°1 – Nodal involvement (induction ITT)

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**TOTAL**

95 | 100 | 76 | 100

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**Listing 6.6-11 Progression/relapse n°1 – Other nodal involvement (induction ITT)**

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**Table 6.6-22 Progression/relapse n°1 – Extra-nodal involvement bis (induction ITT)**

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**Listing 6.6-12 Progression/relapse n°1 – Other extra-nodal involvement (induction ITT)**

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Table 6.6-23 Progression/relapse n°1 – Documentation (induction ITT)

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Listing 6.6-13 Progression/relapse n°1 - Chemotherapy (induction ITT)

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<td>R-ICE</td>
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<td>30/05/2008</td>
<td>GEMCITABINE, DACARB AZINE, CYCLOPHOSPHAMIDE, VINCRI STINE, PREDNISOLONE</td>
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<td>DEXA-BEAM</td>
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<td>2 G VINCRI STIN FOLLOWED BY 6EM DEX OX</td>
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### Listing 6.6-14 Progression/relapse n°1 - Radiotherapy (induction ITT)

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<th>Dose of radiotherapy (Gy)</th>
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<td>TONSIL RIGHT AND CERVICAL RIGHT</td>
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Randomization Number | Arm of treatment | Radiotherapy | Date of radiotherapy | Site of radiotherapy | Dose of radiotherapy (Gy)
--- | --- | --- | --- | --- | ---
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5003601801003 | ARM B / R-DHAP | Yes | 17/05/2005 | INGUINAL + ILIAC | 39
5003602001204 | ARM B / R-DHAP | Yes | 05/03/2005 | RIGHT SHOULDER, MEDIASTINUM | 30
5003603001007 | ARM B / R-DHAP | Yes | 19/06/2006 | MEDIASTINUM + SUPRACLAVICULAR REGION | 21
5003603801009 | ARM B / R-DHAP | Yes | 11/12/2006 | RIGHT AXILLA AND RIGHT ARM | 40
5003604001006 | ARM B / R-DHAP | Yes | 04/09/2006 | | 44
5003604801405 | ARM B / R-DHAP | Yes | 15/04/2008 | PARA-AORTIC | 40
5003604901004 | ARM B / R-DHAP | Yes | 29/04/2007 | D8 AND APARASPINAL MASS | 40
5003605301203 | ARM B / R-DHAP | Yes | 25/05/2004 | THYROID | 18
5003605301610 | ARM B / R-DHAP | Yes | 29/05/2006 | LEFT NECK | 30
5003605701404 | ARM B / R-DHAP | Yes | 08/08/2008 | WHOLE BRAIN | 36
5003606301606 | ARM B / R-DHAP | Yes | 15/04/2005 | ABDOMINAL TUMOR MASS | 5
5003606701005 | ARM B / R-DHAP | Yes | 06/03/2006 | RIGHT FOREARM | 30
5003607201408 | ARM B / R-DHAP | Yes | 27/01/2009 | NASOPHARYNX, LEFT CERVICAL SUBMENTAL, SUPRACLAVICULAR BDS | 40
5003608701008 | ARM B / R-DHAP | Yes | 06/07/2006 | AXILLA RIGHT | 40
5003609301620 | ARM B / R-DHAP | Yes | 05/06/2008 | PARANASAL SINUSES | 36
5003612301623 | ARM B / R-DHAP | Yes | 14/04/2008 | BASE OF BRAIN | 12
5003614301407 | ARM B / R-DHAP | Yes | 07/03/2010 | PARA-AORTIC NODES | 30
5003616501003 | ARM B / R-DHAP | Yes | 18/04/2008 | ENTIRE SPINE C2-L3 INCLUSIVE | 30
5003618301005 | ARM B / R-DHAP | Yes | 09/08/2006 | RIGHT HEMIPELVIS | 30
5003619301016 | ARM B / R-DHAP | Yes | 08/05/2008 | DUODENUM AND PANCREAS | 31
5003620201017 | ARM B / R-DHAP | Yes | 22/11/2005 | INVOLVED SITE ABDOMINAL | 36
5003621501412 | ARM B / R-DHAP | Yes | 09/11/2009 | CHEST WALL | 25
5003628201044 | ARM B / R-DHAP | Yes | 01/02/2009 | CERVICAL MASS | -
5003632201015 | ARM B / R-DHAP | Yes | 15/07/2005 | LEFT SOLE OF FOOT, LEFT LOWER LEG, LEFT THIGH | 21

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**Listing 6.6-15 Progression/relapse n°1 - Immunotherapy (induction ITT)**

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<td>05/03/2006</td>
<td>MABTHERA AND ZEVALIN (THE 09.03.06)</td>
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N = 67

**Listing 6.6-16 Progression/relapse n°1 - Transplant (induction ITT)**

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**Listing 6.6-17 Progression/relapse n°1 – Other treatments (induction ITT)**

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**Listing 6.6-19 Progression/relapse n°2 – Other extra-nodal involvement (induction ITT)**

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**Table 6.6-30 Progression/relapse n°2 – Individual factors of IPI (induction ITT)**

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Table 6.6-31 Progression/relapse n°2 – Treatment (induction ITT)

<table>
<thead>
<tr>
<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
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Table 6.6-32 Progression/relapse n°2 – Type of treatment (induction ITT)

<table>
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<th>Arm of treatment</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
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<tr>
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<td>Chemotherapy</td>
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Listing 6.6-20 Progression/relapse n°2 - Chemotherapy (induction ITT)

<table>
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<tr>
<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Chemotherapy</th>
<th>Date of chemotherapy</th>
<th>Specify chemotherapy</th>
<th>Nb of cycles of chemotherapy</th>
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</thead>
<tbody>
<tr>
<td>5003101021027</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>30/01/2006</td>
<td>GEMOX</td>
<td>3</td>
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<tr>
<td>5003101021605</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>11/04/2006</td>
<td>TAXOL - TOPOTECAN</td>
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<tr>
<td>5003101021631</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>28/05/2008</td>
<td>DHAOX</td>
<td>4</td>
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<tr>
<td>5003101071020</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>30/06/2006</td>
<td>GEMOX</td>
<td>4</td>
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<tr>
<td>5003101131409</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>09/05/2007</td>
<td>R-GEMOX</td>
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<tr>
<td>5003101161407</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>-</td>
<td>CYTARABINE-ETOPOSIDE-DEXAMETHASONE</td>
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### Randomization

<table>
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<th>Arm of treatment</th>
<th>Chemotherapy</th>
<th>Date of chemotherapy</th>
<th>Specify chemotherapy</th>
<th>Nb of cycles of chemotherapy</th>
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</thead>
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<tr>
<td>50031010431622</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>05/08/2008</td>
<td>CHOP</td>
<td>3</td>
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<tr>
<td>50031010491042</td>
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<td>Yes</td>
<td>15/01/2007</td>
<td>GEMCITABINE</td>
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<tr>
<td>50031011641618</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>03/08/2007</td>
<td>DHAP</td>
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<tr>
<td>5003102341061</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>17/02/2010</td>
<td>DHAP</td>
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<tr>
<td>5003102341416</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>04/12/2007</td>
<td>ANTIBODIES ANTI CD20 - PROTOCOL ROCHE</td>
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<tr>
<td>5003102491619</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>04/08/2008</td>
<td>IFOSFAMIDE + ETOPOSIDE</td>
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<tr>
<td>5003602901601</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>12/07/2006</td>
<td>VINCristin and BLEOMycin</td>
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<tr>
<td>5003604801205</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>09/08/2007</td>
<td>IVE</td>
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<tr>
<td>5003605701601</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>27/11/2006</td>
<td>CVP (= COP) + RITUXIMAB (STOP 18/12/2006)</td>
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<tr>
<td>5003615501014</td>
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<td>Yes</td>
<td>29/08/2008</td>
<td>GCVP (GEMCITABINE, CYCLOPHOSPHAMIDE, VINCristine, PREDNISOLONE)</td>
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<td>5003101031401</td>
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<td>06/06/2005</td>
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<td>16/11/2006</td>
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<tr>
<td>5003101221057</td>
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<td>Yes</td>
<td>13/03/2008</td>
<td>Navelbine</td>
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<tr>
<td>5003101641047</td>
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<td>Yes</td>
<td>29/03/2007</td>
<td>GEMOX</td>
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<td>26/09/2008</td>
<td>CYTARABINE, ETOPOSIDE</td>
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<td>5003102341003</td>
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<td>GEMCITABINE - OXALIPLATINE - RITUXIMAB</td>
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<td>5003601801003</td>
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<td>12/09/2005</td>
<td>CVP</td>
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<td>5003603201050</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>18/07/2008</td>
<td>SEE MEDICAL REPORT PAGE 2 AND 3 (B-ALL-PROTOCOL)</td>
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<tr>
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<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>02/11/2006</td>
<td>CVP REFRACTORY / 2ND LINE : 4 CEPP (MINUS CYCLOPHOSPHAMIDE) ON 04/01/2007</td>
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<td>16/01/2009</td>
<td>CHOP</td>
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<tr>
<td>5003611301002</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>20/12/2004</td>
<td>CYTARABINE AND METHOTREXATE (INTRATHECAL)</td>
<td>22</td>
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\[ N = 28 \]

### Listing 6.6-21 Progression/relapse n°2 - Radiotherapy (induction ITT)

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<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Radiotherapy</th>
<th>Date of radiotherapy</th>
<th>Site of radiotherapy</th>
<th>Dose of radiotherapy (Gy)</th>
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<tbody>
<tr>
<td>5003101021631</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>07/10/2008</td>
<td>TOTAL BODY IRRADIATION</td>
<td>2</td>
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<tr>
<td>5003102341416</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>28/01/2008</td>
<td>MEDIASTINAL</td>
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<tr>
<td>5003602901601</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>-</td>
<td>RIGHT ADRENA L AND LEFT LEG (SKIN)</td>
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<tr>
<td>5003603801202</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>13/05/2008</td>
<td>RIGHT KNEE + FEMUR</td>
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<tr>
<td>5003604801205</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>24/09/2007</td>
<td>22</td>
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<tr>
<td>5003632201054</td>
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<td>Yes</td>
<td>05/12/2008</td>
<td>LEFT DISTAL SHANK</td>
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<td>5003643501202</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>04/08/2008</td>
<td>RIGHT NECK AND SUPRACLAVICULAR AREA</td>
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<td>5003101221057</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>-</td>
<td>MEDIASTINAL + ABDOMEN</td>
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<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>24/11/2008</td>
<td>ABDOMINAL (ILIAC RIGHT)</td>
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<tr>
<td>5003606701005</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>02/05/2007</td>
<td>RIGHT THIGH (20 GY) + DORSAL LESION (20 GY)</td>
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<td>5003602301620</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>11/03/2009</td>
<td>LEFT ABDOMINAL WALL AND RIGHT NECK</td>
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<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>06/10/2005</td>
<td>HYPODERMIC : INGUINAL, THIGH, LOWER LEG, SOLE OF FOOT, FOOT : LEFT SIDE</td>
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\[ N = 12 \]

### Listing 6.6-22 Progression/relapse n°2 - Immunotherapy (induction ITT)
### Randomization Table

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<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Immunotherapy</th>
<th>Date of immunotherapy</th>
<th>Specify immunotherapy</th>
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<tr>
<td>5003101641047</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
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<td>5003609301620</td>
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<td>Yes</td>
<td>-</td>
<td>RITUXIMAB MAINTENANCE ON GOING</td>
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<td>5003632201015</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>23/02/2006</td>
<td>MABTHERA</td>
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### Listing 6.6-23 Progression/relapse n°2 – Transplant (induction ITT)

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<th>Arm of treatment</th>
<th>Transplantation</th>
<th>Date of transplantation</th>
<th>Conditioning Regimen</th>
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<tr>
<td>5003101021631</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>09/10/2008</td>
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<td>ARM B / R-DHAP</td>
<td>Yes</td>
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### Listing 6.6-24 Progression/relapse n°2 – Other treatments (induction ITT)

<table>
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<tr>
<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>Other treatment</th>
<th>Date of other treatment</th>
<th>Specify other treatment</th>
</tr>
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<tbody>
<tr>
<td>5003102491619</td>
<td>ARM A / R-ICE</td>
<td>Yes</td>
<td>11/08/2008</td>
<td>DONOR LYMPHOCYTES INFUSIONS</td>
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<tr>
<td>5003101071607</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>21/04/2006</td>
<td>SURGERY INGUINAL NODE</td>
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<td>5003605301610</td>
<td>ARM B / R-DHAP</td>
<td>Yes</td>
<td>-</td>
<td>PALLIATIVE CARE</td>
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### Table 6.6-33 Progression/relapse n°2 – Response after additional treatments (induction ITT)

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<th>Arm of treatment</th>
<th>Response after new treatment</th>
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<td>COMPLETE RESPONSE</td>
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<td>ARM A / R-ICE</td>
<td>N 1 % 5</td>
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<tr>
<td>ARM B / R-DHAP</td>
<td>N 3 % 18</td>
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<td>UNCONFIRMED COMPLETE RESPONSE</td>
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<td>N 1 % 5</td>
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<tr>
<td>ARM B / R-DHAP</td>
<td>N 0 % 0</td>
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<tr>
<td></td>
<td>PARTIAL RESPONSE</td>
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<td>ARM A / R-ICE</td>
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<td>ARM B / R-DHAP</td>
<td>N 0 % 0</td>
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<td>STABLE DISEASE</td>
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<td>ARM A / R-ICE</td>
<td>N 1 % 5</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>N 1 % 6</td>
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<td>PROGRESSIVE DISEASE</td>
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<td>ARM A / R-ICE</td>
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<td>ARM B / R-DHAP</td>
<td>N 10 % 59</td>
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<td>ARM A / R-ICE</td>
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<td>ARM B / R-DHAP</td>
<td>N 2 % 12</td>
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<tr>
<td>ARM A / R-ICE</td>
<td>N 1 % 5</td>
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<tr>
<td>ARM B / R-DHAP</td>
<td>N 1 % 6</td>
</tr>
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<td>Total</td>
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<tr>
<td>ARM A / R-ICE</td>
<td>N 19 % 100</td>
</tr>
<tr>
<td>ARM B / R-DHAP</td>
<td>N 17 % 100</td>
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### 6.7. Safety evaluation

**6.7.1. **Extent of exposure to trial medication

Table 6.7-1 Induction – Frequency of percentage of planned dose received by cycle for Rituximab (induction safety population)

<table>
<thead>
<tr>
<th>Rituximab: Dose received (% of planned dose)</th>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
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<tr>
<td>Cycle 1 &lt;75%</td>
<td>23</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>[75-90%]</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>[90-110%]</td>
<td>211</td>
<td>88</td>
<td>201</td>
</tr>
<tr>
<td>[110-125%]</td>
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<td>0</td>
</tr>
<tr>
<td>&gt;125%</td>
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<td>0</td>
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<tr>
<td>Total</td>
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<td>100</td>
<td>228</td>
</tr>
<tr>
<td>Cycle 2 &lt;75%</td>
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<td>2</td>
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<tr>
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<td>2</td>
<td>8</td>
</tr>
<tr>
<td>[90-110%]</td>
<td>215</td>
<td>96</td>
<td>202</td>
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<tr>
<td>&gt;125%</td>
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<td>100</td>
<td>212</td>
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<tr>
<td>Cycle 3 &lt;75%</td>
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<td>[75-90%]</td>
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</tr>
<tr>
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<td>97</td>
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</tr>
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<td>1</td>
</tr>
<tr>
<td>&gt;125%</td>
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<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
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<td>193</td>
</tr>
</tbody>
</table>

Table 6.7-2 Induction – Frequency of percentage of planned dose received by cycle for ICE regimen (induction safety population)

<table>
<thead>
<tr>
<th>Etoposide: Dose received (% of planned dose)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1 &lt;75%</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>[75-90%]</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>[90-110%]</td>
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<td>95</td>
</tr>
<tr>
<td>[110-125%]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;125%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>239</td>
<td>100</td>
</tr>
<tr>
<td>Cycle 2 &lt;75%</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
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<td>7</td>
<td>3</td>
</tr>
<tr>
<td>[90-110%]</td>
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</tr>
<tr>
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</tr>
<tr>
<td>&gt;125%</td>
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<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Etoposide: Dose received (% of planned dose)</td>
<td>N</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------------------</td>
<td>----</td>
</tr>
<tr>
<td><strong>Cycle 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75%</td>
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</tr>
<tr>
<td>[75-90%]</td>
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<td>7</td>
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<tr>
<td>[90-110%]</td>
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<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>204</td>
</tr>
<tr>
<td><strong>Carboplatine: Dose received (% of planned dose)</strong></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Cycle 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>32</td>
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<tr>
<td>&gt;125%</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>238</td>
</tr>
<tr>
<td><strong>Cycle 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75%</td>
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<td>18</td>
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<td><strong>Total</strong></td>
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<td><strong>Cycle 3</strong></td>
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<td></td>
</tr>
<tr>
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<tr>
<td>[90-110%]</td>
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<tr>
<td>[110-125%]</td>
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<td>29</td>
</tr>
<tr>
<td>&gt;125%</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>203</td>
</tr>
<tr>
<td><strong>Ihosfamide: Dose received (% of planned dose)</strong></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>Cycle 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75%</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>[75-90%]</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>[90-110%]</td>
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<td>[110-125%]</td>
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<tr>
<td>&gt;125%</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>238</td>
</tr>
<tr>
<td><strong>Cycle 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75%</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>[75-90%]</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>[90-110%]</td>
<td></td>
<td>209</td>
</tr>
<tr>
<td>[110-125%]</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>&gt;125%</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>224</td>
</tr>
</tbody>
</table>
### Table 6.7-3 Induction – Frequency of percentage of planned dose received by cycle for R-DHAP (induction safety population)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cycle</th>
<th>&lt;75%</th>
<th>[75-90%]</th>
<th>[90-110%]</th>
<th>[110-125%]</th>
<th>&gt;125%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etoposide</strong></td>
<td>Cycle 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>202</td>
</tr>
<tr>
<td></td>
<td>&lt;75%</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[75-90%]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[90-110%]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[110-125%]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;125%</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>202</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

<p>| <strong>Dexamethasone</strong> | Cycle 1 | &lt;75%  | [75-90%] | [90-110%] | [110-125%] | &gt;125% | Total |
|                  | Cycle 2 | &lt;75%  | [75-90%] | [90-110%] | [110-125%] | &gt;125% | Total |
|                  | Cycle 3 | &lt;75%  | [75-90%] | [90-110%] | [110-125%] | &gt;125% | Total |
| <strong>Cisplatine</strong>   | Cycle 1 | &lt;75%  | [75-90%] | [90-110%] | [110-125%] | &gt;125% | Total |
|                  | Cycle 2 | &lt;75%  | [75-90%] | [90-110%] | [110-125%] | &gt;125% | Total |</p>
<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone: Dose received (% of planned dose)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 3</td>
<td>&lt;75%</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>[75-90%]</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>[90-110%]</td>
<td>153</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>[110-125%]</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;125%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>194</td>
<td>100</td>
</tr>
</tbody>
</table>

| Cycle 1            | <75%                                           | 11    | 5 |
|                    | [75-90%]                                       | 11    | 5 |
|                    | [90-110%]                                      | 205   | 90|
|                    | [110-125%]                                     | 1     | 0 |
|                    | >125%                                          | 0     | 0 |
|                    | Total                                          | 228   | 100|

| Cycle 2            | <75%                                           | 11    | 5 |
|                    | [75-90%]                                       | 9     | 4 |
|                    | [90-110%]                                      | 191   | 91|
|                    | [110-125%]                                     | 0     | 0 |
|                    | >125%                                          | 0     | 0 |
|                    | Total                                          | 211   | 100|

| Cycle 3            | <75%                                           | 10    | 5 |
|                    | [75-90%]                                       | 8     | 4 |
|                    | [90-110%]                                      | 176   | 91|
|                    | [110-125%]                                     | 0     | 0 |
|                    | >125%                                          | 0     | 0 |
|                    | Total                                          | 194   | 100|
Table 6.7-4 Induction – G-CSF: number of days (induction safety population)

<table>
<thead>
<tr>
<th>G-CSF - nb of days</th>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>179</td>
<td>186</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.8</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>2.76</td>
<td>2.73</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8.0</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>21</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Cycle 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>185</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>2.89</td>
<td>2.79</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>8.0</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Max</td>
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<td>16</td>
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</tr>
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<td>Cycle 3</td>
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</tr>
<tr>
<td>N</td>
<td>181</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td></td>
</tr>
<tr>
<td>Std</td>
<td>3.06</td>
<td>4.27</td>
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<tr>
<td>Median</td>
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<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>20</td>
<td>43</td>
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</tr>
</tbody>
</table>

Table 6.7-5 Induction – G-CSF: dose at 3rd cycle (induction safety population)

<table>
<thead>
<tr>
<th>G-CSF - dosage (µg/day)</th>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
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</tr>
<tr>
<td>Mean</td>
<td>560.9</td>
<td>535.4</td>
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</tr>
<tr>
<td>Std</td>
<td>857.04</td>
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</tr>
<tr>
<td>Median</td>
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<td>368.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
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<td>6</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>6000</td>
<td>6000</td>
<td></td>
</tr>
<tr>
<td>BCNU : Dose received (% of planned dose)</td>
<td>Actual arm of induction</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>&lt;75%</td>
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<td>5</td>
</tr>
<tr>
<td>[75-90%]</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>[90-110%]</td>
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<td>118</td>
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<td>[110-125%]</td>
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<td>1</td>
</tr>
<tr>
<td>&gt;125%</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
<td>131</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etoposide : Dose received (% of planned dose)</th>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>&lt;75%</td>
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<td>6</td>
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<tr>
<td>[90-110%]</td>
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<td>107</td>
</tr>
<tr>
<td>[110-125%]</td>
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<td>0</td>
<td>2</td>
</tr>
<tr>
<td>&gt;125%</td>
<td>6</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
<td>131</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Melphalan : Dose received (% of planned dose)</th>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>&lt;75%</td>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>[75-90%]</td>
<td>3</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>[90-110%]</td>
<td>116</td>
<td>95</td>
<td>119</td>
</tr>
<tr>
<td>[110-125%]</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>&gt;125%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
<td>131</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytarabine : Dose received (% of planned dose)</th>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>&lt;75%</td>
<td>25</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>[75-90%]</td>
<td>2</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>[90-110%]</td>
<td>94</td>
<td>77</td>
<td>103</td>
</tr>
<tr>
<td>[110-125%]</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&gt;125%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
<td>131</td>
</tr>
</tbody>
</table>
**Listing 6.7-1 Consolidation – Other types of growth factors (induction safety population)**

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Actual arm of induction</th>
<th>Other Growth Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003101051056</td>
<td>ARM A / R-ICE</td>
<td>NEULASTA</td>
</tr>
<tr>
<td>5003102541052</td>
<td>ARM A / R-ICE</td>
<td>PEGFILGASTRIM 6 MG</td>
</tr>
<tr>
<td>5003619301621</td>
<td>ARM A / R-ICE</td>
<td>PEG - GCSF</td>
</tr>
<tr>
<td>5003101051050</td>
<td>ARM B / R-DHAP</td>
<td>PEGFILGASTRIM</td>
</tr>
<tr>
<td>5003102541636</td>
<td>ARM B / R-DHAP</td>
<td>PEGFILGRASTIM 6 MG</td>
</tr>
<tr>
<td>5003607201408</td>
<td>ARM B / R-DHAP</td>
<td>LENOGRASTIM (+ MUG-CSF)</td>
</tr>
</tbody>
</table>

N = 6

**Table 6.7-7 Consolidation – G-CSF: day of administration (induction safety population)**

<table>
<thead>
<tr>
<th>G-CSF</th>
<th>Actual arm of induction</th>
<th>ARM A / R-ICE</th>
<th>%</th>
<th>ARM B / R-DHAP</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAY 1</td>
<td></td>
<td>N  23</td>
<td>27%</td>
<td>N  14</td>
<td>15%</td>
</tr>
<tr>
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GELARC
### 6.7.2. Overview of toxicity profile

#### Table 6.7-8 Incidence of induction toxicities by grade and cycle (induction safety population)

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## Grade infection with febrile neutropenia

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## Grade infection without febrile neutropenia

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N = 472
### Listing 6.7-3 Other toxicities during consolidation (induction safety population)

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<tr>
<td>5003606201620</td>
<td>ARM A / R-ICE</td>
<td>HEADACHES</td>
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<tr>
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<td>ARM B / R-DHAP</td>
<td>AMPHOTERICIN-B ASSOCIATED DRY-FEVER</td>
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<td>IMIPENEM ASSOCIATED RASH</td>
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<td>NEUTROPENIA</td>
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<td>ARM B / R-DHAP</td>
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<td>ARM A / R-ICE</td>
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<td>HYPOTENSION</td>
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<td>FEVER</td>
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<td>5003609301018</td>
<td>ARM B / R-DHAP</td>
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<td>HYPOMAGNESEMIA</td>
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<td>ARM B / R-DHAP</td>
<td>HEADACHES</td>
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<td>HYPOKALEMIA</td>
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<td>LOWER BACK PAIN</td>
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<td>5003610501031</td>
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<td>PYREXIA</td>
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<td>DIARRHOEA</td>
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<td>PULMONARY (COUGH)</td>
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<td>FEBRILE NEUTROPENIA</td>
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<td>NEUTROPENIC TYPHLITIS</td>
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<td>RASH</td>
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<td>PETECHIAE</td>
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<td>NAUSEA</td>
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<td>FOLLICULITIS (FACE + AXILLA)</td>
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<td>5003632201606</td>
<td>ARM B / R-DHAP</td>
<td>THROMBOSIS VENA SUBCLAVIA, JUGULARIS EXTERNA, INTERNA RIGHT AS RESULT OF INFECTION</td>
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N = 78
### 6.7.3. Adverse events

#### Listing 6.7-4 Adverse events of patients receiving no study treatment – Full analysis population

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>First Randomization Date</th>
<th>AE number</th>
<th>Adverse event description</th>
<th>Start date of adverse event</th>
<th>Non hematological toxicity grade</th>
<th>Hematological toxicity grade</th>
<th>Date of outcome</th>
<th>AE outcome</th>
<th>Seriousness criteria</th>
<th>Date of death</th>
<th>Response at death</th>
<th>Reason for death</th>
<th>Specify reason of death</th>
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<tbody>
<tr>
<td>5003603201027</td>
<td>26/03/2006</td>
<td>1</td>
<td>SEVERE PNEUMONIA AND DEATH FROM SEPTIC SHOCK PRIOR TO START WITH STUDY MEDICATION (DEATH 26/01/2006)</td>
<td>25/01/2006</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>FATAL / DEATH</td>
<td>Yes</td>
<td>26/01/2006</td>
<td>NOT EVALUATED</td>
<td>OTHER REASON</td>
<td>SEPTIC SHOCK</td>
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<tr>
<td>5003603201627</td>
<td>28/03/2007</td>
<td>1</td>
<td>SEPSIS WITH REFRACTORY LACTIC ACIDOSIS AFTER GASTRIC PERFORATION</td>
<td>31/03/2007</td>
<td>LIFE THREATENING</td>
<td>SEVERE</td>
<td>-</td>
<td>FATAL / DEATH</td>
<td>Yes</td>
<td>03/04/2007</td>
<td>PROGRESSIVE DISEASE</td>
<td>OTHER REASON</td>
<td>SEE ATTACHED LETTER / PROGRESSION FORM WILL FOLLOW</td>
</tr>
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</table>

N = 2

#### Listing 6.7-5 Adverse events occurring before 1st induction cycle (induction safety population)

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Actual arm of induction</th>
<th>AE number</th>
<th>Adverse event description</th>
<th>Start date of adverse event</th>
<th>Date of 1st cycle</th>
<th>Time from starting date to date of cycle 1 (days)</th>
<th>Seriousness criteria</th>
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</thead>
<tbody>
<tr>
<td>5003101141406</td>
<td>ARM A / R-ICE</td>
<td>1</td>
<td>EDEMA RELATED TO ALLERGIC REACTION</td>
<td>15/09/2005</td>
<td>17/09/2005</td>
<td>-2</td>
<td>No</td>
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<tr>
<td>5003618501008</td>
<td>ARM A / R-ICE</td>
<td>1</td>
<td>INFECTION WITHOUT FEBRILE NEUTROPENIA</td>
<td>21/01/2007</td>
<td>22/01/2007</td>
<td>-1</td>
<td>No</td>
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<tr>
<td>5003101391207</td>
<td>ARM B / R-DHAP</td>
<td>1</td>
<td>RESPIRATORY INFECTION (E. COLEI STREPTOCOCCUS PNEUMONIAE)</td>
<td>01/02/2006</td>
<td>11/02/2006</td>
<td>-10</td>
<td>No</td>
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<tr>
<td>5003604201028</td>
<td>ARM B / R-DHAP</td>
<td>1</td>
<td>ALLERGIC ANAPHYLACTIC REACTION DUE TO RITUXIMAB</td>
<td>02/02/2006</td>
<td>03/02/2006</td>
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<td>Yes</td>
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<tr>
<td>5003604201056</td>
<td>ARM B / R-DHAP</td>
<td>1</td>
<td>RENAL FUNCTION : CLEARANCE DECREASE</td>
<td>29/04/2008</td>
<td>15/05/2008</td>
<td>-16</td>
<td>No</td>
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<tr>
<td>5003609301018</td>
<td>ARM B / R-DHAP</td>
<td>1</td>
<td>CHEST INFECTION</td>
<td>07/06/2008</td>
<td>15/06/2008</td>
<td>-8</td>
<td>Yes</td>
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<tr>
<td>5003612501019</td>
<td>ARM B / R-DHAP</td>
<td>1</td>
<td>HIGH CREATININE LEVEL (GRADE 3)</td>
<td>03/09/2007</td>
<td>06/09/2007</td>
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<td>Yes</td>
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</table>

N = 8
6.7.4. **Serious adverse events**

**Listing 6.7-6 Serious adverse events of patients receiving no study treatment – Full analysis population**

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>First Randomization Date</th>
<th>AE number</th>
<th>Adverse event description</th>
<th>Start date of adverse event</th>
<th>Non hematological toxicity grade</th>
<th>Hematological toxicity grade</th>
<th>Date of outcome</th>
<th>AE outcome</th>
<th>Seriousness criteria</th>
<th>Date of death</th>
<th>Response at death</th>
<th>Reason for death</th>
<th>Specify reason of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003603201027</td>
<td>26/01/2006</td>
<td>1</td>
<td>SEVERE PNEUMONIA AND DEATH FROM SEPTIC SHOCK PRIOR TO START WITH STUDY MEDICATION (DEATH 26/01/2006)</td>
<td>25/01/2006</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>FATAL</td>
<td>Yes</td>
<td>26/01/2006</td>
<td>NOT EVALUATED</td>
<td>OTHER REASON</td>
<td>SEPTIC SHOCK</td>
</tr>
<tr>
<td>5003603201627</td>
<td>28/03/2007</td>
<td>1</td>
<td>SEPSIS WITH REFRACTORY LACTIC ACIDOSIS AFTER GASTRIC PERFORATION</td>
<td>31/03/2007</td>
<td>LIFE THREATENING</td>
<td>SEVERE</td>
<td>03/04/2007</td>
<td>FATAL</td>
<td>Yes</td>
<td>03/04/2007</td>
<td>PROGRESSIVE DISEASE</td>
<td>OTHER REASON</td>
<td>SEE ATTACHED LETTER / PROGRESSION FORM WILL FOLLOW</td>
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</tbody>
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N = 2

**Listing 6.7-7 Serious adverse events declared to Pharmacovigilance department but not present in clinical database**

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>First Randomization Date</th>
<th>Arm of treatment</th>
<th>Date of 2nd randomization</th>
<th>Arm of 2nd randomization</th>
<th>SAE diagnosis</th>
<th>SAE: date of start</th>
<th>AE/SAE: date of end</th>
<th>Outcome</th>
<th>Sponsor Causality</th>
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<tbody>
<tr>
<td>5003613301007</td>
<td>14/11/2006</td>
<td>ARM A / R-ICE</td>
<td>31/01/2007</td>
<td>RITUXIMAB</td>
<td>ACUTE RENAL IMPAIEMENT</td>
<td>03/01/2007</td>
<td>08/01/2007</td>
<td>Recovered without sequelae</td>
<td>Related</td>
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<tr>
<td>5003613301404</td>
<td>14/11/2006</td>
<td>ARM B / R-DHAP</td>
<td>08/02/2007</td>
<td>OBSERVATION</td>
<td>FEVER, NAUSEA AND VOMITING</td>
<td>13/05/2007</td>
<td>-</td>
<td>Not yet recovered</td>
<td>Unrelated</td>
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N = 5
### Listing 6.7-8 Serious adverse events (induction safety population)

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<th>Randomization Number</th>
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<th>Actual arm of maintenance</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Adverse event description</th>
<th>Date of AE become serious</th>
<th>Non hematological toxicity grade</th>
<th>Hematological toxicity grade</th>
<th>Relation with study drugs</th>
<th>Action taken with study drug</th>
<th>AE outcome</th>
<th>Duration of AE serious (days)</th>
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<tbody>
<tr>
<td>5003101031621</td>
<td>ARM A / R-ICE RITUXIMAB</td>
<td>FEMALE 55</td>
<td>SEPTIC SHOCK WITH PNEUMONIA 06/07/2006 LIFE THREATENING LIFE THREATENING Yes Yes RECOVERED 33</td>
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<td>5003101031621</td>
<td>ARM A / R-ICE RITUXIMAB</td>
<td>FEMALE 55</td>
<td>PULMONARY ASPERGILLOSIS 06/07/2006 LIFE THREATENING LIFE THREATENING Yes Yes RECOVERED 50</td>
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<td>5003101031621</td>
<td>ARM A / R-ICE RITUXIMAB</td>
<td>FEMALE 55</td>
<td>BRONCHITIS TO PNEUMOCOCCUS 18/01/2007 SEVERE MILD Yes No RECOVERED 64</td>
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<tr>
<td>5003101031621</td>
<td>ARM A / R-ICE RITUXIMAB</td>
<td>FEMALE 55</td>
<td>PULMONARY INFECTION TO PSEUDOMONAS AERUGINOSA WITH HEMOPTYSIS 02/06/2007 SEVERE MILD Yes No RECOVERED 72</td>
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<td>5003101051056</td>
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<td>MALE 64</td>
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<td>5003101051068</td>
<td>ARM A / R-ICE NOT APPLICABLE</td>
<td>MALE 63</td>
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<td>5003101051068</td>
<td>ARM A / R-ICE NOT APPLICABLE</td>
<td>MALE 63</td>
<td>ESCHERICHIA COLI INFECTION 15/08/2007 SEVERE NORMAL No No RECOVERED 5</td>
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<td>5003101051603</td>
<td>ARM A / R-ICE NOT APPLICABLE</td>
<td>FEMALE 56</td>
<td>OESOPHAGUS CARCINOMA 09/02/2005 LIFE THREATENING - No No FATAL 0</td>
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<td>5003101051612</td>
<td>ARM A / R-ICE OBSERVATION</td>
<td>MALE 36</td>
<td>Cardiac infarction 28/06/2004 SEVERE MILD No No RECOVERED 4</td>
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<td>5003101131030</td>
<td>ARM A / R-ICE NOT APPLICABLE</td>
<td>FEMALE 48</td>
<td>SEPTIC SHOCK DUE TO PROBABLE APLASIA NO DOCUMENTED AT THE ENTRY TO HOSPITAL, PATIENT WITH IRREGULAR TACHYCARDIA AND CARDIAC RESPIRATORY STANDSTILL 16/08/2005 DEATH UNKNOWN Yes Yes FATAL 0</td>
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<td>MALE 54</td>
<td>HYPERTHERMIA 15/07/2004 MODERATE LIFE THREATENING No No RECOVERED 3</td>
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<td>5003101251205</td>
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<td>MALE 54</td>
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<tr>
<td>5003101281017</td>
<td>ARM A / R-ICE NOT APPLICABLE</td>
<td>MALE 60</td>
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<td>5003101281017</td>
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<td>MALE 60</td>
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<td>5003101281017</td>
<td>ARM A / R-ICE NOT APPLICABLE</td>
<td>MALE 60</td>
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<td>5003101281017</td>
<td>ARM A / R-ICE NOT APPLICABLE</td>
<td>MALE 60</td>
<td>SYCONE 25/11/2004 SEVERE SEVERE No Yes RECOVERED 0</td>
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<td>5003101431622</td>
<td>ARM A / R-ICE RITUXIMAB</td>
<td>MALE 49</td>
<td>INTERSTITIAL PNEUMOPATHY 19/09/2005 SEVERE MILD No No RECOVERED -</td>
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<tr>
<td>5003101431622</td>
<td>ARM A / R-ICE RITUXIMAB</td>
<td>MALE 49</td>
<td>BRUTAL NEUTROPENIA APPEARANCE 10/10/2005 UNKNOWN SEVERE Yes Yes RECOVERED 15</td>
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<td>Actual arm of induction</td>
<td>Actual arm of maintenance</td>
<td>Sex</td>
<td>Age (years)</td>
<td>Adverse event description</td>
<td>Date of AE</td>
<td>Non hematological toxicity grade</td>
<td>Hematological toxicity grade</td>
<td>Relation with study drugs</td>
<td>Action taken with study drug</td>
<td>AE outcome</td>
<td>Duration of AE serious (days)</td>
</tr>
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<td>Relation with study drugs</td>
<td>Action taken with study drug</td>
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<td>17/01/2005</td>
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<td>LIFE THREATENING</td>
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<td>Action taken with study drug</td>
<td>AE outcome</td>
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<td>19/11/2003</td>
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<td>03/09/2007</td>
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<td>53</td>
<td>WOKE AT 4AM; 5AM ON 12/06/2006 WITH DEEP ACHIE IN THIGHS + PELVIS ADMITTED ON 12/06/2006 WITH GCSF INDUCED BONE PAIN. NEUTROPENIC INITIALLY, BUT COUNT RECOVERED QUICKLY.</td>
<td>12/06/2006</td>
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<td>Age (years)</td>
<td>Adverse event description</td>
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<td>Non hematological toxicity grade</td>
<td>Hematological toxicity grade</td>
<td>Relation with study drugs</td>
<td>Action taken with study drug</td>
<td>AE outcome</td>
<td>Duration of AE serious (days)</td>
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<td>PATIENT FELL AT HOME, FRACTURED FACE &amp; RIGHT KNEE, 3 DAYS LATER BECAME INFECTED : ADMITTED TO HOSP. NEUTS 0.25</td>
<td>28/05/2007</td>
<td>MILDE</td>
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<td>58</td>
<td>PATIENT DIED OF PNEUMONIA RELATED TO THE LYMPHOMA WHICH HAS BEEN CONFIRMED IN THE CORONER'S AUTOPIFY REPORT</td>
<td>26/07/2007</td>
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<td>-</td>
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<td>No</td>
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<td>FEMALE</td>
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N = 257
### 6.7.5. Deaths

**Listing 6.7-9 Deaths of patients receiving no study treatment – Full analysis population**

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<th>Randomization Number</th>
<th>First Randomization Date</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Date of death</th>
<th>Reason for death</th>
<th>Specify reason of death</th>
<th>Response at death</th>
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<td>5003603201627</td>
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<td>MALE</td>
<td>49</td>
<td>03/04/2007</td>
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<td>SEE ATTACHED LETTER / PROGRESSION FORM WILL FOLLOW</td>
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<td>5003609201013</td>
<td>14/03/2005</td>
<td>MALE</td>
<td>44</td>
<td>20/09/2005</td>
<td>LYMPHOMA</td>
<td></td>
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<td>MALE</td>
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<td>SEPTIC SHOCK</td>
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N = 4
### 6.7.6. Laboratory tests

#### Table 6.7-9 Hemoglobin (induction safety population)

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<th>R-ICE arm</th>
<th>Actual values</th>
<th>Hemoglobin (g/dl)</th>
<th>Change from baseline</th>
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<td>Std</td>
</tr>
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<td>Baseline</td>
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### Table 6.7-10 Leukocytes (induction safety population)

**R-ICE arm**

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### R-DHAP arm

#### Neutrophils (G/L)

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Table 6.7-14 Monoclonal component at relapse diagnosis (induction safety population)

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Table 6.7-15 Serologies at relapse diagnosis (induction safety population)

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6.7.7. Vital signs

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### Table 6.7-17 Cardiac exams at relapse diagnosis (induction safety population)

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**PROTOCOL CORAL: 50-03B / STATISTICAL REPORT: ANALYSIS OF MAINTENANCE PART**

**RANDOMIZED STUDY OF ICE PLUS RITUXIMAB (R-ICE) versus DHAP PLUS RITUXIMAB (R-DHAP) IN PREVIOUSLY TREATED PATIENTS WITH CD 20 POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA, ELIGIBLE FOR TRANSPLANTATION FOLLOWED BY RANDOMIZED MAINTENANCE TREATMENT WITH RITUXIMAB**

Phase III clinical trial

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LIST OF ABBREVIATIONS

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<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>MITT</td>
<td>Full Analysis Set</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-Treat</td>
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<tr>
<td>Max</td>
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<td>Min</td>
<td>Minimum</td>
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<tr>
<td>Q1</td>
<td>First quartile</td>
</tr>
<tr>
<td>Q3</td>
<td>Third quartile</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>Std</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
</tr>
<tr>
<td>95% CI</td>
<td>95% Confidence Interval</td>
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1. INVESTIGATIONAL PLAN

1.1. Overall study design

This study is a multicenter, phase III open-label, randomized trial evaluating the efficacy of R-ICE compared to R-DHAP in patients aged from 18 to 65 years with previously treated diffuse large B-cell lymphoma, followed by high-dose chemotherapy +/- rituximab maintenance therapy. There will be two phases in the study and patients will undergo two randomizations according to induction phase or maintenance phase.

1.2. Study objectives

1.2.1. Primary objective

Part I (induction chemotherapy): Overall response rate (CR and PR) after 2 and/or 3 cycles of ICE+Rituximab in comparison to DHAP+rituximab, adjusted to successful mobilization of stem cells in patients aged from 18 to 65 years with previously treated diffuse large B-cell lymphoma CD20.

Part II (Maintenance vs. observation): Event free survival (EFS) at 2 years after autotransplant with or without maintenance therapy with rituximab. Events are defined as death from any cause, relapse for complete responders and unconfirmed complete responders (CRu), progression during or after treatment for partial responders, and institution of new antilymphoma therapy. The absence of transplantation procedure will be not considered as an event for the intent to treat analysis.

1.2.2. Secondary objectives

- Eligibility for transplant, (independent from whether transplantation was done or not) transplantation done or not.
- Safety toxicities.
- Event-Free Survival, Progression-Free Survival and Overall Survival for the whole randomized population, for patients submitted to ASCT.
- Progression-Free Survival and Overall Survival for patients randomized in maintenance.

2. STATISTICAL METHODOLOGY

2.1. Statistical methods

Statistical analysis was planned and performed as it follows:

Descriptive statistics

Quantitative variables were summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles were presented when considered relevant.

Qualitative variables were described in terms of frequencies of each response category and frequencies converted into percentages of the number of patients or adverse events examined depending on the statistical unit under investigation.

Censored data were presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% CIs. The median time to event was calculated (if reached) with 95% CIs. Estimates of the treatment effect were expressed as hazard ratios based on the Cox regression with 95% confidence interval.
Statistical inference

Statistical tests were two-sided and performed using a 5% level of significance. 95% confidence intervals were also presented when considered relevant. Survival endpoints were analyzed using the log rank test (unstratified) and Cox model for corresponding hazard ratio and p-value of treatment effect and multivariate models. The number and proportion of responders and non responders in each treatment group, together with the two-sided 95% Pearson-Clopper CI were presented, as well as the difference between proportion, the two-sided 95% asymptotic confidence interval and p-value of chi-square test.

All statistical analyses were carried out with SAS 9.1.3 software (SAS Institute, Cary, NC).

2.2. Determination of sample size

Part I induction:
The primary end point is mobilization adjusted response rate after 3 cycles of chemotherapy and it is expected to detect a difference in mobilization adjusted response rate of 15% between R-ICE 60% (75% response rate and 15% mobilization failure) and R-DHAP 45% (65% response rate and 20% mobilization failure) with a 82% power at 5% significance level. 400 patients should be randomized between the two chemotherapy arms. Initially 400 patients are to be randomised 1:1 to either R-ICE or R-DHAP.

It was expected that 40% of these patients will either not achieve Complete Response or Partial Response or drop-out before ASCT. Immediately prior to ASCT it was expected that there will be 240 patients (400 x 60%) available for second randomisation (1:1) into the maintenance or mabthera arms. First safety analysis on 100 patients (reviewed by DSMC on 14th November 2005) and first interim analysis on 200 patients (18th April 2007) showed that the drop-out rate is 50%. Then, in order to keep the planned power with 240 patients for the maintenance or mabthera arms, we increase the initial sample size from 400 to 480 (240 each)

Part II maintenance:
The primary endpoint of event free survival (EFS) was used to assess sample size. If we wish to detect after transplantation a change in the 2 year event-free of 15% in favor of the MabThera arm 65% versus no maintenance 50%, 240 patients transplanted, randomized 1:1 between the two treatment groups recruited over 3 years and followed for a minimum of two years, will provide 80% power at the overall 5% (2-sided) significance level to detect the expected difference.

2.3. Interim analysis

An interim analysis of the two parts, response rate and EFS efficacy parameter was planned after 200 patients, necessitating an adjustment of the nominal significance (α-level) for the final analysis to maintain the overall global significance level. The O’Brien-Fleming adjustment will be used to partition the α-level with α=0.003 at the first interim for response and α=0.05 at the final analysis. An interim analysis of the primary efficacy parameter was planned after the inclusion of 200 patients leading to 100 patients randomized to the maintenance treatment. It necessitates an adjustment of the nominal significance (α-level) for the final analysis to maintain the overall global significance level. The O’Brien-Fleming adjustment will be used to partition the α-level with α=8.10^-5 (40 events) at the first interim and α=0.05 at the final analysis. The expected number of events during the five years is 140 to 145.
3. STUDY PATIENTS

3.1. Disposition of patients

The whole set of 481 patients was first randomized from July 24, 2003 to June 30, 2008 (approximately five years of enrollment). 245 patients were then randomized in the 2nd part of the study from October 21, 2003 to October 21, 2008.

Nevertheless, CRFs for 4 patients could not be recovered.

Listing 3.1-1 Patients with CRF not recovered

<table>
<thead>
<tr>
<th>Arm of treatment=ARM A / R-ICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization Number</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>5003620201405</td>
</tr>
<tr>
<td>5003631201412</td>
</tr>
</tbody>
</table>

N = 3

<table>
<thead>
<tr>
<th>Arm of treatment=ARM B / R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization Number</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>5003613301404</td>
</tr>
</tbody>
</table>

N = 1

Thus, 477 patients, 243 from R-ICE arm and 234 from R-DHAP arm, are evaluable for induction part, and 242 patients, 122 from the rituximab arm and 120 from the observation arm, are evaluable for maintenance part of the study.

This report deals with analysis of the maintenance part of the study.

The following flowcharts describe the disposition of patients during the whole study.
Figure 3.1-1 Disposition of patients according to arm of 1st randomization

Randomized patients
N = 481

CRF not recovered
N = 4

Evaluable patients
N = 477

R-ICE
N = 243

No study treatment received
N = 4
(one death, 3 protocol violations)

R-DHAP
N = 234

No study treatment received
N = 4
(one death, one protocol violation, 2 patient voluntary withdrawals)

Received study treatment
N = 239

Received study treatment
N = 230

Withdrawn during induction
N = 34
(14 after C1, 19 after C2)
(24 for induction treatment failure, 4 for treatment toxicity, 5 for death, one other reason, one unknown)

Withdrawn during induction
N = 34
(14 after C1, 19 after C2)
(24 for induction treatment failure, 4 for treatment toxicity, 5 for death, one other reason)

Completed induction phase
N = 205
(one pt with only 2 cycles)

Completed induction phase
N = 196

Withdrawn during induction but after 3 cycles
N = 82
(74 for induction treatment failure, 1 protocol violation, 1 death, 1 voluntary withdrawal, 5 other reasons)

Withdrawn during induction but after 3 cycles
N = 64
(49 for induction treatment failure, 6 treatment toxicity, 2 voluntary withdrawal, 1 death, 6 other reason)

Received BEAM+ASCT
N = 123

Received BEAM+ASCT
N = 132

Withdrawn during consolidation
N = 7
(2 deaths, 5 other reasons)

Withdrawn during consolidation
N = 6
(one death, 5 other reasons)

Randomized in maintenance
N = 116
(60 rituximab, 56 observation)

Randomized in maintenance
N = 126
(62 rituximab, 64 observation)
Figure 3.1-2 Disposition of patients according to arm of 2nd randomization

Randomized in maintenance
- N = 245

Evaluable patients
- N = 242

Rituximab
- N = 122
  (60 with R-ICE, 62 with R-DHAP)

Observation
- N = 120
  (56 with R-ICE, 64 with R-DHAP)

No study treatment received
- N = 6
  (2 voluntary withdrawals, one lost to FU after ASCT, one missing withdrawal, 2 not treated with rituximab but maintenance visits)

Switched from rituximab arm
- N = 2

Received study treatment (i.e. at least one injection)
- N = 116

Completed maintenance phase (6 injections)
- N = 78

Received study treatment (i.e. at least one visit)
- N = 119

Completed maintenance phase (6 visits)
- N = 30

No maintenance visit
- N = 3
  (one transplantation failure, one voluntary withdrawal, one missing withdrawal)

CRF not recovered
- N = 3
3.2. Patients recruitment

8 patients (3%) did not respect at least one criterion of inclusion/non inclusion: 5 patients (4%) from rituximab arm and 3 patients (3%) from observation arm.

Table 3.2-1 Criteria exceptions (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>AT LEAST ONE CRITERIA EXCEPTION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>117</td>
<td>96</td>
<td>117</td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>122</td>
<td>100</td>
<td>120</td>
</tr>
</tbody>
</table>

The following tables details inclusion and non inclusion criteria.

**Inclusion criteria**
1- Patient with histologically proven, CD20+ diffuse large B cell lymphoma in 1st relapse after CR, less than PR or partial response to first line treatment
2- Aged from 18 to 65 years inclusive
3- Eligible for transplant
4- Previously treated with chemotherapy regimen containing anthracyclin with or without rituximab
5- ECOG performance status ≤ 2
6- With a minimum life expectancy of 3 months
7- Signed informed consent form prior to randomization

The following table presents the number and the percentage of patients respecting or not the inclusion criteria:

Table 3.2-2 Inclusion criteria (MITT)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>FULFILLED</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>Yes</td>
<td>%</td>
</tr>
<tr>
<td>Inclusion Criteria 1</td>
<td>1</td>
<td>0</td>
<td>241</td>
<td>100</td>
</tr>
<tr>
<td>Inclusion Criteria 2</td>
<td>0</td>
<td>0</td>
<td>242</td>
<td>100</td>
</tr>
<tr>
<td>Inclusion Criteria 3</td>
<td>0</td>
<td>0</td>
<td>242</td>
<td>100</td>
</tr>
<tr>
<td>Inclusion Criteria 4</td>
<td>0</td>
<td>0</td>
<td>242</td>
<td>100</td>
</tr>
<tr>
<td>Inclusion Criteria 5</td>
<td>0</td>
<td>0</td>
<td>242</td>
<td>100</td>
</tr>
<tr>
<td>Inclusion Criteria 6</td>
<td>0</td>
<td>0</td>
<td>242</td>
<td>100</td>
</tr>
<tr>
<td>Inclusion Criteria 7</td>
<td>0</td>
<td>0</td>
<td>242</td>
<td>100</td>
</tr>
</tbody>
</table>

**Exclusion criteria**
1- Burkitt, mantle cell, T-cell lymphoma
2- CD20-negative NHL
3- HIV or HBV disease
4- Central nervous system or meningeal involvement by lymphoma
5- Not previously treated with anthracycline containing regimens
6- Prior transplantation
7- Contraindication to any drug contained in the chemotherapy regimens
8- Any serious active disease or co-morbid medical condition (according to the investigator’s decision)
9- Poor renal function (creatinin level > 150 µmol/l), poor hepatic function (total bilirubin level > 30 mmol/l, transaminases > 2.5 maximum normal level) unless these abnormalities are related to the lymphoma
10- Poor bone marrow reserve as defined by neutrophils < 1.5 G/l or platelets < 100 G/l, unless related to bone marrow infiltration
11- Any history of cancer during the last 5 years, with the exception of non-melanoma skin tumors or stage 0 (in situ) cervical carcinoma
12- Treatment with any investigational drug within 30 days before planned first cycle of chemotherapy and during the study
13- Pregnant woman
14- Adult patient unable to give informed consent because of intellectual impairment

The following table presents the number and the percentage of patients respecting or not the non inclusion criteria:

<table>
<thead>
<tr>
<th>Table 3.2-3 Exclusion criteria (MITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FULFILLED</td>
</tr>
<tr>
<td><strong>FULFILLED</strong></td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td><strong>N</strong></td>
</tr>
<tr>
<td>CRITERIA</td>
</tr>
<tr>
<td>Exclusion Criteria 1</td>
</tr>
<tr>
<td>Exclusion Criteria 2</td>
</tr>
<tr>
<td>Exclusion Criteria 3</td>
</tr>
<tr>
<td>Exclusion Criteria 4</td>
</tr>
<tr>
<td>Exclusion Criteria 5</td>
</tr>
<tr>
<td>Exclusion Criteria 6</td>
</tr>
<tr>
<td>Exclusion Criteria 7</td>
</tr>
<tr>
<td>Exclusion Criteria 8</td>
</tr>
<tr>
<td>Exclusion Criteria 9</td>
</tr>
<tr>
<td>Exclusion Criteria 10</td>
</tr>
<tr>
<td>Exclusion Criteria 11</td>
</tr>
<tr>
<td>Exclusion Criteria 12</td>
</tr>
<tr>
<td>Exclusion Criteria 13</td>
</tr>
<tr>
<td>Exclusion Criteria 14</td>
</tr>
</tbody>
</table>

**Listing 3.2-1 Criteria not fulfilled (MITT)**

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Arm of 2nd randomization</th>
<th>Sex</th>
<th>Age (years)</th>
<th>CRITERIA</th>
<th>FULFILLED</th>
</tr>
</thead>
<tbody>
<tr>
<td>5003101031001</td>
<td>RITUXIMAB</td>
<td>MALE</td>
<td>65</td>
<td>Exclusion Criteria 11</td>
<td>No</td>
</tr>
<tr>
<td>5003101061617</td>
<td>RITUXIMAB</td>
<td>FEMALE</td>
<td>54</td>
<td>Exclusion Criteria 9</td>
<td>No</td>
</tr>
<tr>
<td>5003101171637</td>
<td>RITUXIMAB</td>
<td>FEMALE</td>
<td>63</td>
<td>Exclusion Criteria 3</td>
<td>Missing</td>
</tr>
<tr>
<td>5003604701002</td>
<td>RITUXIMAB</td>
<td>FEMALE</td>
<td>30</td>
<td>Exclusion Criteria 10</td>
<td>No</td>
</tr>
<tr>
<td>5003608301205</td>
<td>RITUXIMAB</td>
<td>FEMALE</td>
<td>59</td>
<td>Exclusion Criteria 9</td>
<td>No</td>
</tr>
<tr>
<td>5003638501023</td>
<td>RITUXIMAB</td>
<td>MALE</td>
<td>60</td>
<td>Exclusion Criteria 10</td>
<td>No</td>
</tr>
<tr>
<td>5003101071005</td>
<td>OBSERVATION</td>
<td>MALE</td>
<td>56</td>
<td>Inclusion Criteria 1</td>
<td>No</td>
</tr>
<tr>
<td>5003610201615</td>
<td>OBSERVATION</td>
<td>MALE</td>
<td>62</td>
<td>Exclusion Criteria 9</td>
<td>No</td>
</tr>
<tr>
<td>5003622501604</td>
<td>OBSERVATION</td>
<td>MALE</td>
<td>47</td>
<td>Exclusion Criteria 10</td>
<td>No</td>
</tr>
</tbody>
</table>

N = 9
3.3. Protocol deviations

3.3.1. Protocol violations

Protocol violations in course of the study were described in blind-review document.

3.3.2. Withdrawals

83 premature withdrawals (66%) were observed in maintenance ITT population during follow-up period: 43 patients (35%) in rituximab arm versus 40 patients (33%) in observation arm.

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB N</th>
<th>RITUXIMAB %</th>
<th>OBSERVATION N</th>
<th>OBSERVATION %</th>
<th>All N</th>
<th>All %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMATURE WITHDRAWAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79</td>
<td>65</td>
<td>80</td>
<td>67</td>
<td>159</td>
<td>66</td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td>35</td>
<td>40</td>
<td>33</td>
<td>83</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
<td>120</td>
<td>100</td>
<td>242</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for premature withdrawal</th>
<th>Arm of 2nd randomization</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
</tr>
<tr>
<td>Transplantation failure</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Treatment toxicity</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Patient voluntary withdrawal</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>40</td>
</tr>
</tbody>
</table>

The main reasons for premature withdrawal were other reason (64%), which includes progression during maintenance period, and transplantation failure (23%).

3 patients (7% of withdrawals) were withdrawn in rituximab arm due to treatment toxicity.

All patients that withdrew during maintenance period are listed in section §6.1.
4. EFFICACY EVALUATION

4.1. Eligible patients for analysis

Five populations of patients were identified:

- **Induction full analysis set** (following the intent-to-treat principle) refers to all randomized patients regardless they have received study treatment or not: 477 patients analyzed according the therapy they were randomized to receive (243 in R-ICE arm and 234 in R-DHAP arm).

- **Induction Intent-To-Treat (ITT) population** refers to patients receiving at least one injection of study treatment, regardless the quantity injected: 469 patients analyzed according the therapy they were randomized to receive (239 in R-ICE arm and 230 in R-DHAP arm).

- **Induction safety population** refers to patients receiving at least one injection of study treatment: 469 patients analyzed according the therapy they actually received (239 in R-ICE arm and 230 in R-DHAP arm).

- **Maintenance Intent-To-Treat (ITT) population** refers to all patients formally randomized in the 2nd part of the study: 242 patients analyzed according the therapy they were randomized to receive (122 in rituximab arm and 120 in observation arm).

- **Maintenance safety population** refers to all patients formally randomized in the 2nd part of the study and have received at least one dose of rituximab or have only been observed, and have at least one maintenance follow-up assessment: 235 patients analyzed according the therapy they actually received, i.e. patient will be included in rituximab arm if he/she had received at least one dose of rituximab during any maintenance visit otherwise, he/she will be included in observation arm (thus, 116 in rituximab arm and 119 in observation arm).

Since all patients received randomized induction treatment, induction ITT and safety populations are equivalent.

The following tables summarize the repartition of patients per population and lists present excluded patients.
<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Arm of treatment</th>
<th>Arm of 2nd randomization</th>
<th>Arm of treatment</th>
<th>Arm of 2nd randomization</th>
<th>Arm of treatment</th>
<th>Arm of 2nd randomization</th>
<th>Arm of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Induction full analysis population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60</td>
<td>13</td>
<td>56</td>
<td>12</td>
<td>127</td>
<td>27</td>
<td>243</td>
</tr>
<tr>
<td>Induction ITT population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60</td>
<td>13</td>
<td>56</td>
<td>12</td>
<td>123</td>
<td>26</td>
<td>239</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>Maintenance ITT population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60</td>
<td>25</td>
<td>56</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>116</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>127</td>
<td>54</td>
<td>127</td>
</tr>
<tr>
<td>TOTAL</td>
<td>60</td>
<td>13</td>
<td>56</td>
<td>12</td>
<td>127</td>
<td>27</td>
<td>243</td>
</tr>
</tbody>
</table>
### Table 4.1-2 Eligible patients for analysis per safety populations

<table>
<thead>
<tr>
<th>Arm of induction</th>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>NOT APPLICABLE</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction Safety population</td>
<td>Yes</td>
<td>59</td>
<td>13</td>
<td>56</td>
<td>12</td>
</tr>
<tr>
<td>Maintenance safety population</td>
<td>Yes</td>
<td>59</td>
<td>25</td>
<td>56</td>
<td>24</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>124</td>
</tr>
<tr>
<td>TOTAL</td>
<td>59</td>
<td>13</td>
<td>56</td>
<td>12</td>
<td>124</td>
</tr>
</tbody>
</table>

### Listing 4.1-1 Patients excluded from MITT/safety populations

<table>
<thead>
<tr>
<th>Randomization Number</th>
<th>Arm of treatment</th>
<th>First Randomization Date</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 30101041606</td>
<td>ARM A / R-ICE</td>
<td>03/12/2003</td>
<td>05/12/2003</td>
<td>BEFORE TREATMENT</td>
<td>MAJOR PROTOCOL VIOLATION</td>
<td></td>
</tr>
<tr>
<td>500 3010201627</td>
<td>ARM A / R-ICE</td>
<td>28/03/2007</td>
<td>03/04/2007</td>
<td>BEFORE TREATMENT</td>
<td>DEATH</td>
<td></td>
</tr>
<tr>
<td>500 30109010113</td>
<td>ARM A / R-ICE</td>
<td>14/03/2005</td>
<td>14/03/2005</td>
<td>BEFORE TREATMENT</td>
<td>OTHER</td>
<td>MEET NOT INCLUSION CRITERIAS</td>
</tr>
<tr>
<td>500 3014301614</td>
<td>ARM A / R-ICE</td>
<td>16/06/2005</td>
<td>17/06/2005</td>
<td>BEFORE TREATMENT</td>
<td>MAJOR PROTOCOL VIOLATION</td>
<td></td>
</tr>
<tr>
<td>500 30101017620</td>
<td>ARM B / R-DHAP</td>
<td>29/10/2004</td>
<td>29/10/2004</td>
<td>BEFORE TREATMENT</td>
<td>PATIENT VOLONTARY WITHDRAWAL</td>
<td></td>
</tr>
<tr>
<td>500 3016010104</td>
<td>ARM B / R-DHAP</td>
<td>02/11/2007</td>
<td>04/11/2007</td>
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<td>PATIENT VOLONTARY WITHDRAWAL</td>
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</tr>
<tr>
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<td>08/10/2004</td>
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<td>MAJOR PROTOCOL VIOLATION</td>
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</tr>
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<td>26/01/2006</td>
<td>26/01/2006</td>
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N = 8
### Listing 4.1-2 Patients excluded from maintenance safety population

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<tr>
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<th>Date of 2nd randomization</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
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<tbody>
<tr>
<td>5003601301015</td>
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<td>08/02/2008</td>
<td>18/03/2008</td>
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<td>5003604901602</td>
<td>RITUXIMAB</td>
<td>02/05/2005</td>
<td>28/06/2005</td>
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<td>OTHER</td>
<td>LOST TO FOLLOW-UP AFTER BMT</td>
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<tr>
<td>5003608301605</td>
<td>RITUXIMAB</td>
<td>25/08/2004</td>
<td>13/09/2004</td>
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<td>5003617201613</td>
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<tr>
<td>5003101601610</td>
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<td>11/08/2004</td>
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<td>TRANSPLANTATION FAILURE</td>
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<tr>
<td>5003102361203</td>
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<td>19/02/2004</td>
<td>13/03/2004</td>
<td>FOLLOW UP PERIOD</td>
<td>PATIENT VOLONTARY WITHDRAWAL</td>
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<td>OBSERVATION</td>
<td>14/06/2006</td>
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**N = 7**

### Listing 4.1-3 Patients with actual arm for maintenance treatment different from randomized

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<th>Actual arm of maintenance</th>
<th>Date of 2nd randomization</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
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<td>5003617201021</td>
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<td>OBSERVATION</td>
<td>14/02/2006</td>
<td>17/03/2006</td>
<td>FOLLOW UP PERIOD</td>
<td>OTHER</td>
<td>PATIENT STATUS : DUE TO HEP C INFECTION AFTER APERESIS AND BAD CONDITION WE DECIDED TO STOP RITUXIMAB THERAPY / EXAMINATION ABNORMAL DUE TO LYMPHOMA ; NO B-SYMPTOMS / LDH = 344 U/L (&lt; 250 U/L)</td>
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**N = 2**
4.2. Baseline data

4.2.1. Demography

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<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
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<td>242</td>
</tr>
<tr>
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<td>51.3</td>
<td>50.7</td>
<td>51.0</td>
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<tr>
<td>Std</td>
<td>10.02</td>
<td>11.66</td>
<td>10.85</td>
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<tr>
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<td>53.0</td>
<td>54.0</td>
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<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Max</td>
<td>65</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<td></td>
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</tr>
<tr>
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<tr>
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<td>80.8</td>
<td>78.7</td>
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<td>Height (cm)</td>
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<td>120</td>
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<td>173.0</td>
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<td>Body Area (m²)</td>
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<td>120</td>
<td>241</td>
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<td>Mean</td>
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<td>1.925</td>
<td>1.902</td>
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<td>Median</td>
<td>1.870</td>
<td>1.955</td>
<td>1.900</td>
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<tr>
<td>The median age at 1st randomization was 54 years old (range from 19 to 65).</td>
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<tr>
<th>Table 4.2-2 Age by category and sex ratio (MITT)</th>
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<th>All</th>
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<tbody>
<tr>
<td>Sex</td>
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<td>%</td>
<td>N</td>
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<td>MALE</td>
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<td>62</td>
<td>83</td>
</tr>
<tr>
<td>FEMALE</td>
<td>46</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Age (years)</td>
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</tr>
<tr>
<td>&lt;40 years</td>
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<tr>
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<td>105</td>
<td>86</td>
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### 4.2.2. Initial diagnosis

#### Table 4.2-3 Time between initial diagnosis and 1st randomization (MITT)

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<th>All</th>
</tr>
</thead>
<tbody>
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<td>241</td>
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<td>36.8</td>
<td>37.6</td>
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<td>1</td>
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<tr>
<td>Max</td>
<td>238</td>
<td>174</td>
<td>238</td>
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<tr>
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<td>118</td>
<td>239</td>
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<td>35.7</td>
<td>36.2</td>
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<td>20.7</td>
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<td>197</td>
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#### Table 4.2-4 Time between initial diagnosis and 1st randomization by category (MITT)

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<tr>
<td>Time from initial diagnostic biopsy to 1st randomization</td>
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<tr>
<td>&lt;12 months</td>
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<td>24</td>
<td>40</td>
</tr>
<tr>
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<td>92</td>
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</table>

<table>
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</tr>
</thead>
<tbody>
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<td>N</td>
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<td></td>
</tr>
<tr>
<td>Time from Initial Treatment to 1st randomization</td>
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<td></td>
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</tr>
<tr>
<td>&lt;12 months</td>
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<td>41</td>
</tr>
<tr>
<td>&gt;=12 months</td>
<td>89</td>
<td>73</td>
<td>76</td>
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#### Table 4.2-5 Characteristics at initial diagnosis (MITT)

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</thead>
<tbody>
<tr>
<td>N</td>
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<tr>
<td>Performance Status at initial diagnosis</td>
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<tr>
<td>0</td>
<td>66</td>
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<td>OBSERVATION</td>
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</tr>
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<td>--------------------------</td>
<td>-----------</td>
<td>-------------</td>
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</tr>
<tr>
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<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
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<td></td>
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Table 4.2-6 International Prognostic Index and individual factors at initial diagnosis (MITT)

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<td>100</td>
<td>108</td>
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<tr>
<td>Ann Arbor Stage at initial diagnosis</td>
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</tr>
<tr>
<td>I-II</td>
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### ARM OF 2ND RANDOMIZATION

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**Table 4.2-7 p-values of Chi-2 test for characteristics at initial diagnosis (MITT)**

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<th>Parameter</th>
<th>P-value (Chi-2)</th>
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<td>Ann Arbor Stage at diagnosis (I-II Vs III-IV)</td>
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</tr>
<tr>
<td>LDH at diagnosis (&lt;= 1 N Vs &gt; 1 N)</td>
<td>0.5237</td>
</tr>
<tr>
<td>Age adjusted IPI at diagnosis (0-1 Vs 2-3)</td>
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<tr>
<td>Extra nodal involvement at diagnosis (&lt;=1 Vs &gt;1)</td>
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</tr>
<tr>
<td>IPI at diagnosis (0-2 Vs 3-5)</td>
<td>0.0666</td>
</tr>
<tr>
<td>B Symptoms at diagnosis (No Vs Yes)</td>
<td>0.5128</td>
</tr>
</tbody>
</table>

**Table 4.2-8 Anatomopathological report at initial diagnosis - review (MITT)**

<table>
<thead>
<tr>
<th></th>
<th>RITUXIMAB</th>
<th></th>
<th>OBSERVATION</th>
<th></th>
<th>All</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Histology (review) at initial diagnosis</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B</td>
<td>33</td>
<td>46</td>
<td>29</td>
<td>45</td>
<td>62</td>
<td>45</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (centroblastique)</td>
<td>7</td>
<td>10</td>
<td>9</td>
<td>14</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire</td>
<td>8</td>
<td>11</td>
<td>5</td>
<td>8</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (immunoblastique)</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (B riche en T / histiocytes)</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B thymique</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Lymphome folliculaire grade 2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à “petites cellules” sans précision</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Final anatomo-pathological review was done for 137 patients (57%). Considering local diagnosis (only reported for non Gela patients) if review was not done, histology is available for 173 patients (71%).

Table 4.2-9 Anatomopathological report at initial diagnosis – review or if missing, local (MITT)
### 4.2.3. Initial treatment

Table 4.2-10 Time between initial treatment and 1st randomization (MITT)

<table>
<thead>
<tr>
<th>Time from initial treatment to 1st randomization (months)</th>
<th>Arm of 2nd randomization</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
</tr>
<tr>
<td>N</td>
<td>122</td>
<td>117</td>
</tr>
<tr>
<td>Mean</td>
<td>37.3</td>
<td>35.8</td>
</tr>
<tr>
<td>Std</td>
<td>40.92</td>
<td>41.31</td>
</tr>
<tr>
<td>Median</td>
<td>22.2</td>
<td>17.9</td>
</tr>
<tr>
<td>Min</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Max</td>
<td>238</td>
<td>173</td>
</tr>
</tbody>
</table>
Table 4.2-11 Characteristics of initial treatment (MITT)

<table>
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<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP - LIKE</td>
<td>102</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>ACVB - LIKE</td>
<td>19</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>OTHER</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>63</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>48</td>
<td>57</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCAL</td>
<td>34</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>OTHER</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>68</td>
<td>85</td>
</tr>
<tr>
<td>TOTAL</td>
<td>122</td>
<td>100</td>
<td>120</td>
</tr>
</tbody>
</table>

Overall 202 patients (83%) received CHOP-like chemotherapy as initial treatment and 125 patients (52%) received rituximab.

Details of other chemotherapy regimens and doses of radiotherapy are listed in section §6.2.

Table 4.2-12 Response at 1st line (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Response after first line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMPLETE RESPONSE</td>
<td>85</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>8</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>PARTIAL RESPONSE</td>
<td>19</td>
<td>16</td>
<td>21</td>
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<tr>
<td>STABLE DISEASE</td>
<td>6</td>
<td>5</td>
<td>5</td>
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<tr>
<td>PROGRESSIVE DISEASE</td>
<td>3</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>NOT EVALUATED</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>122</td>
<td>100</td>
<td>120</td>
</tr>
</tbody>
</table>

Table 4.2-13 p-value of Chi-2 test for response after 1st line (MITT)

<table>
<thead>
<tr>
<th>Variable/Treatment</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response after first line (CR/CRu vs others)</td>
<td>0.4187</td>
</tr>
</tbody>
</table>
### 4.2.4. Progression/relapse diagnosis

Table 4.2-14 Time intervals with progression/relapse diagnosis (MITT)

<table>
<thead>
<tr>
<th>Time intervals with progression/relapse diagnosis (MITT)</th>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from 1st treatment to relapse diagnostic biopsy (months)</td>
<td>N</td>
<td>96</td>
<td>94</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>43.5</td>
<td>41.3</td>
<td>42.4</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>43.24</td>
<td>43.56</td>
<td>43.30</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>28.6</td>
<td>22.9</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>237</td>
<td>172</td>
<td>237</td>
</tr>
<tr>
<td>Time from relapse diagnostic biopsy to 1st randomization (months)</td>
<td>N</td>
<td>96</td>
<td>97</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>0.8</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>0.72</td>
<td>0.43</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>0.6</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Min</td>
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<td>0</td>
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<tr>
<td></td>
<td>Max</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

The following tables present the number and percentage of patients for baseline clinical assessments:

Table 4.2-15 Characteristics at relapse (MITT)

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<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Status at relapse</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>0</td>
<td>72</td>
<td>59</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>38</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Ann Arbor stage at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAGE 1</td>
<td>20</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>STAGE 2</td>
<td>33</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>STAGE 3</td>
<td>22</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>STAGE 4</td>
<td>47</td>
<td>39</td>
<td>53</td>
</tr>
<tr>
<td>TOTAL</td>
<td>122</td>
<td>100</td>
<td>119</td>
</tr>
<tr>
<td>B symptoms at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>97</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>TOTAL</td>
<td>121</td>
<td>100</td>
<td>117</td>
</tr>
<tr>
<td>Total of extra-nodal sites at relapse</td>
<td>Arm of 2nd randomization</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>122</td>
<td>119</td>
<td>241</td>
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<tr>
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<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Std</td>
<td>1.37</td>
<td>1.12</td>
<td>1.25</td>
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<tr>
<td>Median</td>
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<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Min</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Max</td>
<td>6</td>
<td>5</td>
<td>6</td>
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</tbody>
</table>

The median number of extra nodal sites was 1 in both arms.
The details of nodal and extra-nodal involvement are listed in section §6.3.
Table 4.2-17 International Prognostic Index and individual factors at relapse (MITT)

<table>
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<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Performance Status at relapse</td>
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<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>118</td>
<td>97</td>
<td>111</td>
</tr>
<tr>
<td>&gt;=2</td>
<td>4</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>122</td>
<td>100</td>
<td>119</td>
</tr>
<tr>
<td>Ann Arbor stage at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>53</td>
<td>43</td>
<td>48</td>
</tr>
<tr>
<td>III-IV</td>
<td>69</td>
<td>57</td>
<td>71</td>
</tr>
<tr>
<td>TOTAL</td>
<td>122</td>
<td>100</td>
<td>119</td>
</tr>
<tr>
<td>LDH at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=Normal</td>
<td>66</td>
<td>55</td>
<td>67</td>
</tr>
<tr>
<td>&gt;Normal</td>
<td>54</td>
<td>45</td>
<td>51</td>
</tr>
<tr>
<td>TOTAL</td>
<td>120</td>
<td>100</td>
<td>118</td>
</tr>
<tr>
<td>Age-adjusted IPI at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
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<td>28</td>
<td>28</td>
</tr>
<tr>
<td>1</td>
<td>51</td>
<td>43</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
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<td>3</td>
</tr>
<tr>
<td>Subtotal 0-1</td>
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<td>70</td>
<td>81</td>
</tr>
<tr>
<td>Subtotal 2-3</td>
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<td>30</td>
<td>36</td>
</tr>
<tr>
<td>TOTAL</td>
<td>120</td>
<td>100</td>
<td>117</td>
</tr>
<tr>
<td>Nb of extra-nodal sites at relapse</td>
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</tr>
<tr>
<td>&lt;=1</td>
<td>92</td>
<td>75</td>
<td>89</td>
</tr>
<tr>
<td>&gt;1</td>
<td>30</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>TOTAL</td>
<td>122</td>
<td>100</td>
<td>119</td>
</tr>
<tr>
<td>IPI at relapse</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>32</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
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<td>20</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Subtotal 0-2</td>
<td>93</td>
<td>78</td>
<td>95</td>
</tr>
<tr>
<td>Subtotal 3-5</td>
<td>27</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>TOTAL</td>
<td>120</td>
<td>100</td>
<td>117</td>
</tr>
</tbody>
</table>
Table 4.2-18 p-values of Chi-2 test for individual factors of IPI at progression/relapse diagnosis (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance Status at relapse (&lt;2 Vs &gt;=2)</td>
<td>0.2191</td>
</tr>
<tr>
<td>Ann Arbor stage at relapse (I-II Vs III-IV)</td>
<td>0.6251</td>
</tr>
<tr>
<td>LDH at relapse (=&lt; 1 N Vs &gt; 1 N)</td>
<td>0.7822</td>
</tr>
<tr>
<td>Age adjusted IPI at relapse (0-1 Vs 2-3)</td>
<td>0.8976</td>
</tr>
<tr>
<td>Total of extra nodal site at relapse (&lt;=1 Vs &gt;1)</td>
<td>0.9114</td>
</tr>
<tr>
<td>B Symptoms at relapse (No Vs Yes)</td>
<td>0.8963</td>
</tr>
<tr>
<td>IPI at relapse (0-2 Vs 3-5)</td>
<td>0.4823</td>
</tr>
</tbody>
</table>

Table 4.2-19 Other characteristics at relapse (MITT)

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<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Beta 2 microglobulin (mg/l)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;3</td>
<td>76</td>
<td>88</td>
<td>78</td>
</tr>
<tr>
<td>&gt;=3</td>
<td>10</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>86</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>Albumin (G/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=35</td>
<td>15</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>&gt;35</td>
<td>97</td>
<td>87</td>
<td>96</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>100</td>
<td>110</td>
</tr>
</tbody>
</table>

Table 4.2-20 Bone marrow biopsy at relapse (MITT)

<table>
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<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Bone marrow Biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not involved</td>
<td>99</td>
<td>82</td>
<td>98</td>
</tr>
<tr>
<td>Involved</td>
<td>13</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Not Done</td>
<td>8</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>TOTAL</td>
<td>121</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>If BM involved, type of cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LARGE CELLS</td>
<td>7</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>SMALL CELLS</td>
<td>6</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>13</td>
<td>100</td>
<td>8</td>
</tr>
</tbody>
</table>

Overall, 21 patients (9%) presented an involved bone marrow biopsy at relapse, mainly with large cells (62%).
Table 4.2-21 PET scan at relapse (MITT)

|                        | Arm of 2nd randomization |               |               |               |               |               |
|------------------------|--------------------------|---------------|---------------|---------------|---------------|
|                        | RITUXIMAB                | OBSERVATION   | All           |               |               |
| PET Scan at relapse    | N            | %          | N            | %          | N            | %          |
| NEGATIVE               | 2        | 2          | 2        | 2          | 4        | 2          |
| POSITIVE               | 51       | 42         | 40       | 34         | 91       | 38         |
| NOT DONE               | 68       | 56         | 76       | 64         | 144      | 60         |
| Total                  | 121      | 100        | 118      | 100        | 239      | 100        |

PET scan at relapse is available for 95 patients (40%).

Table 4.2-22 Number of sites used for response evaluation at relapse diagnosis (MITT)

<table>
<thead>
<tr>
<th></th>
<th>Arm of 2nd randomization</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of sites used</td>
<td>N</td>
<td>122</td>
<td>120</td>
<td>242</td>
<td></td>
</tr>
<tr>
<td>for evaluation of</td>
<td>Mean</td>
<td>2.5</td>
<td>2.3</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>response per patient</td>
<td>Std</td>
<td>1.45</td>
<td>1.39</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td>307</td>
<td>271</td>
<td>578</td>
<td></td>
</tr>
</tbody>
</table>

The median number of sites used for response evaluation was 2 (range: 1 to 6). The lesions' codification is presented in section §6.3.
### Table 4.2-23 Anatomopathological report at relapse - review (MITT)

<table>
<thead>
<tr>
<th>Histology (review) at relapse</th>
<th>Arm of 2nd randomization</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm of 2nd randomization RITUXIMAB</td>
<td>OBSERVATION</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>73</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology (review) at relapse</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphome diffus à grandes cellules B</td>
<td>31</td>
<td>42</td>
<td>63</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (centroblastique)</td>
<td>14</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (immunoblastique)</td>
<td>5</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Lymphome B folliculaire grade 2</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 B</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 A</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (B riche en T / histiocytes)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hodgkin à prédominance lymphocytaire nodulaire (paragramulome nodulaire)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome B à &quot;petites cellules&quot; non classable pour raisons techniques</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>lymphome B agressif non classable</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphome folliculaire et diffus</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lymphome folliculaire non gradable</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zone grise entre Hodgkin / lymphoprolifération EBV</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Insuffisance de matériel</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Final anatomo-pathological review was done for 139 patients (57%).
Considering local diagnosis (only reported for non Gela patients) if review was not done, histology is available for 167 patients (69%).
<table>
<thead>
<tr>
<th>Table 4.2-24 Anatomopathological report at relapse – review or if missing, local (MITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arm of 2nd randomization</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Histology (review if available, otherwise local) at relapse</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (centroblastique)</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B thymique</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (immunoblastique)</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (B riche en T / histiocytes)</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 2</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale</td>
</tr>
<tr>
<td>Lymphome B non classable pour raisons techniques</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 B</td>
</tr>
<tr>
<td>Lymphome T angio-immunoblastique</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 3 A</td>
</tr>
<tr>
<td>Lymphome diffus à grandes cellules B (anaplasique)</td>
</tr>
<tr>
<td>Lymphome à grandes cellules B plasmoblastique</td>
</tr>
<tr>
<td>Insuffisance de matériel</td>
</tr>
<tr>
<td>Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)</td>
</tr>
<tr>
<td>Lymphome B à &quot;petites cellules&quot; non classable pour raisons techniques</td>
</tr>
<tr>
<td>lymphome B agressif non classable</td>
</tr>
<tr>
<td>Lymphome à grandes cellules non classable</td>
</tr>
<tr>
<td>Lymphome folliculaire grade 1</td>
</tr>
<tr>
<td>Lymphome folliculaire et diffus</td>
</tr>
<tr>
<td>Lymphome folliculaire non gradable</td>
</tr>
<tr>
<td>Zone grise entre Hodgkin / lymphoprolifération EBV</td>
</tr>
<tr>
<td>TOTAL</td>
</tr>
</tbody>
</table>
4.2.5. Medical history

168 patients (69%) presented with medical relevant history and 125 patients (52%) presented at least one persisting disease at baseline.

Table 4.2-25 Medical history (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Medical relevant history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83</td>
<td>68</td>
<td>85</td>
</tr>
<tr>
<td>No</td>
<td>39</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>At least one persisting disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>59</td>
<td>48</td>
<td>66</td>
</tr>
<tr>
<td>No</td>
<td>63</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
<td>120</td>
</tr>
</tbody>
</table>

4.2.6. Concomitant treatments

142 patients (59%) presented at least one concomitant treatment at inclusion and 41 patients (17%) presented at least one prescription due to lymphoma.

Table 4.2-26 Concomitant treatments (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Concomitant treatment at randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67</td>
<td>55</td>
<td>75</td>
</tr>
<tr>
<td>No</td>
<td>55</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>At least one due to symptoms related to lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>No</td>
<td>109</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
<td>120</td>
</tr>
</tbody>
</table>
### 4.3. Evaluation after induction treatment

#### Table 4.3-1 Bone marrow biopsy after induction (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Bone marrow biopsy after induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL negative</td>
<td>15</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>NHL positive</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Not Done</td>
<td>106</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>122</td>
<td>100</td>
<td>117</td>
</tr>
</tbody>
</table>

#### Table 4.3-2 PET scan after induction (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>PET scan after induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>36</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>15</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>NOT DONE</td>
<td>69</td>
<td>58</td>
<td>78</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>120</td>
<td>100</td>
<td>116</td>
</tr>
</tbody>
</table>

#### Table 4.3-3 Number of sites used for response evaluation after induction (MITT)

<table>
<thead>
<tr>
<th>Number of sites used for evaluation of response per patient</th>
<th>Arm of 2nd randomization</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
</tr>
<tr>
<td>N</td>
<td>122</td>
<td>118</td>
</tr>
<tr>
<td>Mean</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Std</td>
<td>1.45</td>
<td>1.44</td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Min</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Max</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Sum</td>
<td>307</td>
<td>270</td>
</tr>
</tbody>
</table>

The lesions’ codification is presented in section §6.4.
Table 4.3-4 Response after induction (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>COMPLETE RESPONSE</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>PARTIAL RESPONSE</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td>STABLE DISEASE</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
</tr>
</tbody>
</table>

7 patients (2 in rituximab arm and 5 in observation arm) were in stable disease after induction. One patient in observation arm had a missing response.

Table 4.3-5 Complete response rate after induction (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu)</th>
<th>CR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>122</td>
<td>73</td>
<td>59.8</td>
<td>50.6</td>
<td>68.6</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>120</td>
<td>69</td>
<td>57.5</td>
<td>48.1</td>
<td>66.5</td>
</tr>
</tbody>
</table>

Table 4.3-6 Difference between CR rates after induction (MITT)

<table>
<thead>
<tr>
<th>Difference between CR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab vs Observation</td>
<td>2.3</td>
<td>-10.1</td>
<td>14.7</td>
</tr>
</tbody>
</table>

Following tables describe details about mobilization:

Table 4.3-7 Collection failure (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>COLLECTION FAILURE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NO</td>
<td>119</td>
<td>98</td>
</tr>
<tr>
<td>YES</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4.3-8 Reason of collection failure (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>COLLECTION FAILURE - REASON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOT ENOUGH CELLS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OTHER CAUSE</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 4.3-9 Mobilization – Collected cells (MITT)

<table>
<thead>
<tr>
<th>Collection failure</th>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>N</td>
<td>119</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>6.217</td>
<td>17.421</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>4.0184</td>
<td>75.5999</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>5.240</td>
<td>5.220</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>1.36</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>28.54</td>
<td>629.00</td>
</tr>
<tr>
<td>Yes</td>
<td>N</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>6.250</td>
<td>7.313</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>4.4831</td>
<td>6.9400</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>6.250</td>
<td>5.100</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>3.08</td>
<td>1.75</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>9.42</td>
<td>15.09</td>
</tr>
<tr>
<td>All</td>
<td>N</td>
<td>121</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>6.217</td>
<td>17.162</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>4.0057</td>
<td>74.6387</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>5.240</td>
<td>5.220</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>1.36</td>
<td>1.75</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>28.54</td>
<td>629.00</td>
</tr>
</tbody>
</table>

Table 4.3-10 Mobilization – Number of collections (MITT)

<table>
<thead>
<tr>
<th>Collection failure</th>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>N</td>
<td>119</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>0.93</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>0.00</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
### Table 4.3-11 Mobilization – Source of stem cells (MITT)

<table>
<thead>
<tr>
<th>Source of Stem Cells</th>
<th>Arm of 2nd randomization</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Peripheral source</td>
<td>118</td>
<td>98</td>
<td>117</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral source + Bone marrow</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>100</td>
<td>118</td>
</tr>
</tbody>
</table>

### Table 4.3-12 Consolidation – Period of collection (MITT)

<table>
<thead>
<tr>
<th>Period of collections</th>
<th>Arm of 2nd randomization</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RITUXIMAB</td>
<td>OBSERVATION</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Before C1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C1-C2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>C2-C3</td>
<td>35</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>After C3</td>
<td>83</td>
<td>69</td>
<td>87</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
<td>100</td>
<td>117</td>
</tr>
</tbody>
</table>
Thus, results on overall response rate adjusted with successful mobilization are the following ones:

**Table 4.3-13 Overall Response Rate adjusted with successful mobilization (MITT)**

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>CR/CRu/PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>117</td>
<td>96</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
</tr>
</tbody>
</table>

15 patients underwent randomization in maintenance part without respect of response (at least PR) or successful mobilization criteria:
- 7 patients (2 in rituximab arm and 5 in observation arm) in stable disease but successful mobilization.
- One patient (in observation arm) with missing response but successful mobilization.
- 5 responder patients (2 in rituximab arm and 3 in observation arm) with no mobilization according to protocol rules but who have had a previous collection.
- One patient (in observation arm) who was reported with collection failure (only 1.75 10^6 CD34/KG) but underwent transplant.
- One patient (in rituximab arm) who, after failure of the first collection, received an additional treatment to undergo a second one (a 2nd collect was done on 20/05/2008 after 1 cycle of ifosfamide etoposide (4.19 10^6 cd34/kg) / transplantation done after 1 cycle of ifosfamide etoposide (25/05/08) / cells infused = 3.96: issue of 2nd collection because failure of 1st collection).

**Table 4.3-14 Mobilization Adjusted Response Rate (MITT)**

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Nb patients</th>
<th>Nb responders with successful mobilization</th>
<th>MARR (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>122</td>
<td>117</td>
<td>95.9</td>
<td>1.3</td>
<td>9.3</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>120</td>
<td>110</td>
<td>91.7</td>
<td>4.1</td>
<td>14.8</td>
</tr>
</tbody>
</table>

**Table 4.3-15 Mobilization Adjusted Response Rate (MITT)**

<table>
<thead>
<tr>
<th>Difference between MARR (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab vs Observation</td>
<td>4.2</td>
<td>-1.8</td>
<td>10.3</td>
</tr>
</tbody>
</table>
### Table 4.3-16 Consolidation – Time intervals with collection and transplantation (MITT)

<table>
<thead>
<tr>
<th>Time from C3 to 1st collection date (days)</th>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>121</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.9</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>89.40</td>
<td>61.19</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13.0</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>-966</td>
<td>-580</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>56</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Time from 1st collection date to 1st administration of BEAM (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>121</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.3</td>
<td>41.2</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>91.11</td>
<td>62.14</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>28.0</td>
<td>28.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>1017</td>
<td>625</td>
<td></td>
</tr>
<tr>
<td>Time from 1st collection date to transplantation (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>121</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>46.6</td>
<td>47.4</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>91.08</td>
<td>62.08</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>35.0</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>1023</td>
<td>631</td>
<td></td>
</tr>
<tr>
<td>Time from 1st administration of BEAM to transplantation (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>122</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.3</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>0.60</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6.0</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Time from transplantation to 2nd randomization date (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>122</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.2</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>17.38</td>
<td>16.10</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.5</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Min</td>
<td>-77</td>
<td>-84</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>68</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>
4.4. Follow-up

Stopping date was set to June 1, 2010 since last event occurred on this date. 92% of patients had a date of last contact after September 1, 2009.

Table 4.4-1 Stopping date (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Date of last contact earlier than 01/06/2010 (stopping date)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>68</td>
<td>56</td>
</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>44</td>
</tr>
<tr>
<td>Date of last contact earlier than 01/09/2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>114</td>
<td>93</td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
</tr>
</tbody>
</table>

The list of the 18 patients with a date of contact earlier than September 1, 2009 is presented in section §6.5.

Table 4.4-2 Follow-up duration (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>N</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (months) ALL 242 44 1 76</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (months) RITUXIMAB 122 43 1 76</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (months) OBSERVATION 120 44 1 74</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With date of last contact censored at stopping date, the median duration of follow-up for the MITT population (calculated from date of 2nd randomization) is 44 months overall (range from 1 to 76 months), 43 months in the rituximab arm and 44 months in the observation arm.
4.5. Efficacy results

4.5.1. Primary criterion

The aim of the 2nd part of the study was to evaluate the efficacy of rituximab given every eight weeks starting at day 28 after ASCT for a maximum of 6 doses in comparison to observation as measured by the event-free survival (EFS), events defined as death from any cause, relapse for complete responders and undocumented complete responders, progression during or after treatment, changes of therapy during allocated treatment.

140 events were required to conclude. Nevertheless, due to low rate of events since more than one year, analysis is performed with 111 events.

According to the definition of events, 55 patients in the rituximab arm and 56 patients in observation arm presented with an event (respectively 45% and 47%): 1 and 4 (respectively 1% and 3%) with a new treatment out of progression, 46 and 46 (respectively 38% and 38%) with progression/relapse, and 8 and 6 (respectively 7% and 5%) with death without progression.

![Table 4.5-1 Primary criterion – Events for survival analysis (MITT)](image)

Event-Free survival is measured from date of 2nd randomization to date of first event.
Figure 4.5-1 Primary criterion – Event-Free Survival (MITT)

Table 4.5-2 Primary criterion – Duration of Event-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>67.2</td>
<td>60.9</td>
<td>72.8</td>
<td>158</td>
</tr>
<tr>
<td>24</td>
<td>59.2</td>
<td>52.6</td>
<td>65.2</td>
<td>118</td>
</tr>
<tr>
<td>36</td>
<td>53.8</td>
<td>47.0</td>
<td>60.1</td>
<td>86</td>
</tr>
<tr>
<td>48</td>
<td>52.8</td>
<td>45.8</td>
<td>59.3</td>
<td>53</td>
</tr>
<tr>
<td>60</td>
<td>47.8</td>
<td>39.5</td>
<td>55.6</td>
<td>26</td>
</tr>
<tr>
<td>72</td>
<td>45.6</td>
<td>36.6</td>
<td>54.1</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 4.5-3 Primary criterion – Kaplan-Meier estimates for Event-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>67.2</td>
<td>60.9</td>
<td>72.8</td>
<td>158</td>
</tr>
<tr>
<td>24</td>
<td>59.2</td>
<td>52.6</td>
<td>65.2</td>
<td>118</td>
</tr>
<tr>
<td>36</td>
<td>53.8</td>
<td>47.0</td>
<td>60.1</td>
<td>86</td>
</tr>
<tr>
<td>48</td>
<td>52.8</td>
<td>45.8</td>
<td>59.3</td>
<td>53</td>
</tr>
<tr>
<td>60</td>
<td>47.8</td>
<td>39.5</td>
<td>55.6</td>
<td>26</td>
</tr>
<tr>
<td>72</td>
<td>45.6</td>
<td>36.6</td>
<td>54.1</td>
<td>6</td>
</tr>
</tbody>
</table>

No. of Subjects | Event | Censored | Median Survival (95% CL)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>242</td>
<td>46% (111)</td>
<td>54% (131)</td>
<td>57.59 (28.78 NA)</td>
</tr>
</tbody>
</table>
Figure 4.5-2 Primary criterion – Event-Free Survival according to treatment arm (MITT)

![Graph showing survival probability over time for different treatment arms.](image)

Logrank p=0.7435

Table 4.5-4 Primary criterion – Duration of Event-Free Survival according to treatment arm (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>122</td>
<td>58</td>
<td>25</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>120</td>
<td>58</td>
<td>26</td>
<td>-</td>
<td>1</td>
<td>74</td>
</tr>
</tbody>
</table>
Table 4.5-5 Primary criterion – Kaplan-Meier estimates for Event-Free Survival according to treatment arm (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>12</td>
<td>69.8</td>
<td>60.7</td>
<td>77.2</td>
<td>82</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>24</td>
<td>59.2</td>
<td>49.7</td>
<td>67.5</td>
<td>62</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>36</td>
<td>53.9</td>
<td>44.3</td>
<td>62.6</td>
<td>44</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>48</td>
<td>52.0</td>
<td>42.0</td>
<td>61.1</td>
<td>27</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>60</td>
<td>48.5</td>
<td>37.1</td>
<td>59.1</td>
<td>14</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>72</td>
<td>48.5</td>
<td>37.1</td>
<td>59.1</td>
<td>4</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>12</td>
<td>64.6</td>
<td>55.3</td>
<td>72.5</td>
<td>76</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>24</td>
<td>59.3</td>
<td>49.8</td>
<td>67.5</td>
<td>56</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>36</td>
<td>53.7</td>
<td>43.9</td>
<td>62.5</td>
<td>42</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>48</td>
<td>53.7</td>
<td>43.9</td>
<td>62.5</td>
<td>26</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>60</td>
<td>47.2</td>
<td>35.0</td>
<td>58.3</td>
<td>12</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>72</td>
<td>42.4</td>
<td>28.6</td>
<td>55.6</td>
<td>2</td>
</tr>
</tbody>
</table>

The 3-yr EFS is 54% in both arms.

Table 4.5-6 Primary criterion – Hazard ratio of rituximab arm for Event-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>0.7436</td>
<td>0.940</td>
<td>0.648 1.363</td>
</tr>
</tbody>
</table>

Table 4.5-7 Primary criterion – Stratified Analysis according to induction treatment and response to induction (CR/CRu vs others) - Hazard ratio of rituximab arm for Event-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>0.7373</td>
<td>0.938</td>
<td>0.643 1.367</td>
</tr>
</tbody>
</table>
4.5.2. Secondary criteria

4.5.2.1. Progression-Free Survival

Progression-Free survival is measured from date of 2\textsuperscript{nd} randomization to date of progression/relapse or death from any cause.

**Figure 4.5-3 Secondary criteria – Progression-Free Survival (MITT)**

![Graph showing progression-free survival over time with key metrics and data points.]

**Table 4.5-8 Secondary criteria – Duration of Progression-Free Survival (MITT)**

<table>
<thead>
<tr>
<th>PFS (months)</th>
<th>N</th>
<th>Median</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>58</td>
<td>32</td>
<td>-</td>
<td>47.0</td>
<td>1</td>
<td>76</td>
</tr>
</tbody>
</table>

**Table 4.5-9 Secondary criteria – Kaplan-Meier estimates for Progression-Free Survival (MITT)**

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>68.9</td>
<td>62.6</td>
<td>74.4</td>
<td>162</td>
</tr>
<tr>
<td>24</td>
<td>60.8</td>
<td>54.2</td>
<td>66.8</td>
<td>120</td>
</tr>
<tr>
<td>36</td>
<td>55.4</td>
<td>48.6</td>
<td>61.7</td>
<td>86</td>
</tr>
<tr>
<td>48</td>
<td>54.4</td>
<td>47.4</td>
<td>60.8</td>
<td>53</td>
</tr>
<tr>
<td>60</td>
<td>49.2</td>
<td>40.7</td>
<td>57.1</td>
<td>26</td>
</tr>
<tr>
<td>72</td>
<td>47.0</td>
<td>37.8</td>
<td>55.6</td>
<td>6</td>
</tr>
</tbody>
</table>
Figure 4.5-4 Secondary criteria – Progression-Free Survival according to treatment arm (MITT)

![Graph showing survival probability over time for RITUXIMAB and OBSERVATION arms, with Logrank p=0.8314]

Table 4.5-10 Secondary criteria – Duration of Progression-Free Survival according to treatment arm (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Time Point (months)</th>
<th>PFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>12</td>
<td>69.8</td>
<td>60.7</td>
<td>77.2</td>
<td>82</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>24</td>
<td>59.2</td>
<td>49.7</td>
<td>67.5</td>
<td>62</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>36</td>
<td>53.9</td>
<td>44.3</td>
<td>62.6</td>
<td>44</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>48</td>
<td>52.0</td>
<td>42.0</td>
<td>61.1</td>
<td>27</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>60</td>
<td>48.5</td>
<td>37.1</td>
<td>59.1</td>
<td>14</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>72</td>
<td>48.5</td>
<td>37.1</td>
<td>59.1</td>
<td>4</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>12</td>
<td>68.0</td>
<td>58.8</td>
<td>75.6</td>
<td>80</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>24</td>
<td>62.6</td>
<td>53.1</td>
<td>70.7</td>
<td>58</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>36</td>
<td>56.9</td>
<td>47.1</td>
<td>65.6</td>
<td>42</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>48</td>
<td>56.9</td>
<td>47.1</td>
<td>65.6</td>
<td>26</td>
</tr>
</tbody>
</table>
The 3-yr PFS is 54% in the rituximab arm vs 57% in the observation arm.

### Table 4.5-12 Secondary criteria – Hazard ratio of rituximab arm for Progression-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>0.8316</td>
<td>1.042</td>
<td>0.713 - 1.522</td>
</tr>
</tbody>
</table>

### Table 4.5-13 Secondary criteria – Stratified Analysis according to induction treatment and response to induction (CR/CRu vs others) - Hazard ratio of rituximab arm for Progression-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>0.8219</td>
<td>1.045</td>
<td>0.712 - 1.535</td>
</tr>
</tbody>
</table>

### 4.5.2.2. Overall Survival

Overall survival is measured from date of 2nd randomization to date of death from any cause.

![Overall Survival](image-url)
Table 4.5-14 Secondary criteria – Duration of Overall Survival (MITT)

<table>
<thead>
<tr>
<th>OS (months)</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>242</td>
<td></td>
<td>58</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 4.5-15 Secondary criteria – Kaplan-Meier estimates for Overall Survival (MITT)

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>84.4</td>
<td>79.2</td>
<td>88.5</td>
<td>199</td>
</tr>
<tr>
<td>24</td>
<td>73.7</td>
<td>67.5</td>
<td>78.9</td>
<td>145</td>
</tr>
<tr>
<td>36</td>
<td>67.7</td>
<td>61.0</td>
<td>73.5</td>
<td>104</td>
</tr>
<tr>
<td>48</td>
<td>63.1</td>
<td>55.9</td>
<td>69.5</td>
<td>63</td>
</tr>
<tr>
<td>60</td>
<td>54.8</td>
<td>45.4</td>
<td>63.3</td>
<td>30</td>
</tr>
<tr>
<td>72</td>
<td>51.9</td>
<td>41.3</td>
<td>61.5</td>
<td>6</td>
</tr>
</tbody>
</table>

Figure 4.5-6 Secondary criteria – Overall Survival according to treatment arm (MITT)

Table 4.5-16 Secondary criteria – Duration of Overall Survival according to treatment arm (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS (months)</td>
<td>RITUXIMAB</td>
<td>58</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>OS (months)</td>
<td>OBSERVATION</td>
<td>63</td>
<td>57</td>
<td>1</td>
<td>74</td>
</tr>
</tbody>
</table>
### Table 4.5-17 Secondary criteria – Kaplan-Meier estimates for Overall Survival according to treatment arm (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Time Point (months)</th>
<th>OS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>12</td>
<td>85.7</td>
<td>78.0</td>
<td>90.9</td>
<td>101</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>24</td>
<td>69.1</td>
<td>59.8</td>
<td>76.6</td>
<td>73</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>36</td>
<td>66.0</td>
<td>56.5</td>
<td>74.0</td>
<td>54</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>48</td>
<td>61.5</td>
<td>51.2</td>
<td>70.3</td>
<td>32</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>60</td>
<td>55.0</td>
<td>42.2</td>
<td>66.1</td>
<td>17</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>72</td>
<td>55.0</td>
<td>42.2</td>
<td>66.1</td>
<td>4</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>12</td>
<td>83.2</td>
<td>75.1</td>
<td>88.8</td>
<td>98</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>24</td>
<td>78.8</td>
<td>70.2</td>
<td>85.1</td>
<td>72</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>36</td>
<td>69.5</td>
<td>59.6</td>
<td>77.4</td>
<td>50</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>48</td>
<td>64.9</td>
<td>54.3</td>
<td>73.7</td>
<td>31</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>60</td>
<td>55.0</td>
<td>40.8</td>
<td>67.1</td>
<td>13</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>72</td>
<td>48.1</td>
<td>30.4</td>
<td>63.8</td>
<td>2</td>
</tr>
</tbody>
</table>

The 3-yr OS is 66% in the rituximab arm vs 69% in the observation arm.

### Table 4.5-18 Secondary criteria – Hazard ratio of rituximab arm for Overall Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>0.7550</td>
<td>1.071</td>
<td>0.698 1.643</td>
</tr>
</tbody>
</table>

### Table 4.5-19 Secondary criteria – Stratified Analysis according to induction treatment and response to induction (CR/CRu vs others) - Hazard ratio of rituximab arm for Progression-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>0.9110</td>
<td>1.025</td>
<td>0.664 1.583</td>
</tr>
</tbody>
</table>
4.5.2.3. Response at the end of maintenance

Considering response reported at follow-up M12 post transplant if patient was not withdrawn before, otherwise response at withdrawal, results are the following ones:

**Table 4.5-20 Secondary criteria – Response at the end of maintenance (MITT)**

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response at the end of maintenance (including deaths for not evaluated patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMPLETE RESPONSE</td>
<td>65</td>
<td>53</td>
<td>53</td>
<td>44</td>
</tr>
<tr>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>PARTIAL RESPONSE</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>STABLE DISEASE</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PROGRESSIVE DISEASE</td>
<td>31</td>
<td>25</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>DEATH</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>NOT EVALUATED</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>122</td>
<td>100</td>
<td>120</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 4.5-21 Overall response rate at the end of maintenance (MITT)**

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu/PR)</th>
<th>OR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>122</td>
<td>80</td>
<td>65.6</td>
<td>56.4</td>
<td>73.9</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>120</td>
<td>70</td>
<td>58.3</td>
<td>49.0</td>
<td>67.3</td>
</tr>
</tbody>
</table>

**Table 4.5-22 Difference between CR rates at the end of maintenance (MITT)**

<table>
<thead>
<tr>
<th>Difference between CR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab vs Observation</td>
<td>7.2</td>
<td>-5.0</td>
<td>19.4</td>
</tr>
</tbody>
</table>

**Table 4.5-23 Complete response rate at the end of maintenance (MITT)**

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu)</th>
<th>CR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>122</td>
<td>73</td>
<td>59.8</td>
<td>50.6</td>
<td>68.6</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>120</td>
<td>61</td>
<td>50.8</td>
<td>41.6</td>
<td>60.1</td>
</tr>
</tbody>
</table>

**Table 4.5-24 Difference between CR rates at the end of maintenance (MITT)**

<table>
<thead>
<tr>
<th>Difference between CR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab vs Observation</td>
<td>9.0</td>
<td>-3.5</td>
<td>21.5</td>
</tr>
</tbody>
</table>
Considering all deaths reported within one year after transplant (even if patient had a previous response), 17 deaths in rituximab arm and 19 deaths in observation arm were reported:

**Table 4.5-25 Secondary criteria – Response at the end of maintenance including all deaths during maintenance period (MITT)**

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Response at the end of maintenance (including deaths for all patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMPLETE RESPONSE</td>
<td>62</td>
<td>51</td>
</tr>
<tr>
<td>UNCONFIRMED COMPLETE RESPONSE</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>PARTIAL RESPONSE</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>STABLE DISEASE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PROGRESSIVE DISEASE</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>DEATH</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>NOT EVALUATED</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>122</td>
<td>100</td>
</tr>
</tbody>
</table>

The list of the 17 patients in rituximab arm and 19 patients in observation arm who died in maintenance period is shown in section §6.6.1.

**Table 4.5-26 Overall response rate at the end of maintenance, including all deaths during maintenance period (MITT)**

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu/PR)</th>
<th>OR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>122</td>
<td>76</td>
<td>62.3</td>
<td>53.1</td>
<td>70.9</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>120</td>
<td>70</td>
<td>58.3</td>
<td>49.0</td>
<td>67.3</td>
</tr>
</tbody>
</table>

**Table 4.5-27 Difference between CR rates at the end of maintenance, including all deaths during maintenance period (MITT)**

<table>
<thead>
<tr>
<th>Difference between OR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab vs Observation</td>
<td>4.0</td>
<td>-8.4</td>
<td>16.3</td>
</tr>
</tbody>
</table>

**Table 4.5-28 Complete response rate at the end of maintenance, including all deaths during maintenance period (MITT)**

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Nb patients</th>
<th>Nb responders (CR/CRu)</th>
<th>CR rate (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITUXIMAB</td>
<td>122</td>
<td>70</td>
<td>57.4</td>
<td>48.1</td>
<td>66.3</td>
</tr>
<tr>
<td>OBSERVATION</td>
<td>120</td>
<td>61</td>
<td>50.8</td>
<td>41.6</td>
<td>60.1</td>
</tr>
</tbody>
</table>

**Table 4.5-29 Difference between CR rates at the end of maintenance, including all deaths during maintenance period (MITT)**

<table>
<thead>
<tr>
<th>Difference between CR rates (%)</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab vs Observation</td>
<td>6.5</td>
<td>-6.0</td>
<td>19.1</td>
</tr>
</tbody>
</table>
4.5.3. Exploratory analyses

4.5.3.1. Subgroup analysis

4.5.3.1.1. By induction treatment

Figure 4.5-7 Exploratory analyses – Event-Free Survival according to treatment arm by induction treatment (MITT)

**Induction treatment=ARM A / R-ICE**

![Graph showing Event-Free Survival (EFS) for ARM A and R-ICE, with Logrank p=0.4978.]

- **Observation**
- **Rituximab**

**Induction treatment=ARM B / R-DHAP**

![Graph showing Event-Free Survival (EFS) for ARM B and R-DHAP, with Logrank p=0.7769.]

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>56</td>
<td>54%</td>
<td>46%</td>
<td>28.22 (9.99, NA)</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>60</td>
<td>47%</td>
<td>53%</td>
<td>31.67 (22.14, NA)</td>
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</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM B / R-DHAP</td>
<td>64</td>
<td>41%</td>
<td>59%</td>
<td>NA (31.61, NA)</td>
</tr>
<tr>
<td>RITUXIMAB</td>
<td>62</td>
<td>44%</td>
<td>56%</td>
<td>57.59 (15.87, NA)</td>
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### Table 4.5-30 Exploratory analyses – Duration of Event-Free Survival according to treatment arm by induction treatment (MITT)

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<th>Induction treatment</th>
<th>Arm of 2nd randomization</th>
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<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
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### Table 4.5-31 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to treatment arm by induction treatment (MITT)

<table>
<thead>
<tr>
<th>Induction treatment</th>
<th>Arm of 2nd randomization</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
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<td>ARM A / R-ICE</td>
<td>RITUXIMAB</td>
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<td>59.6</td>
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<td>44.3</td>
<td>69.8</td>
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### Table 4.5-32 Exploratory analyses – Hazard ratio of rituximab arm by induction treatment for Event-Free Survival (MITT)

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<th>Induction treatment</th>
<th>Parameter</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
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</thead>
<tbody>
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<td>rituximab</td>
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<td>0.805 0.480 1.348</td>
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<td>rituximab</td>
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<td>1.081 0.631 1.853</td>
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</table>
Figure 4.5-8 Exploratory analyses – Progression-Free Survival according to treatment arm by induction treatment (MITT)

Induction treatment=ARM A / R-ICE

<table>
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<tr>
<th></th>
<th>Observation</th>
<th>R-ICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>Event</td>
<td>52% (29)</td>
<td>47% (28)</td>
</tr>
<tr>
<td>Censored</td>
<td>48% (27)</td>
<td>53% (32)</td>
</tr>
<tr>
<td>Median Survival (95% CL)</td>
<td>31.44 (11.70, NA)</td>
<td>31.67 (22.14, NA)</td>
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</table>

Logrank p=0.5313

Induction treatment=ARM B / R-DHAP

<table>
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<tr>
<th></th>
<th>Observation</th>
<th>R-DHAP</th>
</tr>
</thead>
<tbody>
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<td>No. of Subjects</td>
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<td>62</td>
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<tr>
<td>Event</td>
<td>36% (23)</td>
<td>44% (27)</td>
</tr>
<tr>
<td>Censored</td>
<td>64% (41)</td>
<td>56% (35)</td>
</tr>
<tr>
<td>Median Survival (95% CL)</td>
<td>NA (56.97, NA)</td>
<td>57.59 (15.67, NA)</td>
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</table>

Logrank p=0.3974
### Table 4.5-33 Exploratory analyses – Duration of Progression-Free Survival according to treatment arm by induction treatment (MITT)

<table>
<thead>
<tr>
<th>Induction treatment</th>
<th>Arm of 2nd randomization</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>RITUXIMAB</td>
<td>60</td>
<td>32</td>
<td>22</td>
<td>-</td>
<td>1</td>
<td>73</td>
</tr>
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<td>ARM A / R-ICE</td>
<td>OBSERVATION</td>
<td>56</td>
<td>31</td>
<td>12</td>
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<td>1</td>
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<td>OBSERVATION</td>
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<td>-</td>
<td>57</td>
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<td>1</td>
<td>74</td>
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</table>

### Table 4.5-34 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to treatment arm by induction treatment (MITT)

<table>
<thead>
<tr>
<th>Induction treatment</th>
<th>Arm of 2nd randomization</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>RITUXIMAB</td>
<td>12</td>
<td>72.9</td>
<td>59.6</td>
<td>82.4</td>
<td>42</td>
</tr>
<tr>
<td>ARM A / R-ICE</td>
<td>RITUXIMAB</td>
<td>24</td>
<td>58.2</td>
<td>44.3</td>
<td>69.8</td>
<td>30</td>
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<tr>
<td>ARM A / R-ICE</td>
<td>RITUXIMAB</td>
<td>36</td>
<td>49.9</td>
<td>36.0</td>
<td>62.3</td>
<td>18</td>
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<td>ARM A / R-ICE</td>
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<td>49.9</td>
<td>36.0</td>
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<td>44.2</td>
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<td>40.9</td>
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### Table 4.5-35 Exploratory analyses – Hazard ratio of rituximab arm by induction treatment for Progression-Free Survival (MITT)

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<th>Induction treatment</th>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM A / R-ICE</td>
<td>rituximab</td>
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<td>0.847</td>
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<td>rituximab</td>
<td>0.3989</td>
<td>1.271</td>
<td>0.728 2.217</td>
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Figure 4.5-9 Exploratory analyses – Overall Survival according to treatment arm by induction treatment (MITT)

Induction treatment=ARM A / R-ICE

Induction treatment=ARM B / R-DHAP

Logrank p=0.3794

Logrank p=0.1849

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<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
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<td><strong>OBSERVATION</strong></td>
<td>56</td>
<td>45% (25)</td>
<td>55% (31) 58.22 (34.20 NA)</td>
</tr>
<tr>
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<td>60</td>
<td>37% (22)</td>
<td>63% (35) NA (39.20 NA)</td>
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</tbody>
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<table>
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<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
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<td>77% (49) NA (56.97 NA)</td>
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Table 4.5-36 Exploratory analyses – Duration of Overall Survival according to treatment arm by induction treatment (MITT)

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<th>Arm of 2nd randomization</th>
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<th>95% CI lower</th>
<th>95% CI Upper</th>
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<td>67</td>
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Table 4.5-37 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to treatment arm by induction treatment (MITT)

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<th>Induction treatment</th>
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<th>Survival (%)</th>
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<th>Patients at risk</th>
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Table 4.5-38 Exploratory analyses – Hazard ratio of rituximab arm by induction treatment for Overall Survival (MITT)

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<th>Induction treatment</th>
<th>Parameter</th>
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<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
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4.5.3.1.2. By response to induction

Figure 4.5-10 Exploratory analyses – Event-Free Survival according to treatment arm by response to induction (MITT)

Response to induction=CR/CRu

Response to induction=PR
Table 4.5-39 Exploratory analyses – Duration of Event-Free Survival according to treatment arm by response to induction (MITT)

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<th>Response to induction</th>
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<th>Median</th>
<th>95% CI lower</th>
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Table 4.5-40 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to treatment arm by response to induction (MITT)

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<tr>
<th>Response to induction</th>
<th>Arm of 2nd randomization</th>
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<th>Survival (%)</th>
<th>95% CI Lower</th>
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<th>Patients at risk</th>
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Table 4.5-41 Exploratory analyses – Hazard ratio of rituximab arm by response to induction for Event-Free Survival (MITT)

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<th>95% Hazard Ratio Confidence Limits</th>
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Figure 4.5-11 Exploratory analyses – Progression-Free Survival according to treatment arm by response to induction (MITT)

Response to induction=CR/CRu

Response to induction=PR
### Table 4.5-42 Exploratory analyses – Duration of Progression-Free Survival according to treatment arm by response to induction (MITT)

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### Table 4.5-43 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to treatment arm by response to induction (MITT)

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<th>Arm of 2nd randomization</th>
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<th>Survival (%)</th>
<th>95% CI Lower</th>
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<tr>
<td>PR</td>
<td>OBSERVATION</td>
<td>60</td>
<td>58.0</td>
<td>41.5</td>
<td>71.4</td>
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</tr>
<tr>
<td>PR</td>
<td>OBSERVATION</td>
<td>72</td>
<td>58.0</td>
<td>41.5</td>
<td>71.4</td>
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</tr>
</tbody>
</table>

### Table 4.5-44 Exploratory analyses – Hazard ratio of rituximab arm by response to induction for Progression-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Response to induction</th>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>rituximab</td>
<td>0.5453</td>
<td>0.853</td>
<td>0.509</td>
</tr>
<tr>
<td>PR</td>
<td>rituximab</td>
<td>0.2155</td>
<td>1.468</td>
<td>0.800</td>
</tr>
</tbody>
</table>
Figure 4.5-12 Exploratory analyses – Overall Survival according to treatment arm by response to induction (MITT)

Response to induction=CR/CRu

Logrank p=0.5199

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>69</td>
<td>73</td>
</tr>
<tr>
<td>Event</td>
<td>36% (25)</td>
<td>32% (23)</td>
</tr>
<tr>
<td>Censored</td>
<td>64% (44)</td>
<td>68% (50)</td>
</tr>
<tr>
<td>Median Survival (95% CL)</td>
<td>62.92 (53.72 NA)</td>
<td>NA (68.26 NA)</td>
</tr>
</tbody>
</table>

Response to induction=PR

Logrank p=0.2487

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>Event</td>
<td>31% (14)</td>
<td>43% (20)</td>
</tr>
<tr>
<td>Censored</td>
<td>69% (31)</td>
<td>57% (27)</td>
</tr>
<tr>
<td>Median Survival (95% CL)</td>
<td>NA (40.87 NA)</td>
<td>56.05 (23.56 NA)</td>
</tr>
</tbody>
</table>
Table 4.5-45 Exploratory analyses – Duration of Overall Survival according to treatment arm by response to induction (MITT)

<table>
<thead>
<tr>
<th>Response to induction</th>
<th>Arm of 2nd randomization</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
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<td>73</td>
<td>-</td>
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<tr>
<td>CR/CRu</td>
<td>OBSERVATION</td>
<td>69</td>
<td>63</td>
<td>54</td>
<td>-</td>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>RITUXIMAB</td>
<td>47</td>
<td>58</td>
<td>24</td>
<td>-</td>
<td>1</td>
<td>76</td>
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<tr>
<td>PR</td>
<td>OBSERVATION</td>
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<td>-</td>
<td>41</td>
<td>-</td>
<td>3</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 4.5-46 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to treatment arm by response to induction (MITT)

<table>
<thead>
<tr>
<th>Response to induction</th>
<th>Arm of 2nd randomization</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
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<tbody>
<tr>
<td>CR/CRu</td>
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<td>84.7</td>
<td>74.1</td>
<td>91.2</td>
<td>60</td>
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<tr>
<td>CR/CRu</td>
<td>RITUXIMAB</td>
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<td>62.9</td>
<td>83.2</td>
<td>48</td>
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<td>CR/CRu</td>
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<td>48</td>
<td>66.7</td>
<td>53.5</td>
<td>77.0</td>
<td>25</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>RITUXIMAB</td>
<td>60</td>
<td>61.2</td>
<td>44.5</td>
<td>74.2</td>
<td>11</td>
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<tr>
<td>CR/CRu</td>
<td>OBSERVATION</td>
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<td>85.2</td>
<td>74.3</td>
<td>91.8</td>
<td>57</td>
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<tr>
<td>CR/CRu</td>
<td>OBSERVATION</td>
<td>24</td>
<td>80.6</td>
<td>68.9</td>
<td>88.3</td>
<td>43</td>
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<td>CR/CRu</td>
<td>OBSERVATION</td>
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<td>69.0</td>
<td>55.4</td>
<td>79.1</td>
<td>31</td>
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<td>CR/CRu</td>
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<td>32.5</td>
<td>66.0</td>
<td>9</td>
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<td>OBSERVATION</td>
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<td>23.7</td>
<td>61.5</td>
<td>1</td>
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<td>45.4</td>
<td>24.5</td>
<td>64.3</td>
<td>3</td>
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<td>65.1</td>
<td>89.1</td>
<td>36</td>
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<tr>
<td>PR</td>
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<td>60.2</td>
<td>85.6</td>
<td>27</td>
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<tr>
<td>PR</td>
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<td>69.0</td>
<td>52.1</td>
<td>80.9</td>
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<td>OBSERVATION</td>
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<td>64.7</td>
<td>46.6</td>
<td>78.0</td>
<td>9</td>
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<td>OBSERVATION</td>
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<td>46.6</td>
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<td>46.6</td>
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</tbody>
</table>

Table 4.5-47 Exploratory analyses – Hazard ratio of rituximab arm by response to induction for Overall Survival (MITT)

<table>
<thead>
<tr>
<th>Response to induction</th>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>rituximab</td>
<td>0.5197</td>
<td>0.830</td>
<td>0.471 1.463</td>
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<tr>
<td>PR</td>
<td>rituximab</td>
<td>0.2518</td>
<td>1.493</td>
<td>0.752 2.962</td>
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</tbody>
</table>
4.5.3.2. Prognostic factors

4.5.3.2.1. According to response after induction

Only patients in CR, CRu or PR are taken into account.

**Figure 4.5-13 Exploratory analyses – Event-Free Survival according to response after induction (MITT)**

![Graph showing Event-Free Survival (EFS) probability over time for CR/CRu and PR responses.](image)

**Table 4.5-48 Exploratory analyses – Duration of Event-Free Survival according to response after induction (MITT)**

<table>
<thead>
<tr>
<th>Response after induction</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>142</td>
<td>62</td>
<td>48</td>
<td>-</td>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>92</td>
<td>31</td>
<td>15</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
</tbody>
</table>

**Table 4.5-49 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to response after induction (MITT)**

<table>
<thead>
<tr>
<th>Response after induction</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>12</td>
<td>72.8</td>
<td>64.6</td>
<td>79.4</td>
<td>100</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>24</td>
<td>64.5</td>
<td>55.9</td>
<td>71.9</td>
<td>74</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>36</td>
<td>60.0</td>
<td>51.1</td>
<td>67.8</td>
<td>60</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>48</td>
<td>58.5</td>
<td>49.4</td>
<td>66.6</td>
<td>40</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>60</td>
<td>53.1</td>
<td>41.9</td>
<td>63.0</td>
<td>18</td>
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</tbody>
</table>
### Table 4.5-50 Exploratory analyses – Hazard ratio of CR/CRu after induction for Event-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>0.0748</td>
<td>0.703</td>
<td>0.477 1.036</td>
</tr>
</tbody>
</table>

### Figure 4.5-14 Exploratory analyses – Progression-Free Survival according to response after induction (MITT)

![Graph showing progression-free survival (PFS) for response after induction]

Logrank p=0.2014

---

### Table 4.5-51 Exploratory analyses – Duration of Progression-Free Survival according to response after induction (MITT)

<table>
<thead>
<tr>
<th>Response after induction</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>142</td>
<td>62</td>
<td>48</td>
<td>-</td>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>92</td>
<td>58</td>
<td>23</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
</tbody>
</table>
### Table 4.5-52 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to response after induction (MITT)

<table>
<thead>
<tr>
<th>Response after induction</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>12</td>
<td>72.8</td>
<td>64.6</td>
<td>79.4</td>
<td>100</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>24</td>
<td>64.5</td>
<td>55.9</td>
<td>71.9</td>
<td>74</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>36</td>
<td>60.0</td>
<td>51.1</td>
<td>67.8</td>
<td>60</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>48</td>
<td>58.5</td>
<td>49.4</td>
<td>66.6</td>
<td>40</td>
</tr>
<tr>
<td>CR/CRu</td>
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<td>53.1</td>
<td>41.9</td>
<td>63.0</td>
<td>18</td>
</tr>
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<td>CR/CRu</td>
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<td>36.7</td>
<td>60.8</td>
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<tr>
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<td>64.5</td>
<td>53.7</td>
<td>73.4</td>
<td>58</td>
</tr>
<tr>
<td>PR</td>
<td>24</td>
<td>58.4</td>
<td>47.4</td>
<td>67.9</td>
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<td>PR</td>
<td>36</td>
<td>50.8</td>
<td>39.4</td>
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<td>26</td>
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<td>PR</td>
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<td>39.4</td>
<td>61.1</td>
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<tr>
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<td>45.7</td>
<td>31.8</td>
<td>58.6</td>
<td>8</td>
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<tr>
<td>PR</td>
<td>72</td>
<td>45.7</td>
<td>31.8</td>
<td>58.6</td>
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</table>

### Table 4.5-53 Exploratory analyses – Hazard ratio of CR/CRu after induction for Progression-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>0.2028</td>
<td>0.774</td>
<td>0.521</td>
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Figure 4.5-15 Exploratory analyses – Overall Survival according to response after induction (MITT)

Table 4.5-54 Exploratory analyses – Duration of Overall Survival according to response after induction (MITT)

<table>
<thead>
<tr>
<th>Response after induction</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>142</td>
<td>-</td>
<td>58</td>
<td>-</td>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>92</td>
<td>-</td>
<td>41</td>
<td>-</td>
<td>1</td>
<td>76</td>
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</tbody>
</table>

Table 4.5-55 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to response after induction (MITT)

<table>
<thead>
<tr>
<th>Response after induction</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>12</td>
<td>85.0</td>
<td>77.9</td>
<td>89.9</td>
<td>117</td>
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<td>CR/CRu</td>
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<td>77.5</td>
<td>69.5</td>
<td>83.6</td>
<td>91</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>36</td>
<td>71.3</td>
<td>62.7</td>
<td>78.3</td>
<td>73</td>
</tr>
<tr>
<td>CR/CRu</td>
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<td>65.7</td>
<td>56.3</td>
<td>73.5</td>
<td>46</td>
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<td>55.5</td>
<td>43.1</td>
<td>66.3</td>
<td>20</td>
</tr>
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<td>2</td>
</tr>
<tr>
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<td>73.9</td>
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<tr>
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Table 4.5-56: Exploratory analyses – Hazard ratio of CR/CRu after induction for Overall Survival (MITT)

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<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRu</td>
<td>0.3242</td>
<td>0.801</td>
<td>0.516 1.245</td>
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4.5.3.2.2. According to prior rituximab

Figure 4.5-16: Exploratory analyses – Event-Free Survival according to prior rituximab (MITT)

Table 4.5-57: Exploratory analyses – Duration of Event-Free Survival according to prior rituximab (MITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
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<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
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<td>-</td>
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<td>25</td>
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<td>-</td>
<td>1</td>
<td>74</td>
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</table>
### Table 4.5-58 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to prior rituximab (MITT)

<table>
<thead>
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<th>Prior treatment with Rituximab</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
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### Table 4.5-59 Exploratory analyses – Hazard ratio of no prior rituximab for Event-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.0089</td>
<td>0.602</td>
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**Figure 4.5-17 Exploratory analyses – Progression-Free Survival according to prior rituximab (MITT)**

![Survival Probability](image)

Logrank p=0.0331

**Table 4.5-60 Exploratory analyses – Duration of Progression-Free Survival according to prior rituximab (MITT)**

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
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<td>74</td>
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**Table 4.5-61 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to prior rituximab (MITT)**

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
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</thead>
<tbody>
<tr>
<td>No</td>
<td>12</td>
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<td>85.4</td>
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<td>50.3</td>
<td>40.9</td>
<td>59.0</td>
<td>17</td>
</tr>
</tbody>
</table>
Prior treatment with Rituximab | Time Point (years) | Survival (%) | 95% CI Lower | 95% CI Upper | Patients at risk
--- | --- | --- | --- | --- | ---
Yes | 60 | 50.3 | 40.9 | 59.0 | 8
Yes | 72 | 41.9 | 25.2 | 57.8 | 1

Table 4.5-62 Exploratory analyses – Hazard ratio of no prior rituximab for Progression-Free Survival (MITT)

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<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.0344</td>
<td>0.660</td>
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Figure 4.5-18 Exploratory analyses – Overall Survival according to prior rituximab (MITT)

Table 4.5-63 Exploratory analyses – Duration of Overall Survival according to prior rituximab (MITT)

<table>
<thead>
<tr>
<th>Prior treatment with Rituximab</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
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Table 4.5-64 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to prior rituximab (MITT)

<table>
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<tr>
<th>Prior treatment with Rituximab</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
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Table 4.5-65 Exploratory analyses – Hazard ratio of no prior rituximab for Overall Survival (MITT)

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<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior rituximab: No</td>
<td>0.0287</td>
<td>0.614</td>
<td>0.397 0.951</td>
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4.5.3.2.3. According to failure from diagnosis

Figure 4.5-19 Exploratory analyses – Event-Free Survival according to failure from diagnosis (MITT)

Table 4.5-66 Exploratory analyses – Duration of Event-Free Survival according to failure from diagnosis (MITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
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<td>76</td>
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Table 4.5-67 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to failure from diagnosis (MITT)

<table>
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<th>Failure from diagnosis</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
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<td>Failure from diagnosis</td>
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<td>Survival (%)</td>
<td>95% CI Lower</td>
<td>95% CI Upper</td>
<td>Patients at risk</td>
</tr>
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<td>52</td>
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<tr>
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<td>46.1</td>
<td>64.5</td>
<td>28</td>
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<tr>
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<td>49.3</td>
<td>37.1</td>
<td>60.4</td>
<td>13</td>
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<td>&gt;= 12 months</td>
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Table 4.5-68 Exploratory analyses – Hazard ratio of failure from diagnosis <12 months for Event-Free Survival (MITT)

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<tr>
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<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>0.0453</td>
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<td>1.008</td>
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</table>

Figure 4.5-20 Exploratory analyses – Progression-Free Survival according to failure from diagnosis (MITT)

<table>
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<th>Failure from diagnosis</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>105</td>
<td>58</td>
<td>12</td>
<td>-</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>137</td>
<td>58</td>
<td>32</td>
<td>-</td>
<td>1</td>
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Table 4.5-69 Exploratory analyses – Duration of Progression-Free Survival according to failure from diagnosis (MITT)
### Table 4.5-70 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to failure from diagnosis (MITT)

<table>
<thead>
<tr>
<th>Failure from diagnosis</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
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<td>12</td>
<td>59.2</td>
<td>49.0</td>
<td>68.0</td>
<td>60</td>
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<td>55.1</td>
<td>45.0</td>
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<tr>
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<td>51.3</td>
<td>41.0</td>
<td>60.7</td>
<td>34</td>
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<td>&lt; 12 months</td>
<td>48</td>
<td>51.3</td>
<td>41.0</td>
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<td>25</td>
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<td>47.9</td>
<td>36.3</td>
<td>58.6</td>
<td>13</td>
</tr>
<tr>
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<td>56.0</td>
<td>1</td>
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<tr>
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<td>72</td>
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<td>49.2</td>
<td>66.6</td>
<td>52</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>48</td>
<td>56.4</td>
<td>46.7</td>
<td>65.1</td>
<td>28</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
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<td>49.8</td>
<td>37.5</td>
<td>61.0</td>
<td>13</td>
</tr>
<tr>
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<td>61.0</td>
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### Table 4.5-71 Exploratory analyses – Hazard ratio of no failure from diagnosis <12 months for Progression-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>0.1041</td>
<td>1.370</td>
<td>0.937 2.003</td>
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Figure 4.5-21 Exploratory analyses – Overall Survival according to failure from diagnosis (MITT)

Table 4.5-72 Exploratory analyses – Duration of Overall Survival according to failure from diagnosis (MITT)

<table>
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<tr>
<th>Failure from diagnosis</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 months</td>
<td>105</td>
<td>63</td>
<td>41</td>
<td>-</td>
<td>1</td>
<td>74</td>
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<tr>
<td>&gt;= 12 months</td>
<td>137</td>
<td>-</td>
<td>57</td>
<td>-</td>
<td>1</td>
<td>76</td>
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</table>

Table 4.5-73 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to failure from diagnosis (MITT)

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<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
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</thead>
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<td>122</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>24</td>
<td>80.9</td>
<td>73.0</td>
<td>86.7</td>
<td>90</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>36</td>
<td>73.1</td>
<td>64.2</td>
<td>80.2</td>
<td>64</td>
</tr>
<tr>
<td>&gt;= 12 months</td>
<td>48</td>
<td>66.3</td>
<td>56.1</td>
<td>74.7</td>
<td>34</td>
</tr>
</tbody>
</table>
Table 4.5-74 Exploratory analyses – Hazard ratio of no failure from diagnosis < 12 months for Overall Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>0.0730</td>
<td>1.480</td>
<td>0.964 2.270</td>
</tr>
</tbody>
</table>

4.5.3.2.4. According to age-adjusted IPI (at relapse)

Figure 4.5-22 Exploratory analyses – Event-Free Survival according to age-adjusted IPI (MITT)

Table 4.5-75 Exploratory analyses – Duration of Event-Free Survival according to age-adjusted IPI (MITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>165</td>
<td>-</td>
<td>57</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>2-3</td>
<td>72</td>
<td>21</td>
<td>8</td>
<td>58</td>
<td>1</td>
<td>71</td>
</tr>
</tbody>
</table>
### Table 4.5-76 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to age-adjusted IPI (MITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>12</td>
<td>72.8</td>
<td>65.3</td>
<td>79.0</td>
<td>118</td>
</tr>
<tr>
<td>0-1</td>
<td>24</td>
<td>66.3</td>
<td>58.3</td>
<td>73.0</td>
<td>89</td>
</tr>
<tr>
<td>0-1</td>
<td>36</td>
<td>60.7</td>
<td>52.5</td>
<td>68.0</td>
<td>69</td>
</tr>
<tr>
<td>0-1</td>
<td>48</td>
<td>60.7</td>
<td>52.5</td>
<td>68.0</td>
<td>42</td>
</tr>
<tr>
<td>0-1</td>
<td>60</td>
<td>55.4</td>
<td>44.9</td>
<td>64.8</td>
<td>19</td>
</tr>
<tr>
<td>0-1</td>
<td>72</td>
<td>52.2</td>
<td>40.4</td>
<td>62.7</td>
<td>6</td>
</tr>
<tr>
<td>2-3</td>
<td>12</td>
<td>56.3</td>
<td>44.0</td>
<td>66.9</td>
<td>38</td>
</tr>
<tr>
<td>2-3</td>
<td>24</td>
<td>44.5</td>
<td>32.6</td>
<td>55.7</td>
<td>28</td>
</tr>
<tr>
<td>2-3</td>
<td>36</td>
<td>41.0</td>
<td>29.3</td>
<td>52.4</td>
<td>17</td>
</tr>
<tr>
<td>2-3</td>
<td>48</td>
<td>37.6</td>
<td>25.3</td>
<td>49.8</td>
<td>11</td>
</tr>
<tr>
<td>2-3</td>
<td>60</td>
<td>32.9</td>
<td>19.6</td>
<td>46.8</td>
<td>7</td>
</tr>
<tr>
<td>2-3</td>
<td>72</td>
<td>32.9</td>
<td>19.6</td>
<td>46.8</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 4.5-77 Exploratory analyses – Hazard ratio of no age-adjusted IPI for Event-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>0.0018</td>
<td>0.539</td>
<td>0.366 0.794</td>
</tr>
</tbody>
</table>
**Figure 4.5-23 Exploratory analyses – Progression-Free Survival according to age-adjusted IPI (MITT)**

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>165</td>
<td>-</td>
<td>58</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>2-3</td>
<td>72</td>
<td>21</td>
<td>8</td>
<td>58</td>
<td>1</td>
<td>71</td>
</tr>
</tbody>
</table>

**Table 4.5-78 Exploratory analyses – Duration of Progression-Free Survival according to age-adjusted IPI (MITT)**

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>12</td>
<td>75.3</td>
<td>67.9</td>
<td>81.2</td>
<td>122</td>
</tr>
<tr>
<td>0-1</td>
<td>24</td>
<td>68.7</td>
<td>60.9</td>
<td>75.3</td>
<td>91</td>
</tr>
<tr>
<td>0-1</td>
<td>36</td>
<td>63.1</td>
<td>54.8</td>
<td>70.3</td>
<td>69</td>
</tr>
<tr>
<td>0-1</td>
<td>48</td>
<td>63.1</td>
<td>54.8</td>
<td>70.3</td>
<td>42</td>
</tr>
<tr>
<td>0-1</td>
<td>60</td>
<td>57.6</td>
<td>46.8</td>
<td>67.0</td>
<td>19</td>
</tr>
<tr>
<td>0-1</td>
<td>72</td>
<td>54.2</td>
<td>42.1</td>
<td>64.9</td>
<td>6</td>
</tr>
<tr>
<td>2-3</td>
<td>12</td>
<td>56.3</td>
<td>44.0</td>
<td>66.9</td>
<td>38</td>
</tr>
<tr>
<td>2-3</td>
<td>24</td>
<td>44.5</td>
<td>32.6</td>
<td>55.7</td>
<td>28</td>
</tr>
<tr>
<td>2-3</td>
<td>36</td>
<td>41.0</td>
<td>29.3</td>
<td>52.4</td>
<td>17</td>
</tr>
<tr>
<td>2-3</td>
<td>48</td>
<td>37.6</td>
<td>25.3</td>
<td>49.8</td>
<td>11</td>
</tr>
</tbody>
</table>
### Table 4.5-80 Exploratory analyses – Hazard ratio of no age-adjusted IPI for Progression-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>0.0004</td>
<td>0.493</td>
<td>0.333 0.730</td>
</tr>
</tbody>
</table>

### Figure 4.5-24 Exploratory analyses – Overall Survival according to age-adjusted IPI (MITT)

![Graph showing overall survival probability over time for different age-adjusted IPI categories.](image)

Logrank p<0.0001

<table>
<thead>
<tr>
<th>OS (months)</th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>165</td>
<td>27% (44)</td>
<td>73% (121)</td>
<td>NA (62.92 NA)</td>
</tr>
<tr>
<td>Age adjusted IPI 2-3</td>
<td>72</td>
<td>51% (37)</td>
<td>49% (35)</td>
<td>39.20 (20.67 NA)</td>
</tr>
</tbody>
</table>

### Table 4.5-81 Exploratory analyses – Duration of Overall Survival according to age-adjusted IPI (MITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>165</td>
<td>-</td>
<td>63</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>2-3</td>
<td>72</td>
<td>39</td>
<td>21</td>
<td>-</td>
<td>2</td>
<td>71</td>
</tr>
</tbody>
</table>
Table 4.5-82 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to age-adjusted IPI (MITT)

<table>
<thead>
<tr>
<th>Age-adjusted IPI</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>12</td>
<td>90.1</td>
<td>84.4</td>
<td>93.8</td>
<td>146</td>
</tr>
<tr>
<td>0-1</td>
<td>24</td>
<td>80.8</td>
<td>73.6</td>
<td>86.2</td>
<td>106</td>
</tr>
<tr>
<td>0-1</td>
<td>36</td>
<td>76.0</td>
<td>68.2</td>
<td>82.1</td>
<td>83</td>
</tr>
<tr>
<td>0-1</td>
<td>48</td>
<td>72.0</td>
<td>63.5</td>
<td>78.8</td>
<td>50</td>
</tr>
<tr>
<td>0-1</td>
<td>60</td>
<td>63.8</td>
<td>51.8</td>
<td>73.6</td>
<td>22</td>
</tr>
<tr>
<td>0-1</td>
<td>72</td>
<td>59.9</td>
<td>45.9</td>
<td>71.3</td>
<td>6</td>
</tr>
<tr>
<td>2-3</td>
<td>12</td>
<td>71.7</td>
<td>59.7</td>
<td>80.7</td>
<td>49</td>
</tr>
<tr>
<td>2-3</td>
<td>24</td>
<td>58.4</td>
<td>46.0</td>
<td>69.0</td>
<td>37</td>
</tr>
<tr>
<td>2-3</td>
<td>36</td>
<td>51.2</td>
<td>38.6</td>
<td>62.5</td>
<td>21</td>
</tr>
<tr>
<td>2-3</td>
<td>48</td>
<td>45.1</td>
<td>31.4</td>
<td>57.8</td>
<td>13</td>
</tr>
<tr>
<td>2-3</td>
<td>60</td>
<td>36.4</td>
<td>21.6</td>
<td>51.4</td>
<td>8</td>
</tr>
<tr>
<td>2-3</td>
<td>72</td>
<td>36.4</td>
<td>21.6</td>
<td>51.4</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4.5-83 Exploratory analyses – Hazard ratio of no age-adjusted IPI for Overall Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age adjusted IPI 0-1</td>
<td>&lt;.0001</td>
<td>0.413</td>
<td>0.266 0.640</td>
</tr>
</tbody>
</table>

4.5.3.3. Multivariate Cox models

Table 4.5-84 Exploratory analyses – Multivariate Cox model for Event-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment with Rituximab: No</td>
<td>0.1979</td>
<td>0.748</td>
<td>0.481 1.164</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>0.4658</td>
<td>1.179</td>
<td>0.757 1.836</td>
</tr>
<tr>
<td>Age-adjusted IPI 2-3</td>
<td>0.0030</td>
<td>1.846</td>
<td>1.231 2.769</td>
</tr>
<tr>
<td>Response after complete induction: PR</td>
<td>0.2050</td>
<td>1.295</td>
<td>0.868 1.933</td>
</tr>
<tr>
<td>Arm of treatment: ARM A / R-ICE</td>
<td>0.0853</td>
<td>1.417</td>
<td>0.953 2.106</td>
</tr>
<tr>
<td>Arm of 2nd randomization: RITUXIMAB</td>
<td>0.9208</td>
<td>1.020</td>
<td>0.685 1.520</td>
</tr>
</tbody>
</table>

Table 4.5-85 Exploratory analyses – Multivariate Cox model for Progression-Free Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment with Rituximab: No</td>
<td>0.3509</td>
<td>0.808</td>
<td>0.516 1.265</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>0.4536</td>
<td>1.188</td>
<td>0.757 1.863</td>
</tr>
<tr>
<td>Age-adjusted IPI 2-3</td>
<td>0.0007</td>
<td>2.028</td>
<td>1.348 3.052</td>
</tr>
<tr>
<td>Response after complete induction: PR</td>
<td>0.4286</td>
<td>1.180</td>
<td>0.784 1.776</td>
</tr>
<tr>
<td>Arm of treatment: ARM A / R-ICE</td>
<td>0.0676</td>
<td>1.457</td>
<td>0.973 2.181</td>
</tr>
<tr>
<td>Arm of 2nd randomization: RITUXIMAB</td>
<td>0.6104</td>
<td>1.111</td>
<td>0.741 1.666</td>
</tr>
</tbody>
</table>
Table 4.5-86 Exploratory analyses – Multivariate Cox model for Overall Survival (MITT)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment with Rituximab: No</td>
<td>0.2874</td>
<td>0.760</td>
<td>0.459 1.260</td>
</tr>
<tr>
<td>Failure from diagnosis &lt; 12 months</td>
<td>0.5665</td>
<td>1.159</td>
<td>0.700 1.917</td>
</tr>
<tr>
<td>Age-adjusted IPI 2-3</td>
<td>0.0004</td>
<td>2.252</td>
<td>1.433 3.539</td>
</tr>
<tr>
<td>Response after complete induction: PR</td>
<td>0.4638</td>
<td>1.186</td>
<td>0.752 1.871</td>
</tr>
<tr>
<td>Arm of treatment: ARM A / R-ICE</td>
<td>0.0716</td>
<td>1.511</td>
<td>0.964 2.368</td>
</tr>
<tr>
<td>Arm of 2nd randomization: RITUXIMAB</td>
<td>0.4822</td>
<td>1.175</td>
<td>0.749 1.842</td>
</tr>
</tbody>
</table>

4.5.4. Non study or new treatment out of progression

One patient (1%) in rituximab arm and 4 patients (3%) in observation arm presented a new treatment out of progression (corresponding to the 5 events due to change of therapy for Event-Free survival).

Table 4.5-87 Patients with non study or new treatment out of progression (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>New treatment out of progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>121</td>
<td>99</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4.5-88 Type of non study or new treatment out of progression (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
<th>NOT APPLICABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
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<td>100</td>
<td>4</td>
</tr>
<tr>
<td>Transplantation</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>Other treatment</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>100</td>
<td>4</td>
</tr>
</tbody>
</table>

Details of treatment are listed in section §6.6.2.
### 4.5.5. Progression/relapse

47 patients (39%) in rituximab arm and 46 patients (38%) in observation arm presented a first progression/relapse.

#### Table 4.5-89 Patients with progression/relapse (MITT)

<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Progression/relapse n°1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td>No</td>
<td>75</td>
<td>61</td>
</tr>
<tr>
<td><strong>Progression/relapse n°2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>9</td>
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<tr>
<td>No</td>
<td>111</td>
<td>91</td>
</tr>
<tr>
<td><strong>Progression/relapse n°3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
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#### Table 4.5-90 Progression/relapse n°1 – Period (MITT)

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Table 4.5-91 Progression/relapse n°1 – Involvement (MITT)

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Details of extra-nodal involvement are listed in section §6.6.3.

Table 4.5-92 Progression/relapse n°1 – Individual factors of IPI (MITT)

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Table 4.5-94 Progression/relapse n°1 – Type of progression/relapse treatment (MITT)

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<td>N</td>
<td>%</td>
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Details of treatment are listed in section §6.6.3.
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5. SAFETY EVALUATION

5.1. Extent of exposure to trial medication

The number of maintenance visits received by each patient is summarized in the following table; in this summary, patients in the rituximab arm were considered to have received a cycle if they were given a dose of rituximab.

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78 patients (67%) in the rituximab arm received the complete maintenance treatment (6 cycles). 30 patients (25%) in the observation arm had 6 visits during maintenance period. Nevertheless, considering last maintenance visit, 48 patients (40%) had the 6th visit (M11 post transplant):

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### Table 5.1-4 Maintenance - Percentage of planned dose received by cycle for rituximab (MSAP)

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<td>N</td>
<td>91</td>
</tr>
<tr>
<td>Mean</td>
<td>98.8</td>
</tr>
<tr>
<td>Std</td>
<td>4.27</td>
</tr>
<tr>
<td>Median</td>
<td>99.8</td>
</tr>
<tr>
<td>Min</td>
<td>85</td>
</tr>
<tr>
<td>Max</td>
<td>107</td>
</tr>
<tr>
<td>Cycle 4</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>89</td>
</tr>
<tr>
<td>Mean</td>
<td>98.7</td>
</tr>
<tr>
<td>Std</td>
<td>4.36</td>
</tr>
<tr>
<td>Median</td>
<td>99.9</td>
</tr>
<tr>
<td>Min</td>
<td>85</td>
</tr>
<tr>
<td>Max</td>
<td>107</td>
</tr>
<tr>
<td>Cycle 5</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>80</td>
</tr>
<tr>
<td>Mean</td>
<td>98.6</td>
</tr>
<tr>
<td>Std</td>
<td>4.44</td>
</tr>
<tr>
<td>Median</td>
<td>99.6</td>
</tr>
<tr>
<td>Min</td>
<td>85</td>
</tr>
<tr>
<td>Max</td>
<td>107</td>
</tr>
<tr>
<td>Cycle 6</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>78</td>
</tr>
<tr>
<td>Mean</td>
<td>98.7</td>
</tr>
<tr>
<td>Std</td>
<td>4.50</td>
</tr>
<tr>
<td>Median</td>
<td>99.7</td>
</tr>
<tr>
<td>Min</td>
<td>85</td>
</tr>
<tr>
<td>Max</td>
<td>107</td>
</tr>
</tbody>
</table>

Same results are described in terms of frequency in section §6.7.1.
5.2. Adverse events

All adverse events occurring were graded with CTCAE v3.0.

5.2.1. Overview of toxicity profile

The following tables describe the toxicity profile of consolidation (BEAM+ASCT).

<table>
<thead>
<tr>
<th>Grade Infection</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Infection</td>
<td>All Tox.</td>
<td>Grade</td>
</tr>
<tr>
<td>N</td>
<td>91</td>
<td>25</td>
</tr>
<tr>
<td>%</td>
<td>78</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade Neurologic</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Neurologic</td>
<td>All Tox.</td>
<td>Grade</td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>113</td>
</tr>
<tr>
<td>%</td>
<td>3</td>
<td>97</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade Muscositis</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Muscositis</td>
<td>All Tox.</td>
<td>Grade</td>
</tr>
<tr>
<td>N</td>
<td>80</td>
<td>36</td>
</tr>
<tr>
<td>%</td>
<td>69</td>
<td>31</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade Hepatic</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Hepatic</td>
<td>All Tox.</td>
<td>Grade</td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>98</td>
</tr>
<tr>
<td>%</td>
<td>16</td>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade Gastrointestinal</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Gastrointestinal</td>
<td>All Tox.</td>
<td>Grade</td>
</tr>
<tr>
<td>N</td>
<td>69</td>
<td>47</td>
</tr>
<tr>
<td>%</td>
<td>59</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade Renal</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Renal</td>
<td>All Tox.</td>
<td>Grade</td>
</tr>
<tr>
<td>N</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td>%</td>
<td>14</td>
<td>86</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade Cardiovascular</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Cardiovascular</td>
<td>All Tox.</td>
<td>Grade</td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>98</td>
</tr>
<tr>
<td>%</td>
<td>16</td>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other toxicity</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other toxicity</td>
<td>All Tox.</td>
<td>Grade</td>
</tr>
<tr>
<td>N</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>%</td>
<td>29</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 5.2-2 Patients with RBC and platelets transfusions during consolidation (MSAP)

<table>
<thead>
<tr>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>At least one RBC transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Yes</td>
<td>96</td>
<td>83</td>
</tr>
<tr>
<td>At least one platelets transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Yes</td>
<td>113</td>
<td>97</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 5.2-3 Time intervals for hematological recovery after transplant (MSAP)

<table>
<thead>
<tr>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>Neutrophils &gt; 1 Giga/l (days after transplant)</td>
<td></td>
<td>113</td>
</tr>
<tr>
<td>Neutrophils &gt; 0.5 Giga/l (days after transplant)</td>
<td></td>
<td>114</td>
</tr>
<tr>
<td>Platelets &gt; 20 Giga/l (days after transplant)</td>
<td></td>
<td>114</td>
</tr>
</tbody>
</table>
The toxicity profile during the maintenance phase (starting one month after transplant) is summarized by the worst grade reported per patient in the following tables:

### Table 5.2-4 Incidence of toxicities by worst grade per patient during maintenance phase (MSAP)

<table>
<thead>
<tr>
<th>Grade of toxicity</th>
<th>RITUXIMAB</th>
<th>Actual arm of maintenance</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Tox.</td>
<td>Grade</td>
<td>All Tox.</td>
</tr>
<tr>
<td></td>
<td>0  1  2  3 4 5 &gt;=3 NE</td>
<td>Total</td>
<td>0  1  2  3 4 &gt;=3 NE</td>
</tr>
<tr>
<td>Grade allergy</td>
<td>N 109 0 0 1 0 0 6 116</td>
<td>1 95 0 0 1 0 1 23</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 1 94 0 0 1 0 5 100</td>
<td>1 80 0 0 1 0 1 19</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade auditory</td>
<td>N 102 2 4 2 0 0 2 6 116</td>
<td>0 96 0 0 0 0 0 23</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 7 88 2 3 2 0 2 5 100</td>
<td>0 81 0 0 0 0 0 19</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade blood</td>
<td>N 79 18 13 25 0 48 6 116</td>
<td>56 41 14 16 9 17 26</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 68 27 16 11 22 0 41 5 100</td>
<td>47 34 12 13 8 14 22</td>
<td>N 100</td>
</tr>
<tr>
<td>Grade cardiovascular</td>
<td>N 105 3 2 0 0 0 6 116</td>
<td>5 92 1 3 0 1 1 22</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 4 91 3 2 0 0 0 5 100</td>
<td>4 77 1 3 0 1 1 18</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade coagulation</td>
<td>N 103 3 0 3 0 0 3 7 116</td>
<td>1 94 1 0 0 0 0 24</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 5 89 3 0 3 0 3 6 100</td>
<td>1 79 1 0 0 0 0 20</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade skin</td>
<td>N 89 6 0 0 0 0 0 5 116</td>
<td>20 77 12 6 2 0 2 22</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 18 77 13 5 0 0 0 5 100</td>
<td>17 65 10 5 2 0 2 18</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade gastrointestinal</td>
<td>N 77 22 11 0 0 0 0 6 116</td>
<td>31 66 15 12 2 2 4</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 28 66 19 9 0 0 0 5 100</td>
<td>26 55 13 10 2 2 3</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade hepatic</td>
<td>N 11 6 2 1 0 0 1 6 116</td>
<td>12 84 9 2 1 1 2</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 12 83 9 2 1 0 1 5 100</td>
<td>11 71 8 2 1 1 2</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade infection</td>
<td>N 77 22 11 0 0 0 0 6 116</td>
<td>31 66 15 12 2 2 4</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 28 66 19 9 0 0 0 5 100</td>
<td>26 55 13 10 2 2 3</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade viral infection</td>
<td>N 11 6 2 1 0 0 1 6 116</td>
<td>12 84 9 2 1 1 2</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 12 83 9 2 1 0 1 5 100</td>
<td>11 71 8 2 1 1 2</td>
<td>% 100</td>
</tr>
<tr>
<td>Grade metabolic</td>
<td>N 77 22 11 0 0 0 0 6 116</td>
<td>31 66 15 12 2 2 4</td>
<td>N 119</td>
</tr>
<tr>
<td></td>
<td>% 28 66 19 9 0 0 0 5 100</td>
<td>26 55 13 10 2 2 3</td>
<td>% 100</td>
</tr>
</tbody>
</table>
The toxicity profile is also summarized by grade and maintenance visit for each designation in section §6.7.2. In this summary, the denominator is the number of patients who received treatment at each cycle for rituximab arm or had a maintenance visit for observation arm.

Other toxicities are listed in section §6.7.2.
Table 5.2-5 Patients with neutrophils <1 G/L during M3-M12 post transplant (MSAP)

<table>
<thead>
<tr>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>At least one neutrophils value &lt;1 G/L during M3-M12 post transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>No</td>
<td>80</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>100</td>
</tr>
</tbody>
</table>

36 patients (31%) in rituximab arm had a neutropenia of grade 3 or more during M3-M12 post transplant versus 30 patients (25%) in observation arm. Nevertheless, patients could have received a new treatment during this period.

If values after an additional treatment are excluded, results are the following ones:

Table 5.2-6 Patients with neutrophils <1 G/L during M3-M12 post transplant, excluding values after additional treatment (MSAP)

<table>
<thead>
<tr>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>At least one neutrophils value &lt;1 G/L during M3-M12 post transplant (excluding values after additional treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>No</td>
<td>105</td>
<td>91</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>100</td>
</tr>
</tbody>
</table>

11 patients (9%) in rituximab arm had a neutropenia of grade 3 or more during M3-M12 post transplant excluding values after additional treatment versus 7 patients (6%) in observation arm.

Table 5.2-7 Patients with RBC and platelets transfusions during maintenance (MSAP)

<table>
<thead>
<tr>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>At least one RBC transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>103</td>
<td>89</td>
</tr>
<tr>
<td>At least one platelets transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>103</td>
<td>89</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>100</td>
</tr>
</tbody>
</table>
5.2.2. Description of adverse events

Among maintenance safety population, regarding only AEs post 2\textsuperscript{nd} randomization, a total of 162 AEs in rituximab arm and 99 in the observation arm were reported, concerning respectively 67 patients (58\%) and 58 patients (49\%).

In both arms, the most common System Organ Class was infections and infestations (respectively 76 and 37 AEs in rituximab and observation arm, 47\% and 37\% of AEs), then blood and lymphatic system disorders (36 and 19 AEs, 22\% and 19\% of AEs).

### Table 5.2-8 Patients with at least one AE (MSAP)

<table>
<thead>
<tr>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>(%)</th>
<th>OBSERVATION</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with at least one AE</td>
<td>Yes</td>
<td>67</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Patient with at least one AE within 100 days after ASCT</td>
<td>Yes</td>
<td>54</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>Patient with at least one AE more than 100 days after ASCT</td>
<td>Yes</td>
<td>35</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>116</td>
<td>100</td>
<td>119</td>
</tr>
</tbody>
</table>

Regarding AEs within 100 days after ASCT, a total of 87 SAEs in rituximab arm and 75 in observation arm were reported, concerning respectively 54 patients (47\%) and 50 patients (42\%).

Regarding AEs more than 100 days after ASCT, a total of 75 SAEs in rituximab arm and 24 in observation arm were reported, concerning respectively 35 patients (30\%) and 20 patients (17\%).

See details about AEs (overall, within 100 days after ASCT and more than 100 days after ASCT) in the following tables.

The following table summarizes the incidence of AEs by System Organ Class and Preferred Term, ordered by frequency.

### Table 5.2-9 Summary of adverse events by frequency of SOC and PT (MSAP)

<table>
<thead>
<tr>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>(%)</th>
<th>OBSERVATION</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td></td>
<td>162</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Actual arm of maintenance</td>
<td>RITUXIMAB</td>
<td></td>
<td>OBSERVATION</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------</td>
<td>----------</td>
<td>---</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Total number of AEs</td>
<td>76</td>
<td>47</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Preferred Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFECTION</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>HERPES ZOSTER</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>BRONCHITIS</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SEPSIS</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PNEUMONIA</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LOWER RESPIRATORY TRACT INFECTION</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CATHETER RELATED INFECTION</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>NEUTROPENIC INFECTION</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>FOLLICULITIS</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BRONCHOPNEUMONIA</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ESCHERICHIA URINARY TRACT INFECTION</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CENTRAL LINE INFECTION</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NEUTROPENIC SEPSIS</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CATHETER SEPSIS</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CANDIDIASIS</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ORAL HERPES</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>URINARY TRACT INFECTION</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SEPTIC SHOCK</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SINUSITIS</td>
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3 other malignancies in rituximab arm and 2 in observation arm were reported (corresponding to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps)).

Table 5.2-10 Summary of adverse events within 100 days after ASCT by frequency of SOC and PT (MSAP)
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Table 5.2-11 Summary of adverse events more than 100 days after ASCT by frequency of SOC and PT (MSAP)

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- **RITUXIMAB**
  - N: 45
  - %: 60

- **OBSERVATION**
  - N: 13
  - %: 54
<p>| System and Disorder                                                                 | RITUXIMAB |   |   | OBSERVATION |   |   |
|------------------------------------------------------------------------------------|------------|--|--|--|------------|--|--|
| <strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong>                                          | N | % | N | % |
| Total number of AEs                                                               | 14 | 19 | 4 | 17 |
| Preferred Term                                                                    |   |   |   |   |
| NEUTROPENIA                                                                       | 7 | 9 | 1 | 4 |
| LEUKOPENIA                                                                        | 3 | 4 | 2 | 8 |
| FEBRILE NEUTROPENIA                                                               | 1 | 1 | 1 | 4 |
| LYMPHOPENIA                                                                       | 1 | 1 | 0 | 0 |
| THROMBOTIC THROMBOCYTOPENIC PURPURA                                                | 1 | 1 | 0 | 0 |
| THROMBOCYTOPENIA                                                                  | 1 | 1 | 0 | 0 |
| <strong>NERVOUS SYSTEM DISORDERS</strong>                                                      |   |   |   |   |
| Total number of AEs                                                               | 3 | 4 | 2 | 8 |
| Preferred Term                                                                    |   |   |   |   |
| LOSS OF CONSCIOUSNESS                                                             | 0 | 0 | 1 | 4 |
| CEREBRAL ISCHAEMIA                                                                | 0 | 0 | 1 | 4 |
| TRANSIENT ISCHAEMIC ATTACK                                                        | 1 | 1 | 0 | 0 |
| LEUKOENCEPHALOPATHY                                                               | 1 | 1 | 0 | 0 |
| HYPOAESTHESIA                                                                     | 1 | 1 | 0 | 0 |
| <strong>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)</strong>          |   |   |   |   |
| Total number of AEs                                                               | 3 | 4 | 2 | 8 |
| Preferred Term                                                                    |   |   |   |   |
| HEPATIC NEOPLASM MALIGNANT                                                        | 1 | 1 | 0 | 0 |
| MALIGNANT MELANOMA                                                                | 1 | 1 | 0 | 0 |
| ACUTE LEUKAEMIA                                                                   | 1 | 1 | 0 | 0 |
| TRANSITIONAL CELL CARCINOMA                                                       | 0 | 0 | 1 | 4 |
| MYELODYSPLASTIC SYNDROME                                                          | 0 | 0 | 1 | 4 |
| <strong>IMMUNE SYSTEM DISORDERS</strong>                                                       |   |   |   |   |
| Total number of AEs                                                               | 3 | 4 | 1 | 4 |
| Preferred Term                                                                    |   |   |   |   |
| HYPOGAMMAGLOBULINAEMIA                                                            | 3 | 4 | 1 | 4 |
| <strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong>                         |   |   |   |   |
| Total number of AEs                                                               | 2 | 3 | 1 | 4 |
| Preferred Term                                                                    |   |   |   |   |
| PYREXIA                                                                           | 2 | 3 | 0 | 0 |
| MUCOSAL INFLAMMATION                                                              | 0 | 0 | 1 | 4 |
| <strong>GASTROINTESTINAL DISORDERS</strong>                                                    |   |   |   |   |
| Total number of AEs                                                               | 1 | 1 | 1 | 4 |
| Preferred Term                                                                    |   |   |   |   |
| VOMITING                                                                          | 0 | 0 | 1 | 4 |
| GINGIVAL PAIN                                                                      | 1 | 1 | 0 | 0 |
| <strong>VASCULAR DISORDERS</strong>                                                            |   |   |   |   |
| Total number of AEs                                                               | 1 | 1 | 0 | 0 |
| Preferred Term                                                                    |   |   |   |   |
| JUGULAR VEIN THROMBOSIS                                                            | 1 | 1 | 0 | 0 |
| <strong>RENAL AND URINARY DISORDERS</strong>                                                   |   |   |   |   |
| Total number of AEs                                                               | 1 | 1 | 0 | 0 |
| Preferred Term                                                                    |   |   |   |   |
| RENAL FAILURE                                                                      | 1 | 1 | 0 | 0 |</p>
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Table 5.2-12 Characteristics of adverse events (MSAP)

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Table 5.2-13 Action taken with study drugs due to AEs (MSAP)

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Table 5.2-14 Characteristics of adverse events within 100 days after ASCT (MSAP)

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### Table 5.2-15 Action taken with study drugs due to AEs within 100 days after ASCT (MSAP)

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### Table 5.2-16 Characteristics of adverse events more than 100 days after ASCT (MSAP)

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<td>Actual arm of maintenance</td>
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Table 5.2-17 Action taken with study drugs due to AEs more than 100 days after ASCT (MSAP)

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<td>TEMPORARY TREATMENT DISCONTINUATION</td>
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<tr>
<td>DOSE REGIMEN ADAPTATION</td>
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<tr>
<td>Total</td>
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5.2.3. Corrective treatments

Among patients with at least one AE, 57 patients (85%) received a corrective treatment in rituximab arm versus 50 patients (86%) in the observation arm.

Table 5.2-18 Patients with corrective treatment (MSAP)

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137 AEs in rituximab arm (85%) were associated with a corrective treatment versus 83 AEs (84%) in observation arm.

Table 5.2-19 Corrective treatments for AE (MSAP)

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5.3. Deaths and other serious adverse events

5.3.1. Serious adverse events

5.3.1.1. Description of serious adverse events

Among maintenance safety population, regarding only SAEs post 2\textsuperscript{nd} randomization, a total of 43 SAEs in rituximab arm and 22 in observation arm were reported, concerning respectively 24 patients (21\%) and 16 patients (13\%).

In both arms, the most common System Organ Class was infections and infestations (respectively 25 and 6 SAEs in rituximab and observation arms, 58\% and 27\% of SAEs).

All serious adverse events during maintenance period are listed (one listing for SAEs within 100 days after ASCT and one for AEs more than 100 days after ASCT) in section §6.7.3.

5 SAEs were declared to Pharmacovigilance department concerning 2 patients not evaluable due to CRF not recovered. They are listed in section §6.7.3.

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<tr>
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</tr>
<tr>
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<td>116</td>
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</table>

Regarding SAEs within 100 days after ASCT, a total of 20 SAEs in rituximab arm and 17 in observation arm were reported, concerning respectively 14 patients (12\%) and 15 patients (13\%).

Regarding SAEs more than 100 days after ASCT, a total of 23 SAEs in rituximab arm and 5 in observation arm were reported, concerning respectively 14 patients (12\%) and 15 patients (4\%).
### Listing 5.3-1 Serious adverse events with fatal outcome (MSAP)

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See details about SAEs (overall, within 100 days after ASCT and more than 100 days after ASCT) in the following tables.

**Table 5.3-2 Summary of serious adverse events by frequency of SOC and PT (MSAP)**

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Table 5.3-3 Summary of serious adverse events within 100 days after ASCT by frequency of SOC and PT (MSAP)

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<td>Action taken with study drug</td>
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<td>70</td>
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### Table 5.3-10 Action taken with study drugs due to SAE more than 100 days after ASCT (MSAP)

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<th>RITUXIMAB</th>
<th>OBSERVATION</th>
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<td></td>
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<td>N</td>
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</tr>
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5.3.1.2. Corrective treatments

### Table 5.3-11 Patients with corrective treatment (MSAP)

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<td></td>
<td>N</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
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### Table 5.3-12 Corrective treatments for AE (MSAP)

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<tr>
<td>No</td>
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</tr>
<tr>
<td>Yes</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>13</td>
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</table>
5.3.2. Deaths

3 patients who were randomized in observation arm but had no maintenance follow-up assessment, and thus were excluded from maintenance safety population, died due to lymphoma, within one year post transplant for 2 of them. Among maintenance safety population, 43 deaths (37% of patients) in the rituximab arm and 38 deaths (32%) in the observation arm occurred at time of analysis, mainly due to lymphoma (respectively 70% and 79% of deaths).

Table 5.3-13 Summary of deaths (MSAP)

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<thead>
<tr>
<th>Actual arm of maintenance</th>
<th>RITUXIMAB</th>
<th>OBSERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>43</td>
<td>38</td>
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<tr>
<td></td>
<td>37%</td>
<td>32%</td>
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<tr>
<td>No</td>
<td>73</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>63%</td>
<td>68%</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>119</td>
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<td></td>
<td>100%</td>
<td>100%</td>
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</table>

Table 5.3-14 Cause of death (MSAP)

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<tr>
<th>Reason for death</th>
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<th>OBSERVATION</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>LYMPHOMA</td>
<td>30</td>
<td>70%</td>
<td>30</td>
</tr>
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<td>0</td>
</tr>
<tr>
<td>OTHER CANCER</td>
<td>2</td>
<td>5%</td>
<td>2</td>
</tr>
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<td>TOXICITY OF ADDITIONAL TREATMENT</td>
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<td>7%</td>
<td>3</td>
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<td>OTHER REASON</td>
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<td>5%</td>
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<tr>
<td>Total</td>
<td>43</td>
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<td>38</td>
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See details of deaths in the following lists:
## Listing 5.3-2 Deaths (MSAP)

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<th>Sex</th>
<th>Age (years)</th>
<th>Date of death</th>
<th>Reason for death</th>
<th>Specify reason of death</th>
<th>Response at death</th>
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<td>57</td>
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<td>LYMPHOMA</td>
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<td>ORGANIC BRAIN SYNDROME</td>
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**Note:** CMV-PNEUMONIA, RENAL FAILURE, MULTIPLE ORGAN FAILURE AFTER AUTOLOGOUS TRANSPLANT ON 19/03/2007.
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<th>Transplantation date</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Date of death</th>
<th>Reason for death</th>
<th>Specify reason of death</th>
<th>Response at death</th>
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<td>MALE</td>
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N = 81
5.4. Clinical laboratory evaluation

The following tables show statistics summary of parameters registered only at baseline.

**Table 5.4-1 Summary of laboratory tests at relapse diagnosis (MSAP)**

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<tr>
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### Table 5.4-2 Serum electrophoresis values at relapse diagnosis (induction safety population)

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<th>OBSERVATION</th>
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<td><strong>Albumin (G/L)</strong></td>
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<td><strong>Monoclonal component value (G/L)</strong></td>
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For each parameter registered at different time over the course of the study, the mean, standard deviation, median, range and changes from baseline are described in section §6.7.4.

### 5.5. Vitals signs, physical finding and other observations related to safety

Vital signs are described in section §6.7.5.

For clinical examination, a frequency table summarizes the results at each visit.
6. TABLES, LISTINGS AND FIGURES NOT INCLUDED IN THE REPORT

6.1. Withdrawals
### Listing 6.1-1 Withdrawals (MITT)

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<th>Date of 2nd randomization</th>
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<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
<th>Response at withdrawal</th>
<th>Transplantation date</th>
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### 6.2. Initial treatment

#### Listing 6.2-1 Initial treatment - Patients with other chemotherapy (MITT)

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#### Listing 6.2-2 Initial treatment – Doses of radiotherapy (MITT)

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### 6.3. Progression/relapse diagnosis

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GELARC
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<td>Colon</td>
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<td>Caecum</td>
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<td>Ileum</td>
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<td>Other extra-nodal involvement</td>
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### 6.4. Evaluation after complete induction treatment

Table 6.4-1 Codification of sites used for response evaluation after induction treatment, sorted by most frequent (MITT)

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<th>Lesion Codification</th>
<th>Arm of 2nd randomization</th>
<th></th>
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<td>RITUXIMAB</td>
<td>OBSERVATION</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Para-aortic / Portal</td>
<td>36</td>
<td>12%</td>
<td>43</td>
</tr>
<tr>
<td>Mediastinal / Paratracheal</td>
<td>37</td>
<td>12%</td>
<td>34</td>
</tr>
<tr>
<td>Celiac / Mesenteric</td>
<td>28</td>
<td>9%</td>
<td>28</td>
</tr>
<tr>
<td>Cervical / Post_cervical / Upper cervical / Pre_auricular : Left</td>
<td>27</td>
<td>9%</td>
<td>20</td>
</tr>
<tr>
<td>Axillary : Left</td>
<td>22</td>
<td>7%</td>
<td>13</td>
</tr>
<tr>
<td>Cervical / Post_cervical / Upper cervical / Pre_auricular : Right</td>
<td>18</td>
<td>6%</td>
<td>15</td>
</tr>
<tr>
<td>Inguinal / Femoral / Retrocrural : Left</td>
<td>11</td>
<td>4%</td>
<td>10</td>
</tr>
<tr>
<td>Axillary : Right</td>
<td>9</td>
<td>3%</td>
<td>11</td>
</tr>
<tr>
<td>Inguinal / Femoral / Retrocrural : Right</td>
<td>14</td>
<td>5%</td>
<td>6</td>
</tr>
<tr>
<td>External iliac / Iliac : Left</td>
<td>10</td>
<td>3%</td>
<td>10</td>
</tr>
<tr>
<td>Spleen</td>
<td>11</td>
<td>4%</td>
<td>8</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td>1%</td>
<td>12</td>
</tr>
<tr>
<td>External iliac / Iliac : Right</td>
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<td>2%</td>
<td>8</td>
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<tr>
<td>Soft Tissues</td>
<td>7</td>
<td>2%</td>
<td>5</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
<td>1%</td>
<td>8</td>
</tr>
<tr>
<td>Skin</td>
<td>5</td>
<td>2%</td>
<td>6</td>
</tr>
<tr>
<td>Tonsil / Waldeyer's ring</td>
<td>9</td>
<td>3%</td>
<td>1</td>
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<tr>
<td>Kidney</td>
<td>5</td>
<td>2%</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary hilar</td>
<td>4</td>
<td>1%</td>
<td>4</td>
</tr>
<tr>
<td>Infraclavicular / Supraclavicular : Left</td>
<td>6</td>
<td>2%</td>
<td>1</td>
</tr>
<tr>
<td>Bone</td>
<td>3</td>
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<td>3</td>
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<tr>
<td>Stomach</td>
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<tr>
<td>Epitrochlear Right or Left / Other</td>
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<td>1</td>
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<tr>
<td>Infraclavicular / Supraclavicular : Right</td>
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<td>2</td>
</tr>
<tr>
<td>Splenic hilar</td>
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<tr>
<td>Adrenal</td>
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<td>2</td>
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<td>OBSERVATION</td>
<td>All</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
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</tr>
<tr>
<td>Colon</td>
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</tr>
<tr>
<td>Caecum</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ileum</td>
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</tr>
<tr>
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<tr>
<td>Other extra-nodal involvement</td>
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<td>1</td>
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<tr>
<td>Cavum</td>
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<tr>
<td>Urinary Tract</td>
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</tr>
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<td>Parotid</td>
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</tr>
<tr>
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<td>0</td>
</tr>
<tr>
<td>Pleura</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ascites</td>
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<tr>
<td>Oesophagus</td>
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<td><strong>Total</strong></td>
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6.5. Follow-up

Listing 6.5- Patients with date of last contact earlier than September 1, 2009 (MITT)

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<th>Date of last contact</th>
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<td>RITUXIMAB</td>
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<tr>
<td>5003604701602</td>
<td>RITUXIMAB</td>
<td>21/08/2008</td>
</tr>
<tr>
<td>5003604901602</td>
<td>RITUXIMAB</td>
<td>28/06/2005</td>
</tr>
<tr>
<td>5003606301204</td>
<td>RITUXIMAB</td>
<td>23/06/2008</td>
</tr>
<tr>
<td>5003608301605</td>
<td>RITUXIMAB</td>
<td>13/09/2004</td>
</tr>
<tr>
<td>5003613301611</td>
<td>RITUXIMAB</td>
<td>25/05/2006</td>
</tr>
<tr>
<td>5003628201044</td>
<td>RITUXIMAB</td>
<td>12/06/2009</td>
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<tr>
<td>5003628201618</td>
<td>RITUXIMAB</td>
<td>03/06/2009</td>
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<td>18/01/2008</td>
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<td>OBSERVATION</td>
<td>09/06/2009</td>
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<td>5003604301013</td>
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<td>17/06/2009</td>
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<td>5003604701011</td>
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<td>18/05/2009</td>
</tr>
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<td>5003606201620</td>
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<td>11/07/2008</td>
</tr>
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<td>5003607201623</td>
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</tr>
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</tr>
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<td>5003622201607</td>
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<td>04/01/2007</td>
</tr>
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<td>5003628201402</td>
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<td>22/04/2009</td>
</tr>
<tr>
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N = 18
## 6.6 Efficacy results

### 6.6.1 Secondary criteria

**Listing 6.6-1 Patients who died during maintenance period (MITT)**

<table>
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<tr>
<th>Randomization Number</th>
<th>Date of 2nd randomization</th>
<th>Arm of 2nd randomization</th>
<th>Actual arm of maintenance</th>
<th>Transplantation date</th>
<th>Date of 2nd randomization</th>
<th>Date of withdrawal</th>
<th>Treatment period at withdrawal</th>
<th>Reason for premature withdrawal</th>
<th>Other reason for premature withdrawal</th>
<th>Response at withdrawal</th>
<th>Date of death</th>
<th>Reason for death</th>
<th>Response at death</th>
<th>Nb of maintenance visits</th>
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<td>5003101031001</td>
<td>21/10/2003</td>
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<td>PROGRESSIVE DISEASE</td>
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<td>06/05/2004</td>
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<td>11/10/2006</td>
<td>13/01/2007</td>
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<td>23/11/2006</td>
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<td>OTHER</td>
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<td>10/01/2006</td>
<td>FOLLOW UP PERIOD</td>
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<td>31/07/2006</td>
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<td>Arm of 2nd randomization</td>
<td>Actual arm of maintenance</td>
<td>Transplantation date</td>
<td>Date of withdrawal</td>
<td>Treatment period at withdrawal</td>
<td>Reason for premature withdrawal</td>
<td>Other reason for premature withdrawal</td>
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<td>Reason for death</td>
<td>Response at death</td>
<td>Nb of maintenance visits</td>
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<td>----------------------</td>
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6.6.2. Non study or new treatment out of progression

**Listing 6.6-2 New treatment out of progression - Chemotherapy (MITT)**

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**Listing 6.6-3 New treatment out of progression - Radiotherapy (MITT)**

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6.6.3. Progression/relapse

**Table 6.6-1 Progression/relapse n°1 – Extra-nodal involvement (MITT)**

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Table 6.6-2 Progression/relapse n°1 – Nodal involvement (MITT)

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**Table 6.6-3 Progression/relapse n°1 – Details of extra-nodal involvement (MITT)**

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**Caecum**

| Normal | 6 | 22 | 9 | 33 |
| Involved | 0 | 0 | 1 | 4 |
| Not evaluated | 3 | 11 | 0 | 0 |
| | 18 | 67 | 17 | 63 |

**Rectum**

| Normal | 6 | 22 | 9 | 33 |
| Involved | 0 | 0 | 1 | 4 |
| Not evaluated | 3 | 11 | 0 | 0 |
| | 18 | 67 | 17 | 63 |

**Other extra-nodal involvement**

| No | 5 | 19 | 4 | 15 |
| Yes | 5 | 19 | 5 | 19 |
| | 17 | 63 | 18 | 67 |

**TOTAL**

| 27 | 100 | 27 | 100 |

**Listing 6.6-5 Progression/relapse n°1 – Other extra-nodal involvement (MITT)**

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<th>Progression/relapse number</th>
<th>Other extra-nodal involvement - localization</th>
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N = 3
Table 6.6-4 Progression/relapse n°1 – Documentation (MITT)

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Listing 6.6-6 Progression/relapse n°1 - Chemotherapy (MITT)

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<td>GEMCITABINE, VINORELBINE</td>
<td>1</td>
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<td>OBSERVATION</td>
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<td>20/11/2008</td>
<td>R-ICE</td>
<td>2</td>
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<td>5003614301407</td>
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<td>24/06/2009</td>
<td>ICE</td>
<td>6</td>
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<td>5003617301619</td>
<td>OBSERVATION</td>
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<td>09/05/2007</td>
<td>GEMCITABINE ; IFOSFAMIDE ; PREDNISOLONE</td>
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<td>5003618301005</td>
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<td>R-VGF</td>
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<td>28/04/2006</td>
<td>DEXAMETHASONE / CYTARABINE / METHOTREXATE</td>
<td>2</td>
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<td>5003631201619</td>
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<td>ICE C IFOSFAMIDE 50%</td>
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N = 67
### Listing 6.6-7 Progression/relapse n°1 - Radiotherapy (MITT)

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<th>Randomization Number</th>
<th>Arm of 2nd randomization</th>
<th>Radiotherapy</th>
<th>Date of radiotherapy</th>
<th>Site of radiotherapy</th>
<th>Dose of radiotherapy (Gy)</th>
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<tr>
<td>5003101031001</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>16/01/2004</td>
<td>LEFT ARM</td>
<td>47</td>
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<td>5003101031401</td>
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<td>Yes</td>
<td>-</td>
<td>ENCEPHALON</td>
<td>45</td>
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<tr>
<td>5003603801203</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>16/05/2005</td>
<td>RIGHT INGUINA AND RIGHT ILIAC REGION</td>
<td>40</td>
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<tr>
<td>5003604801006</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>04/09/2006</td>
<td>-</td>
<td>44</td>
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<td>5003604901004</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>29/04/2007</td>
<td>D8 AND APARASPINAL MASS</td>
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<td>5003604901005</td>
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<td>Yes</td>
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<td>ILIAC BONE</td>
<td>36</td>
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<td>RITUXIMAB</td>
<td>Yes</td>
<td>29/05/2006</td>
<td>LEFT NECK</td>
<td>30</td>
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<td>RITUXIMAB</td>
<td>Yes</td>
<td>05/06/2008</td>
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<td>RITUXIMAB</td>
<td>Yes</td>
<td>14/04/2008</td>
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<td>5003616501003</td>
<td>RITUXIMAB</td>
<td>Yes</td>
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<td>ENTIRE SPINE C2-L3 INCLUSIVE</td>
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<td>Yes</td>
<td>01/02/2009</td>
<td>CERVICAL MASS</td>
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<td>RIGHT LEG</td>
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<td>LEFT ILIAC + LEFT INGUINAL</td>
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<td>Yes</td>
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<td>Yes</td>
<td>29/07/2008</td>
<td>LEFT PELVIC WALL</td>
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<td>Yes</td>
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<td>RIGHT ADRENAL</td>
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<td>Yes</td>
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<td>11/12/2006</td>
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<td>07/01/2010</td>
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<td>5003618301005</td>
<td>OBSERVATION</td>
<td>Yes</td>
<td>09/08/2006</td>
<td>RIGHT HEMIPELVIS</td>
<td>30</td>
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<td>5003621201020</td>
<td>OBSERVATION</td>
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<td>27/06/2006</td>
<td>TONSILLA RIGHT, ZONA LEG LEFT</td>
<td>8</td>
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<tr>
<td>5003621501412</td>
<td>OBSERVATION</td>
<td>Yes</td>
<td>09/11/2009</td>
<td>CHEST WALL</td>
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N = 27

### Listing 6.6-8 Progression/relapse n°1 - Immunotherapy (MITT)

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<th>Arm of 2nd randomization</th>
<th>Immunotherapy</th>
<th>Date of immunotherapy</th>
<th>Specify immunotherapy</th>
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<tr>
<td>50031010121631</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>14/06/2007</td>
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<td>500310101771008</td>
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<td>Yes</td>
<td>05/04/2007</td>
<td>IBRITUMOMAB TIUXETAN + RITUXIMAB</td>
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<td>5003101251035</td>
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<td>Yes</td>
<td>17/07/2006</td>
<td>RITUXIMAB</td>
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<td>5003101281033</td>
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<td>Yes</td>
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<td>5003102341641</td>
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<td>Yes</td>
<td>12/11/2009</td>
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<td>26/11/2007</td>
<td>RITUXIMAB (IN CONJUNCTION WITH CHEMOTHERAPY)</td>
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<td>5003615501014</td>
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<td>12/03/2008</td>
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<td>Date of immunotherapy</td>
<td>Specify immunotherapy</td>
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<td>18/12/2006</td>
<td>RITUXIMAB (4 CYCLES)</td>
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<td>5003101141624</td>
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<td>10/06/2009</td>
<td>RITUXIMAB</td>
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<td>5003101161407</td>
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<td>Yes</td>
<td>28/03/2007</td>
<td>RITUXIMAB THEN ANTI CD20</td>
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<td>5003101621615</td>
<td>OBSERVATION</td>
<td>Yes</td>
<td>27/08/2005</td>
<td>RITUXIMAB 8 CURES</td>
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<td>25/01/2007</td>
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<td>OBSERVATION</td>
<td>Yes</td>
<td>14/08/2008</td>
<td>RITUXIMAB W/GEMCITABINE AND DACETUZUMAB (INVESTIGATIONAL)</td>
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<td>OBSERVATION</td>
<td>Yes</td>
<td>17/01/2006</td>
<td>MABTHERA</td>
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<td>5003603801602</td>
<td>OBSERVATION</td>
<td>Yes</td>
<td>13/10/2006</td>
<td>RITUXIMAB IN COMBINATION WITH FND</td>
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<tr>
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<td>OBSERVATION</td>
<td>Yes</td>
<td>28/07/2006</td>
<td>RITUXIMAB (STOP: 04.08.2006)</td>
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<td>5003606201609</td>
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<td>RITUXIMAB EVERY 3 MONTHS</td>
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<td>Yes</td>
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<td>MABTHERA 2 CYCLES</td>
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**N = 22**

**Listing 6.6-9 Progression/relapse n°1 - Transplant (MITT)**

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<th>Arm of 2nd randomization</th>
<th>Transplantation</th>
<th>Date of transplantation</th>
<th>Conditioning Regimen</th>
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<tr>
<td>5003102341061</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>26/05/2008</td>
<td>FLUDARABINE, ENDOXAN, IRRADIATION</td>
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<td>Yes</td>
<td>18/02/2010</td>
<td>IBRITUMOMAB TIUXETAN (ETUDE ZEVALLO)</td>
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<td>5003102491619</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>06/09/2007</td>
<td>FLUDARABINE BUSULFAN AND ATG</td>
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<td>5003102541640</td>
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<td>Yes</td>
<td>21/04/2008</td>
<td>CPA, FLUDA, ATG, MPD, CYCLO</td>
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<td>5003601881401</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>11/12/2007</td>
<td>FLUDARABINE / BUSULFAN / SAL</td>
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<td>5003602801605</td>
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<td>Yes</td>
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<td>FLUDARABIN, BUSULFAN, ANTITHYMOCYTE GLOBULIN</td>
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<td>5003604701002</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>30/12/2005</td>
<td>POMP</td>
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<td>RITUXIMAB</td>
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<td>22/12/2006</td>
<td>BU-CY</td>
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<td>Yes</td>
<td>19/03/2007</td>
<td>HD MELPHALAN</td>
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<td>5003617201021</td>
<td>RITUXIMAB</td>
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<td>13/11/2007</td>
<td>FLUDARABIN, BUSULFAN, CYCLOPHOSPHAMIDE, ATG</td>
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<td>14/01/2009</td>
<td>CYCLOPHOSPHAMIDE, FLUDARABINE, METHOTREXATE</td>
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<td>19/09/2007</td>
<td>MELPHALAN + FLUDARABIN</td>
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<td>OBSERVATION</td>
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<td>08/03/2007</td>
<td>TBI + ALEMTUZUMAB + CYCLOPHOSPHAMIDE</td>
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<td>Yes</td>
<td>28/01/2009</td>
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**N = 15**
### Listing 6.6-10 Progression/relapse n°1 – Other treatments (MITT)

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<th>Arm of 2nd randomization</th>
<th>Other treatment</th>
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<td>IBRITUMOMAB TIUXETAN</td>
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<td>23/12/2003</td>
<td>CORTICOIDES</td>
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<td>5003101251035</td>
<td>RITUXIMAB</td>
<td>Yes</td>
<td>05/03/2007</td>
<td>MERCA TOPURINE METHOTREXATE</td>
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<td>RITUXIMAB</td>
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<tr>
<td>5003103161041</td>
<td>RITUXIMAB</td>
<td>Yes</td>
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<td>HUMAN IMMUNOGLOBULIN</td>
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<td>RITUXIMAB</td>
<td>Yes</td>
<td>08/06/2006</td>
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<td>MABTHERA</td>
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<td>Yes</td>
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<td>RITUXIMAB - BENDAMUSTIN</td>
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<td>CORTICOIDS</td>
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<td>SPLENECTOMY</td>
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<td>09/05/2006</td>
<td>MTX HIGH DOSE 2 CYCLES</td>
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N = 13
### 6.7. Safety evaluation

#### 6.7.1. Extent of exposure to trial medication

Table 6.7-1 Maintenance – Frequency of percentage of planned dose received by cycle for Rituximab (MSAP)

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<th>Actual arm of maintenance</th>
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<td>[110-125%]</td>
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<td>&gt;125%</td>
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<td>Cycle 4</td>
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### Table: Randomization and Toxicity

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N = 253
### 6.7.3. Serious adverse events

**Listing 6.7-2 Serious adverse events declared to Pharmacovigilance department but not present in clinical database**

<table>
<thead>
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<th>Randomization Number</th>
<th>First Randomization Date</th>
<th>Arm of treatment</th>
<th>Date of 2nd randomization</th>
<th>Arm of 2nd randomization</th>
<th>SAE diagnosis</th>
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<th>AE/SAE: date of end</th>
<th>Outcome</th>
<th>Sponsor</th>
<th>Causality</th>
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<td>5003613301007</td>
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<td>31/01/2007</td>
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<td>ACUTE RENAL IMPAIEMENT</td>
<td>03/01/2007</td>
<td>08/01/2007</td>
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<td>Related</td>
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<td>Not yet recovered</td>
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N = 5

**Listing 6.7-3 Serious adverse events within 100 days after ASCT (MSAP)**

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<th>Actual arm of maintenance</th>
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<th>Age (years)</th>
<th>Adverse event description</th>
<th>Date of AE become serious</th>
<th>Non hematological toxicity grade</th>
<th>Hematological toxicity grade</th>
<th>Relation with study drugs</th>
<th>Action taken with study drug</th>
<th>AE outcome</th>
<th>Duration of AE serious (days)</th>
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<td>49</td>
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<td>No</td>
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<td>Duration of AE serious (days)</td>
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N = 37
### Listing 6.7-4 Serious adverse events more than 100 days after ASCT (MSAP)

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<th>Date of AE become serious</th>
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N = 28
### 6.7.4. Laboratory tests

#### Table 6.7-3 Hemoglobin (MSAP)

Actual arm of maintenance=RITUXIMAB

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### 6.7.5. Vital signs

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<th>Actual arm of maintenance</th>
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<th>OBSERVATION</th>
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#### Table 6.7-11 Cardiac exams at relapse diagnosis (MSAP)

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<td>%</td>
<td>N</td>
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<td>Abnormal</td>
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<td>5</td>
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<td>Not done</td>
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<td>28</td>
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<tr>
<td>Total</td>
<td>116</td>
<td>100</td>
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</tbody>
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| Echocardiography / Isotopic method | | | | |
| Normal | 81 | 70 | 82 | 69 |
| Abnormal | 14 | 12 | 17 | 14 |
| Not done | 20 | 17 | 20 | 17 |
| Total | 115 | 100 | 119 | 100 |

#### Table 6.7-12 Other exams at relapse diagnosis (MSAP)

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<tbody>
<tr>
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<td>%</td>
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## Exploratory analysis

**Frequency table of overall response rate after induction by Response after 1st line - Induction ITT**

<table>
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<tr>
<th>Response after first line</th>
<th>Response after complete induction (including deaths for all patients)</th>
<th>Arm of treatment</th>
<th>P-value (Chi-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR/CRu/PR</td>
<td>ARM A / R-ICE</td>
<td>ARM B / R-DHAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
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<td>CR/CRu/PR</td>
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<td>49</td>
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<td>Other</td>
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<td>CR/CRu/PR</td>
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<table>
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<th>P-value (Chi-2)</th>
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### Frequency table of overall response rate after induction by Response after 1st line - Induction ITT

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<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
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<th>Response after complete induction (including deaths for all patients) by Treatment</th>
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### Frequency table of complete response rate after induction by Response after 1st line - Induction ITT

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<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
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<td>46</td>
<td>68</td>
<td>48</td>
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<td>19</td>
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<tr>
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<table>
<thead>
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<th>Response after complete induction (including deaths for all patients) by Treatment</th>
<th>P-value (Chi-2)</th>
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</thead>
<tbody>
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<td>Response after 1st line (Other)</td>
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### Event-Free Survival according to Response after 1st line - induction ITT

#### Median and 95% CI

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<th>N</th>
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<th>95% CI Lower</th>
<th>95% CI Upper</th>
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<th>Max</th>
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#### Survival Probability

- Logrank p < 0.0001
- EFS (months)
- Time Point (months)
- EFS (%)
- 95% CI Lower
- 95% CI Upper
- Patients at risk

<table>
<thead>
<tr>
<th>Response after first line</th>
<th>Time Point (months)</th>
<th>EFS (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
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<tr>
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<tr>
<td>Response after first line</td>
<td>Time Point (months)</td>
<td>EFS (%)</td>
<td>95% CI Lower</td>
<td>95% CI Upper</td>
<td>Patients at risk</td>
</tr>
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Progression-Free Survival according to Response after 1st line - induction ITT

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<th>Max</th>
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<th>PFS (%)</th>
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<th>95% CI Upper</th>
<th>Patients at risk</th>
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<td>Patients at risk</td>
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### Overall Survival according to Response after 1st line - induction ITT

**Response after first line**
- **N**: Number of patients
- **Median**: Median survival time
- **95% CI Lower**: Lower confidence interval for 95% confidence interval
- **95% CI Upper**: Upper confidence interval for 95% confidence interval
- **Min**: Minimum survival time
- **Max**: Maximum survival time

#### OS (months)

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#### Response after first line - Time Point (months)

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Prognostic factors

Gender

2nd randomization: EFS (MITT)

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Model with gender and maintenance arm:

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Model with gender, maintenance arm and interaction:

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Arm of 2nd randomization = RITUXIMAB

![](image1)

Arm of 2nd randomization = OBSERVATION

![](image2)
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### Arm of 2nd randomization = RITUXIMAB

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<th>Chi-Square</th>
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<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
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### Arm of 2nd randomization = OBSERVATION

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### Sex = FEMALE

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Prognostic factors

Gender

2nd randomization : PFS (MITT)

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<th>Patients at risk</th>
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Model with gender only:

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<th>Standard Error</th>
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<th>Variable Label</th>
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Model with gender and maintenance arm:

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Model with gender, maintenance arm and interaction:

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Arm of 2nd randomization = RITUXIMAB

Survival Probability

PFS (months)

Logrank p=0.0044

No. of Subjects | Event | Censored | Median Survival (95% CL)
FEMALE | 46 | 28% (13) | 72% (33) | NA (NA NA)
MALE | 76 | 55% (42) | 45% (34) | 25.30 (15.87 57.59)

Arm of 2nd randomization = OBSERVATION

Survival Probability

PFS (months)

Logrank p=0.5921

No. of Subjects | Event | Censored | Median Survival (95% CL)
FEMALE | 37 | 43% (16) | 57% (21) | 61.60 (26.89 NA)
MALE | 83 | 43% (36) | 57% (47) | 58.22 (20.90 NA)
<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Sex</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
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<th>Survival (%)</th>
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### Arm of 2nd randomization=RITUXIMAB

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<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
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<td>0.220 0.773</td>
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### Arm of 2nd randomization=OBSERVATION

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### Sex=MALE

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<th>95% Hazard Ratio Confidence Limits</th>
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### Sex=FEMALE

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Prognostic factors

Gender

2nd randomization : OS (MITT)

<table>
<thead>
<tr>
<th>Sex</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
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<tbody>
<tr>
<td>MALE</td>
<td>159</td>
<td>58</td>
<td>40</td>
<td>-</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>FEMALE</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>76</td>
</tr>
</tbody>
</table>

No. of Subjects | Event | Censored | Median Survival (95% CL)
FEMALE    | 83    | 25% (21) | 75% (62) | NA | NA | NA |
MALE      | 159   | 40% (63) | 60% (96) | 58.05 | 40.48 | NA |
Model with gender only:

<table>
<thead>
<tr>
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<th>DF</th>
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<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
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<th>95% Hazard Ratio Confidence Limits</th>
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Model with gender and maintenance arm:

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<th>Standard Error</th>
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<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
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<th>Variable Label</th>
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</table>

Model with gender and maintenance arm:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
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<tbody>
<tr>
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<td>0.3298</td>
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<td>0.25315</td>
<td>1.3028</td>
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</table>
Arm of 2nd randomization = RITUXIMAB

![Survival Probability graph for RITUXIMAB group with Logrank p=0.0071.](image)

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEMALE</td>
<td>46</td>
<td>22% (10)</td>
<td>78% (36) NA (NA NA)</td>
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<tr>
<td>MALE</td>
<td>76</td>
<td>45% (34)</td>
<td>55% (42) 58.05 (25.56 NA)</td>
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</table>

Arm of 2nd randomization = OBSERVATION

![Survival Probability graph for OBSERVATION group with Logrank p=0.2983.](image)

<table>
<thead>
<tr>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEMALE</td>
<td>37</td>
<td>30% (11)</td>
<td>70% (26) 62.92 (53.72 NA)</td>
</tr>
<tr>
<td>MALE</td>
<td>83</td>
<td>35% (29)</td>
<td>65% (54) 58.22 (40.87 NA)</td>
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</tbody>
</table>
Sex=MALE

Logrank p=0.2362

Sex=FEMALE

Logrank p=0.4233
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<thead>
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<th>Sex</th>
<th>N</th>
<th>Median</th>
<th>95% CI lower</th>
<th>95% CI Upper</th>
<th>Min</th>
<th>Max</th>
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</thead>
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<tr>
<td>RITUXIMAB</td>
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<td>58</td>
<td>26</td>
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<tr>
<td>RITUXIMAB</td>
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<td>46</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
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<td>58</td>
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<table>
<thead>
<tr>
<th>Arm of 2nd randomization</th>
<th>Sex</th>
<th>Time Point (years)</th>
<th>Survival (%)</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Patients at risk</th>
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**Arm of 2nd randomization=RITUXIMAB**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>Variable Label</th>
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</thead>
<tbody>
<tr>
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<td>-0.95023</td>
<td>0.36531</td>
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<td>0.387</td>
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**Arm of 2nd randomization=OBSERVATION**

<table>
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<tr>
<th>Parameter</th>
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<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>Variable Label</th>
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</thead>
<tbody>
<tr>
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<td>0.3012</td>
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**Sex=MALE**

<table>
<thead>
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<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>Variable Label</th>
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</thead>
<tbody>
<tr>
<td>brasrand2 1</td>
<td>RITUXIMAB</td>
<td>0.29959</td>
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<td>0.821</td>
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</table>

**Sex=FEMALE**

<table>
<thead>
<tr>
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<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>Variable Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>brasrand2 1</td>
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</table>

**Coral study**

*Cox models - maintenance population (excluding SD patients)*

*PFS from 2nd randomization*

| Number of Observations Read | 234 |
| Number of Observations Used | 229 |
## Testing Global Null Hypothesis: BETA=0

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Pr &gt; ChiSq</th>
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<tbody>
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<tr>
<td>Wald</td>
<td>20.6540</td>
<td>3</td>
<td>0.0001</td>
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</table>

## Analysis of Maximum Likelihood Estimates

<table>
<thead>
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<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>Variable Label</th>
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<tbody>
<tr>
<td>brasrand2</td>
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<td>0.20445</td>
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<td>1.136</td>
<td>0.761 1.696</td>
<td>Arm of 2nd randomization RITUXIMAB</td>
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<td>0.78873</td>
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</tbody>
</table>
### CORAL study

*Cox models - maintenance population (excluding SD patients)*

*PFS from 2nd randomization*

<table>
<thead>
<tr>
<th>Number of Observations Read</th>
<th>234</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Observations Used</td>
<td>229</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>DF</th>
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<tbody>
<tr>
<td>Likelihood Ratio</td>
<td>27.0463</td>
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<td>Wald</td>
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</table>

### Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
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<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm of 2nd randomization RITUXIMAB</td>
<td>1</td>
<td>0.13214</td>
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<tr>
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**Coral study**

*Cox models - maintenance population (excluding SD patients)*

2nd randomization: OS

<table>
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<tr>
<th>Number of Observations Read</th>
<th>234</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Observations Used</td>
<td>229</td>
</tr>
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### Testing Global Null Hypothesis: BETA=0

<table>
<thead>
<tr>
<th>Test</th>
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### Analysis of Maximum Likelihood Estimates

<table>
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<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
<th>Variable Label</th>
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<tbody>
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### CORAL study

Cox models - maintenance population (excluding SD patients)

2nd randomization: OS

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<tbody>
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#### Testing Global Null Hypothesis: BETA=0

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<tr>
<td>Wald</td>
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#### Analysis of Maximum Likelihood Estimates

<table>
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<th>95% Hazard Ratio Confidence Limits</th>
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<tbody>
<tr>
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<td>0.22899</td>
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<td>1.213</td>
<td>0.775 - 1.901</td>
</tr>
<tr>
<td>Age-adjusted IPI 2-3</td>
<td>1</td>
<td>0.84439</td>
<td>0.22978</td>
<td>13.5035</td>
<td>0.0002</td>
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</tr>
<tr>
<td>Sex MALE</td>
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<td>0.61535</td>
<td>0.25988</td>
<td>5.6067</td>
<td>0.0179</td>
<td>1.850</td>
<td>1.112 - 3.079</td>
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<tr>
<td>Prior treatment with Rituximab No</td>
<td>1</td>
<td>-0.24360</td>
<td>0.25747</td>
<td>0.8951</td>
<td>0.3441</td>
<td>0.784</td>
<td>0.473 - 1.298</td>
</tr>
<tr>
<td>Failure from diagnosis (&lt; 12 months)</td>
<td>1</td>
<td>0.18435</td>
<td>0.25763</td>
<td>0.5120</td>
<td>0.4743</td>
<td>1.202</td>
<td>0.726 - 1.992</td>
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<tr>
<td>Response after complete induction PR</td>
<td>1</td>
<td>0.13211</td>
<td>0.23275</td>
<td>0.3222</td>
<td>0.5703</td>
<td>1.141</td>
<td>0.723 - 1.801</td>
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<tr>
<td>Arm of treatment ARM A / R-ICE</td>
<td>1</td>
<td>0.41014</td>
<td>0.22914</td>
<td>3.2037</td>
<td>0.0735</td>
<td>1.507</td>
<td>0.962 - 2.361</td>
</tr>
</tbody>
</table>
**CORAL study**

**PET scan in PR patients after induction**

<table>
<thead>
<tr>
<th>PET scan after induction chemo</th>
<th>N</th>
<th>%</th>
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</thead>
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<tr>
<td>NEGATIVE</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>NOT DONE</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>89</td>
<td>100</td>
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</table>
### CORAL study

**PET scan in PR patients after induction**

*List of PET positive and PR patients after induction*

<table>
<thead>
<tr>
<th>No.</th>
<th>PET scan after induction</th>
<th>PET scan at M3 post transplant</th>
<th>Transplantation date</th>
<th>Progression / Relapse</th>
<th>Date of Progression / Relapse</th>
<th>PFS (months) from 1st rando</th>
<th>PFS (months) from 2nd rando</th>
<th>Date of death</th>
<th>OS (months) from 1st rando</th>
</tr>
</thead>
<tbody>
<tr>
<td>02</td>
<td>POSITIVE</td>
<td>POSITIVE</td>
<td>11/10/2006</td>
<td>Yes</td>
<td>04/01/2007</td>
<td>5.7495</td>
<td>2.6283</td>
<td>19/02/2007</td>
<td>7.2608</td>
</tr>
<tr>
<td>03</td>
<td>POSITIVE</td>
<td>NOT DONE</td>
<td>21/12/2004</td>
<td>-</td>
<td>67.0838</td>
<td>62.5544</td>
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<td>67.0883</td>
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<tr>
<td>04</td>
<td>POSITIVE</td>
<td>NOT DONE</td>
<td>27/12/2007</td>
<td>-</td>
<td>27.8275</td>
<td>24.4107</td>
<td>-</td>
<td>27.8275</td>
<td></td>
</tr>
<tr>
<td>05</td>
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<td>NOT DONE</td>
<td>04/10/2005</td>
<td>Yes</td>
<td>10/01/2006</td>
<td>5.8809</td>
<td>1.8398</td>
<td>16/02/2006</td>
<td>7.0965</td>
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<td>06</td>
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<td>21/11/2005</td>
<td>-</td>
<td>49.6756</td>
<td>46.6530</td>
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</tr>
<tr>
<td>07</td>
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<td>28/11/2005</td>
<td>-</td>
<td>50.6612</td>
<td>47.6715</td>
<td>-</td>
<td>50.6612</td>
<td></td>
</tr>
<tr>
<td>08</td>
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<td>17/05/2004</td>
<td>-</td>
<td>75.2033</td>
<td>72.3450</td>
<td>-</td>
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</tr>
<tr>
<td>10</td>
<td>POSITIVE</td>
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<td>15/07/2008</td>
<td>-</td>
<td>22.1766</td>
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<td>-</td>
<td>22.1766</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>POSITIVE</td>
<td>POSITIVE</td>
<td>21/06/2006</td>
<td>-</td>
<td>38.3409</td>
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<td>-</td>
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<tr>
<td>12</td>
<td>POSITIVE</td>
<td>NOT DONE</td>
<td>28/11/2007</td>
<td>Yes</td>
<td>21/10/2009</td>
<td>25.5606</td>
<td>22.7680</td>
<td>32.0000</td>
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<tr>
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<td>2.9240</td>
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<tr>
<td>15</td>
<td>POSITIVE</td>
<td>-</td>
<td>14/02/2008</td>
<td>-</td>
<td>3.8768</td>
<td>1.2813</td>
<td>-</td>
<td>3.8768</td>
<td></td>
</tr>
<tr>
<td>16</td>
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<td>NEGATIVE</td>
<td>10/03/2008</td>
<td>-</td>
<td>29.6674</td>
<td>25.7248</td>
<td>-</td>
<td>29.6674</td>
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</tr>
<tr>
<td>17</td>
<td>POSITIVE</td>
<td>NEGATIVE</td>
<td>14/11/2007</td>
<td>-</td>
<td>33.7413</td>
<td>30.7187</td>
<td>-</td>
<td>33.7413</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>POSITIVE</td>
<td>POSITIVE</td>
<td>19/05/2008</td>
<td>-</td>
<td>26.7433</td>
<td>21.6509</td>
<td>-</td>
<td>26.7433</td>
<td></td>
</tr>
<tr>
<td>20</td>
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<td>Yes</td>
<td>13/01/2006</td>
<td>10.1520</td>
<td>7.2279</td>
<td>-</td>
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<tr>
<td>21</td>
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<td>16/09/2008</td>
<td>-</td>
<td>23.8850</td>
<td>19.6797</td>
<td>-</td>
<td>23.8850</td>
<td></td>
</tr>
</tbody>
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N = 24
SAFETY REPORT
CORAL: 50-03B

03/07/2003 – 02/07/2011 (96 MONTHS)

PHASE III MULTICENTRE OPEN-LABEL RANDOMIZED STUDY OF ICE PLUS RITUXIMAB (R-ICE) VERSUS DHAP PLUS RITUXIMAB (R-DHAP) IN PREVIOUSLY TREATED PATIENTS WITH CD 20 POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA, ELIGIBLE FOR TRANSPLANTATION FOLLOWED BY RANDOMIZED MAINTENANCE TREATMENT WITH RITUXIMAB

EudraCT number: 2004-002103-32

Sponsor
GELARC, CORAL GROUP

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Intergroup Protocol Coordinator

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☎: 33 1 42 49 98 11
Fax: 33 1 42 49 99 72
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFSSAPS</td>
<td>French Health Authority</td>
</tr>
<tr>
<td>GELA</td>
<td>Study Group of Adults' Lymphoma</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Event</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
</tbody>
</table>
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1. Introduction

This document is a safety report for CORAL study, covering the period between 03 July 2003 and 02 July 2011 (96 months).

This study is sponsored by GELA and was registered by the French Health Authority (AFSSaPS) on 03 July 2003.

The first subject was included to the study on July 24, 2003. The last included patient has completed his study treatment in November 2009. All the patients are now in the post-treatment follow up period.

The study is conducting in 8 European countries (Austria, Belgium, Czech Republic, Germany, France, Sweden, United Kingdom, Ireland) and 5 other countries (Australia, New Zealand, USA, Israel, Switzerland).

The objectives of the study

Part I, induction therapy: To evaluate the efficacy and the safety of ICE plus rituximab (R-ICE) in comparison with DHAP plus rituximab (R-DHAP) in previously-treated patients with CD20-positive large B-cell lymphoma eligible for autologous transplantation.

Part II, maintenance therapy: To evaluate the efficacy and safety of rituximab maintenance therapy after transplantation.

The primary endpoint of the study

Part I, induction therapy: Overall response rate (ORR) (Complete Response CR and Partial Response PR) adjusted with successful mobilization at the end of 3 cycles of induction chemotherapy treatment before high-dose chemotherapy and autologous transplantation.

Part II, maintenance therapy: Event free survival (EFS) at 2 years post transplantation: events being death from any cause, relapse for complete responders and unconfirmed complete responders, progression during and after treatment and changes of therapy.
1.1 Study medication

Induction phase:
There are 2 treatment arms: arm A (R-ICE) and arm B (R-DHAP). The patients are stratified by the investigator.

Arm A: 3 cycles of R-ICE in 3–weekly intervals.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC (5) max 800 mg</td>
</tr>
<tr>
<td>Ifosfamide + Mesna</td>
<td>5 g/m²</td>
</tr>
<tr>
<td>Lenograstim</td>
<td></td>
</tr>
</tbody>
</table>

Arm B: 3 cycles of R-DHAP in 3–weekly intervals.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-DHAP</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
</tr>
<tr>
<td>Cisplatin c.i.</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>2000 mg/m²/12 h</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg/m²</td>
</tr>
<tr>
<td>Lenograstim</td>
<td></td>
</tr>
</tbody>
</table>

Consolidation:
All patients in CR (complete response) or PR (partial response) will be submitted to consolidation treatment with BEAM and then the autologous stem cell transplantation (ASCT) will be performed.

BEAM

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmustine</td>
<td>300 mg/m²</td>
</tr>
<tr>
<td>Etoposide</td>
<td>200 mg/m²</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>200 mg/m²</td>
</tr>
<tr>
<td>Melphalan</td>
<td>140 mg/m²</td>
</tr>
</tbody>
</table>

Maintenance: Randomization to Rituximab post transplant versus Observation after restaging at the end of induction remission treatment.

The investigational medicinal products in this study are the following:

- **Rituximab**: reference document for expectedness is SmPC
- **Carboplatin**: reference document for expectedness is SmPC
- **Ifosfamide**: reference document for expectedness is SmPC
- **Mesna**: reference document for expectedness is SmPC
- **Lenograstim**: reference document for expectedness is SmPC
- **Dexamethasone**: reference document for expectedness is SmPC
- **Cisplatin**: reference document for expectedness is SmPC
Carmustine: reference document for expectedness is SmPC
Etoposide: reference document for expectedness is SmPC
Cytarabine: reference document for expectedness is SmPC
Melphalan: reference document for expectedness is SmPC

**Autologous stem cell transplantation (ASCT)**

All events in this report are coded with MedDRA version 10.0.

1.2  **Protocol safety parameters**

Serious Adverse Events (SAEs) that occurred after the informed consent up to 30 days after the last study drug administration or last maintenance visit, whether or not ascribed to the study, are recorded in the SAE pages. A SAE that occurs after this time will be reported only if considered related to the study.

- SAE is not recorded if related to lymphoma progression.
- Severe hematologic toxicity is never to be declared as AE. Febrile neutropenia requiring hospitalization less than 8 days, nausea, vomiting and hair loss, are not to be reported as SAE but only as AE.
- Hospitalizations for previously planned procedure or convenience are not to be reported as SAE.

2. **Protocol amendments**

*Amendment N°1* - June 20th, 2003
- Aracytine perfusion 200 mg/m²/12 h.

*Amendment N°2* - January 16th, 2006
- Increase of the inclusion period of 24 months (January 2008).
- The investigators are allowed to mobilize and collect the patient after the 2nd and/or 3rd cycles of chemotherapy. It is a usual practice in the majority of centers.
- Collection of more data particularly on the relapse post transplantation: Addition of 2 pages at the Case Report Form.
- Collection of the number of transfusion episode in the CRF instead of units.
3. Serious Adverse Events cases information

A total of 309 SAE cases were received between July 03, 2003 and July 02, 2011.

3.1 SAE cases nullification

Out of 309 cases received, 47 SAE cases were cancelled as they did not meet the reporting criteria defined in the protocol. The cancellation reasons are summarized in the table below:

<table>
<thead>
<tr>
<th>Cancellation reason</th>
<th>Nb of SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>10</td>
</tr>
<tr>
<td>Duplicate</td>
<td>6</td>
</tr>
<tr>
<td>Reporting out of protocol</td>
<td>10</td>
</tr>
<tr>
<td>Adverse event (non serious) according to the protocol</td>
<td>19</td>
</tr>
<tr>
<td>Patient not randomized</td>
<td>1</td>
</tr>
<tr>
<td>Existing at inclusion condition</td>
<td>1</td>
</tr>
</tbody>
</table>

A total of 262 SAE cases were captured in the Gelarc Pharmacovigilance database.

3.2 SAE cases characteristics

Out of 262, 230 SAE cases were assessed by the investigator and/or by the sponsor as related to the study.

Of them, 198 events were listed and 32 events have not been listed yet in the reference documents, current version at the moment of the SAE reporting. The related and unexpected SAEs have been notified to the Health Authorities and Ethics Committees as Suspected Unexpected Serious Adverse Reactions (SUSARs) and are described in Section 4.4.

<table>
<thead>
<tr>
<th>Causality by the investigator or by the sponsor</th>
<th>Listed in the reference document</th>
<th>Unlisted in the reference document</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related</td>
<td>198</td>
<td>32</td>
<td>230</td>
</tr>
<tr>
<td>Unrelated</td>
<td>NA</td>
<td>NA</td>
<td>32</td>
</tr>
</tbody>
</table>
A total of **22 related to the study** cases that referred to 21 subjects, were received with fatal outcome and they are described in Section 4.3.

**A total of 230 cases assessed as related to the study (by the investigator or/sponsor) have been analyzed in the current document.** These related cases will be further mentioned as SAR (Serious Adverse Reaction).

179 SAR cases were reported from induction phase and 51 - from maintenance phase.

32 cases were considered as unrelated to the study, they are summarized in the line listing of unrelated cases (cf Appendix 4). 7 of them were reported with fatal outcome.

None pregnancy case was received during the 8-years reference period.

### 3.3 Subject’s characteristics

A total of **481** subjects have been included to the CORAL study (246 and 235 in the R-ICE arm and in the R-DHAP arm respectively), **245** subjects have been randomized to the maintenance phase since February, 04 2004.

A total of **153** subjects experienced serious adverse events (SAE) during the period between July 03, 2003 and July 02, 2011.

Of them, a total of **141** subjects experienced serious adverse reactions (SAR). Subject’s age was ranged between 19 and 67-year-old with a mean age of 56-year-old. There were 85 male and 56 female patients.

During induction, 116 of 481 included patients experienced SAR.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total Number of subjects included</th>
<th>Nb SAR reports</th>
<th>Nb of patients Involved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ICE +/− BEAM</td>
<td>246</td>
<td>75</td>
<td>49 patients (19.9%)</td>
</tr>
<tr>
<td>R-DHAP +/− BEAM</td>
<td>235</td>
<td>104</td>
<td>67 patients (28.5%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>481</td>
<td>179</td>
<td>116</td>
</tr>
</tbody>
</table>

*Table I: SARs and number of patients involved during induction*
During maintenance phase, 35 patients of 245 randomized, developed at least one SAR

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total Number of subjects included</th>
<th>Nb SAE reports</th>
<th>Nb of patients involved (% of randomized to the arm subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>124</td>
<td>35</td>
<td>23 subjects (18.5%)</td>
</tr>
<tr>
<td>Observation</td>
<td>121</td>
<td>16</td>
<td>12 subjects (13.2%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>245</td>
<td>51</td>
<td>35</td>
</tr>
</tbody>
</table>

*Table II: SARs and number of patients involved during maintenance*

4. **Summary of the serious adverse reactions**

4.1  **Induction phase: Summary of the serious adverse reactions by SOC**

**R-ICE versus R-DHAP**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Arm R-ICE +/- BEAM, ASCT</th>
<th>Arm R-DHAP +/- BEAM, ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total of patients included</strong></td>
<td>246</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia b)</td>
<td>21</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Bicytopenia</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hematotoxicity</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>11</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Atrial fibrillation a)b)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac insufficiency a)b)</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest a)b)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
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GELARC – Annual Safety Report-Coral–09August 2011 – Pharmacovigilance@gela.org
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*a some events have been associated with fatal outcomes
*b some events have been declared as suspected unexpected serious adverse reaction
Summary of the induction SARs by SOC and by arm

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4.2 Maintenance phase: Summary of the serious adverse reactions by SOC

In order to compare the 2 maintenance arms: with rituximab and without rituximab, all SAE cases from the maintenance either related or unrelated to the study are summarized in the table below. 11 additional cases from the maintenance phase were assessed as unrelated (*) to the study, 6 from observation arm, and 5 from rituximab arm.

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<tr>
<td><strong>Nervous system disorders</strong></td>
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<tr>
<td>Leukoencephalopathy a)b)</td>
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<tr>
<td>Hypoesthesia</td>
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<td>Paresis</td>
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<tr>
<td>Loss of consciousness</td>
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<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>3</td>
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<td>2</td>
</tr>
<tr>
<td>Acute Renal failure</td>
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</tr>
<tr>
<td>Renal Acidosis Tubular b)</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Nephropathy toxic</td>
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<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Interstitial pneumonitis</td>
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</tr>
<tr>
<td>Pulmonary infiltration</td>
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<td>-</td>
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</tr>
<tr>
<td>Pneumopathy</td>
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<td>-</td>
<td>1</td>
</tr>
<tr>
<td><strong>Social circumstances</strong></td>
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<td>-</td>
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</tr>
<tr>
<td>Social stay hospitalization</td>
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<tr>
<td><strong>Total</strong></td>
<td>62</td>
<td>40</td>
<td>22</td>
</tr>
</tbody>
</table>

*a some events have been associated with fatal outcomes
b some events have been declared as suspected unexpected serious adverse reaction
*unrelated cases

### 4.3 Fatal cases

A total of 22 related to the study cases were reported with fatal outcome, they involved 21 patients. Of them, 8 subjects were from R-DHAP arm, 6 from R-ICE arm and 7 cases involved the subjects who were randomized to the maintenance phase, 5 from the arm with rituximab and 2 - from the observation arm.
## Table of Adverse Events

<table>
<thead>
<tr>
<th>SAE number</th>
<th>inclusion number</th>
<th>SAE occurrence</th>
<th>chemotherapy regimen</th>
<th>MedDRA reaction</th>
<th>LLT:</th>
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<tbody>
<tr>
<td>002</td>
<td>5003101071002</td>
<td>Induction</td>
<td>R-DHAP</td>
<td>Septic shock</td>
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<tr>
<td>009</td>
<td>5003603201001</td>
<td>Induction</td>
<td>R-DHAP</td>
<td>Neutropenic sepsis</td>
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<td>5003601601402</td>
<td>Induction</td>
<td>R-DHAP</td>
<td>Respiratory failure</td>
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<td>Induction</td>
<td>R-DHAP</td>
<td>Septicemia Gram-Negative</td>
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<td>5003619501010</td>
<td>Induction</td>
<td>R-DHAP</td>
<td>Respiratory failure</td>
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<td>Induction</td>
<td>R-DHAP</td>
<td>Pneumonia</td>
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<td>252</td>
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<td>Induction</td>
<td>R-DHAP</td>
<td>Cardiac insufficiency</td>
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<td>303 304</td>
<td>5003606301012</td>
<td>Induction</td>
<td>R-DHAP+BEAM</td>
<td>Septicemia candida CMV infection</td>
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<td>013</td>
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<td>R-ICE</td>
<td>Cardiac arrest</td>
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<td>Induction</td>
<td>R-ICE</td>
<td>Septic shock</td>
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<td>R-ICE</td>
<td>Septic shock</td>
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<td>Induction</td>
<td>R-ICE</td>
<td>Septic shock</td>
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</tr>
<tr>
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<td>5003616501005</td>
<td>Induction</td>
<td>R-ICE+BEAM</td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>206</td>
<td>5003606301045</td>
<td>Induction</td>
<td>R-ICE+BEAM</td>
<td>Septic shock</td>
<td></td>
</tr>
<tr>
<td>127</td>
<td>5003601401602</td>
<td>Maintenance</td>
<td>Rituximab</td>
<td>Myocarditis</td>
<td></td>
</tr>
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<td>Maintenance</td>
<td>Rituximab</td>
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<td>5003601401004</td>
<td>Maintenance</td>
<td>Rituximab</td>
<td>Leukoencephalopathy</td>
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<td>Rituximab</td>
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<td>Maintenance</td>
<td>Observation</td>
<td>Myelodysplastic syndrome</td>
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<td>293</td>
<td>5003606301207</td>
<td>Maintenance</td>
<td>Observation</td>
<td>Urothelial carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

These fatal cases were assessed as SUSARs and are described in the Section 4.4.

In addition, 7 fatal SAEs were assessed as unrelated to the study (see line listing of unrelated cases, Appendix 4): 2 patients died after inclusion but before starting the study treatment, 2 other deaths occurred after the lymphoma progression and new chemotherapy regimen (SAE
cases 098, 101, 172, 197). One patient died during observation period of Septicemia, 3 months after the ASCT (SAE case 290)

2 patients died of esophagus (SAE case 274) and hepatic (SAE case 263) carcinoma. In the case 274, the patient completed the induction treatment with R-ICE on 17/12/2004, he was not randomized to the maintenance phase because of induction treatment failure. On 06/01/2005 he was diagnosed with esophageus carcinoma and died a month later of this event. The event of esophageus carcinoma was assessed as unrelated to the study.

In the case 263, the patient completed his induction phase with R-DHAP and then the maintenance phase with rituximab on 02/03/2005. He was diagnosed with hepatic adenocarcinoma on 24/04/2007 and died from this event one year later. The investigator assessed the event as unrelated to the study drugs.

### 4.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

32 SARs were assessed as being unexpected according to the study drugs reference documents. They involved twenty nine (29) SUSARs notifications, 2 of them were further re-evaluated by the investigator, and consequently nullified.

**SUSARs occurred in the induction phase – R-ICE Regimen**

**SAE 013** (patient incl. N 5003605301601)

**MedDRA LLT:** CARDIAC ARREST  
**Outcome:** Fatal  
This case occurred in NEW-ZEALAND and referred to a 61-year-old male subject with a past medical history of aortic stenosis. The patient was included in the arm R-ICE of the study, he received 3 complete cycles of R-ICE between 05 April 2004 and 05 June 2004. On 20 June 2004, 15 days after the last study drugs administration, the patient died suddenly. The investigator presumed that the patient died of a myocardial event. The investigator assessed the event as unrelated to study drugs. No more details were reported.

**SAE 053** (patient incl. N 5003602901002)

**MedDRA LLT:** PNEUMONIA STREPTOCOCCAL  
**Outcome:** Recovered  
This case occurred in ISRAEL and referred to a 64-year-old male subject. Patient received R-ICE regimen from 28 January 2005 to 07 February 2005. On 17 February 2005, the patient developed cavitating pneumonia associated with non-serious bilateral hearing loss, probably related to carboplatin. Following to the bronchoalveolar lavage, Streptococcus pneumoniae was identified in the sputum. The patient was prescribed intravenous ceftriaxon and recovered on 06 March 2005 from the cavitating pneumonia. The outcome of the ototoxicity is unknown, carboplatin was permanently stopped. The investigator assessed the event of cavitating pneumonia as related to the study.
SAE 082 (patient incl. N 5003101131030)
MedDRA LLT: SEPTIC SHOCK
Outcome: Fatal
The case was reported from France and involved a 48-year-old female patient with a history of irregular tachycardia and cardiac standstill. The patient had received R-ICE regimen between 22 June and 04 August 2005. Twelve days after the second cycle of R-ICE treatment, on 16 August 2005, she died of septic shock probably due to bone marrow aplasia, not documented. The investigator assessed the event as related to the study drugs.

SAE 083 (patient incl. N 5003603701004)
MedDRA LLT: SEPTIC SHOCK
Outcome: Fatal
The case reported from Switzerland and involved a 64-year-old male patient. He started R-ICE regimen on 12 August 2005. On 18 August 2005, 6 days after the last R-ICE administration, he experienced status febrile and progression of neutropenia. He was hospitalized and prescribed antibiotics. The patient’s status gradually decreased and he died on 01 September 2005 of multiorgan failure due to septic shock in febrile neutropenia, two weeks after the onset. The investigator assessed the event as definitely related to the study treatment.

SAE 162 (patient incl. N 5003604801014)
MedDRA LLT: LEUKOENCEPHALOPATHY
Outcome: Recovered
This case occurred in Republic Czech and referred to a 63-year-old male subject. Past medical history included hypertension and mild renal failure of prerenal etiology. The patient was included in the R-ICE arm of the study. On 19 February 2007, the patient completed his first cycle of chemotherapy. On 21 February 2007, reported as day 3 of treatment, the subject developed life threatening leukoencephalopathy and cardiac arrhythmia. Treatment with rituximab, carboplatin, ifosfamide and etoposide was permanently discontinued. The patient was considered recovered with completely restored neurological and renal functions, normal EF, he was discharged on 12 April 2007. The investigator assessed the event as related to the study drugs.

SAE 175 (patient incl. N 5003102161413)
MedDRA LLT: SEPTIC SHOCK
Outcome: Fatal
This SAE was reported from France and involved a 49-year-old male patient experienced septic shock 5 days after the first cycle of R-ICE. He died on 05 November 2006, two days after the onset. No more details given. The investigator assessed the event as related to study drugs.

SUSARs occurred in the induction phase – R-ICE Regimen + BEAM

SAE 159 (patient incl. N 5003616501005)
MedDRA LLT: SEPSIS
Outcome: Fatal
This case was reported from United Kingdom and referring to a 59-year-old female subject. Past medical history included diffuse large B-cell lymphoma. The patient was included in the arm R-ICE of the Coral study and received 3 cycles of rituximab, etoposide, carboplatine, ifosfamide and G-CSF from 03 November 2006 to 20 December 2006 that were well tolerated. On 11 February 2007 the subject has received a consolidation treatment with BEAM (BCNU, etoposide, cytarabine and melphalan) and underwent autologous stem cell
transplantation (ASCT) on 14 February 2007 that was complicated with severe neutropenia. On 16 February 2007, patient presented with fever at 38.8°C, Hb was 6.4 g/dl, leucocytes 0 and platelets 9 Giga/l. The patient developed acidosis and acute renal failure. Despite the intensive care with intravenous antibiotics and hydration, the patient expired on 21 February 2007 due to sepsis and multi-organ failure (intestinal, marrow, cardiac and renal failure). The investigator assessed the relationship of these events as unrelated to the study drugs.

SAE 206 (patient incl. N 5003607201045)

MedDRA LLT: SEPTIC SHOCK
Outcome: Fatal
This case occurred in Germany and referred to a 48-year-old male subject. Past medical history included diffuse large B-cell lymphoma, sleep apnoea syndrome, chronic obstructive pulmonary disease, Hepatitis B reactivation. The patient was included to the arm R-ICE on 07 May 2007.
On 03 August 2007, patient was hospitalized for receiving the consolidation treatment with BEAM and a graft. On 13 August 2007, he presented with fever and diarrhea in a context of neutropenia, following by septic shock and was transferred to the intensive care unit. Then, he developed a bladder tamponade associated with hemorrhagic cystitis and anuria, so a catheter was placed. The patient’s health status progressively deteriorated and he was put under artificial respiration. He presented a circulatory failure with a supraventricular tachycardia. The patient died on 18 August 2007 of multiple organ failure in a context of pancytopenia.
The investigator assessed the relationship of these events as possibly related to the study.

SAE 254 (patient incl. N 5003610501031)

MedDRA LLT: VENOOCCLUSIVE DISEASE
Outcome: Recovered/resolved with sequelae
This case was reported from IRELAND and referred to a 54-year-old male subject. Past medical history was diffuse large B-cell lymphoma. The patient was included in the arm R-ICE of the Coral study and received 3 cycles of rituximab, etoposide, carboplatine, ifosfamide and G-CSF from March 2008 and April 2008. On 27th June 2008, the patient was admitted at the hospital for suspicion of venoocclusive disease. The investigator assessed the relationship of this event as being related with the study drugs. Follow up information has been received from the site on 05 September 2008. The patient received a consolidation cycle with BEAM (carmustine, etoposide, cytarabine, melphalan) from 5 to 11 June 2008 and underwent the autologous stem cell transplantation on 11 June 2008. On 26 June 2008, he had elevated liver function tests (LFTs) especially elevated bilirubin, distended abdomen and tender hepatomegaly, he also developed concurrent sepsis of unknown origin that was managed by antibiotics. Abdominal ultrasound and liver Doppler revealed hepatomegaly, ascite, portal vein patent with no flow reversal in hepatic veins. On 30 June 2008, the probable multifactorial liver damage secondary to sepsis, drugs or venoocclusive disease (VOD) was suspected. The corrective treatments included supportive care, fluid balance management, and diuretic therapy. On 30 June, LFTs were improving; bilirubin was stabilized (40-50) on 20 July, patient’s weight back to baseline on 10 July, diuretics and antibiotics were discontinued on 15 and 25 July respectively. The patient was considered recovered from VOD with sequelae on 20 July 2008, although his LFTs were persistently abnormal. On 29 July 2008, the PET scan showed progressive lymphoma disease. Despite further chemotherapy with gemcitabine, vinorelbine the patient’s lymphoma continued progressing. The patient expired on 01st of September 2008 of progressive disease. The follow up information regarding study drugs dosing and concomitant treatment has been received from the investigator on 10th of September 2008: Study drugs dosing regimen was: Rituximab, 780 mg, intravenous: 1st dose was administered on 21 March 2008, 2nd dose – on 23 March 2008, 3rd – 10 April 2008, and 4th – 01 May 2008. Rituximab was given as part of R-ICE regimen, 3 cycles 3 weekly,
includes etoposide, carboplatin, ifosfamid/mesna. Patient had rituximab previously, pre trial as part of R-CHOP regimen – rituximab 375 mg/m², cyclophosphamide, doxorubicin, vincristine and prednisolone, commenced on 28 February 2008. BEAM consolidation – from 5 to 11 June 2008. Reinfusion of stem cells 11th -12th June 2008.

**SUSARs occurred in the induction phase – R-DHAP Regimen**

**SAE 002** (patient incl. N 5003101071002)
**MedDRA LLT: SEPTIC SHOCK**
**Outcome: Fatal**
This SAE was reported from France and involved a 64-year-old male patient. He was included to R-DHAP arm on 16 October 2003 and developed pancytopenia ten days after the first cycle of the R-DHAP. He died of septic shock of non-identified origin 23 days after the onset of the event. The investigator assessed the event as related to the study treatment.

**SAE 009** (patient incl. N 5003603201001)
**MedDRA LLT: NEUTROPENIC SEPSIS**
**Outcome: Fatal**
This SAE was reported from Germany and involved a 51-year-old male patient with no relevant medical history. He was included to the R-DHAP arm and received study drugs from 14 March to 11 May 2004. On 11 May 2004 he experienced colitis, peritonitis and sepsis secondary to neutropenia. He died of hypovolemic shock two days after the onset, on 13th of May 2004. The investigator assessed the event as related to the study treatment.

**SAE 049** (patient incl. N 5003601601402)
**MedDRA LLT: RESPIRATORY FAILURE**
**Outcome: Fatal**
This case occurred in USA and referred to a 65-year-old female subject. The patient was included in the arm R-DHAP of the study. Past medical history included stage 4 diffuse large B-cell lymphoma. She received her third cycle of R-DHAP on 17 December 2004 and was undergoing stem cell harvesting and high dose GCSF. On January 3, 2005, during stem cell pheresis, she developed electrolyte abnormalities and dyspnea. She was transferred to ICU. On the next day, respiratory failure progressed, she was intubated. Chest CT showed bilateral infiltrates and pleural effusion, cardiac echo revealed ejection fraction of 50%. Right-side thoracocentesis removed of 1L of fluids. The patient experienced recurrent respiratory failure on 08 January 2005. She refused any further treatment and life-saving intervention. She expired ten days after the onset, on 13 January 2005. The investigator assessed the event as unrelated to study drugs.

**SAE 160** (patient incl. N 5003607301622)
**MedDRA LLT: SEPTICEMIA GRAM-NEGATIVE**
**Outcome: Fatal**
This SAE was reported from New Zealand and involved a 65-year-old female patient who was included to R-DHAP arm on 11 December 2006. Following to the second cycle of the R-DHAP, which was delayed because of neutropenia, she experienced a severe headache and mild renal dysfunction with blood creatinine of 0.2. She also had experienced renal failure and headache after the first cycle but her status returned to normal by the second cycle. Seven days after the second cycle she developed septic shock secondary to gram negative septicemia. Her clinical condition continued to deteriorate and she died the day after the onset, on 26 January 2007. The investigator assessed the event as related to the study drugs.
SAE 173 (patient incl. N 5003619501010)
**MedDRA LLT: RESPIRATORY FAILURE**
**Outcome: Fatal**
This case was reported from United Kingdom and referring to a 45-year-old female subject. The subject received her 2nd cycle of R-DHAP regimen on March 15, 2007. On April 4, 2007 she suffered from respiratory arrest due to chest sepsis. Chest X-ray showed ongoing basal atelectasis. She was intubated and ventilated and prescribed antibiotics. The next day she was not improving requiring increasing amounts of noradrenalin. She died on 6 April 2007. The investigator assessed the event as unrelated to study drugs.

The next 4 SAEs describe serious adverse reactions in the same patient occurred at the same period of time and linked by the final fatal outcome (patient incl. N 5003604701012).

SAE 178
**MedDRA LLT: FEBRILE NEUTROPENIA**
**Outcome: Not yet recovered at death**
SAE 250
**MedDRA LLT: RESPIRATORY INSUFFICIENCY**
**Outcome: Not yet recovered at death**
SAE 251
**MedDRA LLT: EMBOLIC CEREBRAL INFARCTION**
**Outcome: Not yet recovered at death**
SAE 252
**MedDRA LLT: CARDIAC INSUFFICIENCY**
**Outcome: Fatal**
This case was reported from Switzerland and involved a 62-year-old male patient who experienced severe febrile neutropenia on 30 April 2007, 5 days after the first cycle of the R-DHAP. He was admitted to the intensive care unit. Secondary to febrile neutropenia he also experienced respiratory and cardiac insufficiency, tachycardia, atrial fibrillation and thromboembolic cerebral infarction. There was no evidence of a source of infection. He died on 04 May 2007, 4 days after the onset of cardiac insufficiency. The investigator assessed the events as definitely related to the study treatment.

SAE 193 (patient incl. N 5003623501405).
**MedDRA LLT: PEUMONIA**
**Outcome: Fatal**
This case occurred in UNITED KINGDOM and referred to a 58-year-old male subject. Past medical history included diffuse large B-cell lymphoma. The patient was included in the arm R-DHAP of the study on 05 July 2007 and received his first cycle on 07 July 2007. On 26 July 2007 he was found dead at home. As per autopsy, the cause of the death was lobar pneumonia (left upper lobe) due to or as a consequence of lymphoma: “the immediate cause of death appears to be lobar pneumonia. Predisposing factors for pneumonia would include neutropenia (which may be induced either by the lymphoma itself or by the chemotherapy) and infiltration of the liver by lymphoma”. The investigator did not report the relationship of the death with study drugs.

**SUSARs occurred in induction phase – Regimen R-DHAP + BEAM**

The 3 cases above occurred in the same time. They were all deemed as the reason of the death (patient incl. N 5003606301012).
SAE 228
MedDRA PT: CARDIAC ARREST
Outcome: Ongoing at death
SAE 303
MedDRA PT: CANDIDA SEPTICEMIA
Outcome: Fatal
SAE 304
MedDRA PT: CMV INFECTION
Outcome: Fatal
This case was reported from Australia and referring to a 64-year-old female subject. Past medical history included diffuse large B-cell lymphoma since March 2007. The patient achieved a brief remission with chemotherapy but relapsed on October 2007. The patient was included in the arm R-DHAP of the Coral study on 11 October 2007. She underwent autologous stem cell transplant (ASCT) on 17 January 2008. The patient developed anemia and neutropenia and an episode of nausea and vomiting associated with diarrhea after the stem transplant. The patient collapsed and developed hypoxic cardiac arrest on 21 January 2008 following to the aspiration of vomitus. She was resuscitated and admitted to the Intensive Care Unit. She showed some signs of recovery initially but that was followed by the gradual deterioration of her condition. Subsequently she developed acute renal failure, CMV enterocolitis, pulmonary infection, candida septicemia; she died on 12 February 2008. The investigator assessed the relationship of these events as related to study drugs.

SAE 285 (patient incl. N 5003101071643)
MedDRA LLT: HYPONATREMIA
Outcome: Recovered
The case reported from France and involved a 58-year-old female patient. No past/ongoing medical history was reported. On 01 November 2007, the patient started treatment with rituximab, dexamethasone and cisplatin. On day 1 of cycle 1, the patient received 550 mg rituximab, cisplatin 146 mg and dexamethasone 40 mg. On day 2 of cycle 1, the patient received rituximab 548 mg cytarabine 5840 mg and dexamethasone 40 mg. From day 6- day 13 the patient started with G-CSF (dosing unknown). On 20 November 2007, the patient started the second cycle with rituximab 550 mg, dexamethasone 40 mg and cisplatin 146 mg on day 1. On day 2 of cycle 2, the patient received cytarabine 5840 mg and dexamethasone 40 mg. From day 6- day 13 the patient started with G-CSF 526 ug per day. On 11 December 2007, the patient started the third cycle with rituximab 563 mg, dexamethasone 40 mg and cisplatin 150 mg. On day 2 of cycle 2, the patient received cytarabine 6000 mg and dexamethasone 40 mg. On day 3 and day 4 for all the three cycles, the patient received 40 mg dexamethasone. From day 6 day 13, the patient received G-CSF 263 ug per day. On 03 December 2007, 7.50 x 10^6 stem cells from peripheral blood were collected. On 06 December 2007, the patient experienced cutaneous reaction subclavicular left resulting in hospitalisation. Lab tests performed showed hemoglobin 8.8 g/dl, leukocyte 8.8 giga/l and platelets 91 giga/l. In response to the event, the patient received a corrective treatment of pristinamycine. On 08 December 2007, the event of cutaneous reaction subclavicular left resolved and the patient was discharged from the hospital. On 21 February 2008, the patient carried out a consolidation treatment with BCNU 455 mg, etoposide 12220 mg, cytarabine 2440 mg and melphalan 213 mg. On the following day, the patient experienced hyponatremia which was medically significant. Hemoglobin was 14 g/dl, leukocytes were 13.3 giga/l and platelets were 461 giga/l. In response to the event the patient received furosemide as a corrective therapy. Three days later, the event of hyponatremia resolved. On 27 February 2008, the patient had 7.50 x 10^6/ kg cd3+ cells infused. On 29 February 2008, the patient experienced mucositis grade 3 resulting in hospitalisation. Lab tests performed showed haemoglobin as 10.3 g/dl, leukocyte 0.4 giga/l and platelet 92 giga/l. In response to the event, the patient received a corrective therapy with morphine sulphate and local
treatment. On 02 March 2008, the patient experienced renal failure which was considered to be medically significant. Lab tests showed haemoglobin as 9.9 g/dl, leukocyte 0.1 giga/l and platelet 17 giga/l. In response to the event, the patient received a corrective therapy with furosemide. On 07 March 2008, neutrophils > 500 giga/l were transplanted. On the following day, neutrophils > 1000 giga/l were transplanted. On the same day, the patient experienced pulmonary embolism resulting in prolonged hospitalisation. Hemoglobin was 8.4 g/dl, leukocyte 9 giga/l and platelets 19 giga/l. In response to this event, the patient received heparine and 6 utp. On 13 March 2008, platelets > 20,000 giga/l were transplanted. On 20 March 2008, the events of pulmonary embolism and renal failure resolved. On 31 March 2008, the event of mucositis resolved and the patient was discharged from the hospital. The events cutaneus reaction subclavicular left, mucositis, pulmonary embolism, hyponatremia and renal failure had resolved. The investigator assessed the events of mucositis and hyponatremia to be related to the study drugs - rituximab, dexamethasone, cisplatine, cytarabine and G-CSF.

**SUSARs occurred in the maintenance phase – Rituximab Regimen**

The DSMC that met in August 2007 (see appendix 5) assessed the 2 following cases as non-related to the study. Nevertheless these cases were assessed by the investigators as related with the study so that will be maintained by the Gelarc Pharmacovigilance as SUSARs.

**SAE 126** (patient incl. N 5003601401604)  
**MedDRA LLT:** PNEUMOCYSTIS JIROVECI PNEUMONIA  
**Outcome:** Recovered  
This case was reported from Sweden and referring to a 62-year-old female subject. The patient was included in the arm R-DHAP of the study on 28 October 2005. She has completed 3 cycles of R-DHAP and had autologous stem cell transplantation on 19 January 2006 with high doses of chemotherapy, then she was randomized to the rituximab maintenance arm. Last rituximab administration was done on June 14, 2006. On June 20, 2006 she developed fever and cough. She was hospitalized on July 17, 2006, the bronchoalveolar lavage revealed *Pneumocystis jiroveci*. She was prescribed sulfamethoxazol and trimetoprim. Treatment with rituximab was remained ongoing. She recovered on 05 August 2006. The investigator assessed the event as related to the study drugs.

**SAE 127** (patient incl. N 5003601401602)  
**MedDRA PT:** MYOCARDITIS  
**Outcome:** Fatal  
This case was reported from SWEDEN and referred to a 43-year-old male subject. Past medical history included diffuse large B-cell lymphoma with tonsil localization. From December 2000 to May 2001, he received 8 cycles of CHOP and local radiotherapy and reached a complete remission. Progression was documented in July 2004 with tonsil, cervical node, PS 0, LDH elevated, FEVG normal. He was included to the Coral study on 04 August 2004 in the arm R-ICE and has completed his induction therapies: 1st cycle on 09 August 2004, 2nd 30 August 2004, 3rd 24 September 2004 at the same dose. Each cycle complicated with an hematotoxicity of grade 3. He was in incomplete remission at the restaging in October 2004. BEAM regimen delivered at full dose with stem cells transplant on 01 November 2004. Time to recovery was 11 days with infection Grade 4 life threatening with ICU for 3 days and recovery. Randomisation rituximab: 1st cycle was done on 14 December 2004, cycle 6, the last dose of rituximab, - on 11 October 2005 with one report of adverse
event on February 2005- transient neutropenia. He was in complete remission, well being full time working. Several episodes of infection in the follow up were treated with antibiotics, the last one in June 2006 due to low level of IgM, IgG. No gamma globulins prophylaxis were given. Sudden death occurred on 06 August 2006, 10 months after the last rituximab dose, he was found dead in this bed. Autopsy report: **myocarditis** with acute inflammation of the myocardium, cardiac insufficiency. The investigator is concerned by the possible relation with hypogamma globulinemia, related to rituximab and the myocarditis almost one year after last dose.

**SAE 129** (patient incl. N 5003616301615)
**MedDRA PT:** PNEUMONIA
**Outcome:** Fatal
This case reported from Australia and involved a 64-year-old male subject with a history of lobectomy due to lung cancer on 1991. He was included to the arm R-ICE on 29 September 2005. The patient completed his cycles of R-ICE, a consolidation with BEAM and underwent autologous stem cells transplantation on 15 December 2005. The last dose of rituximab was given on 17 May 2006. On the 8th month of maintenance therapy with rituximab, on 15 August 2006 he developed **pneumonia** due to pneumocystis carinii. He died 20 days after the onset. The investigator assessed this event as related to the study.

**SAE 153** (patient incl. N 5003610501402)
**MedDRA PT:** RENAL ACIDOSIS TUBULAR
**Outcome:** Recovered with sequelae
This case was reported from Ireland and referring to a 59-year-old male subject with a history of hypertension and asthma. No allergies were reported. Concomitant medications included allopurinol, sulfamethoxanolen trimethoprim, valacyclovir, lansoprazole, fluconazole, erindoprime, amloidipine besylate, acetaminophen, piperacillin sodium, tazobactam sodium, furosemide, cyclizine, gentamycine sulfate, meropenem, amphotericin B and amikacin. The patient received 3 cycles of R-DHAP as induction therapy and consolidation therapy with BEAM and autologous stem cell transplantation on 14 December 2006. On 28 December 2006 he was randomized to the rituximab maintenance arm. On January 5, 2007 the subject developed **type IV renal tubular acidosis** causing refractory grade 2 hyperkalemia. Treatment included calcium sulfonate, sodium bicarbonate and levoglutamide. The event resolved with sequelae on January 11, 2007. Sequelae were not specified. The investigator assessed the event as related to study drugs.

**SAE 190** (patient incl. N 5003601401004)
**MedDRA PT:** LEUKOENCEPHALOPATHY
**Outcome:** Fatal
This case occurred in Sweden and referred to a 63-year-old female subject. Past medical history included diffuse large B-cell lymphoma. The patient was included in the arm R-DHAP of the study on 27 September 2006. The third and the last dose of rituximab, prior to onset of the event, was done on 03 May 2007. On 26 June 2007, the subject developed fever, mental disturbances (mental disorder), varicella lesions on the skin and varicella zoster virus seen in blisters. The event was assessed as life threatening. The patient received antiviral therapy. The treatment with rituximab was permanently discontinued. Relevant laboratory values included hemoglobin 10.5 g/dl, leukocytes 11.1 giga/l, and platelets 162 giga/l. A brain CT scan on 01 July 2007 that was "without remarks". The subject's spinal fluid showed no varicella or malignant cells. On 17 July 2007, the subject was still unconscious and the event was not resolved. The initial diagnosis encephalitis was changed to varicella zoster vasculopathy with associated demyelination. The patient died on 26 August 2007 of vasculopathy due to varicella zoster infection. The results of the autopsy showed neither signs of lymphoma in the brain nor in the body. In the brain perivascular demyelination was...
found in the Pons consistent with leukoencephalopathy. The investigator assessed the event as definitely related to study drugs.

**SAE 261** (patient incl. N 5003601401002)
**MedDRA PT:** ACUTE LEUKEMIA
**Outcome:** Fatal
This case was reported from Sweden and referring to a 58-year-old male subject. Past medical history: Diffuse large B-cell lymphoma since November 2003 and Gastritis since March 2004 treated by lansoprazol and fluconazol as prophylaxis. The patient achieved a partial response after 6 courses chemotherapy and relapsed on April 2004. The patient was included in the arm R-ICE of the Coral study on 15 April 2004. He underwent autologous stem cell transplantation on 06 July 2004 then he was randomized in the rituximab maintenance arm on 22 July 2004. The patient developed non serious isolated neutropenia on August 2004 and pneumonia on January 2005. On December 2005, the patient experienced bronchitis possibly due to hypogammaglobulinemia which was assessed by the investigator as related to rituximab. The last dose of rituximab was given on the 09 June 2005. The patient was diagnosed with Acute Non-Lymphocytic Leukemia on 15 June 2006 (25 months post transplantation or 1 year after the last rituximab dose administered). At this moment he was on unconfirmed complete response of lymphoma. He was prescribed with antileukemic treatment but died on 09 July 2006. The investigator assessed the relationship of this event as related to study drugs.

**SAE 282** (patient incl. N 5003604901603)
**MedDRA LLT:** ACUTE BRONCHOPNEUMONIA
**Outcome:** Fatal
This case was reported from Israel and referring to a 62-year-old female. Past medical history: Diffuse large B-cell lymphoma, asthma since 1979 treated by ventolin and symbicort turbuhaler. The patient was included in the arm R-DHAP of the Coral study on 03 March 2008. The patient developed acute renal failure on April 2008. She received the consolidation treatment on the 12 June 2008 and underwent autologous stem cell transplantation on 18 June 2008 then she was randomized in the rituximab maintenance arm on 19 June 2008. The patient experienced CMV infection treated by ganciclovir and superficial bleeding after removal porthacat on July 2008. Then she had thrombocytopenia on August 2008 required platelets transfusion. On 04th of September, 2008 the patient was found in a comatous state with no response to stimuli, Babinski sign was positive with decerebration signs, brain CT scanner did not show haemorrhage or infarct. On the 07 September 2008 no change in the neurological status was observed and oxygen desaturation. The patient was intubated and respirated. The patient was treated by antibiotics, repeated plasmapheresis but no change in the neurological status was observed. The patient status deteriorated and she died on 13th of September, 2008.

Post mortem examination was performed. The autopsy report summary stated that the most prominent and severe changes are related to the lungs and are manifested in diffuse alveolar damage, which is most probably a result of chemotherapy and a CMV infection. In addition, changes of a very severe and chronic localized bronchopneumonia, areas of haemorrhagic and thrombotic necrosis in a few small blood vessels were observed. Extensive hypoxia changes were observed in various organs (areas of fatty and parenchymatic necrosis in the pancreas, extensive infarction in the brain, a centrolobular necrosis in the liver and a tubular necrosis in both kidneys). No signs of lymphoma involvement were noted in any of organs examined, in the lymph nodes or in the bone marrow. The final diagnosis is acute bronchopneumonia, extensive diffuse alveolar damage. Hypoxia is a part of diagnosis.
SUSARs occurred in the maintenance phase – Observation

SAE 292 (patient incl. N 5003606301604)
Reaction / Event (MedDRA LLT): Myelodysplastic syndrome
Outcome of Reaction: Fatal
This case was reported from Australia and is referring to a 65-year-old male subject. Past medical history: Asthma since 1950 and gout since 1975. Diffuse large B-cell lymphoma with initial involvement of the right orbital area with mixed lymphoid infiltrate since 2002. The patient received CHOP-like as initial treatment from November 2002 to January 2003 followed by the radiotherapy with 30 Gy. He remained on partial response after the first line treatment until a relapse on 21th May 2004 with right cervical and supraventricular lymph node involvement. The patient was included in the arm R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone and lenograstime) of the Coral study on 1st June 2004 and received his 3 cycles of chemotherapy between 18th June 2004 and 03rd August 2004. The patient developed upper respiratory tract infection on 26 July 2004 and recovered 2 days later. He received the consolidation treatment with BEAM (carmustine, etoposide, melphalan and cytarabine) on the 15 September 2004, and he underwent the autologous stem cell transplantation on 21 September 2004. On the next day he was randomized into the observation maintenance arm. The patient had neutropenia and diarrhea 3 days after the transplantation that lasted 10 days. On 14 October 2004 he developed acute renal failure and nephrotoxicity with creatinine level elevated until May 2005. On 05th of February 2008 the patient developed myelodysplastic syndrome with a severe marrow failure. Severe anaemia and thrombocytopenia required a huge transfusion support. The patient status deteriorated and he died on 22th of June, 2009. The investigator assessed the relationship of myelodysplastic syndrome as related to the Coral study drugs.

SAE 293 (patient incl. N 5003606301207)
Reaction / Event (MedDRA llt): Urothelial carcinoma
Outcome of Reaction: Fatal
This case was reported from Australia and referring to a 41-year-old male subject. Past medical history: Hypertension since 2000 and dental decay over many years. Diffuse large B-cell lymphoma with initial gastric involvement. The patient received 2 cycles of CHOP-like as initial treatment from July 2004 to August 2004. He progressed after the second cycle on the 26th of August, 2004 with inguinal, mediastinal, para-aortic, mesenteric nodes involvement and pleural effusion, stomach and duodenal involvement. The patient was included in the arm R-ICE (Rituximab, Etoposide, Carboplatine, Ifosfamide, Lenograstim) of the Coral study on 27th of August, 2004 and received his 3 cycles of chemotherapy between 30th of August, 2004 and 14th of October, 2004. He received the consolidation treatment with BEAM (carmustine, etoposide, melphalan and cytarabine) on the 17th November 2004 and underwent the autologous stem cell transplantation (ASCT) on 23 November 2004. On 02nd of December he was randomized into the observation maintenance arm. During the study, in December 2004 and February 2005 the patient had dental abscess and dental caries requiring full upper dental clearance. On the 20th of March 2008, 3.5 years after the ASCT, the patient was diagnosed with high grade urothelial carcinoma, he was treated with 4 cycles of cisplatin and gemcitabine. CT Scanner was performed on 13th of May, 2009 and revealed a reoccurrence of urothelial carcinoma. The patient died on 09 October 2009. The investigator assessed the relationship of urothelial carcinoma as related to the Coral study drugs.
2 SAE cases were initially reported as SUSARs but according to the follow-up information, they were reassessed as related and expected for the case 043 and as unrelated to the study for the case 098.

**SAE 043** (patient incl. N 5003631201611), **NEUTROPENIC SEPSIS**
This SAE reported from Germany and involved a 61-year-old female patient who developed sepsis with neutropenia, tachyarrhythmia and acidosis on 21 December 2004, 16 days after the first cycle of the R-DHAP. Sepsis symptoms decreased four days after the onset but the patient died on 29 December 2004, five days after the onset probably of lymphoma progression. LDH were elevated from 800 to 2000 UI/L. The investigator assessed the event as related to the study drugs. Cause of death both neutropenic sepsis and lymphoma progression according to the investigator.
Additional information given by the investigator on 16 July 2007: the patient was considered as recovered from sepsis on 27 December 2004 but she died of lymphoma progression on 29 December 2004. Following this additional information the sponsor reevaluated the case as related and expected.

**SAE 098** (patient incl. N 5003610201612), **PULMONARY ASPERGILLOSIS**
This case was reported from Germany and involved a 57-year-old female subject. The patient was included in the R-ICE of the study and received his first cycle of R-ICE on 13 April 2005. On 09 July 2005, she received the consolidation treatment with BEAM. On 13 July 2005, the patient developed fever and neutropenia. Further investigations evidenced pulmonary infiltrates and an aspergillosis was diagnosed. The patient’s status gradually decreased and she died on 23 July 2005.
According to the follow up information, this event occurred after the subject’s premature withdrawal from the study. The patient received the consolidation treatment with BEAM in the frame of a progression treatment.

## 5. Overview

A total of 141 patients (29.3% of 481 included patients), presented at least one SAR, 116 (24.1%) - during the induction phase and 35 (14.3% of 245 randomized patients) - during the maintenance phase.

**Induction phase – R-ICE regimen**
A total of 246 patients were included, 19.9% of all included patients experienced SARs. A total of 75 SARs were received from this arm.

**SOC reported serious adverse reactions occurred in more than 5% of patients included in R-ICE:**
- Infections and infestations – 13.8%
SOC reported serious adverse reactions occurred in more than 1 % of patients included in R-ICE:

- Blood and lymphatic system disorders – 3.3%
- Gastrointestinal disorders – 2.8%
- General disorders and site administrations-2%
- Cardiac disorders – 2.0%
- Vascular disorders – 1.2%
- Respiratory, thoracic and mediastinal disorders – 1.2%
- Nervous system disorders – 1.2%

Induction phase – R-DHAP regimen

A total of 235 patients were included, 28.5% of included patients experienced serious adverse reaction. A total of 104 SARs were reported from this arm.

SOC reported serious adverse reactions occurred in more than 5 % of patients included in R-DHAP:

- Infections and infestations – 14.4%
- Gastrointestinal disorders – 5.5%
- Blood and lymphatic system disorders – 5.5%

SOC reported serious adverse reactions occurred in more than 1 % of patients included in R-DHAP:

- Nervous system disorders – 3.8%
- Renal and urinary disorders – 3.4%
- Cardiac disorders – 2.6%
- Metabolism and nutrition disorders – 2.6%
- Respiratory, thoracic and mediastinal disorders – 2.1%
- General disorders and administration site conditions – 1.3%

Maintenance phase – Rituximab regimen

A total of 124 subjects were randomized to the rituximab arm, 18.5% of them experienced serious adverse reactions. A total of 40 serious adverse events, either related or unrelated to the study, were received in this arm. The events are summarized in Section 4.2.

Of 40, 22 SAE were reported in Infections and infestations SOC.

Six cases were reported with fatal outcome: SAE N 127, 129, 190, 261, 282 and 263 (unrelated case), and they are described in Section 4.3 and 4.4.

Maintenance phase – Observation

A total of 121 subjects were randomized to the arm without rituximab, 13.2% of them experienced serious adverse reaction. 22 serious adverse events, either related or unrelated to the study, were received in this arm. The events are summarized in Section 4.2.
2 cases were reported with fatal outcome: SAE N 292 and 293. Both of them were considered by the investigator as a secondary malignancy, the cases are described in Section 4.3 and 4.4.

**Infections**
Infections and infestations is the SOC that contains the highest number of Serious Adverse Reactions (SAR) independently of the arm and the chemotherapy regimen. Infection was the reason of 12 subject’s deaths out of 21.
During the maintenance phase, 22 SARs were reported from the arm with rituximab and 3 - from the observational arm.

**Haematological events**
The reporting rules of the protocol required that severe haematological toxicity and febrile neutropenia with a hospitalization for less than 8 days have not to be considered as serious adverse events. Haematological toxicity is a well known adverse reaction following the chemotherapy regimen.

**Respiratory events**
3 pulmonary embolism reported from R-ICE arm versus two from R-DHAP arm. 3 cases of respiratory insufficiency or respiratory failure reported in the R-DHAP arm, two of them were fatal.
In the rituximab maintenance arm, 2 SAR occurred, pulmonary infiltration and interstitial pneumonitis, both are of infectious origin.

**Gastro-intestinal events**
During induction, 7 digestive haemorrhages were reported, 3 from R-ICE arm and 4 in R-DHAP arm.
In the rituximab maintenance phase, 3 gastrointestinal events reported: faecaloma, gastrointestinal bleeding and nausea.
None fatal event occurred in this SOC.

**Nervous system disorders**
9 neurological events have been reported from R-DHAP arm versus 3 from R-ICE arm.
In the maintenance phase, 2 neurological events were reported in each of 2 arms. A case of leukoencephalopathy with a fatal outcome reported from rituximab arm, SAE N 190. A 63-year-old patient developed neurological disturbance and varicella lesions approximately 1.5
month after the third maintenance rituximab administration. He died of leucoencephalopathy 2 months after the onset.

The second case of leucoencephalopathy was reported from the induction phase (SAE N 162), developed 3 days after the first cycle of R-ICE, the patient recovered from this event. Both cases are described in Section 4.4.

**Renal and urinary disorders**

8 cases of renal failure were reported from R-DHAP regimen versus 2 from R-ICE that probably could be explained by the cisplatine known renal toxicity.

**Neoplasms**

3 fatal SAR of secondary malignancy were reported during maintenance phase, 2 of them were reported from the observation arm and related to induction phase treatment (SAEs N 292 & 293)

The third one (SAE N 261), occurred in 58-year-old patient, who started to receive a chemotherapy treatment for his lymphoma in November 2003, he was included to R-ICE arm in April 2004 and then was randomized to rituximab maintenance in July 2004. One year after the last study rituximab, in June 2006, he was diagnosed with *acute non-lymphocytic* leukemia. He expired from this disease in July 2006.

The cases are described in Section 4.4.

6. **Conclusion**

Based on the presented data, no changes to the conduct of this study are warranted.

7. **Line-listings**

The line listings are enclosed:

- **Appendix 1**: Synopsis
- **Appendix 2**: Serious Adverse Reactions from induction phase
- **Appendix 3**: Serious Adverse Reactions from maintenance phase
- **Appendix 4**: Unrelated Serious Adverse Events

8. **DSMC**

- **Appendix 5**: DSMC recommendations dated 10 August 2007.
- **Appendix 6**: DSMC recommendations dated 03 March 2010.
Title

CORAL study: **RANDOMIZED STUDY OF ICE PLUS RITUXIMAB (R-ICE) VERSUS DHAP PLUS RITUXIMAB (R-DHAP) IN PREVIOUSLY TREATED PATIENTS WITH CD 20 POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA, ELIGIBLE FOR TRANSPLANTATION FOLLOWED BY RANDOMIZED MAINTENANCE TREATMENT WITH RITUXIMAB**

Sponsor: GELARC, CORAL group

Lymphoma groups of each country: GELA; DSHNHL; ILL, NCRI, ALLG, SAKK, MSKCC, CLSG, ISH, Nordics centers

Principal Investigator

Prof. Christian Gisselbrecht

Centres

Participating centres of study groups which have been registered according to local government rules

**Objectives**

**Part I, induction therapy:** To evaluate the efficacy and safety of ICE plus rituximab (R-ICE) in comparison with DHAP plus rituximab (R-DHAP) in previously-treated patients with CD20-positive large B-cell lymphoma eligible for autologous transplantation.

**Part II, maintenance therapy:** To evaluate the efficacy and safety of **Mabthera** maintenance therapy after transplantation.

**Primary endpoints**

**Part I, induction therapy:** Overall response rate (ORR) (Complete Response CR and Partial Response PR) **adjusted with successful mobilization** at the end of 2 and/or 3 cycles of induction chemotherapy treatment before high-dose chemotherapy and autologous transplantation.

**Part II, maintenance therapy:** Event free survival (EFS) at 2 years post transplantation: events being death from any cause, relapse for complete responders and unconfirmed complete responders, progression during and after treatment and changes of therapy

- Eligibility for transplant, toxicities with R-ICE and R-DHAP, time to progression or relapse, disease-free survival for complete responders, overall survival.

**Secondary endpoints**

- Eligibility for transplant, toxicities with R-ICE and R-DHAP, time to progression or relapse, disease-free survival for complete responders, overall survival.

**Study design**

Phase III, multicentric, open-label, randomized study

**Number of subjects**

480 patients n=240/arm

**Study Population**

- **Inclusion criteria**
  - Patient with histologically proven, CD 20+ diffuse large B cell lymphoma in 1st relapse after CR, less than PR or partial response to first line treatment
  - Aged from 18 to 65 years inclusive
  - Eligible for transplant
  - Previously treated with chemotherapy regimen containing anthracyclines with or without rituximab
  - ECOG performance status ≤ 2
  - With a minimum life expectancy of 3 months
  - Signed informed consent form prior to randomization
- **Exclusion criteria**
  - Burkitt, mantle cell, T-cell lymphoma.
  - CD 20-negative NHL
  - Documented infection with HIV or HBV disease (in the absence of vaccination).
  - Central nervous system or meningeal involvement by lymphoma.
  - Not previously treated with anthracycline-containing regimens.
  - Prior transplantation
  - Contraindication to any drug contained in the chemotherapy regimens.
  - Any serious active disease or co-morbid medical condition (according to the investigator’s decision).
  - Poor renal function (creatinin level>150μmol/l), poor hepatic function (total bilirubin level>30mmol/l, transaminases>2.5 maximum normal level) unless these abnormalities are related to the lymphoma.
  - Poor bone marrow reserve as defined by neutrophils<1.5G/l or platelets<100G/l, unless related to bone marrow infiltration.
  - Any history of cancer during the last 5 years, with the exception of non-melanoma skin tumors or stage 0 (in situ) cervical carcinoma.
  - Pregnant woman
  - Treatment with any investigational drug within 30 days before planned first cycle of chemotherapy and during the study.
  - Adult patient unable to give informed consent because of intellectual impairment

Appendix 1: synopsis
### Statistical analysis
- **Primary endpoints**
  - Part I induction: Mobilization adjusted response rate will be analyzed using chi-square test and a logistic regression to adjust for prognostic factors.

- **Secondary endpoints**
  - Part II maintenance: Event-free survival post transplant, using a stratified log-rank test. A Kaplan-Meier plot of time to first event for each treatment group will also be produced. Time to progression, overall survival and duration of response or disease free survival will be analyzed using the log rank test.

### Treatment

#### Induction:
Central randomization to one of the two treatment arms: arm A (R-ICE) and arm B (R-DHAP). Patients will be stratified according to the center, prior treatment with Rituximab, refractory disease (PR+ less than PR) and relapse < 12 months.

#### A arm
- **Induction:** 3 cycles of RICE in 3-weekly intervals.

<table>
<thead>
<tr>
<th>RICE</th>
<th>Dose</th>
<th>D-2</th>
<th>D-1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6 to D13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>(X)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Carboplatine</td>
<td>AUC (5) max 800mg</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Ifosfamide + Mesna</td>
<td>5 g/m²</td>
<td>X →</td>
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<tr>
<td>(Continuous infusion 24 h)</td>
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<tr>
<td>G-CSF (SC)</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Rituximab D-2</td>
<td>first cycle only</td>
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</tbody>
</table>

#### B arm
- **Induction:** 3 cycles of R-DHAP, 3 weeks interval.

<table>
<thead>
<tr>
<th>R-DHAP</th>
<th>Dose</th>
<th>D-2</th>
<th>D-1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6 to D13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Cisplatin c.i.</td>
<td>100 mg/m²</td>
<td>X →</td>
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<tr>
<td>Cytosine Arabinoside</td>
<td>2000 mg/m²/12 h</td>
<td>XX</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>G-CSF (sc)</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Rituximab D-2</td>
<td>first cycle only</td>
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#### Mobilization
After the two and/or third chemotherapy cycle patients will be mobilized with G-CSF for peripheral blood stem cell collection at the time of recovery. The minimum amount of stem cells required is: 2 x 10^6 CD 34+/kg.

### Consolidation
All patient in CR, CRu or PR will be submitted to consolidation with R-Beam.

<table>
<thead>
<tr>
<th>BEAM</th>
<th>Dose</th>
<th>D-6</th>
<th>D-5</th>
<th>D-4</th>
<th>D-3</th>
<th>D-2</th>
<th>D-1</th>
<th>D0</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCNU</td>
<td>300mg/m²</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>200 mg/m²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine twice daily</td>
<td>200 mg/m²/12 h</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Melphalan</td>
<td>140 mg/m²</td>
<td>X</td>
<td>A</td>
<td></td>
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</table>

### Maintenance
Prior to ASCT, patients will undergo a central randomization to Rituximab maintenance therapy (1) or observation (2) (A1, A2, B1, B2). Schedule for Rituximab maintenance is 375 mg/m² every eight weeks starting at day 28 after ASCT for a maximum of 6 doses.

### Planned start/end of recruitment
The trial will start in January 2003. The trial will start in January 2003. 480 patients will be randomized within a period of approx. five years, end of recruitment is therefore to by expected by mid/end of 2008. The minimum follow-up time after the end of the recruitment period will be 2 years, with a total study period of 7 years. Interim analysis is planned after 200 patients in year 2006.
CD20+ relapsed/refractory DLCL

R1

R-DHAP

R-DHAP

R-ICE

R-ICE

Clinical evaluation

PBPC

Evaluation

CR / PR

PD / SD

BEAM

OFF

R2

Mabthera 375 mgm²/8 weeks/12 months

Observation
### Induction Phase

#### Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Country</th>
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<th>SAE number</th>
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### Induction Phase

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#### Hepatobiliary disorders

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<th>MedDRA LLT</th>
<th>Onset Date</th>
<th>Latency last administration (D)</th>
<th>Outcome</th>
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#### Immune system disorders

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<th>Latency last administration (D)</th>
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<td>DRUG HYPERSensitivity</td>
<td>02/02/2006</td>
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</table>

(*) Suspected Unexpected Serious Adverse Reaction

Line-listing 03 July 2003 to 02 July 2011
EudraCT number: 2004-002103-32
Appendix 2: Related Serious Adverse Reactions

CORAL STUDY

09/08/2011

Induction Phase

Infections and infestations
Country

Inclusion number

SAE
number

Gender

Age

Induction Arm

MedDRA LLT

Onset Date

BELGIUM
AUSTRALIA
USA
UNITED KINGDOM
AUSTRALIA
IRELAND
ISRAEL
AUSTRALIA
AUSTRALIA
GERMANY
GERMANY
FRANCE
FRANCE
GERMANY
SWITZERLAND
GERMANY
NEW ZELAND
ISRAEL
SWEDEN
GERMANY
SWEDEN
UNITED KINGDOM
AUSTRALIA
AUSTRALIA
ISRAEL
UNITED KINGDOM
UK
GERMANY
UK
GERMANY
USA
GERMANY
NEW ZEALAND
UNITED KINGDOM
UNITED KINGDOM
UNITED KINGDOM
UNITED KINGDOM
UNITED KINGDOM
GERMANY
BELGIUM
ISRAEL
GERMANY
GERMANY
ISRAEL
BELGIUM
ISRAEL
UNITED KINGDOM
ISRAEL
GERMANY

5003101281017
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5003601601005
5003624501017
5003620301017
5003610501031
5003604901004
5003606301012
5003606301207
5003603201034
5003603201034
5003101091025
5003101051068
5003630201055
5003605701601
5003602201601
5003605301010
5003605901003
5003601401002
5003603201034
5003601401006
5003623501408
5003604301607
5003617301619
5003602901401
5003620501602
5003618501025
5003630201055
5003620501602
5003603201001
5003601601401
5003631201011
5003604301618
5003612501011
5003623501408
5003617501026
5003614501032
5003614501002
5003630201055
5003101541415
5003602901201
5003603201001
5003601201201
5003602901002
5003102541034
5003604901004
5003623501405
5003602901002
5003603201205

36
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232
198
235
248
099
304
60
277
279
131
270
296
61
68
202
79
137
280
275
308
22
106
42
187
225
297
306
9
20
43
112
180
219
224
245
289
298
278
8
10
28
52
95
141
193
53
67

MALE
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59
54
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64
37
33
33
61
64
62
62
56
55
48
56
33
62
53
62
19
60
60
59
62
59
50
59
61
55
41
53
59
53
27
62
54
31
50
32
64
27
52
58
64
59

R-ICE
R-ICE
R-ICE
R-ICE
R-ICE
R-ICE
R-DHAP + BEAM
R-DHAP + BEAM
R-ICE + BEAM
R-DHAP
R-DHAP
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R-DHAP + BEAM
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R-DHAP

ASPERGILLOSIS
CELLULITIS
CELLULITIS
CENTRAL LINE INFECTION
CENTRAL LINE INFECTION
CENTRAL LINE INFECTION
CATHETER SEPSIS
CMV INFECTION (*)
DENTAL ABSCESS
DIARRHEA, CLOSTRIDIUM DIFFICILE
DIARRHEA, CLOSTRIDIUM DIFFICILE
ENTEROBACTER SEPTICEMIA
ESCHERICHIA COLI INFECTION
GASTROINTESTINAL CANDIDIASIS
HERPES ZOSTER
HERPES ZOSTER
HERPES ZOSTER
INFECTION
INFECTION
INFECTIOUS DIARRHEA
KLEBSIELLA PNEUMONIAE INFECTION
KLEBSIELLA SEPSIS
LOWER RESPIRATORY TRACT INFECTION
LOWER RESPIRATORY TRACT INFECTION
NEUTROPENIC INFECTION
NEUTROPENIC INFECTION
NEUTROPENIC INFECTION
NEUTROPENIC INFECTION
NEUTROPENIC INFECTION
NEUTROPENIC SEPSIS (*)
NEUTROPENIC SEPSIS
NEUTROPENIC SEPSIS
NEUTROPENIC SEPSIS
NEUTROPENIC SEPSIS
NEUTROPENIC SEPSIS
NEUTROPENIC SEPSIS
NEUTROPENIC SEPSIS
NEUTROPENIC SEPSIS
NEUTROPENIC SEPSIS
STREPTOCOCCUS PNEUMONIAE PNEUMONIA
PNEUMONIA
PNEUMONIA
PNEUMONIA
PNEUMONIA
PNEUMONIA
PNEUMONIA
PNEUMONIA (*)
PNEUMONIA STREPTOCOCCAL (*)
PSEUDOMONAL SEPSIS

03/12/2004
19/11/2004
15/02/2008
19/08/2007
24/03/2008
02/05/2008
21/06/2006
21/01/2008
01/12/2004
01/09/2006
27/02/2007
04/07/2005
15/08/2007
27/04/2008
04/05/2005
09/05/2005
02/09/2007
17/06/2005
09/07/2004
08/03/2007
08/07/2007
25/01/2008
14/09/2004
16/02/2006
20/12/2004
28/05/2007
19/12/2007
27/04/2008
28/06/2007
11/05/2004
03/05/2004
23/12/2004
07/03/2006
20/04/2007
29/11/2007
19/12/2007
16/04/2008
25/09/2006
08/06/2008
14/07/2007
07/04/2004
19/04/2004
01/05/2004
05/02/2005
04/10/2005
08/01/2006
26/07/2007
17/02/2005
14/01/2005

(*) Suspected Unexpected Serious Adverse Reaction
Line-listing 03 July 2003 to 02 July 2011
Page 3/5

Latency last
administration
(D)
9
1
6
9
Not reported
0
33
6
10
8
145
6
40
0
10
5
9
53
3
154
24
7
0
2
0
77
2
0
1
0
0
11
0
0
13
8
6
10
0
122
1
8
0
0
23
12
5
10
32

Outcome
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Not reported
Recovered without sequelae
Died
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
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Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Died
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered with sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Recovered without sequelae
Died
Recovered without sequelae
Recovered without sequelae


**Induction Phase**

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<th>Inclusion number</th>
<th>SAE number</th>
<th>Gender</th>
<th>Age</th>
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<th>MedDRA LLT</th>
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**Injury, poisoning and procedural complications**

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**Metabolism and nutrition disorders**

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<th>Onset Date</th>
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<td>DEHYDRATION</td>
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**Musculoskeletal and connective tissue disorders**

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<th>Age</th>
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<th>Latency last administration (D)</th>
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**Nervous system disorders**

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<th>Outcome</th>
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(*) Suspected Unexpected Serious Adverse Reaction

Line-listing 03 July 2003 to 02 July 2011
Induction Phase

BELGIUM 5003101601610 11 MALE 49 R-DHAP + BEAM EPILEPTIC SEIZURE 24/05/2004 2 Recovered without sequelae
UNITED KINGDOM 5003615501007 154 FEMALE 52 R-DHAP ISCHAEMIC STROKE 19/01/2007 0 Recovered with sequelae
CZECH REPUBLIC 5003604801014 162 MALE 62 R-ICE LEUKOENCEPHALOPATHY (*) 21/02/2007 0 Recovered without sequelae
CZECH REPUBLIC 5003603160103 163 FEMALE 60 R-DHAP NEUROTOXICITY 23/01/2007 5 Recovered with sequelae
FRANCE 5003101431204 3 MALE 56 R-DHAP STROKE 29/12/2003 2 Recovered with sequelae
ISRAEL 5003602901401 54 MALE 60 R-ICE STROKE 20/12/2004 0 Recovered with sequelae
FRANCE 5003101391048 128 MALE 61 R-DHAP STROKE 12/08/2006 1 Recovered without sequelae
FRANCE 5003101031067 189 FEMALE 21 R-DHAP VAGAL REACTION 29/05/2007 4 Recovered without sequelae
UNITED KINGDOM 5003616501411 255 MALE 63 R-DHAP VASOVAGAL REACTION 07/07/2008 1 Recovered without sequelae

Psychiatric disorders

Country Inclusion number SAE number Gender Age Induction Arm MedDRA LLT Onset Date Latency last administration (D) Outcome
SWEDEN 5003601401605 136 FEMALE 57 R-ICE CONFUSION 25/09/2006 1 Recovered without sequelae

Renal and urinary disorders

Country Inclusion number SAE number Gender Age Induction Arm MedDRA LLT Onset Date Latency last administration (D) Outcome
FRANCE 5003101431627 91 MALE 65 R-DHAP ACUTE RENAL FAILURE 10/10/2005 7 Recovered without sequelae
GERMANY 5003622201625 149 MALE 59 R-DHAP ACUTE RENAL FAILURE 02/01/2007 6 Recovered without sequelae
AUSTRALIA 5003613301007 152 MALE 62 R-ICE ACUTE RENAL FAILURE 03/01/2007 not reported Recovered without sequelae
GERMANY 5003603201050 217 MALE 61 R-DHAP ACUTE RENAL FAILURE 26/10/2004 30 Recovered without sequelae
ISRAEL 5003604901603 241 FEMALE 62 R-DHAP ACUTE RENAL FAILURE 27/04/2008 2 Not reported
GERMANY 5003622201607 273 MALE 55 R-DHAP + BEAM ACUTE RENAL FAILURE 29/12/2004 6 Recovered without sequelae
FRANCE 5003101071607 4 MALE 59 R-DHAP RENAL FAILURE 16/01/2004 3 Recovered with sequelae
GERMANY 5003603101012 44 MALE 58 R-DHAP RENAL FAILURE 26/12/2004 7 Recovered without sequelae
FRANCE 5003101071643 287 FEMALE 59 R-DHAP + BEAM RENAL FAILURE 02/03/2008 4 Recovered without sequelae
NEW ZEALAND 5003621301014 260 FEMALE 59 R-ICE RENAL FAILURE ACUTE 01/11/2007 5 Recovered without sequelae

Respiratory, thoracic and mediastinal disorders

Country Inclusion number SAE number Gender Age Induction Arm MedDRA LLT Onset Date Latency last administration (D) Outcome
ISRAEL 5003602901201 7 FEMALE 31 R-ICE PULMONARY EMBOLISM 07/03/2004 0 Recovered without sequelae
AUSTRALIA 5003613301403 116 MALE 37 R-ICE PULMONARY EMBOLISM 07/04/2006 13 Recovered without sequelae
FRANCE 5003101391048 122 MALE 61 R-DHAP PULMONARY EMBOLISM 08/07/2006 1 Recovered without sequelae
UNITED KINGDOM 5003612501012 177 FEMALE 55 R-ICE PULMONARY EMBOLISM 24/04/2007 30 Recovered without sequelae
FRANCE 5003101071643 288 FEMALE 59 R-DHAP + BEAM PULMONARY EMBOLISM 08/03/2008 10 Recovered without sequelae
AMERICA 5003616501402 49 FEMALE 65 R-DHAP RESPIRATORY FAILURE (*) 04/01/2005 0 Died
UNITED KINGDOM 5003619501010 173 FEMALE 45 R-DHAP RESPIRATORY FAILURE (*) 06/04/2007 22 Died
SWITZERLAND 5003604701012 250 MALE 62 R-DHAP RESPIRATORY INSUFFICIENCY (*) 30/04/2007 5 Ongoing at death

Vascular disorders

Country Inclusion number SAE number Gender Age Induction Arm MedDRA LLT Onset Date Latency last administration (D) Outcome
FRANCE 5003103161206 111 FEMALE 35 R-DHAP + BEAM COLLAPSE 06/03/2006 0 Recovered without sequelae
AUSTRALIA 5003613301007 148 MALE 62 R-ICE HYPOTENSION 21/11/2006 not reported Unknown
SWEDEN 5003601401602 271 MALE 42 R-ICE + BEAM HYPOTENSION 04/11/2004 28 Recovered without sequelae
FRANCE 5003103161041 164 FEMALE 49 R-DHAP THROMBOSIS 27/03/2006 7 Recovered without sequelae
IRELAND 5003610501031 254 MALE 54 R-ICE + BEAM VENOOCCLUSIVE DISEASE (*) 27/06/2008 16 Recovered with sequelae

(*) Suspected Unexpected Serious Adverse Reaction

Line-listing 03 July 2003 to 02 July 2011
## Related Serious Adverse Reactions

### Maintenance phase

#### Blood and lymphatic system disorders

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<th>SAE number</th>
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<td>24/03/2008</td>
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#### General disorders and administration site condition

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(*) Suspected Unexpected Serious Adverse Reaction

Line-listing 03 July 2003 to 02 July 2011
### Hepatobiliary disorders

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### Investigations

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(*) Suspected Unexpected Serious Adverse Reaction

Line-listing 03 July 2003 to 02 July 2011
### Neoplasms benign, malignant and unspecified (incl cysts and polyps)

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### Nervous system disorders

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### Renal and urinary disorders

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### Respiratory, thoracic and mediastinal disorders

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(*) Suspected Unexpected Serious Adverse Reaction
### Gastrointestinal disorders

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### General disorders and administration site condition

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### Infections and infestations

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### Investigations

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### Musculoskeletal and connective tissue disorders

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### Neoplasms benign, malignant and unspecified (incl cysts and polyps)

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### Nervous system disorders

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### Renal and urinary disorders

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### Respiratory, thoracic and mediastinal disorders

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### Social circumstances

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### Surgical and medical procedures

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Protocol 50-03B / CORAL – Data Safety Monitoring Committee (DSMC) Meeting
Centre Hayem, Hôpital Saint-Louis – Paris
August 10, 2007
– Minutes of the Meeting –

Attendants: Massimo Federico (Oncologia Medica II, Università di Modena e Reggio Emilia – Modena, Italy), Marc Buyse (International Drug Development Institute – Brussels, Belgium), Armando Lopez-Guillermo (Department of Haematology, Hospital Clinic– Barcelona, Spain)

After confirming Massimo Federico as chairman of the Committee, the participants defined the following Agenda:
1) Review of safety data
2) Review of efficacy data
3) Give an opinion on what can be given on the results to the investigators after DSMC

As planned, the members of the DSMC reviewed data on the first 200 enrolled patients with respect to safety and efficacy of the induction (R-ICE vs R-DHAP) and the maintenance therapy (Rituximab vs observation). Moreover, the committee analysed the updated Safety Report for the CORAL study, covering the period between July 03, 2003 and July 03, 2007. Comments after review of available documentation are hereby reported.

1) Review of safety data
Part I, induction therapy: a total of 163 SAE were reported, involving 108 subjects out of the 385 subjects included in the study within the covered period.

- Fatal and life-threatening SAEs were equally distributed between study Arms and in the range of expected rate considering the study population.
- Hospitalization due to SAEs was more frequent in the standard Arm (R-DHAP); however, based on these data no change in trial conduct or clinical practice has been suggested.
- Based on safety reports and all additional available documentation the DSMC ensures that patients are not put at undue risk.

Part II, maintenance therapy: a total of 35 SAEs occurred during the maintenance period, 14 in the observation arm and 21 in the maintenance arm. In the observation arm these SAEs could be considered as related to the induction treatment (BEAM or ASCT). In the maintenance Arm 4 cases were considered as SUSARs (Suspected Unexpected Serious Adverse Reactions). After review of available information the committee did not confirm one (SAE 127 – 5003601401602) out of the four SUSARs and was puzzled about another (SAE 126 – 5003601401604)

- SAE 127: the patient was found dead in his bed 10 months after the administration of the last dose of Rituximab. He received his ASCT one year earlier. The DSMC is of the opinion that death can not clearly be related to Rituximab treatment but most probably to late toxicity of induction therapy (R-ICE plus BEAM and ASCT).
- SAE 126: the patient developed fever and cough one week after the last administration of Rituximab. Previously she had been treated with R-DHAP, BEAM and ASCT. A bronchiolar lavage revealed pneumocystis jirovecii. She was prescribed appropriate therapy and treatment with Rituximab remained ongoing. She recovered from the pulmonary infection. The DSMC concluded that given the complete recovery under Rituximab, the SUSAR is not clearly related to the study drug.
- SAE 129 and SAE 190: SAE 129 was concerned with a pneumonia by pneumocystic carinii while SAE 190 was related to a reactivation of varicella virus. These two reactions were considered to be related to Rituximab.

Based on these events, the DSMC recommends an appropriate prophylaxis for patients randomised for maintenance with Rituximab.
Modena, March 3rd, 2010

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Subject : Protocol 50-03B / CORAL
Safety Report 03/07/2003 – 02/07/2009 (72 months)

Dear Christian,

Following the review of the 72 months Safety report of the CORAL study I do not need additional details before returning you an answer.

Based on the data presented in the report I do not think that changes in the conduct of the study are to be warranted, due also to the fact that the study already completed the planned accrual. However, I have just one comment on a SAE recorded during maintenance phase and listed in chapter 4.2, page 17 of the Safety report:

- **Ear and labyrinth disorders: Hearing loss**
  The SAE is reported for a patient allocated in the Observational arm, so it can’t be related to “maintenance therapy”; to me this is to be considered as a late effect of induction treatment.

Finally, it seems to me that a phone conference is not needed at the moment, although I am of course available if someone else suggests it is worth of to organize it.

With best regards,

Massimo
2) Review of efficacy data
The DSMC confirms the previously reported comment, i.e. that with respect to efficacy data no differences between arms emerges that would impose a modification or premature termination of the study: actually, the percentage of events (17%) is too small to draw any conclusion.

General comments and suggestions:
- As from study protocol, the primary endpoint of part II (maintenance) of the study used to assess sample size was event free survival: to provide a 80% power at the overall 5% significance level to detect a 15% difference in favor of the Rituximab arm and considering a 40% drop out, 400 patients were planned to be registered to have 240 patients to be transplanted. However, as pointed out during the previous DSMC Meeting, the sample size planned and reported in the study protocol for evaluation of study endpoints is insufficient to fit with study requirements since the drop out for the first 200 patients enrolled is still higher than expected (about 50%). Therefore, an additional 80 patients should be enrolled in the CORAL trial to reach 240 randomized patients for the second part of the study;
- adoption of strict criteria for response assessment to avoid risk of biases in the evaluation between study arms should be considered;
- given the relevance of the ongoing study, the need for a centralized histologic review emerges, and the indication to make any effort to have diagnostic biopsies reviewed is warmly suggested;
- the study was planned to complete accrual in three years; an additional year has already passed without completing patients’ registration: the DSMC approves the prolongation of the study to complete patients’ accrual (even if the suggested modification related to introduction of prophylaxis for patients randomised in the Rituximab arm is not accepted);
- a separate analysis of the subset of patients who received Rituximab as first-line treatment is recommended.

3) What can be given on the results of DSMC analysis to the investigators
The DSMC expresses the opinion that during the next ASH a preliminary disclosure of some study data can be provided to Investigators taking part in the study; information to be given must be related to the following:
   a) Accrual status;
   b) Demographics;
   c) Baseline data, underlining differences between patients who received Rituximab including regimens as front-line therapy and patients first treated with Rituximab in the CORAL study;
   d) Toxicity data;
   e) Overall efficacy data, providing that results per arm remain hidden

The CORAL study DSMC Committee
Massimo Federico, Armando Lopez-Guillermo, Marc Buyse