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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ORIGINAL REPORT

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

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See accompaning 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.

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INTRODUCTION

During the last decade, the addition of the anti-CD20 monoclonal antibody rituximab to various chemotherapies[1-3] 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 years[4] 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 (saaIPI).[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

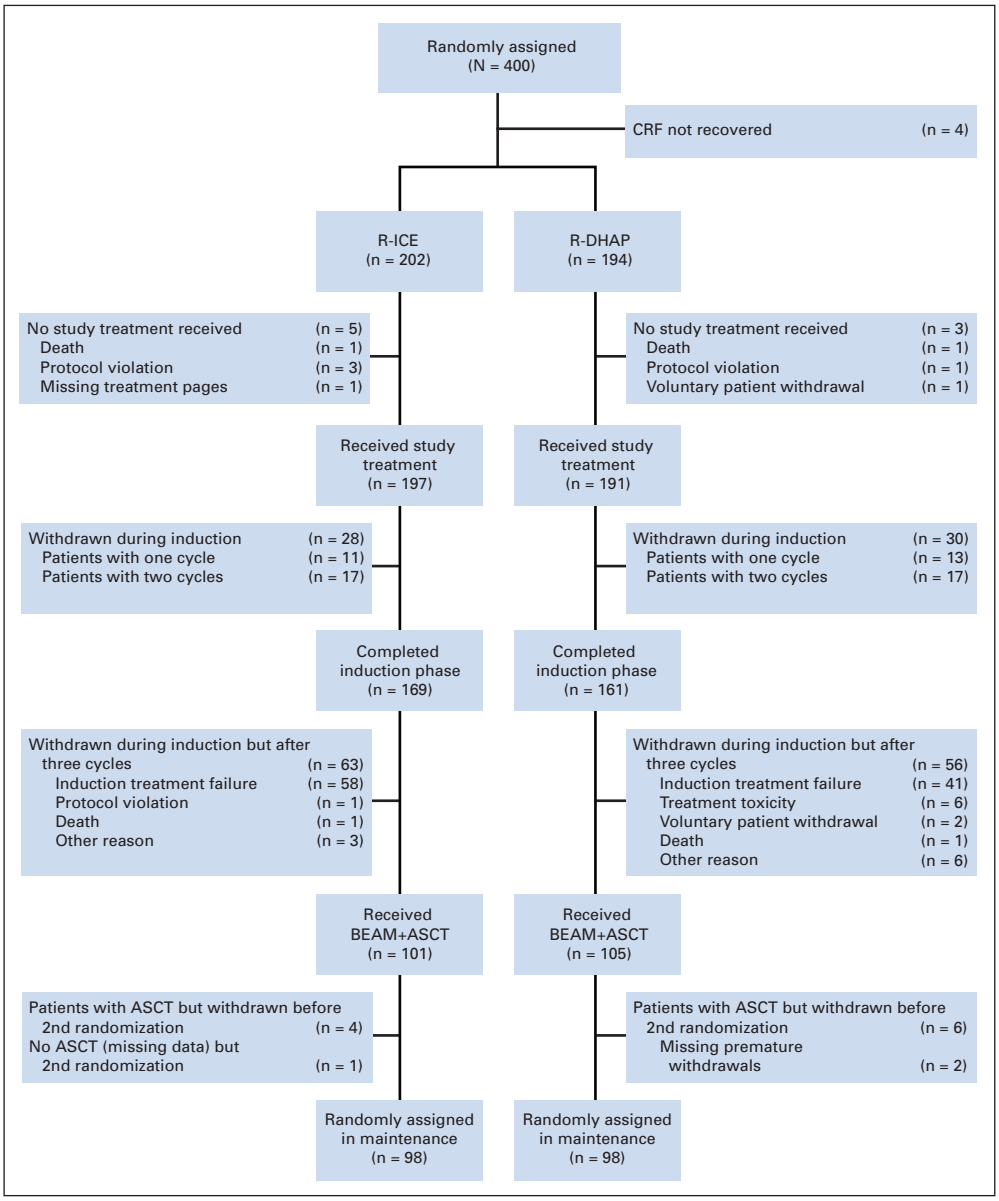

Fig 1. CONSORT diagram of distribution of patients according to arm resulting from the first random assignment. CRF, case report forms; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin; BEAM, carmustine, etoposide, cytarabine, melphalan; ASCT, autologous stem-cell transplantation.

relevant institutional review boards or ethics committees, and all patients gave written informed consent.

The study was registered under Europen 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/m^2) was administered before chemotherapy, and in the first course, additional rituximab was given on day −1. The R-ICE[13] regimen consisted of etoposide (100 mg/m^2) on days 1 through 3, ifosfamide (5,000 mg/m^2) 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[14] consisted of cisplatin (100 mg/m^2) on day 1 via continuous 24-hour infusion, followed on day 2 by cytarabine (2 g/m^2) 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 leukapheresis.

Leukapheresis 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.

Table 1. Baseline Patient Demographics and Clinical Characteristics (intent to treat)

Demographic or Clinical Characteristic	No. of Patients: R-ICE (n = 202)	No. of Patients: R-DHAP (n = 194)	P
Age, years			
Median	54	55	
Range	19-65	19-65	NS
Sex			
Male	125	118	
Female	77	76	NS
Ann Arbor stage			
I-II	81	66	
III-IV	119	121	NS
Extranodal site > 1	55	64	NS
Bone marrow involvement	17	19	NS
Elevated LDH	104	94	NS
saaIPI at relapse			
0-1	119	107	
2-3	75	74	NS
Time to relapse after diagnosis, months	89	87	NS
< 12*	112	103	
≥ 12	122	122	NS
Prior rituximab treatment			
Prior first-line CHOP-like chemotherapy	171	167	NS
Intensified CHOP	28	23	

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.

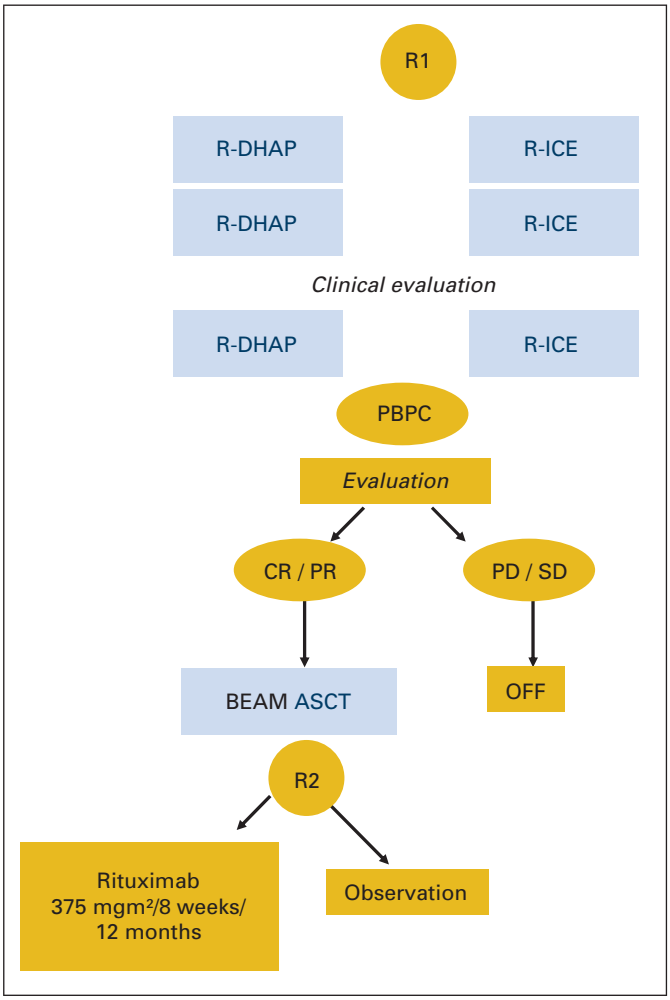

Fig 2. Treatment protocol. R1, first random assignment; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; PBPC, peripheral-blood progenitor cells; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; BEAM, carmustine, etoposide, cytarabine, melphalan; ASCT, autologous stem-cell transplantation; R2, second random assignment.

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.[15] CR was defined by the disappearance of all documented disease; unconfirmed CR (CRu) was used when a residual mass was present without evidence of

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

Response	R-ICE (n = 197) No. of Patients	%	R-DHAP (n = 191) No. of Patients	%
Complete response	48	24	53	28
Unconfirmed complete response	24	12	22	12
Partial response	53	27	45	24
Stable disease	23	12	22	12
Progressive disease	38	19	35	18
Death	6	3	10	5
Premature withdrawal, not evaluated	4	2	4	2
Autologous transplantation				
Median $CD34^+$ cells collected, million/kg	4.5		4.9	
Collection failure < 2,000,000 $CD34^+$ cells	20	10	15	8
Mobilization-adjusted response	103	52.3	104	54.5
Consolidation with BEAM performed per protocol	101	51	105	55

Abbreviations: R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; BEAM, carmustine, etoposide, cytarabine, and melphalan.

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/m^2) on day −6, etoposide (200 mg/m^2), cytarbine (200 mg/m^2) on days −5 to −2, and melphalan (140 mg/m^2) 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.

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. PFS 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, PFS, and OS, and 95% CIs were calculated.[16] Cox regression analysis was used to calculate the hazard ratio between the two arms.[17] 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).

RESULTS

Response to Treatment

At diagnosis, 62% of the patients had been treated with a CHOP-like regimen with rituximab. Before inclusion, after first-line treatment, 65% of patients had achieved a first CR, 20% had achieved a PR, 4% had stable disease, and 11% had progressive disease.

After salvage chemotherapy but before transplantation, the overall response rate, including CR, CRu, and PR, was 63.5% (95% CI, 56.8% to 70.7%) in the R-ICE arm and 62.8% (95% CI, 55.6% to 69.7%) in the R-DHAP arm (Table 2). The factors significantly affecting the overall response rate in the univariate analysis ($P < .001$) were refractory disease/relapse less than 12 months after diagnosis, secondary IPI of 2 to 3, and prior rituximab treatment, but not the treatment arm (Table 3). In total, 206 patients received BEAM and ASCT per protocol, and five more patients had stable disease. The main reason for premature withdrawal from the study was disease progression (Fig 1). Three months after transplantation and random assignment, 132

Table 3. Response Rate and Survival According to Prognostic Factors

Factor	Total No. of Patients	Response CR/CRu/PR No. of Patients	%	*P*	3-Year Event-Free Survival %	*P*	3-Year Overall Survival %	*P*
All patients	398	246	63		31		50	
CR/CRu		148	38		51		70	
Prior rituximab								
No	147	122	83	< .001	47	< .001	66	< .01
Yes	244	124	51		21		40	
Relapse, > 12 months	160	140	88	< .001	45	< .001	64	
Refractory, < 12 months	228	106	46		20		39	< .001
saaIPI								
< 2	224	160	71	< .001	40		62	
> 1	146	76	52		18	< .001	32	< .001

Abbreviations: CR, complete response; CRu, unconfirmed complete response; PR, partial response; saaIPI, secondary age-adjusted International Prognostic Index.

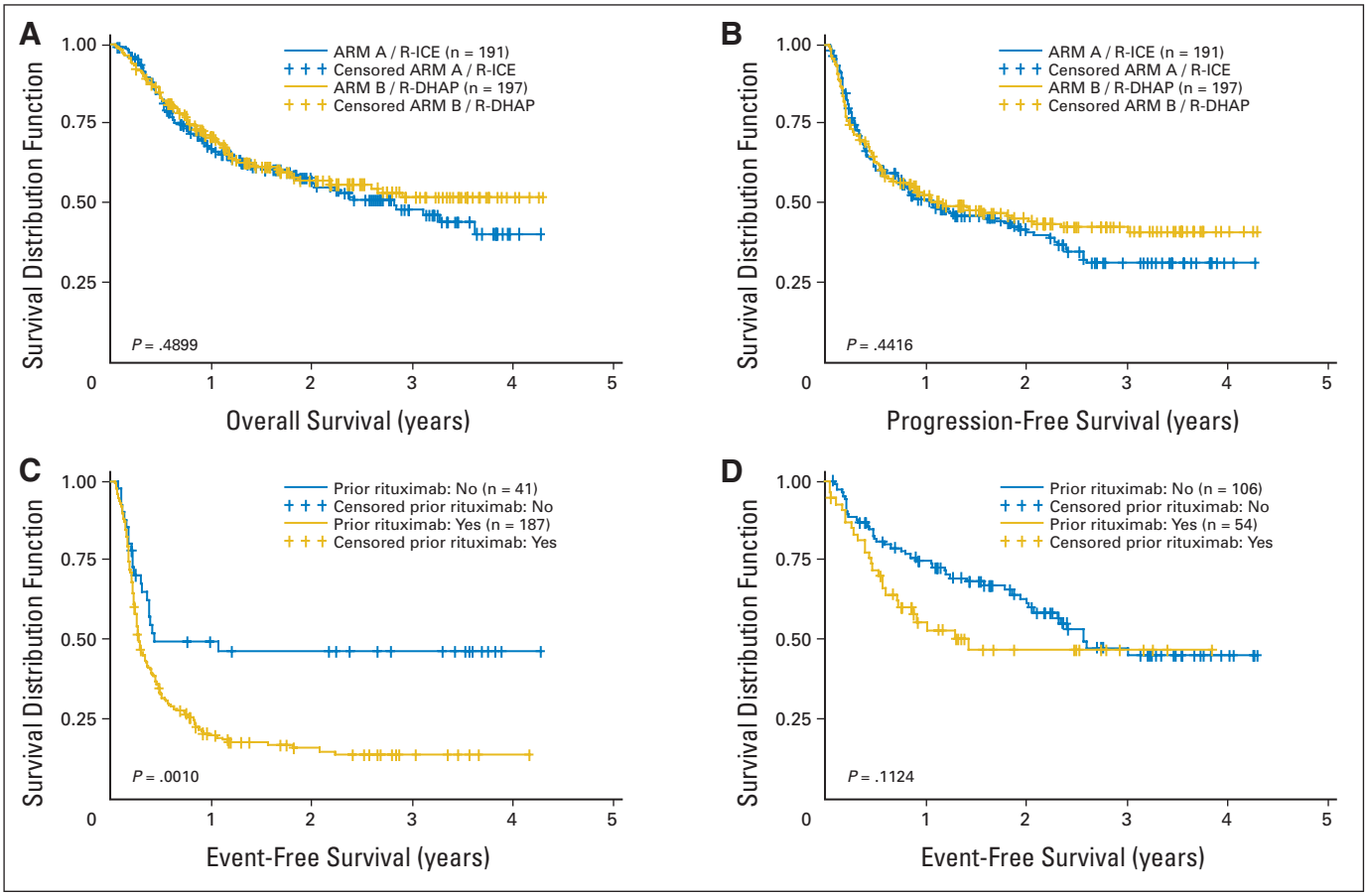

Fig 3. (A) Overall survival according to the first random assignment (intent to treat). (B) Progression-free survival according to treatment arm. (C) Event-free survival (EFS) according to prior rituximab treatment and relapse less than 12 months after diagnosis. (D) EFS according to prior rituximab treatment and relapse more than 12 months after diagnosis. R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin.

(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 ($P = .01$). 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

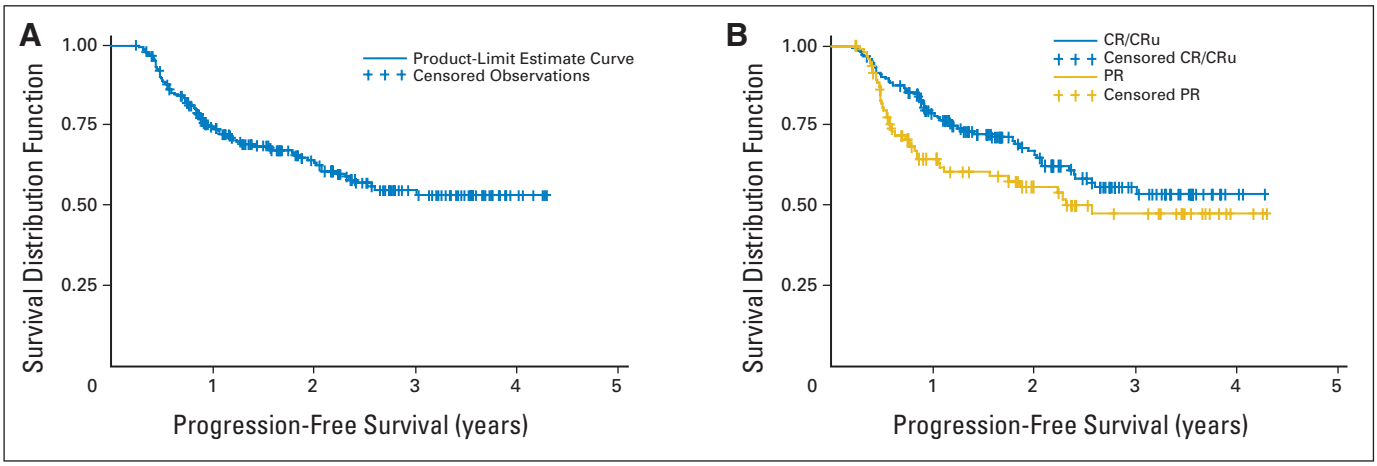

Fig 4. (A) Progression-free survival (PFS) of patients undergoing autologous stem-cell transplantation (intent to treat; n = 206). (B) PFS according to response after salvage regimen (including death) for all patients: complete response (CR) plus unconfirmed complete response (CRu; n = 147) and partial response (PR; n = 98).

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,[6] 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.[12] The R-ICE regimen was chosen because we assumed that rituximab would improve its results, as suggested by the Memorial Sloan-Kettering Cancer Center.[13] 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.[5,12] Both regimens were supplemented with rituximab, which has been shown to improve treatment results of patients with relapsed DLBCL[11-13] 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.[6] 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[13] with R-ICE and in a study using high-dose rituximab before and after transplantation.[18] 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.[13] 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.[19]

Consequently, new drugs designed to increase the response rate of salvage regimens and new approaches,[20] including allogeneic transplantation, should be explored.[21,22] 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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ORIGINAL REPORT

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

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ABSTRACT

Purpose
To evaluate the prognostic value of the cell of origin (COO) in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBLC), 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[1] 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)[3-5] associated with different oncogenic events.[6-10]

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]).[11] Consequently, surrogates of this molecular classification have been developed for routine usage on the basis of immunohistochemical protein expression or genetic markers detected by fluorescent in situ hybridization (FISH),[12-15] the most concordant with the microarray results being the algorithms of Choi[16] and Hans.[17] Published algorithms encompass proteins such as CD10, BCL6, 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,[18] although treatment with rituximab appears to eliminate the unfavorable effect from BCL2 expression.[19,20] 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.[12,21] Smaller, potentially oncogenic FOXP1 isoforms induced by B-cell activation have been found in some ABC-like DLBCLs.[22]

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.[3,4,23] 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[11] 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.[11] 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.[13,16,24-26] 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.[27]

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,[27] 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 $CD20^+$ DLBCL and to test maintenance with or without rituximab. The study was registered under European Union Drug Regulating Authorities Clinical Trials (EudraCT) No. 2004 to 002103-32 and ClinicalTrials.gov NCT 00137995, and it was conducted in accordance with Good Clinical Practice rules. All patients gave written informed consent to participate and to provide tissue material for biologic studies.

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[1] 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, BLC2, 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.[13] The tissue quality was evaluated morphologically on hematoxylin and eosin staining. All evaluable occurrences were given a secondary classification according to the COO algorithms previously published by Hans et al,[14] Muris et al,[15] and Nyman et al.[24]

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, Altlussheim, Germany). The hybridization signal scoring was performed according to Haralambieva et al,[28] 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.[13]

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 hematoxylin and eosin–stained frozen sections. Total RNA quantity and initial quality were estimated by a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA), and quality was assessed by electrophoresis (Agilent 2100 Bioanalyzer; Agilent Technologies, Mississauga, 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.[3] Details of the

Table 1. Index of Variation Considering Immunophenotypes and Chromosomal Abnormalities Between Primary and Relapse Biopsies in Matched Pairs

Parameter	No. of Patients (n = 87)	% Similarities Primary *v* Relapse	*P* by Wilcoxon test
CD10	77	96	.62
BCL6	75	95	.38
MUM1/IRF4	75	91	.80
FOXP1 (Barrans)	68	93	.13
BCL2	75	92	.79
Chromosomal breakpoint			
BCL2/18q21	28	100	1
BCL6/3q27	25	100	1
c-MYC/8q24	24	100	1
GCB/ABC surrogate publication			
Hans et al[14]	77	94	.58
Muris et al[15]	73	88	.42
Nyman et al[24]	67	97	1

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 χ^2 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.[29] 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.[30] All statistical analyses were performed with SAS 9.13 (SAS Institute, Cary, NC) and S-Plus 6.2 (MathSoft, Cambridge, MA) software.

Table 2. Baseline Characteristics of Patients Enrolled Onto Bio-CORAL and CORAL

	Patients									
	At Diagnosis					At Time to Relapse				
	Bio-CORAL (n = 249)		CORAL (n = 396)			Bio-CORAL (n = 249)		CORAL (n = 296)		
Characteristic	No.		No.		*P*	No.		No.		*P*
Sex										
Male	156	63	241	61	.47	156	63	241	61	.47
Female	93	37	152	39		93	37	152	39	
Age, years										
Median	53		54		.9	54		55		.9
Range	19-65		19-65			19-65		19-65		
ECOG PS										
0-1	190	88	300	84	.33	216	88	339	88	.46
2-3	28	22	55	16		31	12	48	12	
Ann Arbor stage										
I-II	111	45	159	41	.16	97	40	147	38	.68
III-IV	133	55	226	59		147	60	237	62	
Elevated LDH	115	27	187	48	.79	119	60	195	51	.37
"B" symptoms	95	38	154	40	.59	60	24	93	24	.27
Extranodal site > 1	55	22.5	93	26	.16	71	29	117	30	.21
Bone marrow involvement	—		—			20	8	35	9	.8
aaIIPI										.59
0-1	138	59	217	62	.12	146	62	226	61	.59
2-3	78	40	131	38		90	38	146	39	
Initial response										
CR-CRU	173	70	255	65	.09	—				
CRU	34	14	47	12		—				
PR	38	15	76	20		—				
Stable disease	9	4	16	4		—				
Progression	27	11	43	11		—				
Time to relapse, months						—				
< 12	134	54	229	58	.02	—				
≥ 12	115	46	164	42		—				
Prior rituximab treatment	152	61	243	62	.67	—				
Treatment at relapse										
R-ICE	—					126	51	201	51	.77
R-DHAP	—					123	49	192	49	
Response at induction										
CR/CRU	—					99	41	147	37	.38
PR	—					63	26	98	26	
Stable disease	—					24	10	46	12	
Progression	—					43	17	78	20	
Not evaluable	—					8	2	11	3	
Death						12	4	16	4	
Transplantation	—					139	56	206	53	.07

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 (aaIPI). 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 aaIPI. At salvage therapy, 123 patients were treated with R-DHAP;126, with R-ICE.

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 aaIPI were the individual risk factors for OS and PFS ($P < .001$, $P < .001$, and $P < .001$, respectively). Moreover, initial aaIPI 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, MUM/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 ($P = .007$ 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 1C and 1D). Analysis realized after removing PMBL and transformed FL occurrences resulted in unchanged results neither in PFS (non-GC Iv GC, 34% Iv 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 aaIIPI ($P = .039$), 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 aaIPI.

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 micr4oarrays (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.

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

Parameter	Diagnosis		Relapse		Pooled Occurrences				
							P		
	No.	%	No.	%	No.	%	OS	PFS	CR
Immunohistochemistry									
CD10	179		82		240		.21	.48	.23
Positive	74	44	40	49	98	59			
Negative	105	57	42	51	140	41			
BCL6	177		81		238		.17	.08	.50
Positive	99	56	50	62	142	60			
Negative	78	44	31	38	96	40			
MUM1/IRF4	176		81		239		.61	.83	.35
Positive	61	37	27	33	100	42			
Negative	115	65	54	67	134	58			
FOXP1 (Barrans)	157		77		217		.036	.024	.56
Positive	104	66	55	71	142	65			
Negative	53	33	22	29	75	35			
BCL2	175		78		241		.63	.3	.56
Positive	123	70	55	70	175	73			
Negative	52	30	23	30	66	27			
Chromosomal break point (FISH)*									
BCL2/18q21	92		45		107		.1	.52	.84
Positive	36	39	16	38	33	31			
Negative	56	61	29	62	74	59			
BCL6/3q27	81		49		94		.89	.65	.06
Positive	15	19	11	23	17	18			
Negative	66	81	38	77	77	82			
c-MYC/8q24	89		49		96		.02	.04	.005
Positive	18	20	10	20	12	13			
Negative	71	80	39	80	84	87			
ImmunoFISH index published by Copie-Bergman et al[13]									
No. of occurrences	154		130		217				
Negative	113	73	92	71	148	68	.72	.35	.09
Positive	41	34	38	29	69	30			
GCB/ABC algorithm publication									
Hans et al[13]	173		82		235		.23	.09	.89
GC	90	52	48	59	116	49			
Non GC	83	48	34	41	119	51			
Muris et al[14]	171		78		237		.89	.51	.46
Group 1	124	73	56	72	171	72			
Group 2	47	27	2	28	66	28			
Nyman et al[21]	160		74		225		.18	.08	.36
ABC	116	72.5	56	76	165	73			
Others	44	27.5	18	24	60	27			

Abbreviations: ABC, activated B-cell; CR, complete response; FISH, flourescent in situ hybridization; GC, germinal cell; GCB, germinal center B; OS, overall survival; PFS, progression-free survival.

*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.

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.[27] Selected patients were representative of the whole population, with similar clinical characteristics and identical clinical prognostic parameters, including aaIPI, early relapse, prior rituximab exposure and secondary aaIPI. 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 aaIIPI, except FOXP1. FOXP1 expression was significantly associated with a poorer PFS and OS but had a marginal prognostic

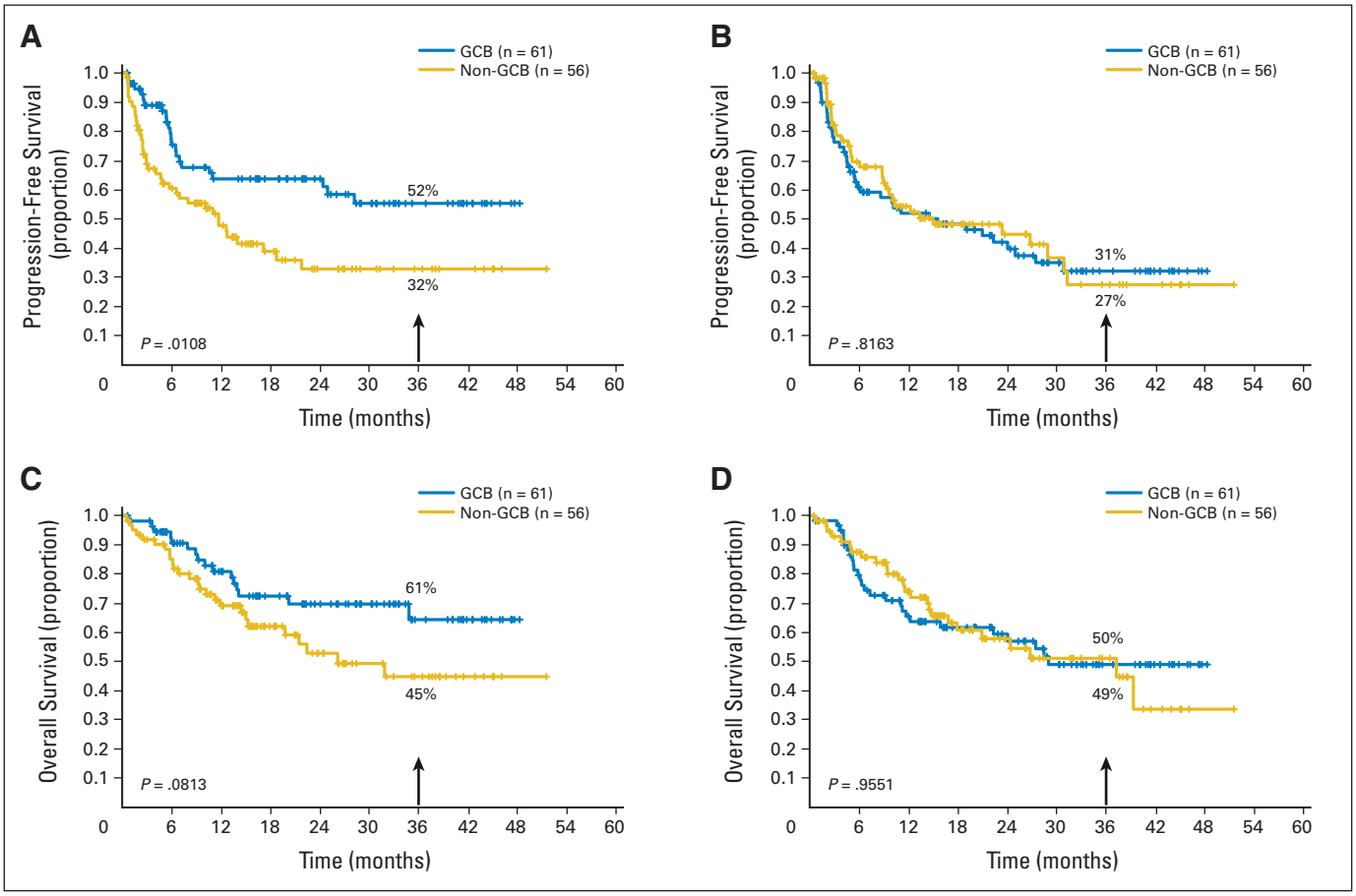

Fig 1. (A, B) Progression-free survival (PFS) and (C, D) overall survival (OS) according to the (A, C) rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) versus (B, D) rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) treatment arms (ie, Collaborative Trial in Relapsed Aggressive Lymphoma [CORAL] first random assignment, intent to treat) and to the Hans algorithm. Among the 232 patients classified on the basis of Hans's algorithm, 115 were treated with R-DHAP and 117, with R-ICE. Blue lines indicate patients who had a germinal cell B (GCB) profile (n = 115; 49.5%) and were treated with R-ICE (n = 61) or treated with R-DHAP (n = 54). Gold lines indicate patients who had a non-GCB profile (n = 117; 50.5%) and were treated with R-ICE (n = 56) or treated with R-DHAP (n = 61).

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 can not 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 immunochemotherapy. 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.

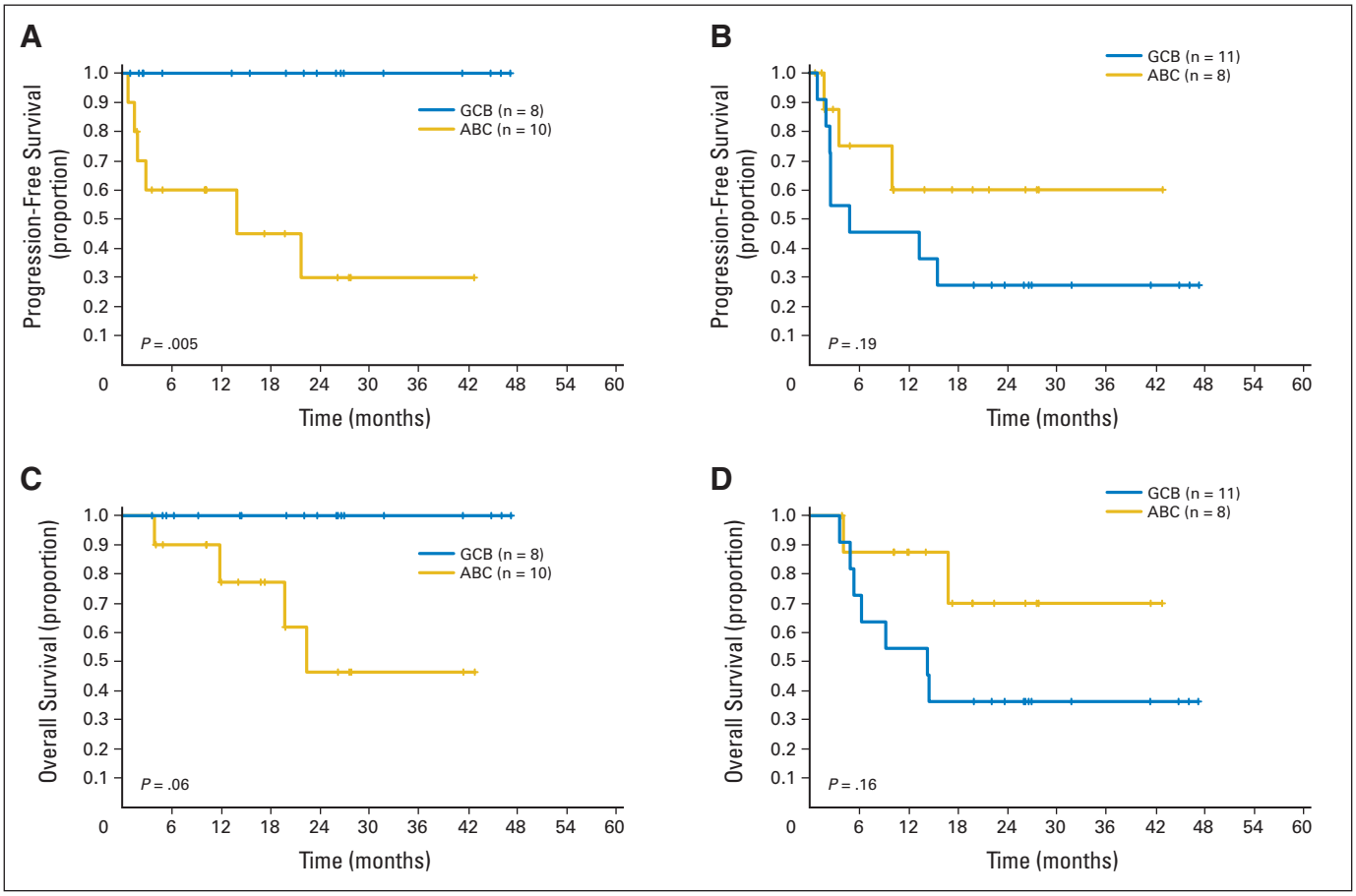

Fig 2. Progression-free survival (PFS; A, B) and overall survival (OS; C, D) according to the treatment and germinal center B (GCB)/activated B-cell (ABC) status as classified by the gene predictor on the basis of gene signatures published by Alizadeh et al.[3] Blue lines indicate patients with a GCB 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) PFS 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.

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[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.[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*.[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 β pathway.[7,40,41] Inhibition of nuclear factor kappa β 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 β degradation.[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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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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Processed as a Rapid Communication manuscript. Listen to the podcast by Dr Rosenblatt at www.jco.org/podcasts

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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,[9] only 10% of these patients obtain long-term disease-free survival with salvage chemotherapy alone.[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.[11]

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

The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study was organized among 12 countries. In this study, patients with refractory or relapsed CD20$^+$ DLBCL were randomly assigned to either rituximab, ifosfamide, carboplatin, and etoposide (R-ICE)[16] or rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP).[17] Patients who responded to the chemotherapy were submitted to HDT and ASCT. The initial results[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 treatment after transplantation.[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 5-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$^+$ 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$^+$ 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.[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).

Patient 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.[18] Briefly, only chemotherapy-sensitive patients (CR, unconfirmed CR [CRu], or PR) after three cycles of R-ICE[16] or R-DHAP[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^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.[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

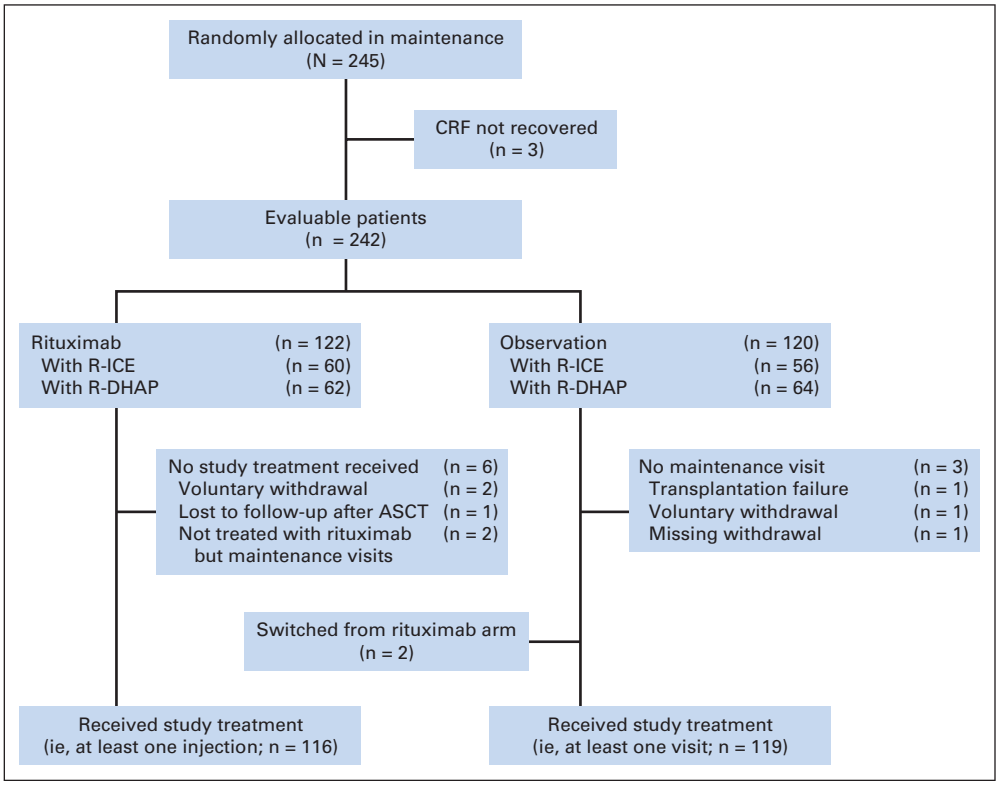

Fig 1. CONSORT diagram of the patient distribution according to the treatment arm resulting from the second random assignment. ASCT, autologous stem-cell transplantation; CRF, case report forms; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide.

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 51% (95% CI, 44% to 58%) for the R-DHAP arm ($P = .3$). The EFS was 26% (95% CI, 20% to 32%) in 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, primarily

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

Characteristic	Rituximab (n = 122)	Observation (n = 120)	*P*
Age, years			
Median	54	54	
Range	19-65	19-65	
< 40	17	22	NS
Sex			
Male	76	83	
Female	46	37	NS
Body mass index, kg/m^2			
Median	25.8	26.7	NS
Range	17.3-36.8	18.3-45.2	
> 30	21	28	
Ann Arbor stage			
I-II	53	48	
III-IV	69	71	NS
Extranodal site > 1	30	30	NS
Bone marrow involvement	13	8	NS
Elevated LDH	54	51	NS
Response after salvage therapy			
CR + CRu	73	69	NS
PR	47	45	
Stable disease	2	5	
saaIPI at relapse			
0-1	84	81	
2-3	36	36	NS
Time to relapse, months			
< 12*	33	41	NS
≥ 12	89	76	
Prior rituximab treatment	63	62	NS
Prior CHOP-like first-line chemotherapy	102	100	NS
Salvage regimen			
R-ICE	60	56	
R-DHAP	62	64	

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, dexamethasone, cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; saaIPI, secondary age-adjusted International Prognostic Index.
*Including patients not achieving CR in first-line treatment.

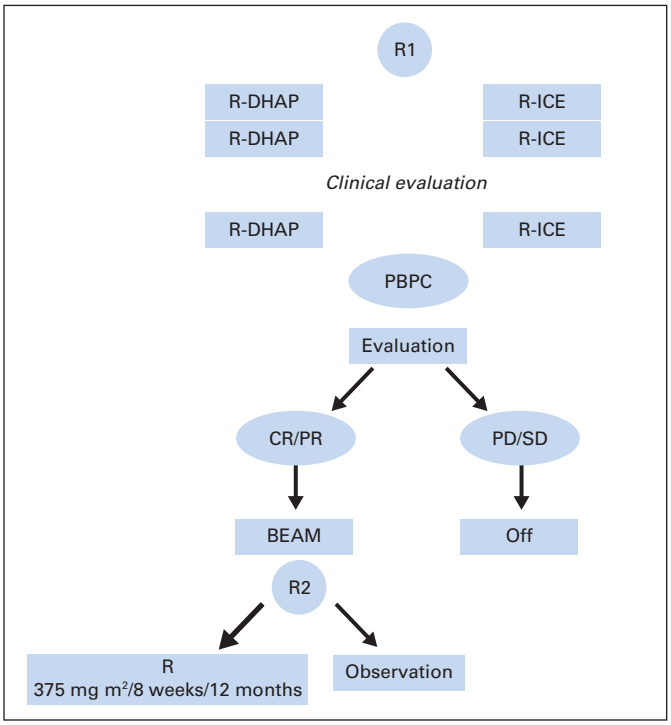

Fig 2. Treatment protocol. BEAM, carmustine, etoposide, cytarabine, melphalan; CR, complete response; PBPC, peripheral-blood progenitor cells; PD, progressive disease; PR, partial response; R, rituximab; R1, first random assignment; R2, second random assignment; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; SD, stable disease.

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

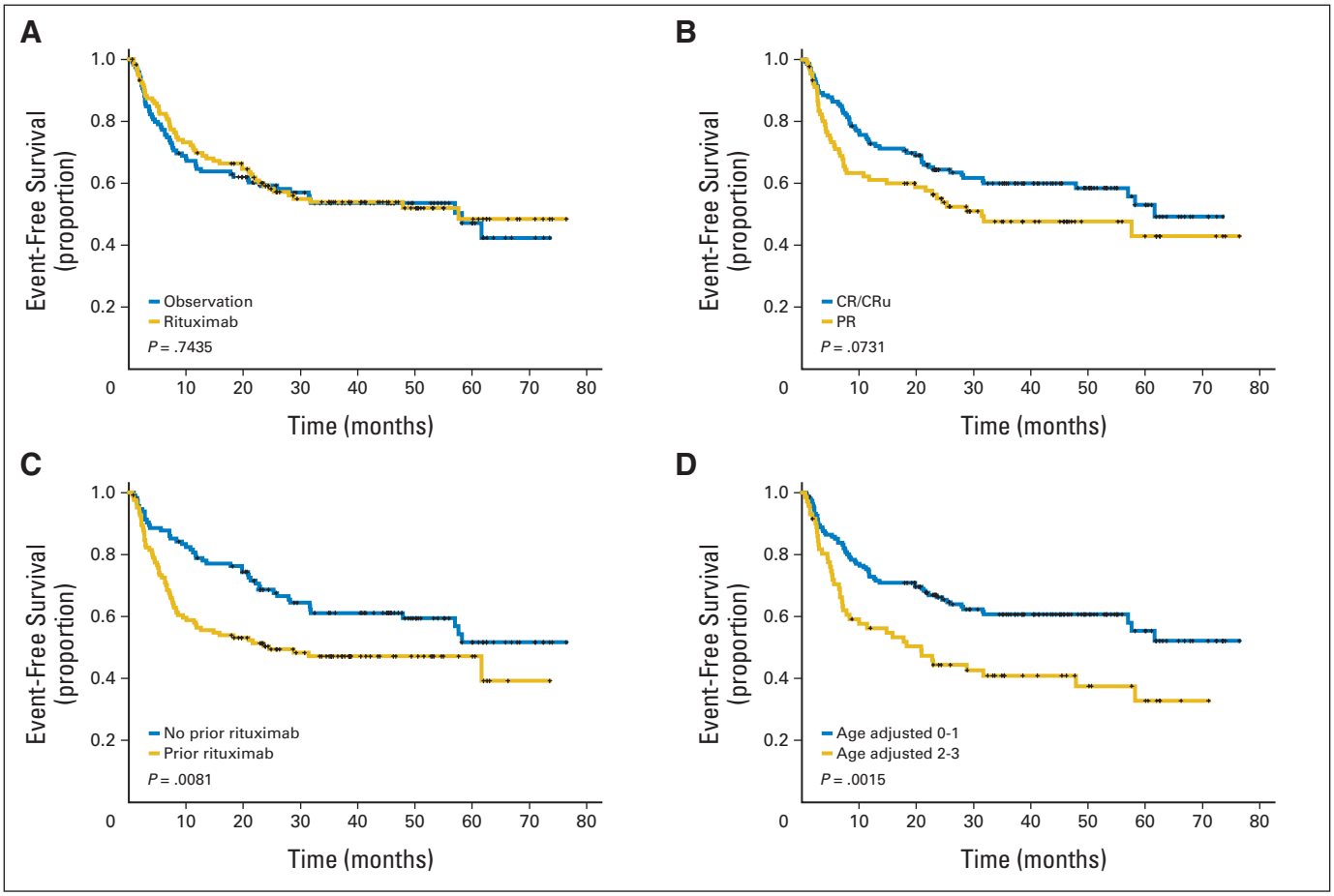

Fig 3. Survival of patients after autologous transplantation. (A) Event-free survival (EFS) according to the second random assignment and treatment arm of rituximab (n = 122) or observation (n = 120). (B) EFS at the second random assignment according to disease status before transplantation (complete response [CR] plus unconfirmed CR [CRu], n = 142; partial response [PR], n = 92). (C) EFS at the second random assignment according to prior rituximab exposure (n = 125) or no prior rituximab (n = 117) during first-line treatment. (D) EFS at the second random assignment according to age-adjusted International Prognostic Index at relapse of 0 to 1 (n = 165) versus 2 to 3 (n = 72).

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; $P = .06$). 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.

Table 2. Prognostic Factors at the Second Random Assignment

Patients	No. of Patients	4-Year EFS (%)	*P*	4-Year PFS (%)	*P*	4-Year OS (%)	*P*
Arm			.7		.8		.7
Rituximab	122	52		52		61	
Observation	120	53		56		65	
R-ICE			.4		.5		.4
Rituximab	60	50		50		61	
Observation	56	47		49		53	
R-DHAP			.7		.4		.2
Rituximab	62	55		55		62	
Observation	64	59		63		77	
Prior rituximab			.009		.03		.03
Yes	125	47		50		58	
No	117	59		59		69	
Treatment failure, months			.04		.1		.07
< 12	105	48		51		59	
≥ 12	137	56		56		66	
saaIPI			.0018		< .001		< .001
0-1	165	61		63		72	
2-3	72	37		37		45	
Response			.07		.2		.3
CR + CRu	142	58		58		66	
PR	92	48		51		59	
Sex			.01		.01		.007
Male	159	46		48		55	
Female	83	63		65		75	
Rituximab arm			.005		.005		.009
Male	76	38		48		50	
Female	46	70		70		76	
Observation arm			.5		.6		.3
Male	83	53		56		60	
Female	37	56		59		77	

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.

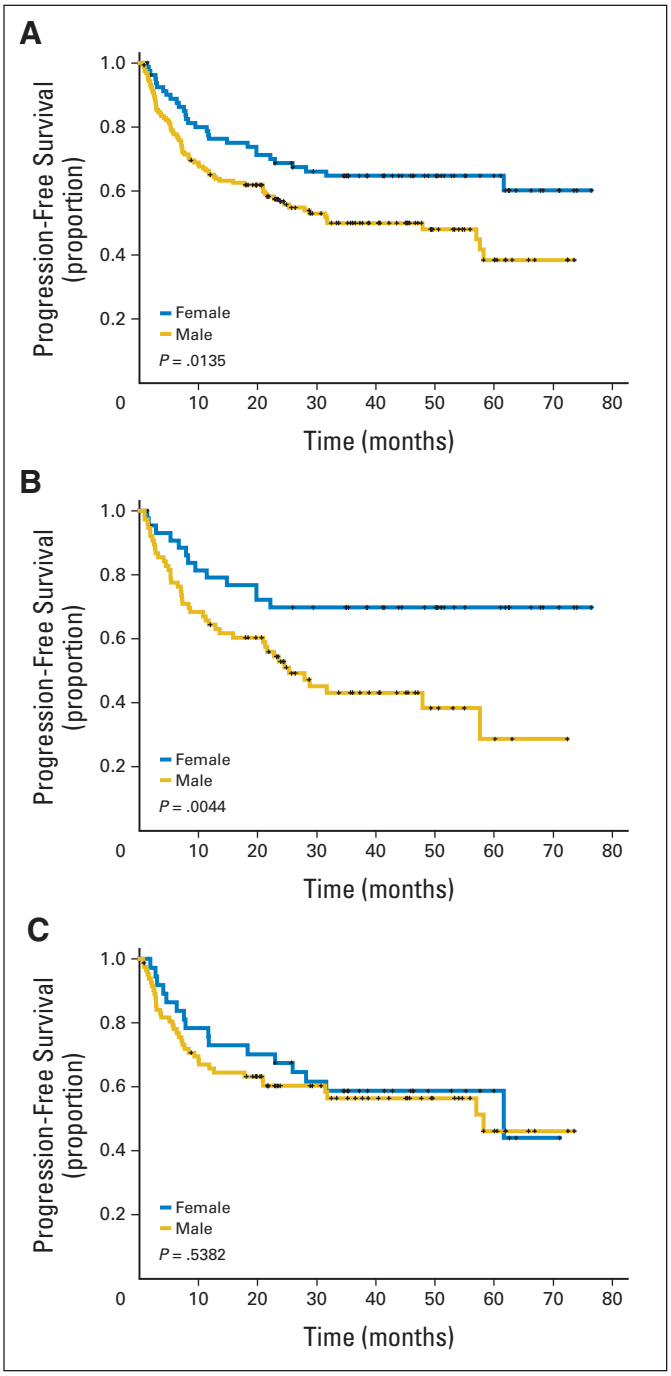

Fig 4. Survival of patients after autologous transplantation according to sex. (A) Progression-free survival (PFS) at the second random assignment according to male (n = 159) or female (n = 83) sex. (B) PFS at the second random assignment according to male (n = 78) or female (n = 46) sex and the rituximab treatment arm. (C) PFS at the second random assignment according to male (n = 83) or female (n = 37) sex and observation.

Male sex is an adverse prognostic factor in follicular lymphomas and DLBCL in the rituximab era.[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.[24] These results are similar to the findings of Ng et al[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.[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.

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.[28] Consequently, new drugs that are designed to increase the response rate of salvage regimens and novel approaches, including allogeneic transplantation, should be explored.[29-31] An improved understanding of the biology of DLBCL derived at least in part from studies of patient tumor specimens[22] will play a key role in the development of novel targeted therapies for this disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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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Final approval of manuscript: All authors

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Appendix

The following centers and principal investigators included patients in the study: Australia (n = 37): J. Trotman, Concord Repatriation General Hospital, Ph. Campbell, Geelong Hospital, I. Lewis, Royal Adelaide Hospital, R. Lowenthal, Royal Hobart Hospital, R. Herrmann, Royal Perth Hospital, D. Ma, St Vincent's Hospital, Sydney, D. Gill, P. Marlton, Princess Alexandra Hospital – Woodville, G. Hill, Royal Brisbane and Women's Hospital – Herston, J. Gibson, Royal Prince Alfred Hospital – Camperdown, K.E. Fay, Royal North Shore – St Leonards – NSW, C.L. Smith, Austin Hospital – Heidelberg, A.P. Grigg, Royal Melbourne Hospital – Parkville – Victoria, G. Cull, Sir Charles Gardiner Hospital – Nedlands – WA. New Zealand (n = 13): P.J. Browett, Auckland Hospital, Christchurch Hospital, C.S. Karapetis, Ch. Musuka, Dunedin Hospital, G. Forgeson, Palmerston North Hospital. Swizterland (n = 24): W. Mingrone, Kantonsspital Aarau AG, C. Beretta, Fmh Onkologie-Hamatologie – Rheinfelden, D.C. Beticher, Inst Fur Medizinische Onkol Der Univ – Bern, M. Ghielmini, Ospedale Civico – Lugano, C. Helg, Hug Geneve – A. Lohri, Geneve, Kantonsspital – Basel, C. Caspar, Kantonsspital – Baden. Sweden (n = 13): B. Malmer, Umea University Hospital, H. Hagberg, Akademiska Sjukhuset – Uppsala. United Kingdom (n = 50): D.W. Milligan, Birmingham Heartlands Hospital, Ch. Pocock, Kent and Canterbury Hospital, M. Joyner, Royal Devon and Exeter Hospital, A. Pettitt, Royal Liverpool University Hospital, D. Linch, University College London Hospitals, S. Montoto, St Bartholomew's Hospital – London, J. Radford, Christie Hospital – Manchester, T. Maughan, Velindre Hospital – Cardiff, A. Kruger, Royal Cornwall Hospital – Truro, Ch. Hatton, John Radcliffe Hospital – Oxford, J. Neilson, Russells Hall Hospital – Dudley, R. Pettengell, St Georges Hospital – London, S.A.J. Rule, Derriford Hospital – Plymouth, M. Macheta, Blackpool Victoria Hospital – Blackpool. Ireland (n = 4): H. Enright, Amnch – Dublin, E. Vandenberghe, St James's Hospital – Dublin. Czech Republic (n = 36): I. Vasova, FN Brno, P. Zak, FN Hradec Kralove, T. Kozak, FN Kralovske Vinohrady, M. Trneny, VFN Praha 2 – Charles University Général Hospital, T. Kozak, FN Kralovske Vinohrady – Praha. Israel (n = 13): H. Rosenbaum, Rambam – Haifa, O. Bairey, Rabin Medical Center – Beilinson Hospital – Petah Tikva, A. Avigdor, Sheba Medical Center – Tel Hashomer, D. Ben Yehuda, Hadassah Medical Center – Jerusalem. United States (n = 9): C. Moskowitz, A. Zelenetz, Memorial Sloan-Kettering Cancer Center – New York, NY. France (n = 128): A. Thyss, Centre

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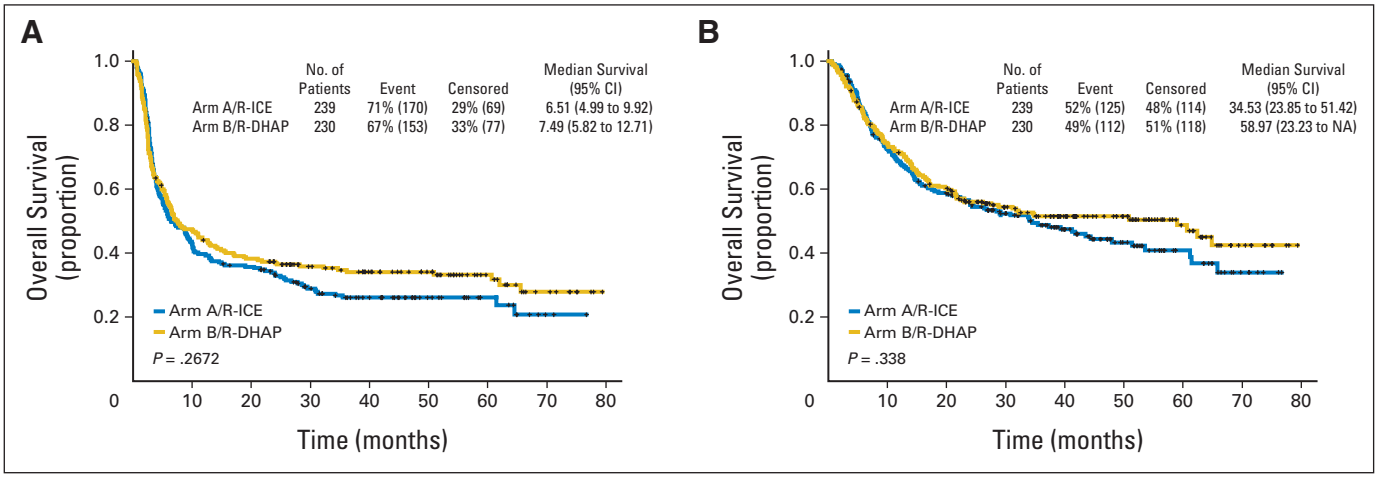

Fig A1. (A) Event-free survival (EFS) according to treatment arm from induction treatment. (B) Overall survival (OS) according to treatment arm (induction intent to treat). NA, not available; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide.

Emetteur : M. Fournier
Date : 24/11/2010
Version : 2

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 $\alpha=8.10^{-5}$ (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

Arm of treatment=ARM A / R-ICE

Randomization Number	Country Code	Initials of family name	Initials of first name	Date of Birth	First Randomization Date	Date of 2nd randomization
5003613301007	Australie - Nouvelle-Zélande	JEN	RO	10/01/1944	14/11/2006	31/01/2007
5003620201405	Allemagne-Autriche	STA	BR	22/06/1950	03/04/2006	18/09/2006
5003631201412	Allemagne-Autriche	WIL	MA	27/02/1952	07/12/2007	-
N = 3						

Arm of treatment=ARM B / R-DHAP

Randomization Number	Country Code	Initials of family name	Initials of first name	Date of Birth	First Randomization Date	Date of 2nd randomization
5003613301404	Australie - Nouvelle-Zélande	KEL	ER	30/01/1946	14/11/2006	08/02/2007
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 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

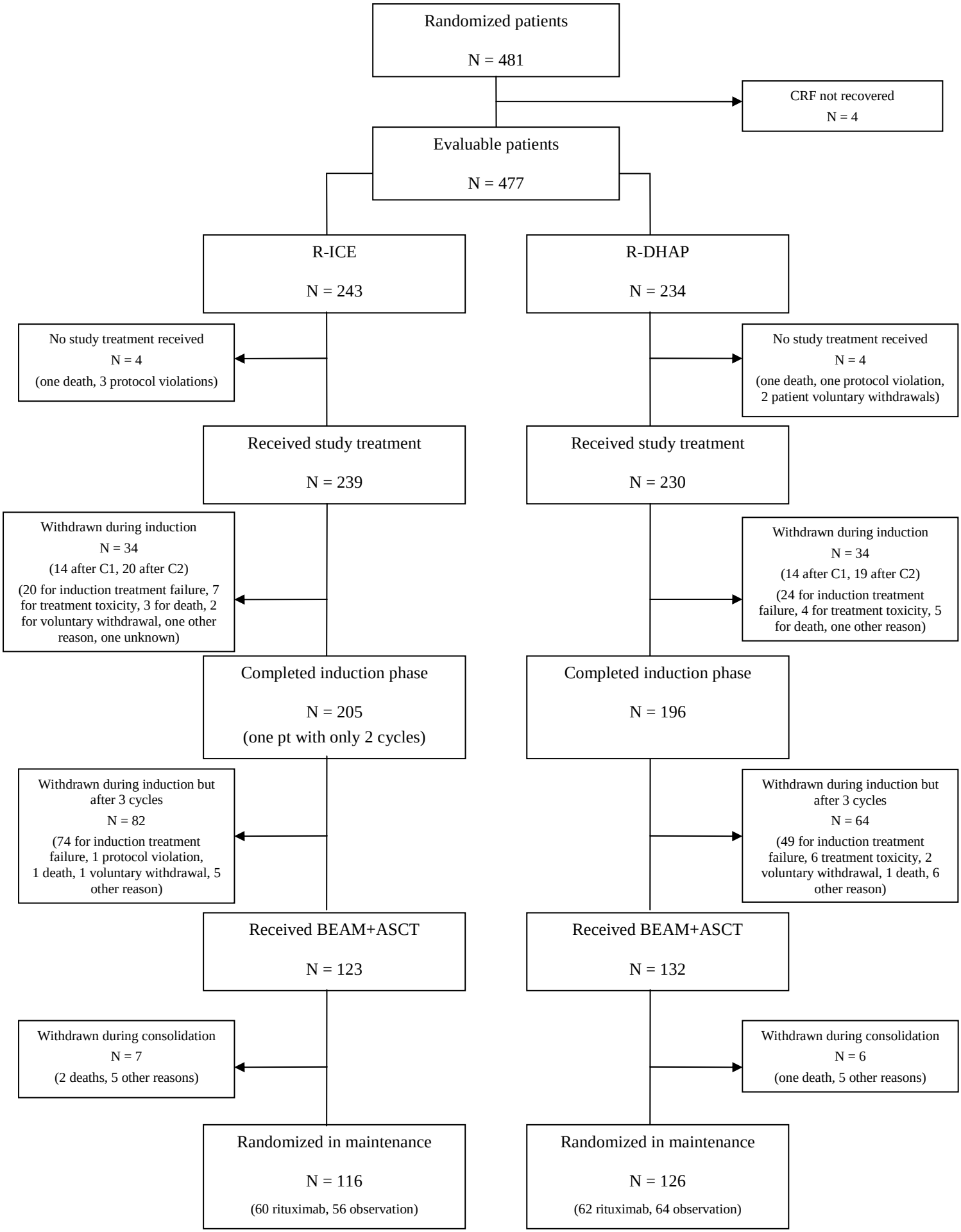
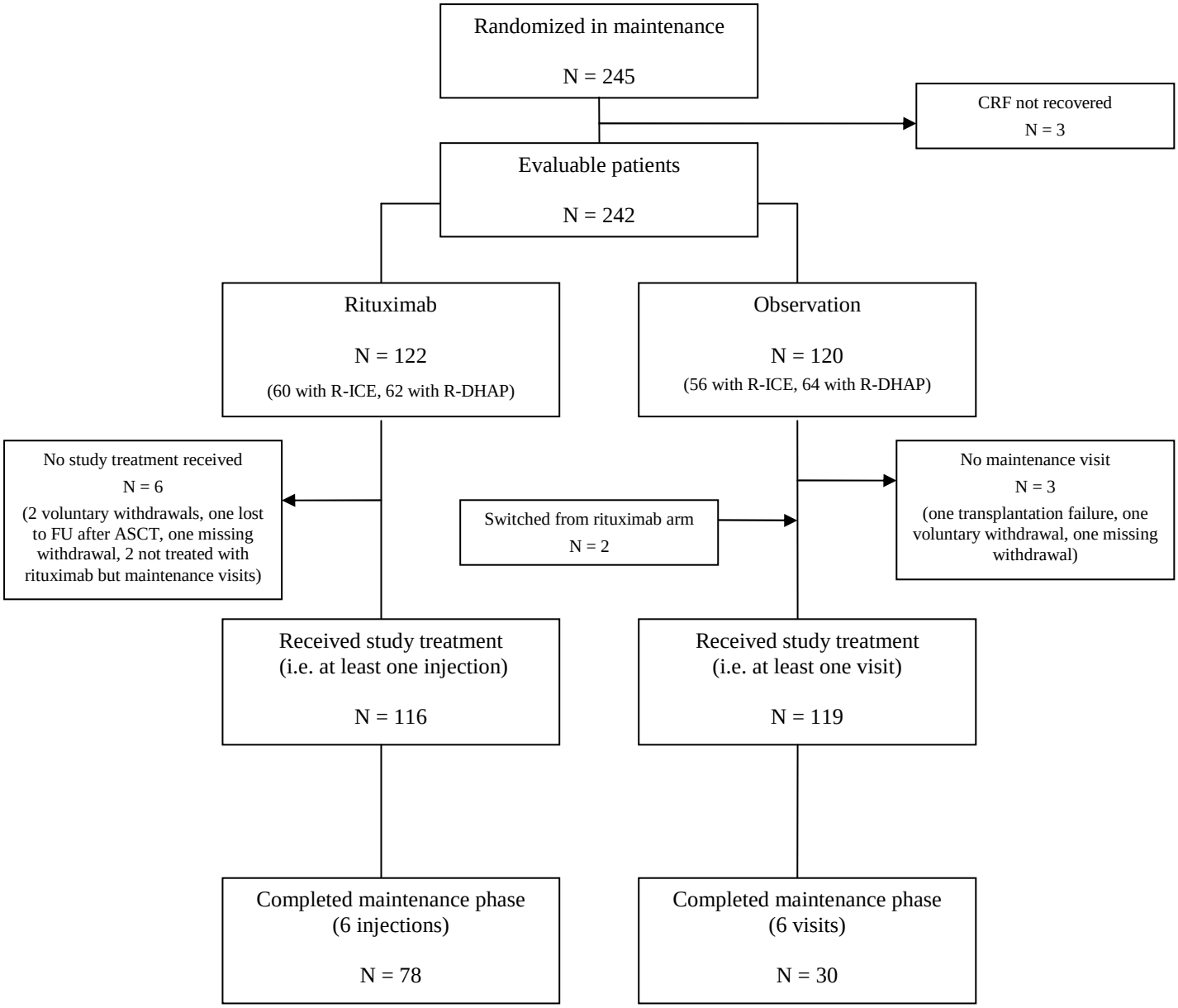


Figure 3.1-2 Disposition of patients according to arm of 2nd randomization



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 3.2-1 Criteria exceptions

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
AT LEAST ONE CRITERIA EXCEPTION						
No	224	92	221	94	445	93
Yes	19	8	13	6	32	7
TOTAL	243	100	234	100	477	100

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

	FULFILLED				Total
	No		Yes		
	N	%	N	%	N
CRITERIA					
Inclusion Criteria 1	7	1	470	99	477
Inclusion Criteria 2	0	0	477	100	477
Inclusion Criteria 3	0	0	477	100	477
Inclusion Criteria 4	0	0	477	100	477
Inclusion Criteria 5	3	1	474	99	477
Inclusion Criteria 6	0	0	477	100	477
Inclusion Criteria 7	1	0	476	100	477

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

	FULFILLED						Total
	Missing		No		Yes		
	N	%	N	%	N	%	N
CRITERIA							
Exclusion Criteria 1	0	0	476	100	1	0	477
Exclusion Criteria 2	0	0	475	100	2	0	477
Exclusion Criteria 3	1	0	472	99	4	1	477
Exclusion Criteria 4	0	0	477	100	0	0	477
Exclusion Criteria 5	0	0	477	100	0	0	477
Exclusion Criteria 6	0	0	477	100	0	0	477
Exclusion Criteria 7	0	0	476	100	1	0	477
Exclusion Criteria 8	0	0	477	100	0	0	477
Exclusion Criteria 9	1	0	467	98	9	2	477
Exlusion Criteria 10	0	0	467	98	10	2	477
Exclusion Criteria 11	0	0	475	100	2	0	477
Exclusion Criteria 12	0	0	477	100	0	0	477
Exclusion Criteria 13	0	0	477	100	0	0	477
Exclusion Criteria 14	0	0	477	100	0	0	477

Listing 3.2-1 Criteria not fulfilled

Randomization Number	Arm of treatment	Sex	Age (years)	CRITERIA	FULFILLED
5003101021027	ARM A / R-ICE	MALE	33	Exclusion Criteria 2	No
5003101021027	ARM A / R-ICE	MALE	33	Inclusion Criteria 1	No
5003101031001	ARM A / R-ICE	MALE	65	Exclusion Criteria 11	No
5003101041606	ARM A / R-ICE	MALE	64	Exclusion Criteria 1	No
5003101041606	ARM A / R-ICE	MALE	64	Exclusion Criteria 2	No
5003101041606	ARM A / R-ICE	MALE	64	Inclusion Criteria 1	No
5003101051004	ARM A / R-ICE	FEMALE	49	Exclusion Criteria 9	No
5003101131030	ARM A / R-ICE	FEMALE	48	Exclusion Criteria 3	No
5003101131030	ARM A / R-ICE	FEMALE	48	Exclusion Criteria 7	No
5003101131030	ARM A / R-ICE	FEMALE	48	Exclusion Criteria 9	No
5003101171637	ARM A / R-ICE	FEMALE	63	Exclusion Criteria 3	Missing
5003102341049	ARM A / R-ICE	MALE	33	Exlusion Criteria 10	No
5003102491616	ARM A / R-ICE	MALE	46	Exlusion Criteria 10	No

Randomization Number	Arm of treatment	Sex	Age (years)	CRITERIA	FULFILLED
5003102541625	ARM A / R-ICE	MALE	25	Exclusion Criteria 3	No
5003602901002	ARM A / R-ICE	MALE	64	Inclusion Criteria 5	No
5003602901201	ARM A / R-ICE	FEMALE	31	Exlusion Criteria 10	No
5003603201627	ARM A / R-ICE	MALE	49	Exlusion Criteria 10	No
5003605201006	ARM A / R-ICE	FEMALE	63	Exclusion Criteria 9	No
5003609201013	ARM A / R-ICE	MALE	44	Inclusion Criteria 1	No
5003610201615	ARM A / R-ICE	MALE	62	Exclusion Criteria 9	No
5003614301614	ARM A / R-ICE	MALE	59	Inclusion Criteria 1	No
5003617501024	ARM A / R-ICE	FEMALE	61	Inclusion Criteria 5	No
5003622201022	ARM A / R-ICE	MALE	60	Exlusion Criteria 10	No
5003622501604	ARM A / R-ICE	MALE	47	Exlusion Criteria 10	No
5003630201055	ARM A / R-ICE	FEMALE	62	Exlusion Criteria 10	No
5003101031019	ARM B / R-DHAP	FEMALE	58	Inclusion Criteria 1	No
5003101061617	ARM B / R-DHAP	FEMALE	54	Exclusion Criteria 9	No
5003101071002	ARM B / R-DHAP	MALE	64	Exclusion Criteria 9	No
5003101071005	ARM B / R-DHAP	MALE	56	Inclusion Criteria 1	No
5003101251044	ARM B / R-DHAP	FEMALE	64	Exclusion Criteria 3	No
5003101251044	ARM B / R-DHAP	FEMALE	64	Inclusion Criteria 1	No
5003603201005	ARM B / R-DHAP	MALE	50	Exclusion Criteria 3	No
5003603201027	ARM B / R-DHAP	MALE	54	Exclusion Criteria 11	No
5003603201027	ARM B / R-DHAP	MALE	54	Exlusion Criteria 10	No
5003603201027	ARM B / R-DHAP	MALE	54	Inclusion Criteria 5	No
5003604701002	ARM B / R-DHAP	FEMALE	30	Exlusion Criteria 10	No
5003608301205	ARM B / R-DHAP	FEMALE	59	Exclusion Criteria 9	No
5003610201212	ARM B / R-DHAP	MALE	23	Inclusion Criteria 7	No
5003617201031	ARM B / R-DHAP	FEMALE	56	Exclusion Criteria 9	Missing
5003623501405	ARM B / R-DHAP	MALE	58	Exclusion Criteria 9	No
5003631201012	ARM B / R-DHAP	FEMALE	58	Exclusion Criteria 9	No
5003638501023	ARM B / R-DHAP	MALE	60	Exlusion Criteria 10	No
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

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
PREMATURE WITHDRAWAL						
No	77	32	82	35	159	33
Yes	166	68	152	65	318	67
Total	243	100	234	100	477	100

Table 3.3-2 Period of withdrawal from study

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Treatment period at withdrawal						
BEFORE TREATMENT	4	2	4	3	8	3
INDUCTION PHASE	116	70	98	64	214	67
CONSOLIDATION PHASE	7	4	6	4	13	4
FOLLOW UP PERIOD	39	23	44	29	83	26
Total	166	100	152	100	318	100

Table 3.3-3 Reason of withdrawal from study

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Reason for premature withdrawal						
INDUCTION TREATMENT FAILURE	94	57	73	48	167	53
TRANSPLANTATION FAILURE	11	7	8	5	19	6
TREATMENT TOXICITY	8	5	12	8	20	6
MAJOR PROTOCOL VIOLATION	3	2	1	1	4	1
PATIENT VOLONTARY WITHDRAWAL	5	3	6	4	11	3
DEATH	9	5	10	7	19	6
OTHER	35	21	42	28	77	24
Missing	1	1	0	0	1	0
Total	166	100	152	100	318	100

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

	Arm of treatment																							
	ARM A / R-ICE								ARM B / R-DHAP								All							
	Arm of 2nd randomization						All		Arm of 2nd randomization						All		Arm of 2nd randomization						All	
	RITUXIMAB		OBSERVATION		NOT APPLICABLE				RITUXIMAB		OBSERVATION		NOT APPLICABLE				RITUXIMAB		OBSERVATION		NOT APPLICABLE			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Induction full analysis population																								
Yes	60	13	56	12	127	27	243	51	62	13	64	13	108	23	234	49	122	26	120	25	235	49	477	100
Induction ITT population																								
Yes	60	13	56	12	123	26	239	51	62	13	64	14	104	22	230	49	122	26	120	26	227	48	469	100
No	0	0	0	0	4	50	4	50	0	0	0	0	4	50	4	50	0	0	0	0	8	100	8	100
Maintenance ITT population																								
Yes	60	25	56	23	0	0	116	48	62	26	64	26	0	0	126	52	122	50	120	50	0	0	242	100
No	0	0	0	0	127	54	127	54	0	0	0	0	108	46	108	46	0	0	0	0	235	100	235	100
TOTAL	60	13	56	12	127	27	243	51	62	13	64	13	108	23	234	49	122	26	120	25	235	49	477	100

Table 4.1-2 Eligible patients for analysis per safety populations

	Actual arm of induction																							
	ARM A / R-ICE								ARM B / R-DHAP								All							
	Actual arm of maintenance						All		Actual arm of maintenance						All		Actual arm of maintenance						All	
	RITUXIMAB		OBSERVATION		NOT APPLICABLE				RITUXIMAB		OBSERVATION		NOT APPLICABLE				RITUXIMAB		OBSERVATION		NOT APPLICABLE			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Induction Safety population																								
Yes	59	13	56	12	124	26	239	51	57	12	63	13	110	23	230	49	116	25	119	25	234	50	469	100
Maintenance safety population																								
Yes	59	25	56	24	0	0	115	49	57	24	63	27	0	0	120	51	116	49	119	51	0	0	235	100
No	0	0	0	0	124	53	124	53	0	0	0	0	110	47	110	47	0	0	0	0	234	100	234	100
TOTAL	59	13	56	12	124	26	239	51	57	12	63	13	110	23	230	49	116	25	119	25	234	50	469	100

Listing 4.1-1 Patients excluded from MITT/safety populations

Randomization Number	Arm of treatment	First Randomization Date	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal
5003101041606	ARM A / R-ICE	03/12/2003	05/12/2003	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION	
5003603201627	ARM A / R-ICE	28/03/2007	03/04/2007	BEFORE TREATMENT	DEATH	
5003609201013	ARM A / R-ICE	14/03/2005	14/03/2005	BEFORE TREATMENT	OTHER	MEET NOT INCLUSION CRITERIAS
5003614301614	ARM A / R-ICE	16/06/2005	17/06/2005	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION	
5003101071620	ARM B / R-DHAP	29/10/2004	29/10/2004	BEFORE TREATMENT	PATIENT VOLONTARY WITHDRAWAL	
5003601601004	ARM B / R-DHAP	02/11/2007	04/11/2007	BEFORE TREATMENT	PATIENT VOLONTARY WITHDRAWAL	
5003603201005	ARM B / R-DHAP	08/10/2004	12/10/2004	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION	
5003603201027	ARM B / R-DHAP	26/01/2006	26/01/2006	BEFORE TREATMENT	DEATH	
N = 8						

Listing 4.1-2 Patients excluded from maintenance safety population

Randomization Number	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal
5003601301015	RITUXIMAB	08/02/2008	18/03/2008	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL	
5003604901602	RITUXIMAB	02/05/2005	28/06/2005	FOLLOW UP PERIOD	OTHER	LOST TO FOLLOW-UP AFTER BMT
5003608301605	RITUXIMAB	25/08/2004	13/09/2004	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL	
5003617201613	RITUXIMAB	22/09/2005	-	-	-	
5003101601610	OBSERVATION	17/05/2004	11/08/2004	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE	
5003102361203	OBSERVATION	19/02/2004	13/03/2004	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL	
5003631201619	OBSERVATION	14/06/2006	-	-	-	
N = 7						

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

Randomization Number	Arm of 2nd randomization	Actual arm of maintenance	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Comments
5003612201401	RITUXIMAB	OBSERVATION	29/09/2005	12/10/2005	FOLLOW UP PERIOD	OTHER	THE PATIENT WAS RANDOMIZED AT RITUXIMAB BUT IT WAS NOT GIVEN BECAUSE OF INCORRECTED COMMUNICATION BETWEEN US AND THE PRIVATE PRAXIS
5003617201021	RITUXIMAB	OBSERVATION	14/02/2006	17/03/2006	FOLLOW UP PERIOD	OTHER	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 (< 250 U/L)
N = 2							

4.2. Baseline data

4.2.1. Demography

Table 4.2-1 Demography (FAS)

		Arm of treatment		All
		ARM A / R-ICE	ARM B / R-DHAP	
Age (years)	**N**	243	234	477
	Mean	50.7	52.3	51.5
	Std	11.10	10.48	10.82
	Median	54.0	55.0	54.0
	Min	19	19	19
	Max	65	65	65
Weight	**N**	243	233	476
	Mean	79.4	77.8	78.6
	Std	17.38	16.30	16.87
	Median	77.0	76.0	76.0
	Min	47	45	45
	Max	176	137	176
Height	**N**	243	233	476
	Mean	172.4	172.5	172.5
	Std	9.47	9.21	9.33
	Median	173.0	173.0	173.0
	Min	147	152	147
	Max	196	198	198
Body Area at baseline	**N**	243	232	475
	Mean	1.914	1.891	1.903
	Std	0.2192	0.2074	0.2136
	Median	1.900	1.900	1.900
	Min	1.46	1.40	1.40
	Max	2.79	2.45	2.79

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)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	**%**	**N**	**%**	**N**	**%**
Sex						
MALE	156	64	147	63	303	64
FEMALE	87	36	87	37	174	36
Age (years)						
<40 years	41	17	32	14	73	15
>=40 years	202	83	202	86	404	85
Total	243	100	234	100	477	100

4.2.2. Initial diagnosis

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

		Arm of treatment		All
		ARM A / R-ICE	ARM B / R-DHAP	
Time from initial diagnosis to 1st randomization (months)	**N**	241	233	474
	Mean	27.1	30.8	28.9
	Std	32.34	40.72	36.70
	Median	14.1	13.8	13.9
	Min	1	1	1
	Max	180	238	238
Time from initial diagnostic biospsy to 1st randomization (months)	**N**	242	230	472
	Mean	27.1	29.3	28.2
	Std	32.29	37.42	34.87
	Median	14.0	13.8	13.9
	Min	1	1	1
	Max	180	197	197

Table 4.2-4 Time between intial diagnosis and 1st randomization by category (FAS)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Time from initial diagnostic biospsy to 1st randomization						
<12 months	104	43	99	43	203	43
>=12 months	138	57	131	57	269	57
TOTAL	242	100	230	100	472	100
Time from Initial Treatment to 1st randomization						
<12 months	107	45	106	46	213	46
>=12 months	133	55	122	54	255	54
TOTAL	240	100	228	100	468	100

Table 4.2-5 Characteristics at initial diagnosis (FAS)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Performance Status at diagnosis						
0	114	52	107	50	221	51
1	76	35	71	33	147	34
2	20	9	27	13	47	11
3	8	4	6	3	14	3
4	2	1	1	0	3	1
TOTAL	220	100	212	100	432	100

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Ann Arbor Stage at diagnosis						
STAGE 1	37	15	44	19	81	17
STAGE 2	60	25	57	25	117	25
STAGE 3	43	18	35	15	78	17
STAGE 4	99	41	96	41	195	41
TOTAL	239	100	232	100	471	100
B Symptom at diagnosis						
Yes	95	40	99	44	194	42
No	141	60	125	56	266	58
TOTAL	236	100	224	100	460	100

Table 4.2-6 International Prognostic Index and individual factors at initial diagnosis (FAS)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Performance Status at diagnosis						
<2	190	86	178	84	368	85
>=2	30	14	34	16	64	15
TOTAL	220	100	212	100	432	100
Ann Arbor Stage at diagnosis						
I-II	97	41	101	44	198	42
III-IV	142	59	131	56	273	58
TOTAL	239	100	232	100	471	100
LDH at diagnosis						
=< 1 N	93	43	97	47	190	45
> 1 N	123	57	108	53	231	55
TOTAL	216	100	205	100	421	100
Age adjusted IPI at initial diagnosis						
0	42	21	42	22	84	21
1	76	37	78	41	154	39
2	66	32	49	26	115	29
3	20	10	21	11	41	10
Subtotal 0-1	118	58	120	63	238	60
Subtotal 2-3	86	42	70	37	156	40
TOTAL	204	100	190	100	394	100
Nb of extra-nodal sites at initial diagnosis						
<=1	170	73	174	76	344	74
>1	64	27	55	24	119	26
TOTAL	234	100	229	100	463	100

	Arm of treatment					
	ARM A / R-ICE		ARM B / R-DHAP		All	
	N	%	N	%	N	%
IPI at initial diagnosis						
0	35	17	34	18	69	18
1	55	27	64	34	119	30
2	62	31	41	22	103	26
3	35	17	35	19	70	18
4	14	7	13	7	27	7
5	2	1	2	1	4	1
Subtotal 0-2	152	75	139	74	291	74
Subtotal 3-5	51	25	50	26	101	26
TOTAL	203	100	189	100	392	100

Table 4.2-7 p-values of Chi-2 test for individual factors of IPI at initial diagnosis (FAS)

Variable/Treatment	P-value (Chi-2)
Performance Status at diagnosis (<2 Vs >=2)	0.4824
Ann Arbor Stage at diagnosis (I-II Vs III-IV)	0.5169
LDH at diagnosis (=< 1 N Vs > 1 N)	0.3798
Age adjusted IPI at diagnosis (0-1 Vs 2-3)	0.2811
Extra nodal involvement at diagnosis (<=1 Vs >1)	0.4119
IPI at diagnosis (0-2 Vs 3-5)	0.7632
B Symptoms at diagnosis (No Vs Yes)	0.3921

Table 4.2-8 Anatomopathological report at initial diagnosis - review (FAS)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Histology (review) at initial diagnosis						
Lymphome diffus à grandes cellules B	65	46	63	51	128	48
Lymphome diffus à grandes cellules B (centroblastique)	25	18	13	10	38	14
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire	9	6	9	7	18	7
Lymphome diffus à grandes cellules B (immunoblastique)	6	4	10	8	16	6
Lymphome à grandes cellules B thymique	6	4	4	3	10	4
Lymphome diffus à grandes cellules B (B riche en T / histiocytes)	4	3	4	3	8	3
Insuffisance de matériel	3	2	3	2	6	2
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale	4	3	1	1	5	2
Lymphome folliculaire grade 2	4	3	1	1	5	2
Lymphome à grandes cellules B non classable pour raisons techniques	1	1	3	2	4	2
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à "petites cellules" sans précision	1	1	3	2	4	2
lymphome B agressif non classable	1	1	3	2	4	2
Lymphome B non classable pour raisons techniques	2	1	1	1	3	1
Lymphome à grandes cellules non classable	3	2	0	0	3	1
Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)	1	1	1	1	2	1
Lymphome à grandes cellules B plasmoblastique	1	1	1	1	2	1
Lymphome T périphérique (sans spécificité)	1	1	0	0	1	0
Lymphome T angio-immunoblastique	1	1	0	0	1	0
Lymphome T angio-immunoblastique avec progression cytologique B	0	0	1	1	1	0
Lymphome folliculaire grade 1	1	1	0	0	1	0
Zone grise entre Hodgkin / lymphoprolifération EBV	1	1	0	0	1	0
Lymphome folliculaire grade 3 B	0	0	1	1	1	0
Lymphome folliculaire grade 1-2	0	0	1	1	1	0
Lymphome folliculaire grade 3 A	0	0	1	1	1	0
TOTAL	140	100	124	100	264	100

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 4.2-9 Anatomopathological report at initial diagnosis – review or if missing, local (FAS)

	Arm of treatment					
	ARM A / R-ICE		ARM B / R-DHAP		All	
	N	%	N	%	N	%
Histology (review if available, otherwise local) at initial diagnosis						
Lymphome diffus à grandes cellules B	95	51	94	55	189	53
Lymphome diffus à grandes cellules B (centroblastique)	28	15	19	11	47	13
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire	9	5	10	6	19	5
Lymphome diffus à grandes cellules B (B riche en T / histiocytes)	9	5	9	5	18	5
Lymphome diffus à grandes cellules B (immunoblastique)	6	3	11	6	17	5
Lymphome à grandes cellules B thymique	11	6	6	3	17	5
Insuffisance de matériel	3	2	3	2	6	2
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale	4	2	1	1	5	1
Lymphome folliculaire grade 2	4	2	1	1	5	1
Lymphome à grandes cellules B non classable pour raisons techniques	1	1	3	2	4	1
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à "petites cellules" sans précision	1	1	3	2	4	1
lymphome B agressif non classable	1	1	3	2	4	1
Lymphome B non classable pour raisons techniques	2	1	1	1	3	1
Lymphome à grandes cellules non classable	3	2	0	0	3	1
Lymphome diffus à grandes cellules B (anaplasique)	1	1	2	1	3	1
Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)	1	1	1	1	2	1
Lymphome à grandes cellules B plasmoblastique	1	1	1	1	2	1
Lymphome T périphérique (sans spécificité)	1	1	0	0	1	0
Lymphome T angio-immunoblastique	1	1	0	0	1	0
Lymphome T angio-immunoblastique avec progression cytologique B	0	0	1	1	1	0
Lymphome folliculaire probable	1	1	0	0	1	0
Lymphome folliculaire grade 1	1	1	0	0	1	0
Lymphome folliculaire et diffus	1	1	0	0	1	0
Zone grise entre Hodgkin / lymphoprolifération EBV	1	1	0	0	1	0
Lymphome folliculaire grade 3 B	0	0	1	1	1	0
Lymphome folliculaire grade 1-2	0	0	1	1	1	0
Lymphome folliculaire grade 3 A	0	0	1	1	1	0
TOTAL	186	100	172	100	358	100

4.2.3. Initial treatment

Table 4.2-10 Time between initial treatment and 1st randomization (FAS)

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

Table 4.2-11 Characteristics of initial treatment (FAS)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Chemotherapy regimen						
CHOP - LIKE	203	84	203	87	406	85
ACVB - LIKE	32	13	27	12	59	12
OTHER	7	3	4	2	11	2
.	1	0	0	0	1	0
Immunotherapy						
RITUXIMAB	155	64	151	65	306	64
UNKNOWN	1	0	1	0	2	0
.	87	36	82	35	169	35
Radiotherapy						
LOCAL	63	26	51	22	114	24
OTHER	2	1	1	0	3	1
UNKNOWN	2	1	7	3	9	2
.	176	72	175	75	351	74
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 1st line (FAS)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Response after first line						
COMPLETE RESPONSE	129	53	122	52	251	53
UNCONFIRMED COMPLETE RESPONSE	31	13	24	10	55	12
PARTIAL RESPONSE	44	18	49	21	93	20
STABLE DISEASE	11	5	13	6	24	5
PROGRESSIVE DISEASE	27	11	25	11	52	11
NOT EVALUATED	0	0	1	0	1	0
TOTAL	242	100	234	100	476	100

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

Variable/Treatment	P-value (Chi-2)
Response after first line (CR/CRu vs other)	0.3968

4.2.4. Progression/relapse diagnosis

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

		Arm of treatment		All
		ARM A / R-ICE	ARM B / R-DHAP	
Time from 1st treatment to relapse diagnostic biopsy (months)	**N**	187	174	361
	Mean	29.6	36.2	32.8
	Std	33.79	44.24	39.26
	Median	15.3	17.9	16.1
	Min	1	3	1
	Max	179	237	237
Time from relapse diagnostic biopsy to 1st randomization (months)	**N**	189	179	368
	Mean	0.8	0.7	0.7
	Std	2.03	0.55	1.50
	Median	0.5	0.5	0.5
	Min	-0	-0	-0
	Max	27	4	27

The following tables present the number and percentage of patients for baseline clinical assessments:

Table 4.2-15 Characteristics at relapse (FAS)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Performance Status at relapse						
0	105	43	113	49	218	46
1	109	45	90	39	199	42
2	26	11	28	12	54	11
3	2	1	0	0	2	0
4	0	0	1	0	1	0
Ann Arbor stage at relapse						
STAGE 1	40	17	32	14	72	15
STAGE 2	53	22	57	25	110	23
STAGE 3	45	19	33	14	78	16
STAGE 4	104	43	110	47	214	45
TOTAL	242	100	232	100	474	100
B symptoms at relapse						
No	178	74	176	77	354	75
Yes	63	26	53	23	116	25
TOTAL	241	100	229	100	470	100

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

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

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)

	Arm of treatment					
	ARM A / R-ICE		ARM B / R-DHAP		All	
	N	%	N	%	N	%
Performance Status at relapse						
<2	214	88	203	88	417	88
>=2	28	12	29	13	57	12
Ann Arbor stage at relapse						
I-II	93	38	89	38	182	38
III-IV	149	62	143	62	292	62
TOTAL	242	100	232	100	474	100
LDH at relapse						
<=Normal	111	47	112	49	223	48
>Normal	126	53	117	51	243	52
TOTAL	237	100	229	100	466	100
Age-adjusted IPI at relapse						
0	47	20	52	23	99	21
1	95	40	87	38	182	39
2	79	34	67	30	146	32
3	14	6	21	9	35	8
Subtotal 0-1	142	60	139	61	281	61
Subtotal 2-3	93	40	88	39	181	39
TOTAL	235	100	227	100	462	100
Nb of extra-nodal sites at relapse						
<=1	175	72	154	66	329	69
>1	67	28	78	34	145	31
TOTAL	242	100	232	100	474	100
IPI at relapse						
0	35	15	46	20	81	18
1	72	31	51	22	123	27
2	67	29	59	26	126	27
3	44	19	40	18	84	18
4	12	5	26	11	38	8
Subtotal 0-2	4	2	5	2	9	2
Subtotal 3-5	174	74	156	69	330	72
TOTAL	60	26	71	31	131	28
Ann Arbor stage at relapse	234	100	227	100	461	100

Table 4.2-18 p-values of Chi-2 test for individual factors of IPI at progression/relapse diagnosis (FAS)

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

Table 4.2-19 Other characteristics at relapse (FAS)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
beta 2 microglobulin (mg/l)						
<3	127	78	124	78	251	78
>=3	35	22	34	22	69	22
Total	162	100	158	100	320	100
Albumin baseline (G/L)						
<=35	35	17	40	19	75	18
>35	171	83	170	81	341	82
Total	206	100	210	100	416	100

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

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Bone marrow Biopsy						
Not involved	196	81	180	77	376	79
Involved	21	9	22	9	43	9
Unspecified	3	1	2	1	5	1
Not Done	23	9	29	12	52	11
TOTAL	243	100	233	100	476	100
If BM involved, type of cells						
LARGE CELLS	14	67	13	59	27	63
SMALL CELLS	5	24	8	36	13	30
UNKNOWN	2	10	1	5	3	7
TOTAL	21	100	22	100	43	100

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)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
PET Scan at relapse						
NEGATIVE	3	1	2	1	5	1
POSITIVE	85	35	84	36	169	36
NOT DONE	152	63	145	63	297	63
Total	240	100	231	100	471	100

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)

		Arm of treatment		
		ARM A / R-ICE	ARM B / R-DHAP	All
Number of sites used for evaluation of response per patient	**N**	243	234	477
	Mean	2.5	2.3	2.4
	Std	1.54	1.43	1.49
	Median	2.0	2.0	2.0
	Min	0	0	0
	Max	6	6	6
	Sum	611	540	1151

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 (FAS)

	Arm of treatment					
	ARM A / R-ICE		ARM B / R-DHAP		All	
	N	%	N	%	N	%
Histology (review) at relapse						
Lymphome diffus à grandes cellules B	51	41	62	49	113	45
Lymphome diffus à grandes cellules B (centroblastique)	29	23	26	20	55	22
Lymphome à grandes cellules B thymique	8	6	3	2	11	4
Lymphome diffus à grandes cellules B (immunoblastique)	5	4	6	5	11	4
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire	4	3	4	3	8	3
Lymphome B non classable pour raisons techniques	2	2	5	4	7	3
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale	4	3	1	1	5	2
Lymphome à grandes cellules B non classable pour raisons techniques	3	2	1	1	4	2
lymphome B agressif non classable	1	1	3	2	4	2
Lymphome folliculaire grade 2	1	1	3	2	4	2
Insuffisance de matériel	3	2	1	1	4	2
Lymphome folliculaire et diffus	1	1	2	2	3	1
Lymphome diffus à grandes cellules B (B riche en T / histiocytes)	1	1	2	2	3	1
Lymphome diffus à grandes cellules B (anaplasique)	2	2	1	1	3	1
Lymphome folliculaire grade 3 B	1	1	1	1	2	1
Lymphome T angio-immunoblastique	1	1	1	1	2	1
Lymphome folliculaire grade 3 A	1	1	1	1	2	1
Lymphome à grandes cellules B plasmoblastique	1	1	1	1	2	1
Lymphome T périphérique (sans spécificité)	1	1	0	0	1	0
Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)	1	1	0	0	1	0
Lymphome folliculaire en transformation possible (en L. à grandes cellules B)	1	1	0	0	1	0
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à "petites cellules" sans précision	0	0	1	1	1	0
Lymphome B à "petites cellules" non classable pour raisons techniques	0	0	1	1	1	0
Lymphome à grandes cellules non classable	1	1	0	0	1	0
Lymphome folliculaire grade 1	1	1	0	0	1	0
Lymphome folliculaire non gradable	0	0	1	1	1	0
Zone grise entre Hodgkin / lymphoprolifération EBV	1	1	0	0	1	0
TOTAL	125	100	127	100	252	100

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)

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

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)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Medical relevant history						
Yes	178	73	165	71	343	72
No	65	27	69	29	134	28
At least one persisting disease						
Yes	132	54	134	57	266	56
No	111	46	100	43	211	44
Total	243	100	234	100	477	100

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)

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Concomitant treatment at randomization						
Yes	146	60	148	63	294	62
No	97	40	86	37	183	38
At least one due to symptoms related to lymphoma						
Yes	50	21	56	24	106	22
No	193	79	178	76	371	78
Total	243	100	234	100	477	100

4.3. Evaluation after induction treatment

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

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Bone marrow biopsy after induction						
NHL negative	23	10	27	12	50	11
NHL positive	4	2	1	0	5	1
Indeterminate	0	0	2	1	2	0
Not Done	199	88	188	86	387	87
TOTAL	226	100	218	100	444	100

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

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
PET scan after induction						
NEGATIVE	35	16	37	17	72	17
POSITIVE	38	17	42	20	80	18
NOT DONE	149	67	135	63	284	65
TOTAL	222	100	214	100	436	100

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

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

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)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Date of last contact earlier than 01/06/2010 (stopping date)				
No	140	59	140	61
Yes	99	41	90	39
Total	239	100	230	100
Date of last contact earlier than 01/09/2009				
No	209	87	208	90
Yes	30	13	22	10
Total	239	100	230	100

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)

	Arm of treatment	N	Median	Min	Max
Follow-up (months)	ALL	469	45	0	79
Follow-up (months)	ARM A / R-ICE	239	45	0	77
Follow-up (months)	ARM B / R-DHAP	230	45	0	79

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 treatement 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 withdrwal. 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)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Response after complete induction (including deaths for not evaluated patients)				
COMPLETE RESPONSE	57	24	60	26
UNCONFIRMED COMPLETE RESPONSE	31	13	25	11
PARTIAL RESPONSE	65	27	63	27
STABLE DISEASE	26	11	27	12
PROGRESSIVE DISEASE	47	20	44	19
DEATH	5	2	5	2
NOT EVALUATED	5	2	4	2
Missing	3	1	2	1
Total	239	100	230	100

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

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

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

	Difference between OR rates (%)	95% CI lower	95% CI upper	p-value
R-ICE vs R-DHAP	-0.3	-9.0	8.3	0.9404

Table 4.5-4 Primary criterion – Complete Response rate after induction treatment (induction ITT)

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

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

	Difference between CR rates (%)	95% CI lower	95% CI upper	p-value
R-ICE vs R-DHAP	-0.1	-8.9	8.6	0.9756

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)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Response after complete induction (including deaths for all patients)				
COMPLETE RESPONSE	57	24	60	26
UNCONFIRMED COMPLETE RESPONSE	30	13	25	11
PARTIAL RESPONSE	65	27	63	27
STABLE DISEASE	26	11	26	11
PROGRESSIVE DISEASE	46	19	39	17
DEATH	7	3	11	5
NOT EVALUATED	5	2	4	2
Missing	3	1	2	1
Total	239	100	230	100

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

Arm of treatment	Nb patients	Nb responders (CR/CRu/PR)	OR rate (%)	95% CI lower	95% CI upper
ARM A / R-ICE	239	152	63.6	57.2	69.7
ARM B / R-DHAP	230	148	64.3	57.8	70.5

Table 4.5-8 Primary criterion – Difference between OR after induction treatment including deaths for all patients (induction ITT)

	Difference between OR rates (%)	95% CI lower	95% CI upper	p-value
R-ICE vs R-DHAP	-0.7	-9.4	7.9	0.8658

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

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

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

	Difference between CR rates (%)	95% CI lower	95% CI upper	p-value
R-ICE vs R-DHAP	-0.6	-9.3	8.2	0.9008

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

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Collection failure				
No	159	65	167	71
Yes	37	15	24	10
Missing	47	19	43	18
Total	243	100	234	100

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Collection failure - reason				
NOT ENOUGH CELLS	29	78	20	83
OTHER CAUSE	6	16	4	17
Missing	2	5	0	0
Total	30	100	24	100

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)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Response after complete induction	**Collection failure**				
CR/CRu/PR	**No**	123	**51**	130	**57**
	Yes	26	11	15	7
	Missing	4	2	3	1
Other	**No**	36	15	37	16
	Yes	11	5	9	4
	Missing	39	16	36	16
Total		239	100	230	100

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

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

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

	Difference between MARR (%)	95% CI lower	95% CI upper	p-value
R-ICE vs R-DHAP	-5.1	-14.1	4.0	0.2720

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

If mobilization adjsuted 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)

			Arm of treatment	
			ARM A / R-ICE	ARM B / R-DHAP
Collection failure				
No	**Collected Cells**	**N**	157	166
		Mean	9.490	16.542
		Std	40.2192	69.8178
		Median	5.300	5.230
		Min	1.14	1.20
		Max	507.15	629.00
Yes	**Collected Cells**	**N**	19	13
		Mean	1.486	2.647
		Std	3.4004	3.3759
		Median	0.520	0.900
		Min	0.00	0.00
		Max	15.09	9.42
All	**Collected Cells**	**N**	176	179
		Mean	8.626	15.533
		Std	38.0704	67.3229
		Median	4.865	5.100
		Min	0.00	0.00
		Max	507.15	629.00

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

			Arm of treatment	
			ARM A / R-ICE	ARM B / R-DHAP
Collection failure				
No	**Number of collections**	**N**	158	167
		Mean	1.9	1.6
		Std	1.02	0.78
		Median	2.0	1.0
		Min	1	1
		Max	6	5
Yes	**Number of collections**	**N**	26	17
		Mean	1.7	1.5
		Std	1.71	1.01
		Median	1.5	2.0
		Min	0	0
		Max	7	3

			Arm of treatment	
			ARM A / R-ICE	ARM B / R-DHAP
Total	Number of collections	N	184	184
		Mean	1.9	1.6
		Std	1.14	0.80
		Median	2.0	1.0
		Min	0	0
		Max	7	5

Table 4.5-18 Mobilization – Source of stem cells (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Source of Stem Cells				
Peripheral source	184	97	178	97
Bone marrow	4	2	4	2
Peripheral source + Bone marrow	2	1	1	1
Total	190	100	183	100

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)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Consolidation treatment (BEAM)				
Yes	123	51	132	57
No	116	49	98	43
Transplantation				
Yes	123	51	132	57
No	116	49	98	43
Total	239	100	230	100

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)

		Arm of treatment	
		ARM A / R-ICE	ARM B / R-DHAP
Time fom C3 to 1st collection date (days)	N	177	179
	Mean	5.6	-0.4
	Std	41.15	86.02
	Median	13.0	13.0
	Min	-413	-966
	Max	122	56
Time from 1st collection date to 1st administration of BEAM (days)	N	120	132
	Mean	38.0	45.7
	Std	47.96	101.28
	Median	29.0	28.0
	Min	2	6
	Max	453	1017
Time from 1st collection date to transplantation (days)	N	120	132
	Mean	44.3	51.9
	Std	47.91	101.24
	Median	35.0	34.0
	Min	9	12
	Max	459	1023
Time from 1st administration of BEAM to transplantation (days)	N	122	132
	Mean	6.3	6.2
	Std	0.49	0.88
	Median	6.0	6.0
	Min	5	0
	Max	8	10
Time from transplantation to 2nd randomization date (days)	N	116	126
	Mean	8.0	7.5
	Std	16.03	17.42
	Median	8.0	7.0
	Min	-84	-77
	Max	53	70

Table 4.5-21 Consolidation – Period of collection (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Period of collection				
Before C1	2	1	2	1
C1-C2	7	4	6	3
C2-C3	34	19	44	24
After C3	134	76	128	71
Total	177	100	180	100

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)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Events				
No event	69	29	77	33
New treatment out of progression	36	15	31	13
Progression/relapse	119	50	107	47
Death without progression	15	6	15	7
TOTAL	239	100	230	100

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)

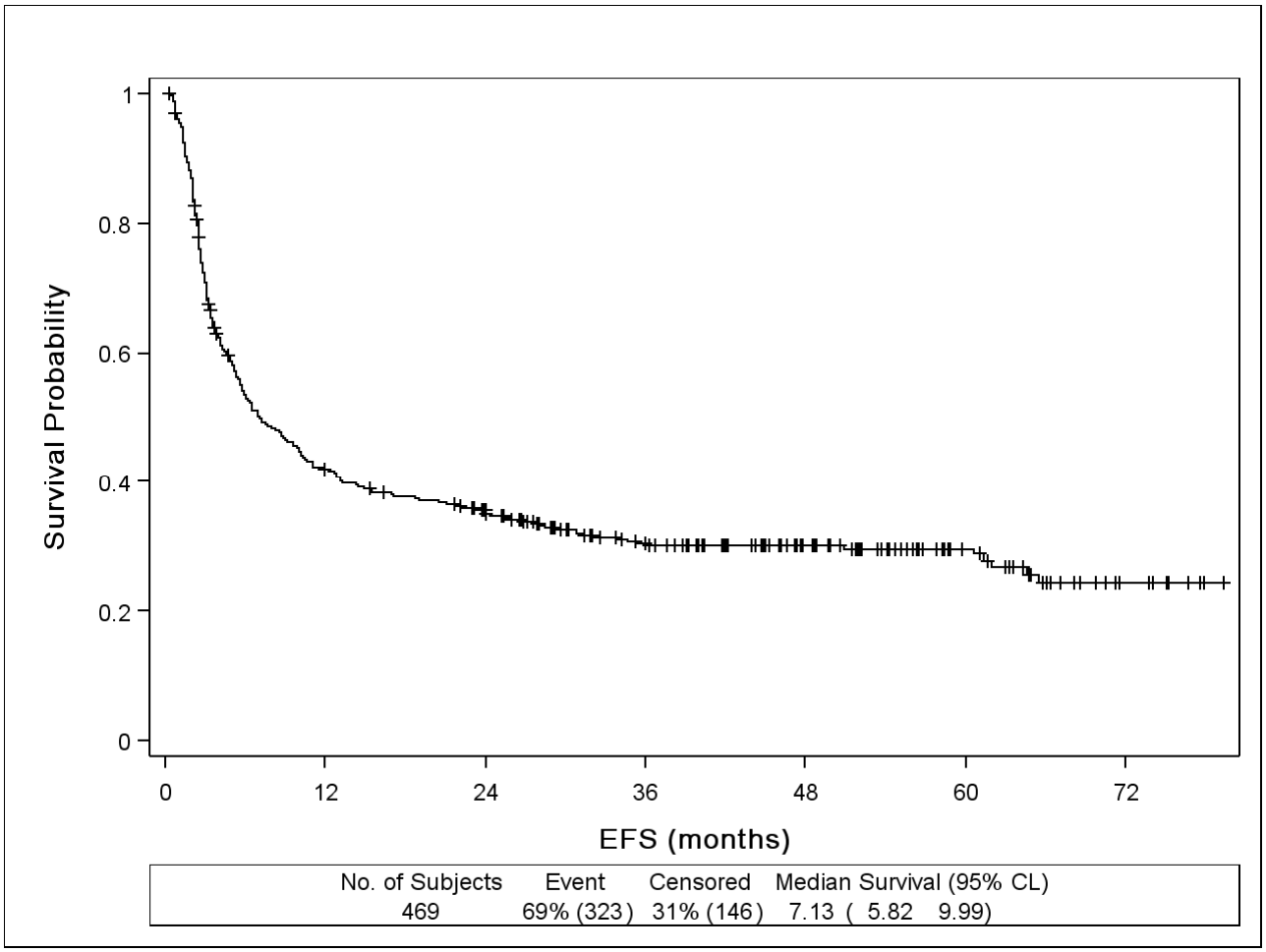


Table 4.5-23 Secondary criteria – Duration of Event-Free Survival (induction ITT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	469	7	6	10	0	79

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

Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
12	41.9	37.4	46.4	190
24	35.5	31.1	39.9	150
36	30.5	26.2	34.8	102
48	30.2	25.9	34.5	67
60	29.7	25.4	34.1	33
72	24.4	19.0	30.1	8

Figure 4.5-2 Secondary criteria – Event-Free Survival according to treatment arm (induction ITT)

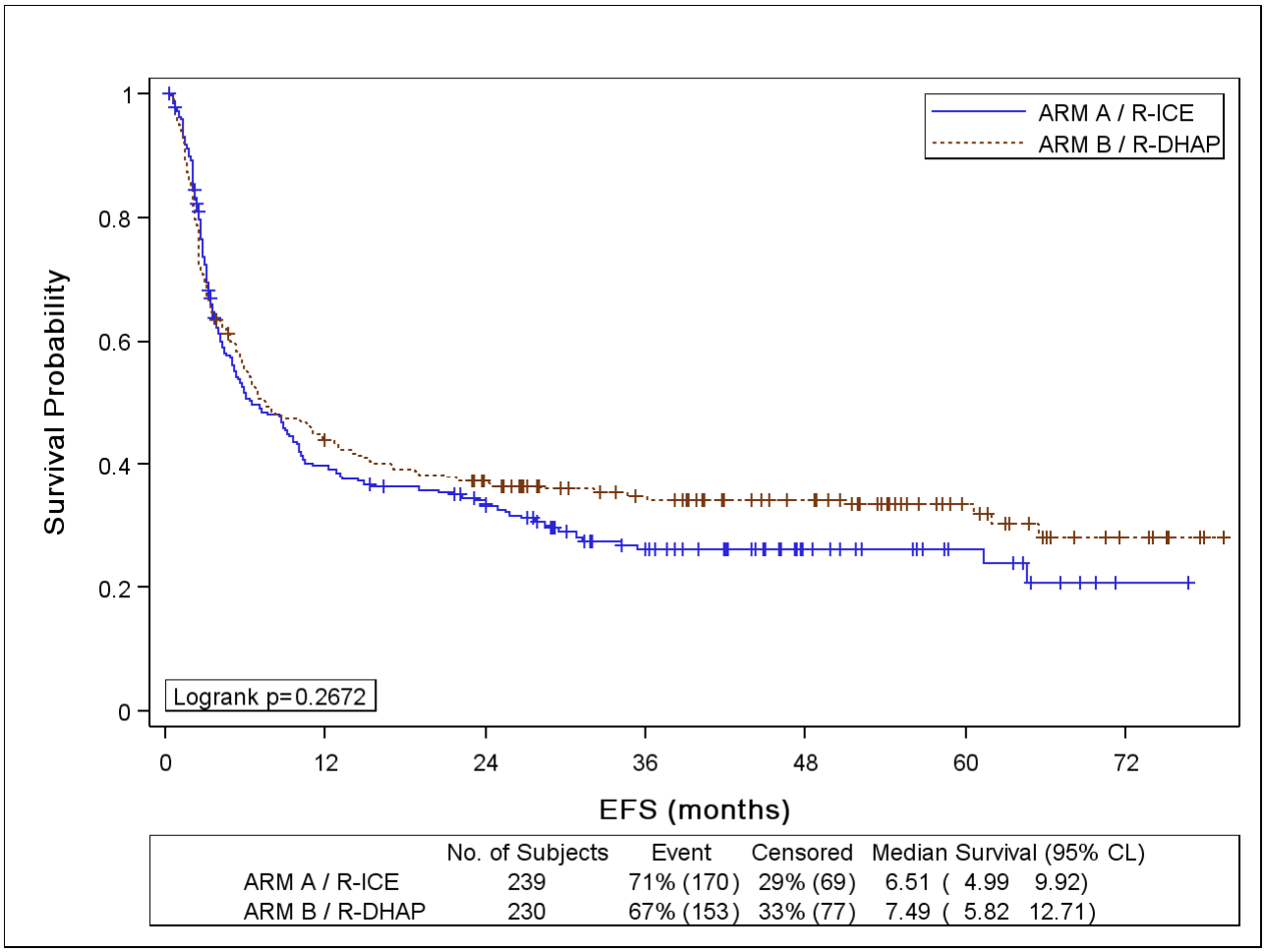


Table 4.5-25 Secondary criteria – Duration of Event-Free Survival according to treatment arm (induction ITT)

	Arm of treatment	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	ARM A / R-ICE	239	7	5	10	0	77
EFS (months)	ARM B / R-DHAP	230	7	6	13	0	79

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

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

Arm of treatment	Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
ARM B / R-DHAP	60	33.3	27.1	39.7	22
ARM B / R-DHAP	72	28.0	20.5	35.9	7

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
R-ICE	0.2687	1.131	0.909	1.408

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.

Figure 4.5-3 Secondary criteria – Progression-Free Survival (induction ITT)

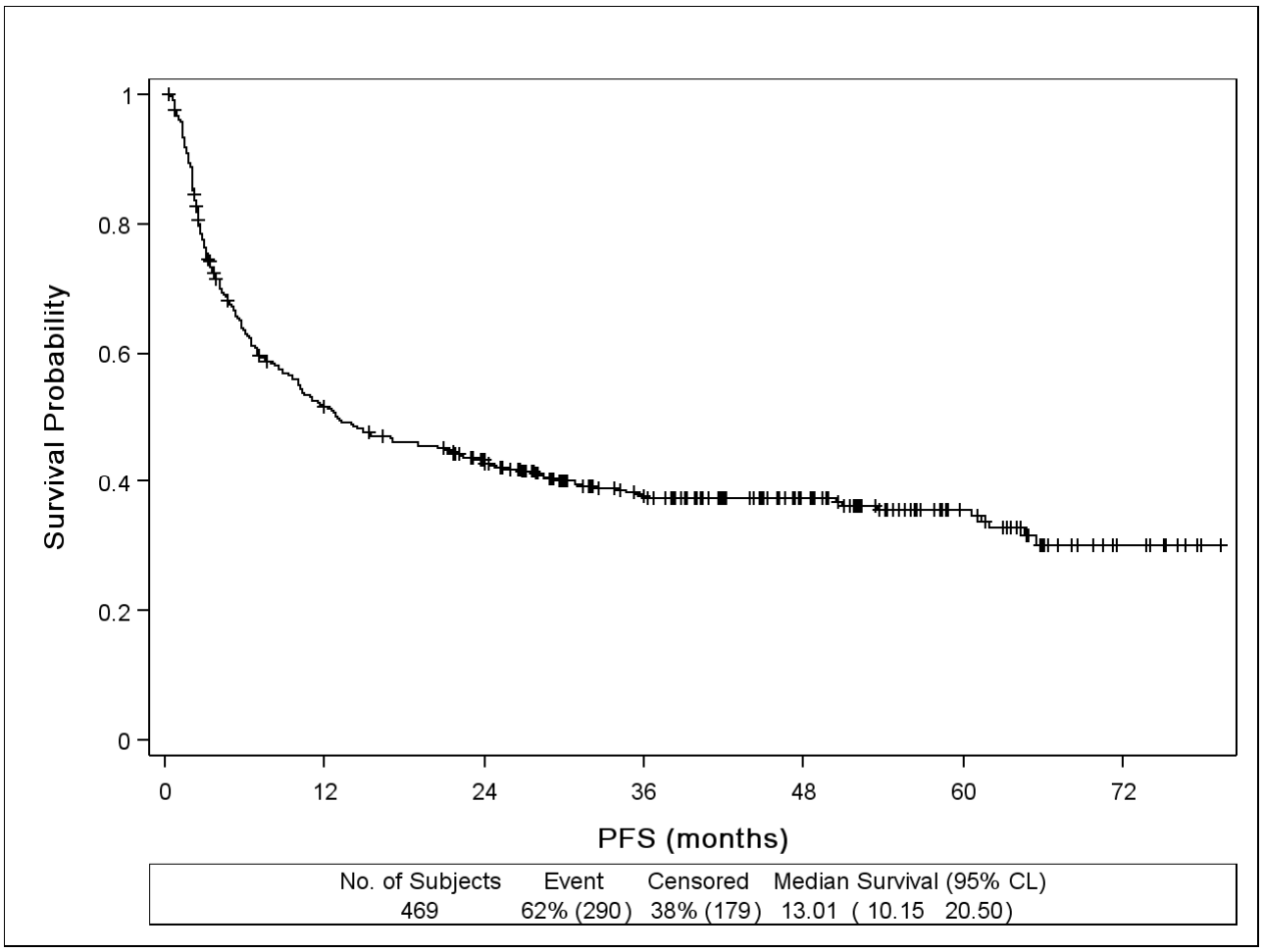


Table 4.5-28 Secondary criteria – Duration of Progression-Free Survival (induction ITT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	469	13	10	21	0	79

Table 4.5-29 Secondary criteria – Kaplan-Meier estimates for Progression-Free Survival (induction ITT)

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

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

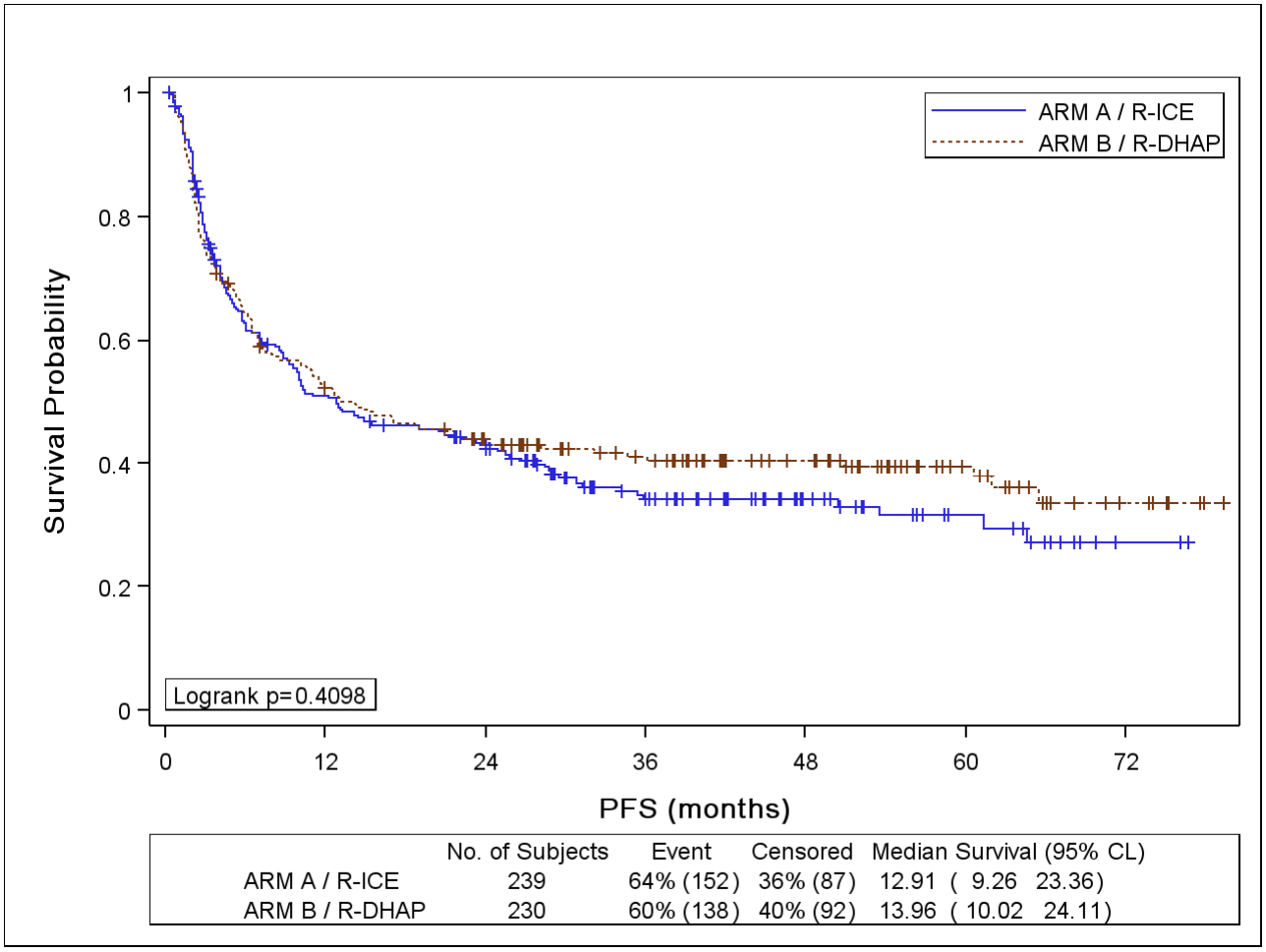


Table 4.5-30 Secondary criteria – Duration of Progression-Free Survival according to treatment arm (induction ITT)

	Arm of treatment	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	ARM A / R-ICE	239	13	9	23	0	77
PFS (months)	ARM B / R-DHAP	230	14	10	24	0	79

Table 4.5-31 Secondary criteria – Kaplan-Meier estimates for Progression-Free Survival according to treatment arm (induction ITT)

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

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
R-ICE	0.4109	1.102	0.875	1.387

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)

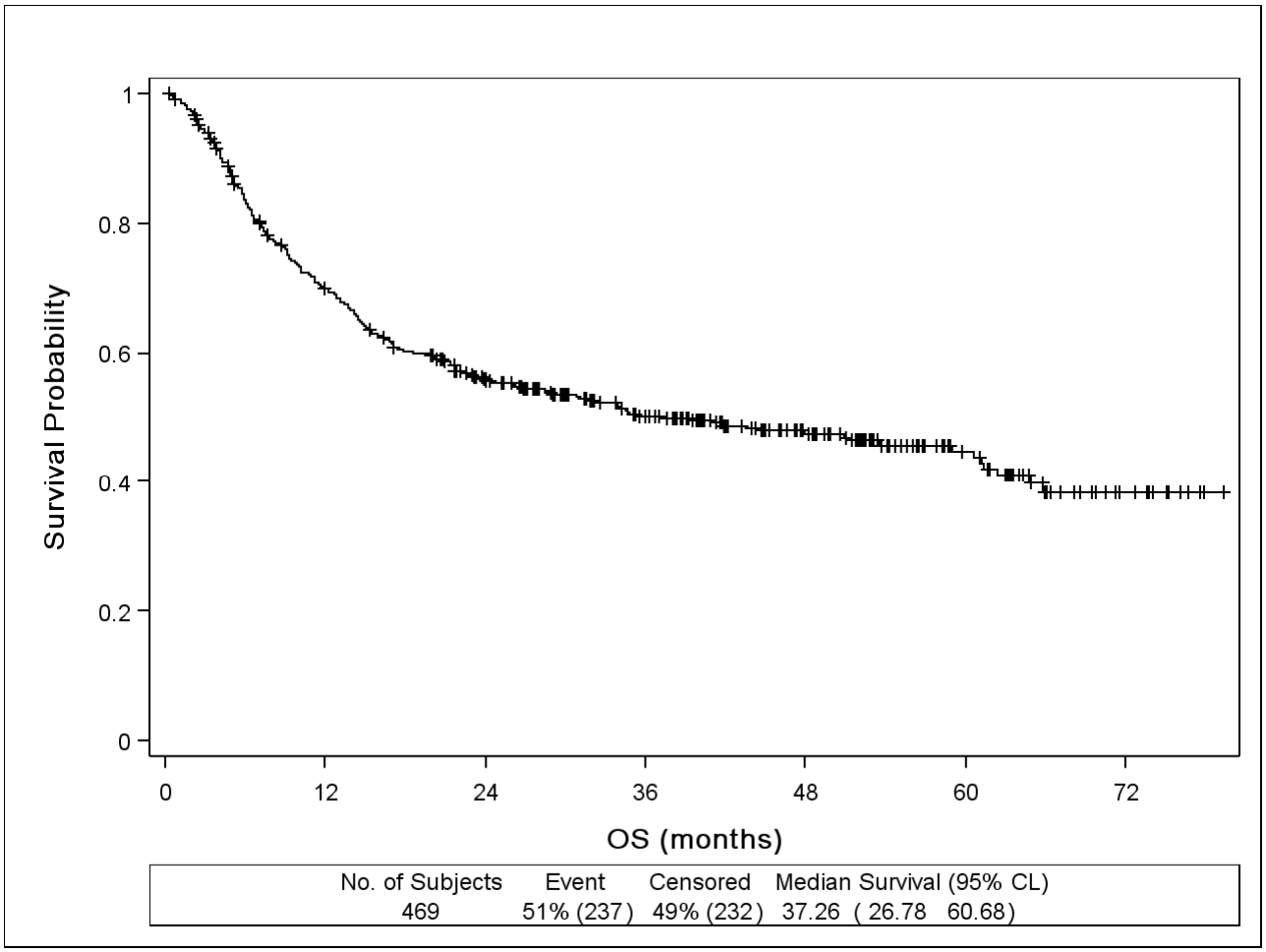


Table 4.5-33 Secondary criteria – Duration of Overall Survival (induction ITT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	469	37	27	61	0	79

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

Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
12	70.1	65.6	74.0	315
24	56.1	51.4	60.5	228
36	50.2	45.4	54.8	162
48	47.5	42.5	52.3	100
60	44.9	39.5	50.1	48
72	38.3	31.6	45.0	11

Figure 4.5-6 Secondary criteria – Overall Survival according to treatment arm (induction ITT)

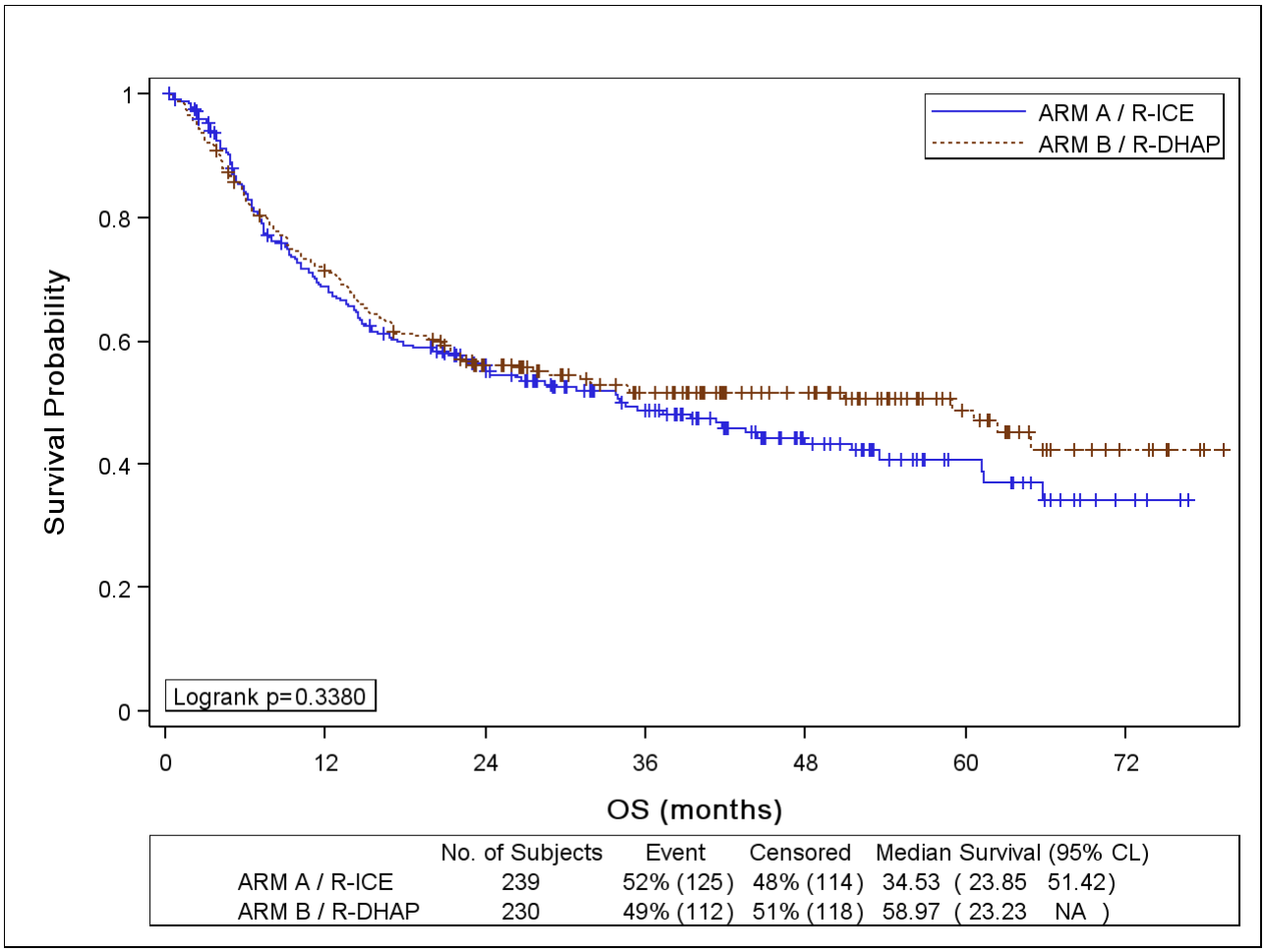


Table 4.5-35 Secondary criteria – Duration of Overall Survival according to treatment arm (induction ITT)

	Arm of treatment	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	ARM A / R-ICE	239	35	24	51	0	77
OS (months)	ARM B / R-DHAP	230	59	23	-	0	79

Table 4.5-36 Secondary criteria – Kaplan-Meier estimates for Overall Survival according to treatment arm (induction ITT)

Arm of treatment	Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
ARM A / R-ICE	12	68.7	62.2	74.2	155
ARM A / R-ICE	24	56.1	49.3	62.2	114
ARM A / R-ICE	36	48.9	42.0	55.4	79
ARM A / R-ICE	48	43.4	36.2	50.4	43
ARM A / R-ICE	60	40.9	33.4	48.3	20
ARM A / R-ICE	72	34.0	24.6	43.6	4
ARM B / R-DHAP	12	71.4	65.1	76.9	160
ARM B / R-DHAP	24	56.1	49.4	62.3	114
ARM B / R-DHAP	36	51.6	44.7	58.0	83
ARM B / R-DHAP	48	51.6	44.7	58.0	57

Arm of treatment	Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
ARM B / R-DHAP	60	48.8	41.3	56.0	28
ARM B / R-DHAP	72	42.5	33.0	51.6	7

Table 4.5-37 Secondary criteria – Hazard ratio of R-ICE arm for Overall Survival (induction ITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
R-ICE	0.3389	1.133	0.878	1.462

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.

Figure 4.5-7 Secondary criteria – Event-Free Survival (patients with ASCT)

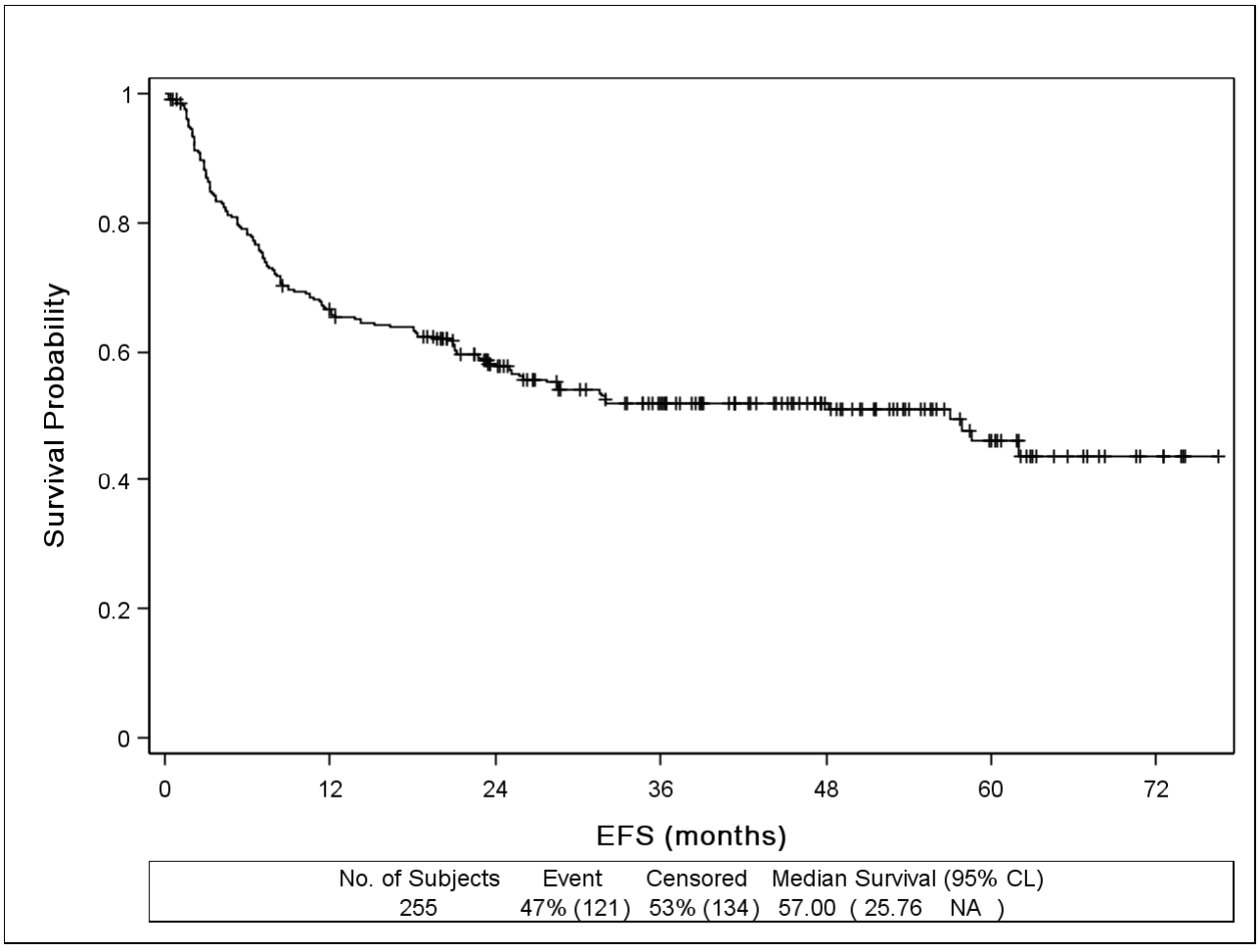


Table 4.5-38 Secondary criteria – Duration of Event-Free Survival (patients with ASCT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	255	57	26	-	0	76

Table 4.5-39 Secondary criteria – Kaplan-Meier estimates for Event-Free Survival (patients with ASCT)

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

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

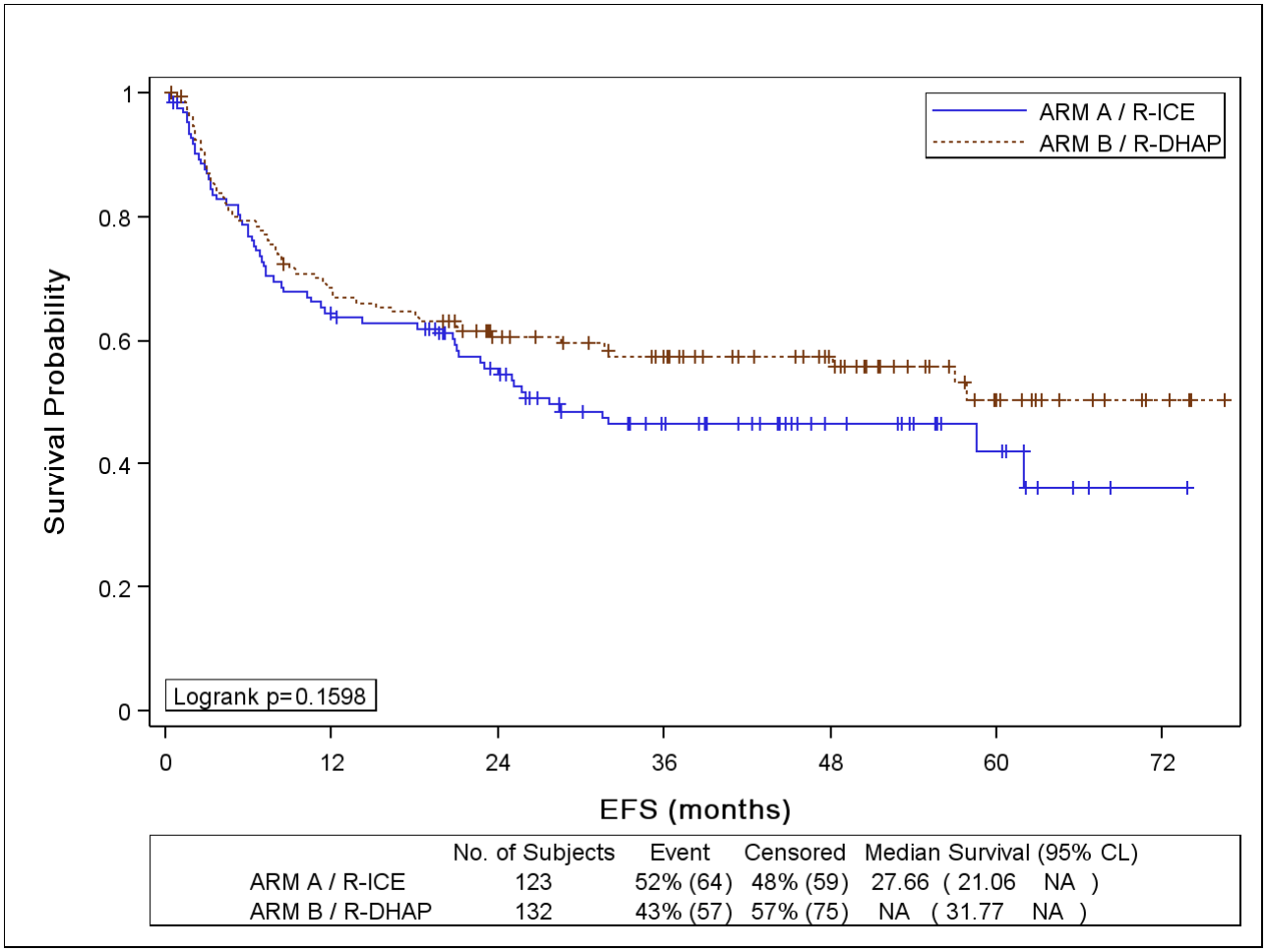


Table 4.5-40 Secondary criteria – Duration of Event-Free Survival according to treatment arm (patients with ASCT)

	Arm of treatment	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	ARM A / R-ICE	123	28	21	-	0	74
EFS (months)	ARM B / R-DHAP	132	-	32	-	0	76

Table 4.5-41 Secondary criteria – Kaplan-Meier estimates for Event-Free Survival according to treatment arm (patients with ASCT)

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

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
R-ICE	0.1612	1.291	0.903	1.846

4.5.2.7. Progression-Free Survival of 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.

Figure 4.5-9 Secondary criteria – Progression-Free Survival (patients with ASCT)

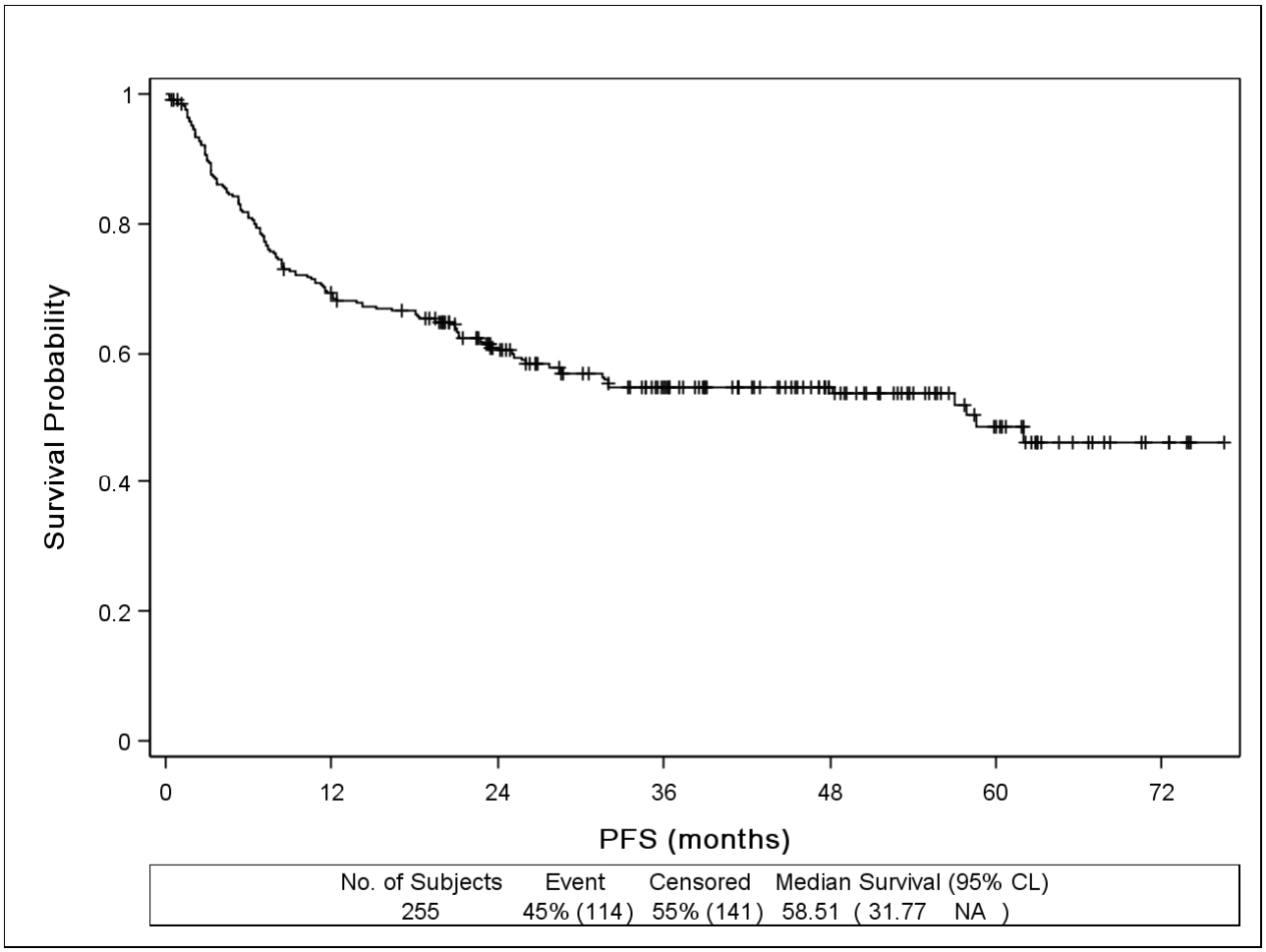


Table 4.5-43 Secondary criteria – Duration of Progression-Free Survival (patients with ASCT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	255	59	32	-	0	76

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

Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
12	69.3	63.2	74.6	172
24	60.9	54.5	66.6	128
36	54.7	48.1	60.9	92
48	54.7	48.1	60.9	56
60	48.7	40.4	56.5	26
72	46.4	37.3	54.9	6

Figure 4.5-10 Secondary criteria – Progression-Free Survival according to treatment arm (patients with ASCT)

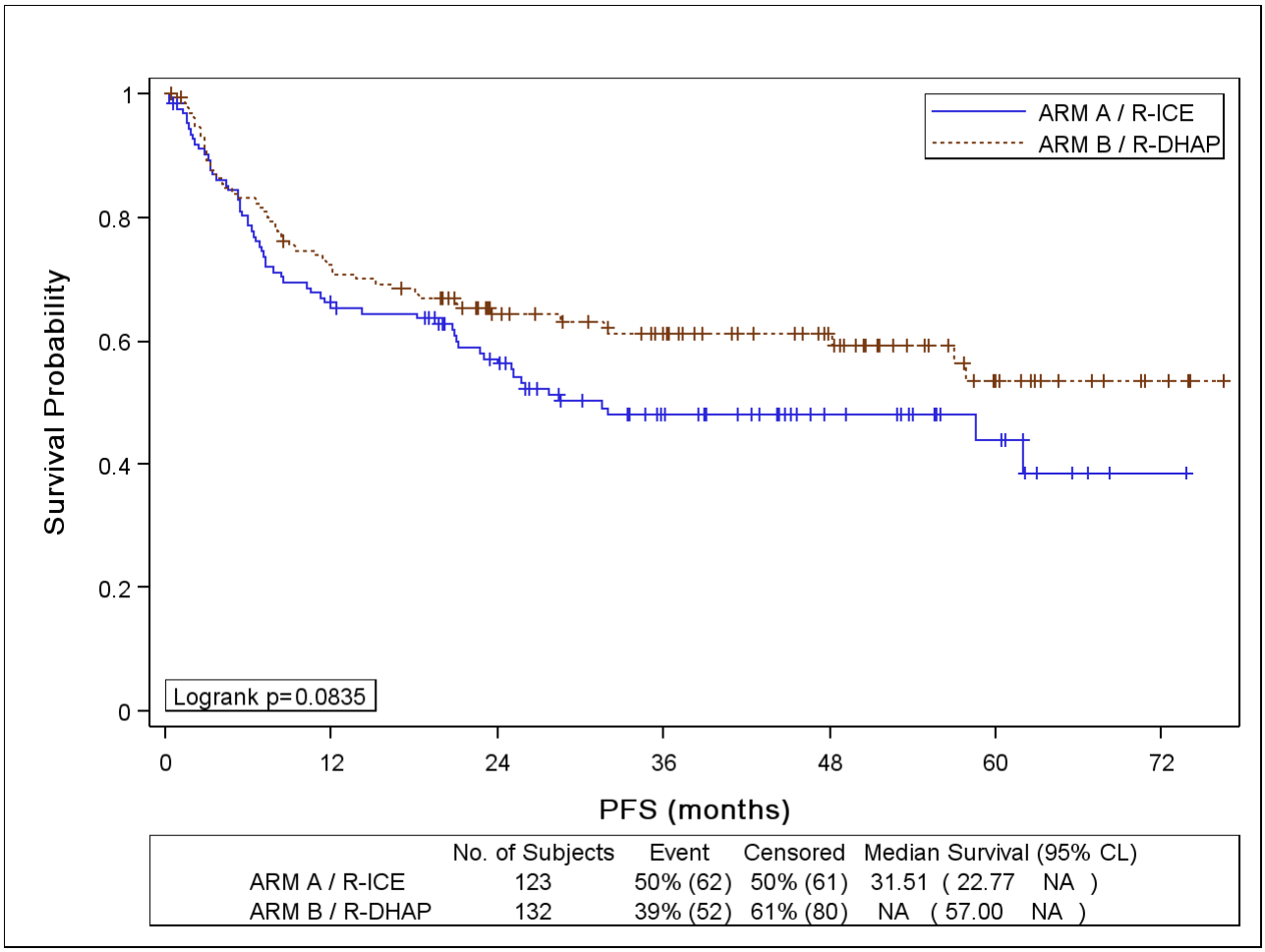


Table 4.5-45 Secondary criteria – Duration of Progression-Free Survival according to treatment arm (patients with ASCT)

	Arm of treatment	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	ARM A / R-ICE	123	32	23	-	0	74
PFS (months)	ARM B / R-DHAP	132	-	57	-	0	76

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

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

Arm of treatment	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
ARM B / R-DHAP	60	53.6	41.8	64.0	15
ARM B / R-DHAP	72	53.6	41.8	64.0	5

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
R-ICE	0.0850	1.383	0.956	2.000

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)

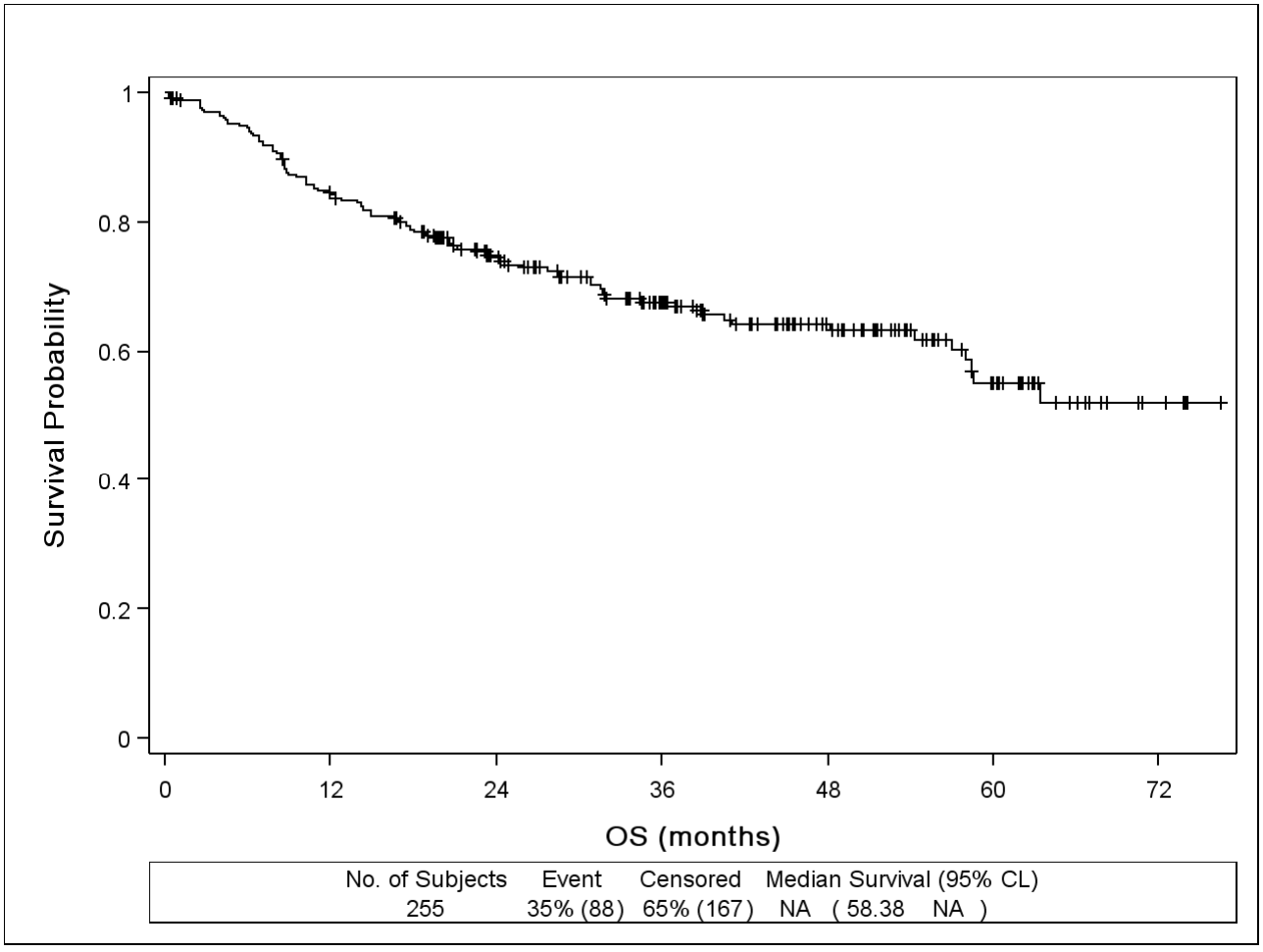


Table 4.5-48 Secondary criteria – Duration of Overall Survival (patients with ASCT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	255	-	58	-	0	76

Table 4.5-49 Secondary criteria – Kaplan-Meier estimates for Overall Survival (patients with ASCT)

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

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

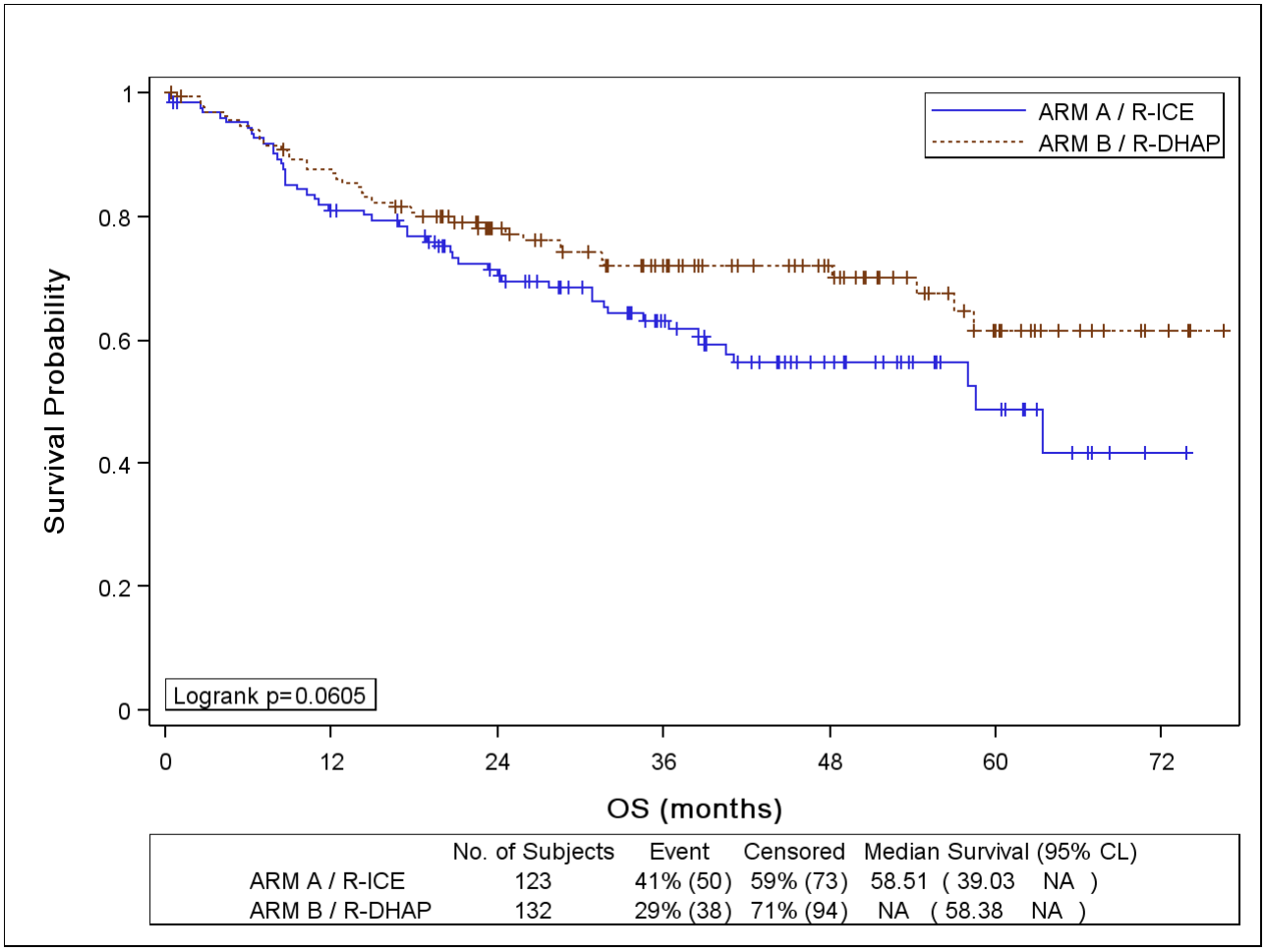


Table 4.5-50 Secondary criteria – Duration of Overall Survival according to treatment arm (patients with ASCT)

	Arm of treatment	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	ARM A / R-ICE	123	59	39	-	0	74
OS (months)	ARM B / R-DHAP	132	-	58	-	0	76

Table 4.5-51 Secondary criteria – Kaplan-Meier estimates for Overall Survival according to treatment arm (patients with ASCT)

Arm of treatment	Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
ARM A / R-ICE	12	81.0	72.8	87.0	97
ARM A / R-ICE	24	71.4	62.3	78.6	77
ARM A / R-ICE	36	63.1	53.3	71.3	51
ARM A / R-ICE	48	56.4	46.0	65.5	27
ARM A / R-ICE	60	48.8	35.5	60.9	13
ARM A / R-ICE	72	41.9	25.1	57.7	1
ARM B / R-DHAP	12	87.7	80.7	92.3	113
ARM B / R-DHAP	24	78.1	69.9	84.4	80
ARM B / R-DHAP	36	71.9	62.8	79.2	61
ARM B / R-DHAP	48	71.9	62.8	79.2	41
ARM B / R-DHAP	60	61.5	48.5	72.2	17
ARM B / R-DHAP	72	61.5	48.5	72.2	5

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
R-ICE	0.0625	1.494	0.979	2.278

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 – Stratificaction factors (induction ITT)

		Arm of treatment				All	
		ARM A / R-ICE		ARM B / R-DHAP			
		N	%	N	%	N	%
Prior treatment with Rituximab							
No		85	36	82	36	167	36
Yes		154	64	148	64	302	64
Failure from diagnosis							
< 12 months		145	61	131	57	276	59
>= 12 months		94	39	99	43	193	41
Prior treatment with Rituximab	**Failure from diagnosis**						
No	**< 12 months**	25	10	19	8	44	9
	>= 12 months	60	25	63	27	123	26
Yes	**< 12 months**	120	50	112	49	232	49
	>= 12 months	34	14	36	16	70	15
Total		239	100	230	100	469	100

	Failure from diagnosis				All	
	< 12 months		>= 12 months			
	N	%	N	%	N	%
Prior treatment with Rituximab						
No	44	16	123	64	167	36
Yes	232	84	70	36	302	64
Total	276	100	193	100	469	100

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

Parameter	P-value (Chi-2)
Prior Rituximab according to arm	0.9842
Failure from diagnosis according to arm	0.4140
Failure from diagnosis according to prior rituximab	<.0001

4.5.3.1. According to prior rituximab

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

	Prior treatment with Rituximab				All	
	No		Yes			
	N	%	N	%	N	%
Performance Status at diagnosis						
<2	126	89	237	83	363	85
>=2	15	11	48	17	63	15
TOTAL	141	100	285	100	426	100
Ann Arbor Stage at diagnosis						
I-II	97	60	99	33	196	42
III-IV	65	40	202	67	267	58
TOTAL	162	100	301	100	463	100
LDH at diagnosis						
<= 1 N	87	63	99	36	186	45
> 1 N	52	37	177	64	229	55
TOTAL	139	100	276	100	415	100
Age adjusted IPI at initial diagnosis						
0	54	43	30	11	84	22
1	38	30	111	42	149	38
2	25	20	89	34	114	29
3	8	6	33	13	41	11
Subtotal 0-1	92	74	141	54	233	60
Subtotal 2-3	33	26	122	46	155	40
TOTAL	125	100	263	100	388	100
Nb of extra nodal sites at diagnosis						
<=1	142	89	197	67	339	74
>1	18	11	99	33	117	26
TOTAL	160	100	296	100	456	100
IPI at initial diagnosis						
0	51	41	18	7	69	18
1	35	28	82	31	117	30
2	24	19	76	29	100	26
3	11	9	59	23	70	18
4	4	3	23	9	27	7
5	0	0	4	2	4	1
Subtotal 0-2	110	88	176	67	286	74
Subtotal 3-5	15	12	86	33	101	26
TOTAL	125	100	262	100	387	100
B Symptom at diagnosis						
No	111	71	153	52	264	58

	Prior treatment with Rituximab				All	
	No		Yes			
	N	%	N	%	N	%
Yes	45	29	144	48	189	42
TOTAL	156	100	297	100	453	100

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

Parameter	P-value (Chi-2)
Performance Status at diagnosis (<2 Vs >=2)	0.0896
Ann Arbor Stage at diagnosis (I-II Vs III-IV)	<.0001
LDH at diagnosis (=< 1 N Vs > 1 N)	<.0001
Age adjusted IPI at diagnosis (0-1 Vs 2-3)	0.0002
Nb of extra nodal sites at diagnosis (<=1 Vs >1)	<.0001
IPI at diagnosis (0-2 Vs 3-5)	<.0001
B Symptoms at diagnosis (No Vs Yes)	<.0001

Table 4.5-57 Exploratory analyses – Characteristics at progression/relapse diagnosis according to prior rituximab (induction ITT)

	Prior treatment with Rituximab				All	
	No		Yes			
	N	%	N	%	N	%
Age (years)						
<40 years	23	14	50	17	73	16
>=40 years	144	86	252	83	396	84
Total	167	100	302	100	469	100
Performance Status at relapse						
<2	155	93	257	86	412	88
>=2	11	7	43	14	54	12
TOTAL	166	100	300	100	466	100
Ann Arbor stage at relapse						
I-II	69	42	110	37	179	38
III-IV	97	58	190	63	287	62
TOTAL	166	100	300	100	466	100
LDH relapse						
<=Normal	83	51	137	46	220	48
>Normal	81	49	158	54	239	52
TOTAL	164	100	295	100	459	100
Age-adjusted IPI at relapse						
0	34	21	63	22	97	21
1	78	48	103	35	181	40
2	45	28	99	34	144	32

	Prior treatment with Rituximab					
	No		Yes		All	
	N	%	N	%	N	%
3	6	4	27	9	33	7
Subtotal 0-1	112	69	166	57	278	61
Subtotal 2-3	51	31	126	43	177	39
TOTAL	163	100	292	100	455	100
Nb of extra nodal sites at relapse						
<=1	125	75	200	67	325	70
>1	41	25	100	33	141	30
TOTAL	166	100	300	100	466	100
IPI at relapse						
0	30	18	49	17	79	17
1	50	31	72	25	122	27
2	50	31	76	26	126	28
3	25	15	58	20	83	18
4	6	4	29	10	35	8
5	2	1	7	2	9	2
Subtotal 0-2	130	80	197	68	327	72
Subtotal 3-5	33	20	94	32	127	28
TOTAL	163	100	291	100	454	100
B symptoms at relapse						
No	130	79	221	74	351	76
Yes	35	21	77	26	112	24
TOTAL	165	100	298	100	463	100

Table 4.5-58 Exploratory analyses – p-value of Chi-2 test for characteristics at progression/relapse diagnosis according to prior rituximab (induction ITT)

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

Table 4.5-59 Exploratory analyses – Overall response rate according to prior rituximab (induction ITT)

	Prior treatment with Rituximab			
	No		Yes	
	N	%	N	%
Response after complete induction				
CR/CRu/PR	137	82	164	54
Other	30	18	138	46
Total	167	100	302	100

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

	Prior treatment with Rituximab			
	No		Yes	
	N	%	N	%
Response after complete induction				
CR/CRu	84	50	89	29
Other	83	50	213	71
Total	167	100	302	100

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

	Prior treatment with Rituximab			
	No		Yes	
	N	%	N	%
Mobilization adjusted overall response rate				
No	44	26	172	57
Yes	123	74	130	43
Total	167	100	302	100

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

Prior rituximab: No	**p-value (Wald Chi-2)**	**Odds ratio estimates**	**95% Wald confidence limits**	
Response to induction CR/CRu/PR	<.0001	3.843	2.437	6.059
Response to induction CR/CRu	<.0001	2.422	1.637	3.582
Mobilization adjusted response rate	<.0001	0.270	0.179	0.409

Figure 4.5-13 Exploratory analyses – Event-Free Survival according to prior rituximab (induction ITT)

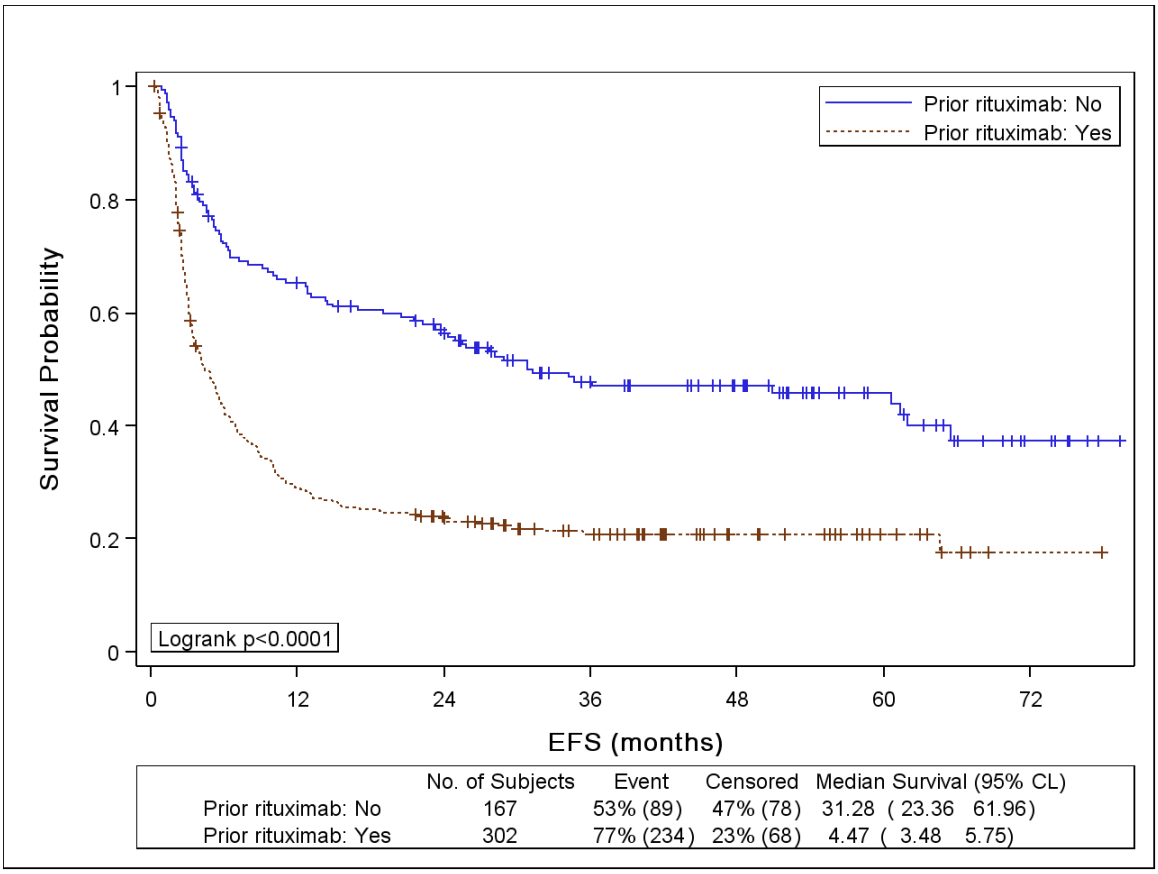


Table 4.5-63 Exploratory analyses – Duration of Event-Free Survival according to prior rituximab (induction ITT)

Prior treatment with Rituximab	N	Median	95% CI lower	95% CI Upper	Min	Max
No	167	31	23	62	1	79
Yes	302	4	3	6	0	78

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

Prior treatment with Rituximab	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
No	12	65.4	57.6	72.1	105
No	24	57.2	49.2	64.4	87
No	36	47.8	39.8	55.5	59
No	48	47.0	38.9	54.7	46
No	60	45.9	37.7	53.7	24
No	72	37.4	27.4	47.3	7
Yes	12	28.9	23.9	34.2	85
Yes	24	23.5	18.8	28.4	63
Yes	36	20.9	16.4	25.8	43
Yes	48	20.9	16.4	25.8	21
Yes	60	20.9	16.4	25.8	9
Yes	72	17.4	10.8	25.4	1

Table 4.5-65 Exploratory analyses – Hazard ratio of prior rituximab for Event-Free Survival (induction ITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior rituximab: No	<.0001	0.439	0.343	0.561

Figure 4.5-14 Exploratory analyses – Progression-Free Survival according to prior rituximab (induction ITT)

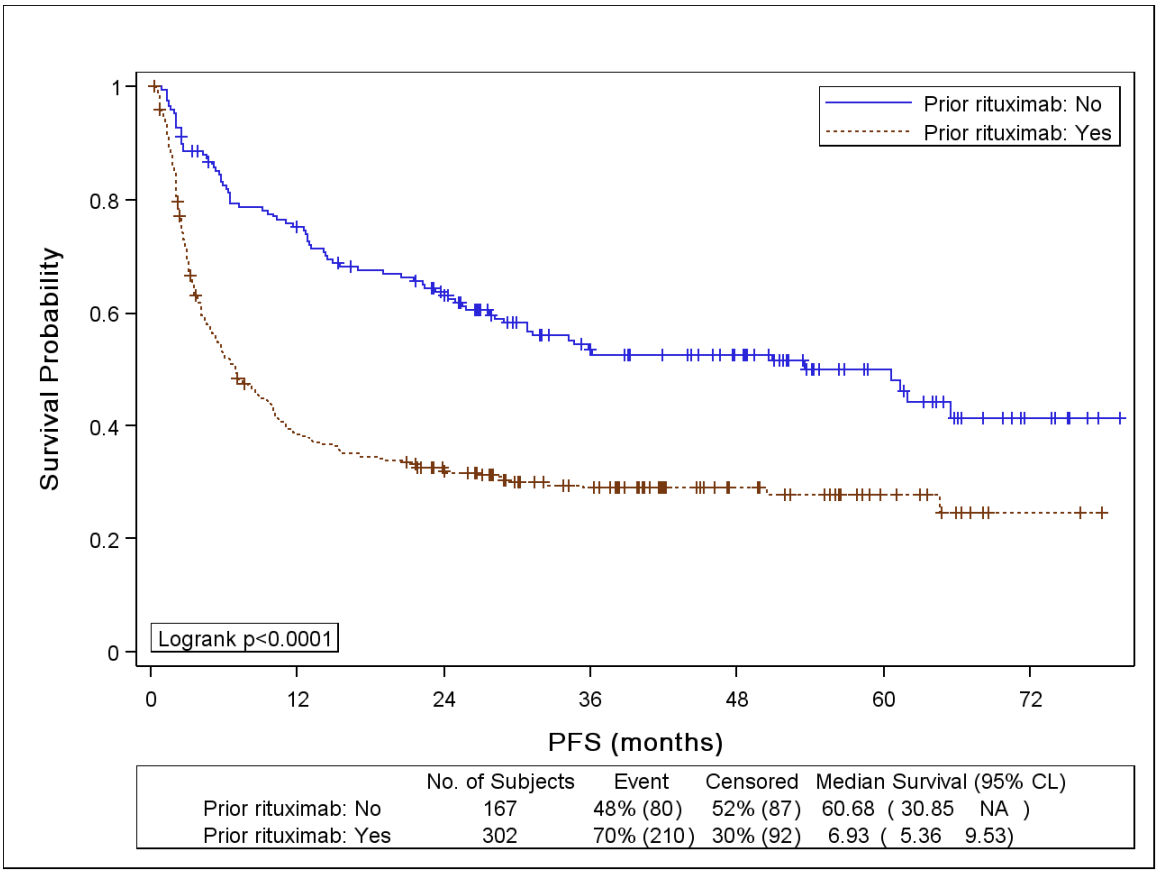


Table 4.5-66 Exploratory analyses – Duration of Progression-Free Survival according to prior rituximab (induction ITT)

Prior treatment with Rituximab	N	Median	95% CI lower	95% CI Upper	Min	Max
No	167	61	31	-	1	79
Yes	302	7	5	10	0	78

Table 4.5-67 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to prior rituximab (induction ITT)

Prior treatment with Rituximab	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
No	12	75.1	67.7	81.0	121
No	24	63.8	55.9	70.7	97
No	36	53.5	45.3	61.1	65
No	48	52.7	44.4	60.3	51
No	60	50.1	41.4	58.1	26
No	72	41.4	30.9	51.6	7
Yes	12	38.6	33.0	44.1	112
Yes	24	32.0	26.7	37.4	84

Prior treatment with Rituximab	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
Yes	36	28.9	23.7	34.3	58
Yes	48	28.9	23.7	34.3	28
Yes	60	27.8	22.4	33.4	12
Yes	72	24.7	17.5	32.5	2

Table 4.5-68 Exploratory analyses – Hazard ratio of prior rituximab for Progression-Free Survival (induction ITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior rituximab: No	<.0001	0.455	0.351	0.589

Figure 4.5-15 Exploratory analyses – Overall Survival according to prior rituximab (induction ITT)

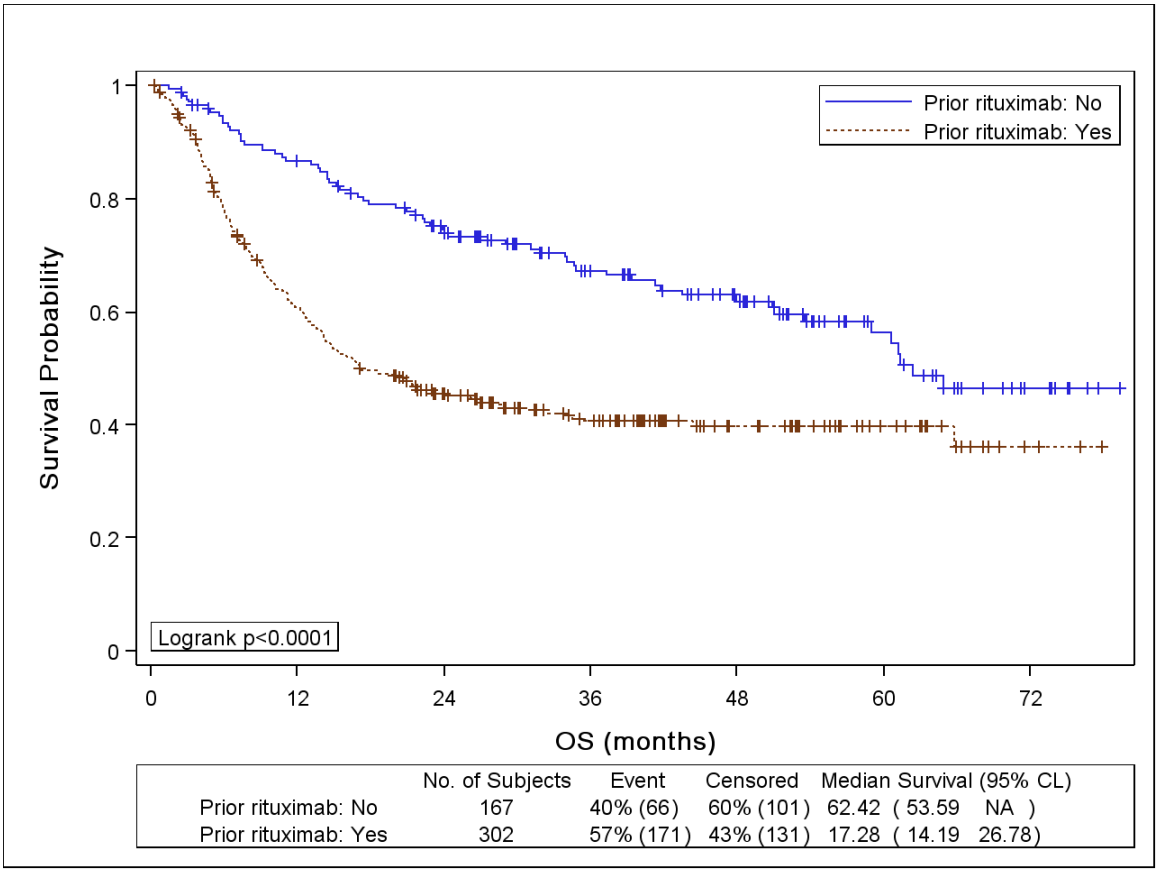


Table 4.5-69 Exploratory analyses – Duration of Overall Survival according to prior rituximab (induction ITT)

Prior treatment with Rituximab	N	Median	95% CI lower	95% CI Upper	Min	Max
No	167	62	54	-	2	79
Yes	302	17	14	27	0	78

Table 4.5-70 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to prior rituximab (induction ITT)

Prior treatment with Rituximab	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
No	12	86.6	80.3	90.9	140
No	24	74.7	67.2	80.7	114
No	36	67.3	59.2	74.1	83
No	48	62.0	53.4	69.4	62
No	60	56.4	46.9	64.9	30
No	72	46.5	35.3	56.9	8
Yes	12	60.8	55.0	66.2	175
Yes	24	45.7	39.9	51.4	114
Yes	36	40.6	34.8	46.4	79
Yes	48	39.8	33.8	45.7	38
Yes	60	39.8	33.8	45.7	18
Yes	72	36.2	27.6	44.8	3

Table 4.5-71 Exploratory analyses – Hazard ratio of prior rituximab for Overall Survival (induction ITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior rituximab: No	<.0001	0.485	0.364	0.646

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)

	Failure from diagnosis					
	< 12 months		>= 12 months		All	
	N	%	N	%	N	%
Performance Status at diagnosis						
<2	211	82	152	90	363	85
>=2	47	18	16	10	63	15
TOTAL	258	100	168	100	426	100
Ann Arbor Stage at diagnosis						
I-II	97	35	99	53	196	42
III-IV	178	65	89	47	267	58
TOTAL	275	100	188	100	463	100
LDH at diagnosis						
<= 1 N	79	32	107	65	186	45
> 1 N	171	68	58	35	229	55
TOTAL	250	100	165	100	415	100
Age adjusted IPI at initial diagnosis						
0	29	12	55	36	84	22
1	87	37	62	41	149	38
2	87	37	27	18	114	29

	Failure from diagnosis					
	< 12 months		>= 12 months		All	
	N	%	N	%	N	%
3	33	14	8	5	41	11
Subtotal 0-1	116	49	117	77	233	60
Subtotal 2-3	120	51	35	23	155	40
TOTAL	236	100	152	100	388	100
Nb of extra nodal sites at diagnosis						
<=1	194	72	145	78	339	74
>1	77	28	40	22	117	26
TOTAL	271	100	185	100	456	100
IPI at initial diagnosis						
0	21	9	48	32	69	18
1	68	29	49	32	117	30
2	65	28	35	23	100	26
3	53	23	17	11	70	18
4	25	11	2	1	27	7
5	3	1	1	1	4	1
Subtotal 0-2	154	66	132	87	286	74
Subtotal 3-5	81	34	20	13	101	26
TOTAL	235	100	152	100	387	100
B Symptom at diagnosis						
No	140	52	124	68	264	58
Yes	131	48	58	32	189	42
TOTAL	271	100	182	100	453	100

Table 4.5-73 Exploratory analyses – p-value of Chi-2 test for characteristics at initial diagnosis according to failure from diagnosis (induction ITT)

Parameter	P-value (Chi-2)
Performance Status at diagnosis (<2 Vs >=2)	0.0135
Ann Arbor Stage at diagnosis (I-II Vs III-IV)	0.0002
LDH at diagnosis (=< 1 N Vs > 1 N)	<.0001
Age adjusted IPI at diagnosis (0-1 Vs 2-3)	<.0001
Nb of extra nodal sites at diagnosis (<=1 Vs >1)	0.1030
IPI at diagnosis (0-2 Vs 3-5)	<.0001
B Symptoms at diagnosis (No Vs Yes)	0.0005

Table 4.5-74 Exploratory analyses – Characteristics at progression/relapse diagnosis according to failure from diagnosis (induction ITT)

	Failure from diagnosis				All	
	< 12 months		>= 12 months			
	N	%	N	%	N	%
Age (years)						
<40 years	57	21	16	8	73	16
>=40 years	219	79	177	92	396	84
Total	276	100	193	100	469	100
Performance Status at relapse						
<2	232	85	180	94	412	88
>=2	42	15	12	6	54	12
TOTAL	274	100	192	100	466	100
Ann Arbor stage at relapse						
I-II	106	39	73	38	179	38
III-IV	169	61	118	62	287	62
TOTAL	275	100	191	100	466	100
LDH at relapse						
<=Normal	114	42	106	56	220	48
>Normal	155	58	84	44	239	52
TOTAL	269	100	190	100	459	100
Age-adjusted IPI at relapse						
0	53	20	44	23	97	21
1	97	36	84	45	181	40
2	90	34	54	29	144	32
3	27	10	6	3	33	7
Subtotal 0-1	150	56	128	68	278	61
Subtotal 2-3	117	44	60	32	177	39
TOTAL	267	100	188	100	455	100
Nb of extra nodal sites at relapse						
<=1	187	68	138	72	325	70
>1	87	32	54	28	141	30
TOTAL	274	100	192	100	466	100
IPI at relapse						
0	41	15	38	20	79	17
1	72	27	50	27	122	27
2	71	27	55	29	126	28
3	49	18	34	18	83	18
4	25	9	10	5	35	8
5	8	3	1	1	9	2
Subtotal 0-2	184	69	143	76	327	72
Subtotal 3-5	82	31	45	24	127	28
TOTAL	266	100	188	100	454	100

	Failure from diagnosis				All	
	< 12 months		>= 12 months			
	N	%	N	%	N	%
B symptoms at relapse						
No	201	74	150	79	351	76
Yes	71	26	41	21	112	24
TOTAL	272	100	191	100	463	100

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)

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

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

	Failure from diagnosis			
	< 12 months		>= 12 months	
	N	%	N	%
Response after complete induction				
CR/CRu/PR	135	49	166	86
Other	141	51	27	14
Total	276	100	193	100

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

	Failure from diagnosis			
	< 12 months		>= 12 months	
	N	%	N	%
Response after complete induction				
CR/CRu	66	24	107	55
Other	210	76	86	45
Total	276	100	193	100

Table 4.5-78 Exploratory analyses – Mobilization adjusted response rate according to failure from diagnosis (induction ITT)

	Failure from diagnosis (Randomization)			
	< 12 months		>= 12 months	
	N	%	N	%
Mobilization adjusted overall response rate				
No	163	59	53	27
Yes	113	41	140	73
Total	276	100	193	100

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

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

Figure 4.5-16 Exploratory analyses – Event-Free Survival according to failure from diagnosis (induction ITT)

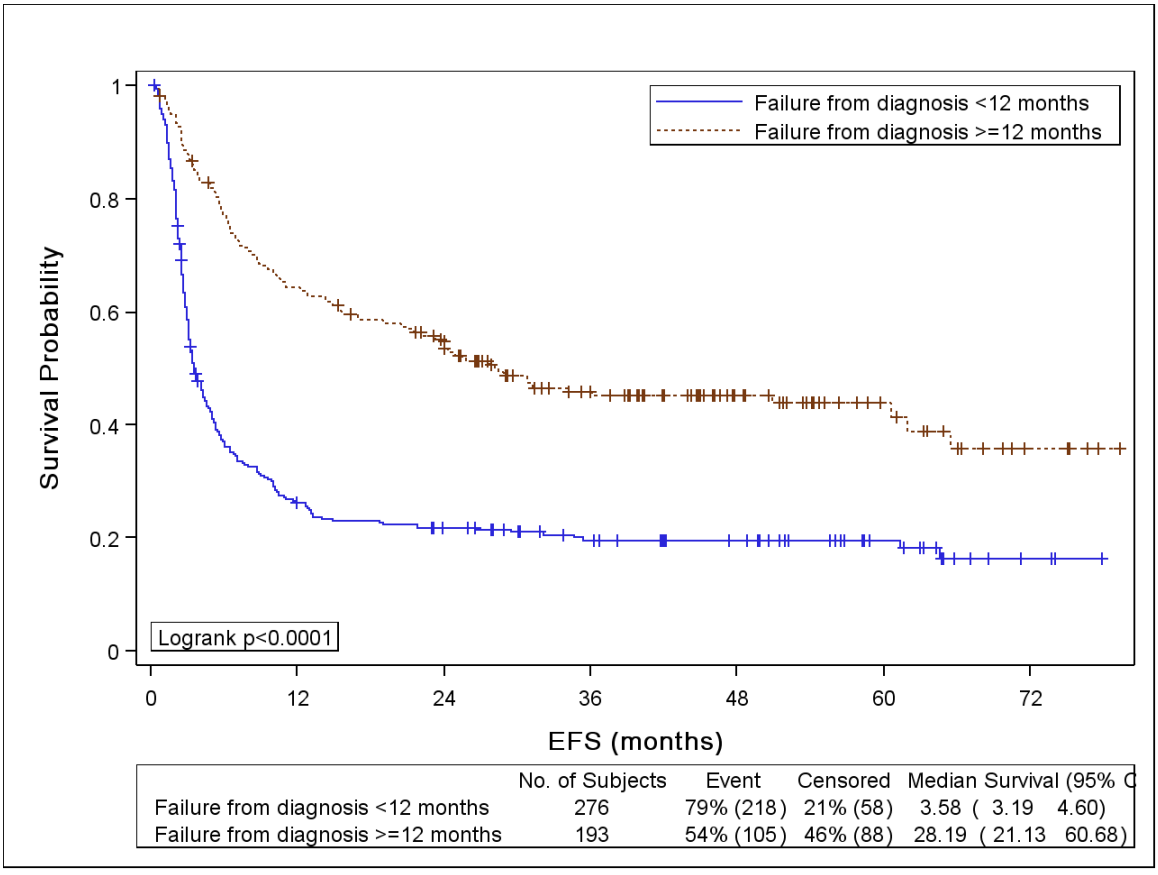


Table 4.5-80 Exploratory analyses – Duration of Event-Free Survival according to failure from diagnosis (induction ITT)

Failure from diagnosis	N	Median	95% CI lower	95% CI Upper	Min	Max
< 12 months	276	4	3	5	0	78
>= 12 months	193	28	21	61	1	79

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

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

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Failure from diagnosis < 12 months	<.0001	2.450	1.936	3.100

Figure 4.5-17 Exploratory analyses – Progression-Free Survival according to failure from diagnosis (induction ITT)

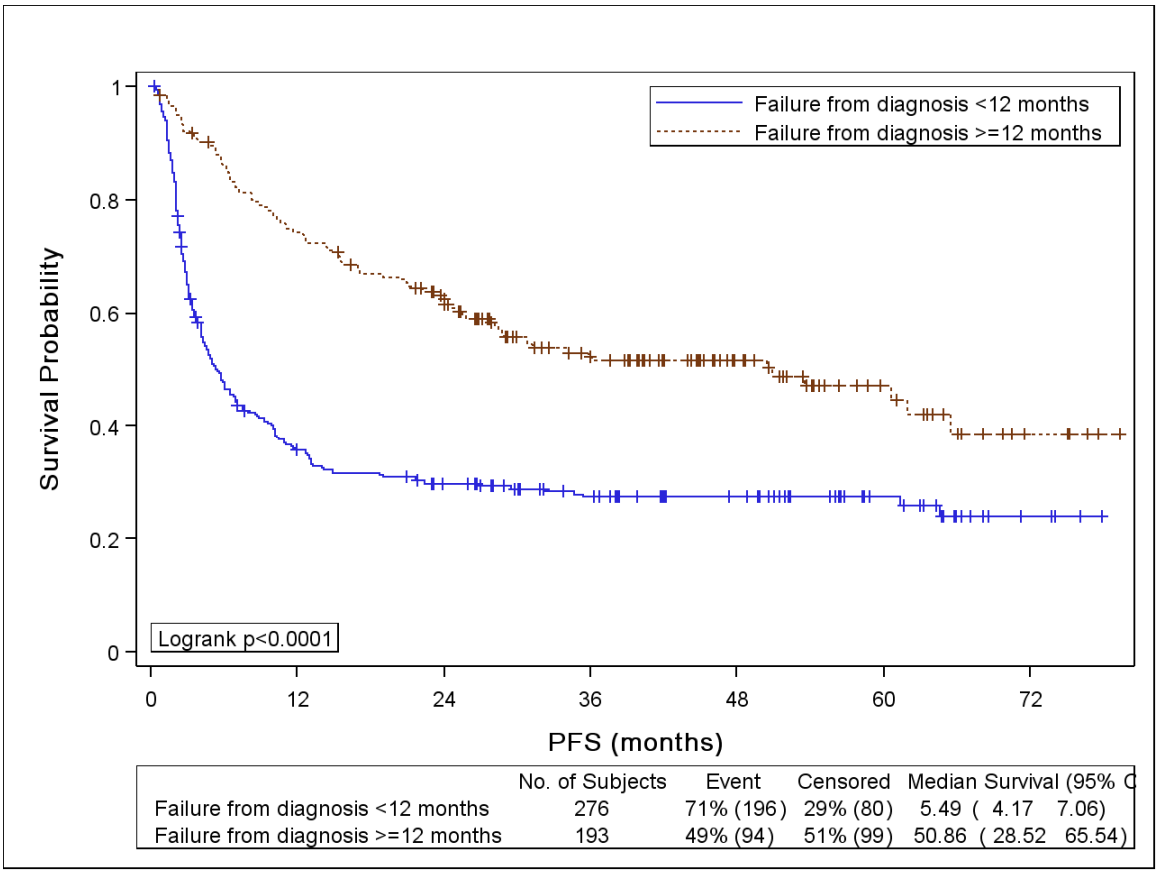


Table 4.5-83 Exploratory analyses – Duration of Progression-Free Survival according to failure from diagnosis (induction ITT)

Failure from diagnosis	N	Median	95% CI lower	95% CI Upper	Min	Max
< 12 months	276	5	4	7	0	78
>= 12 months	193	51	29	66	1	79

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

Failure from diagnosis	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
< 12 months	12	35.6	29.9	41.3	92
< 12 months	24	29.8	24.4	35.3	72
< 12 months	36	27.3	22.0	32.8	52
< 12 months	48	27.3	22.0	32.8	38
< 12 months	60	27.3	22.0	32.8	19
< 12 months	72	24.0	17.8	30.7	4
>= 12 months	12	74.3	67.5	79.9	141
>= 12 months	24	62.5	55.2	69.0	109
>= 12 months	36	52.3	44.7	59.4	71
>= 12 months	48	51.6	43.9	58.7	41
>= 12 months	60	47.1	38.6	55.2	19
>= 12 months	72	38.5	27.4	49.6	5

Table 4.5-85 Exploratory analyses – Hazard ratio of failure from diagnosis for Progression-Free Survival (induction ITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Failure from diagnosis < 12 months	<.0001	2.319	1.810	2.970

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

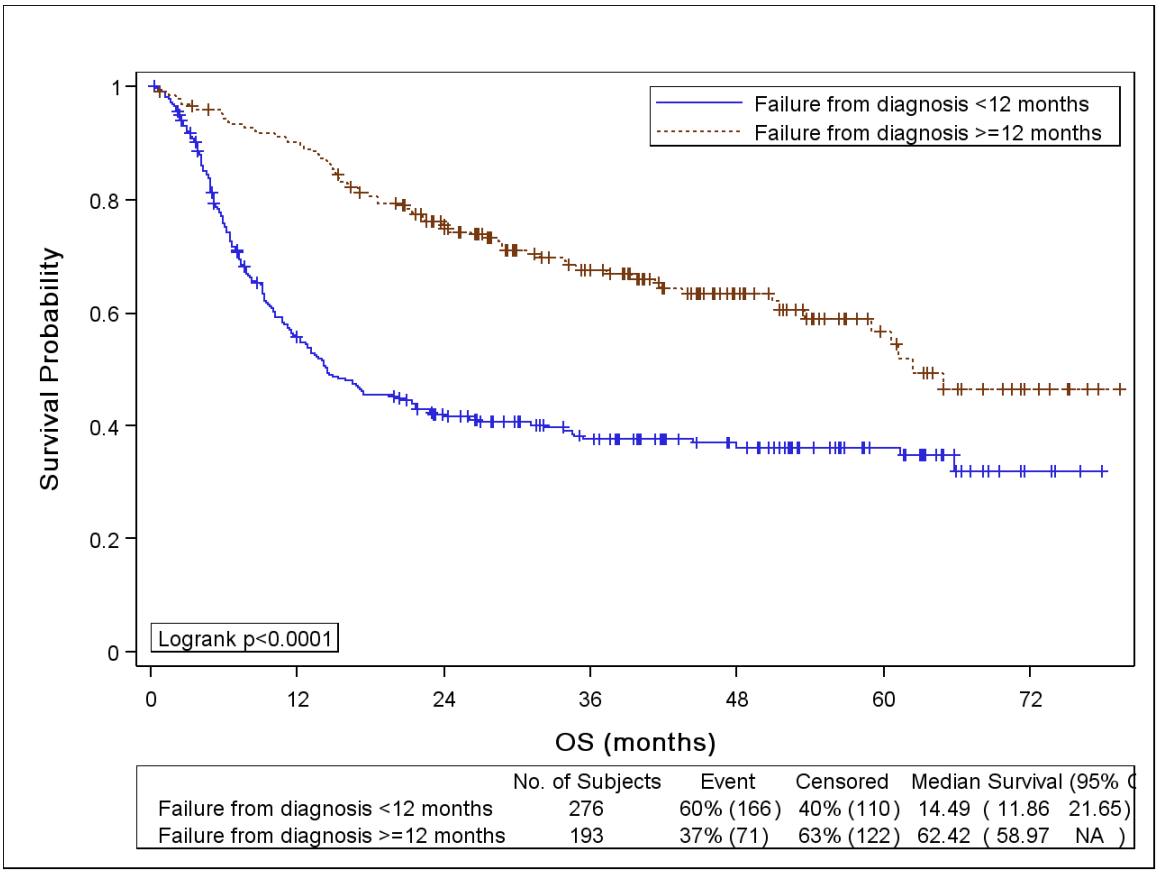


Table 4.5-86 Exploratory analyses – Duration of Overall Survival according to failure from diagnosis (induction ITT)

Failure from diagnosis	N	Median	95% CI lower	95% CI Upper	Min	Max
< 12 months	276	14	12	22	0	78
>= 12 months	193	62	59	-	1	79

Table 4.5-87 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to failure from diagnosis (induction ITT)

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

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Failure from diagnosis < 12 months	<.0001	2.391	1.808	3.161

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)

	Prior treatment with Rituximab							
	No				Yes			
	Failure from diagnosis				Failure from diagnosis			
	< 12 months		>= 12 months		< 12 months		>= 12 months	
	N	%	N	%	N	%	N	%
Response after complete induction								
CR/CRu/PR	28	64	108	88	107	46	57	81
Other	16	36	15	12	125	54	13	19
Total	44	100	123	100	232	100	70	100

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

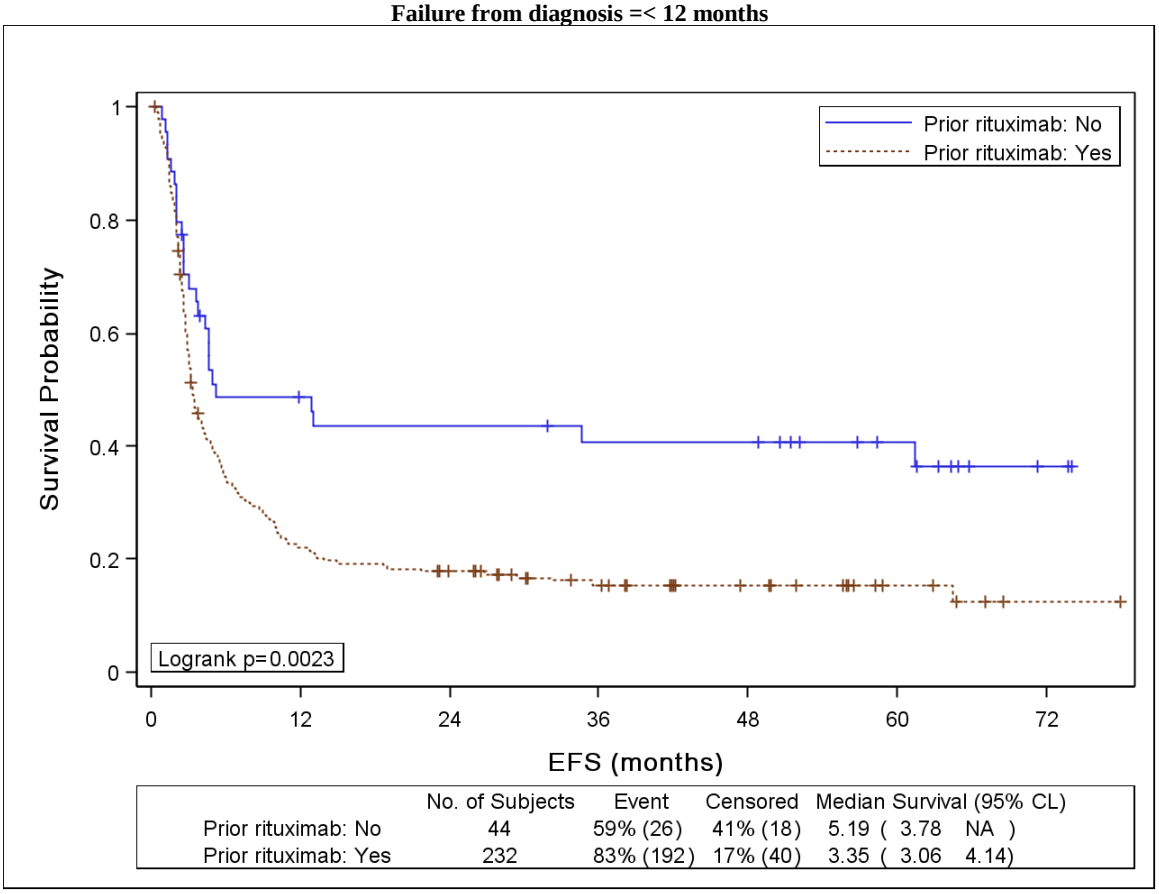
	Prior treatment with Rituximab							
	No				Yes			
	Failure from diagnosis				Failure from diagnosis			
	< 12 months		>= 12 months		< 12 months		>= 12 months	
	N	%	N	%	N	%	N	%
Response after complete induction								
CR/CRu	14	32	69	56	52	22	37	53
Other	30	68	54	44	180	78	33	47
Total	44	100	123	100	232	100	70	100

Table 4.5-91 Exploratory analyses – Mobilization adjusted response rate according to prior rituximab and failure from diagnosis (induction ITT)

	Prior treatment with Rituximab							
	No				Yes			
	Failure from diagnosis				Failure from diagnosis			
	< 12 months		>= 12 months		< 12 months		>= 12 months	
	N	%	N	%	N	%	N	%
Mobilization adjusted overall response rate								
No	18	41	26	21	145	63	27	39
Yes	26	59	97	79	87	38	43	61
Total	44	100	123	100	232	100	70	100

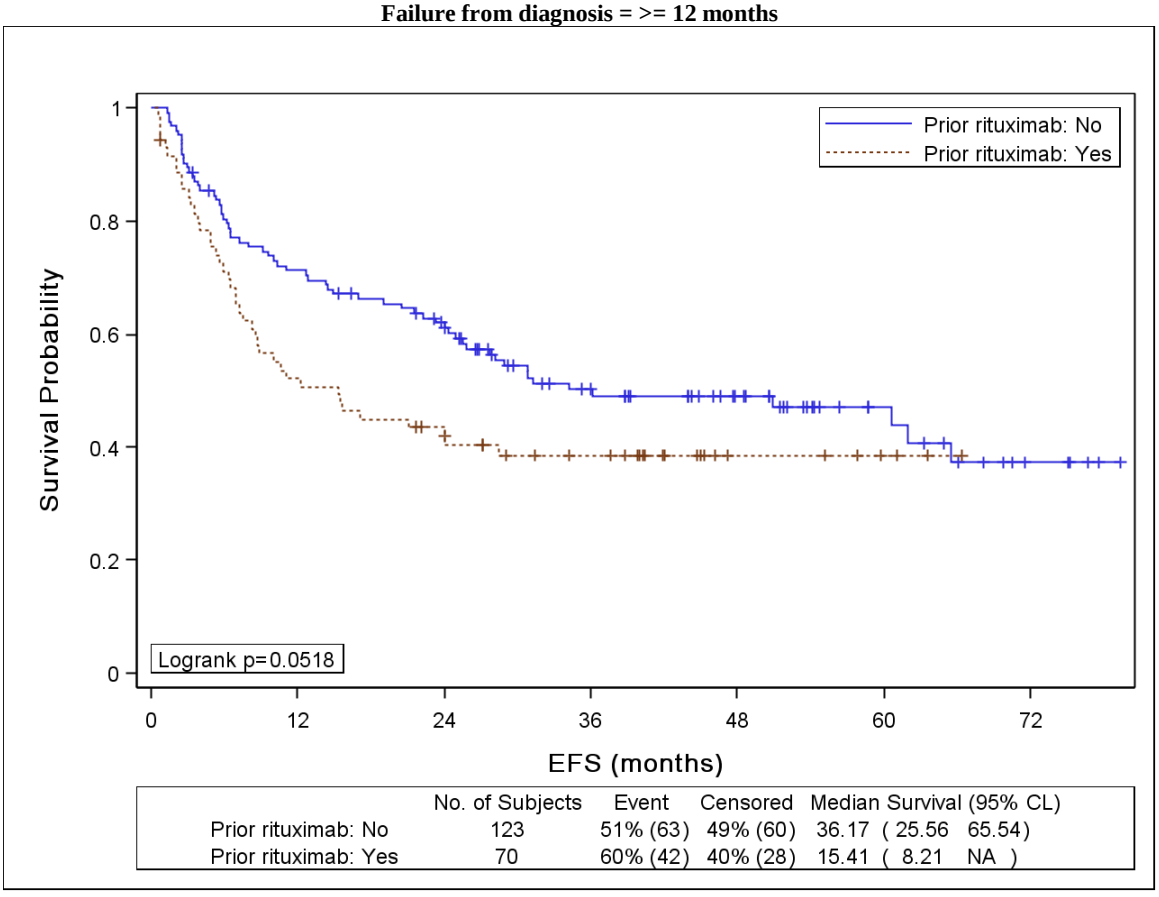
Figure 4.5-19 Exploratory analyses – Event-Free Survival according to prior rituximab by failure from diagnosis (induction ITT)

Failure from diagnosis =< 12 months



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Prior rituximab: No	44	59% (26)	41% (18)	5.19 (3.78 NA)
Prior rituximab: Yes	232	83% (192)	17% (40)	3.35 (3.06 4.14)

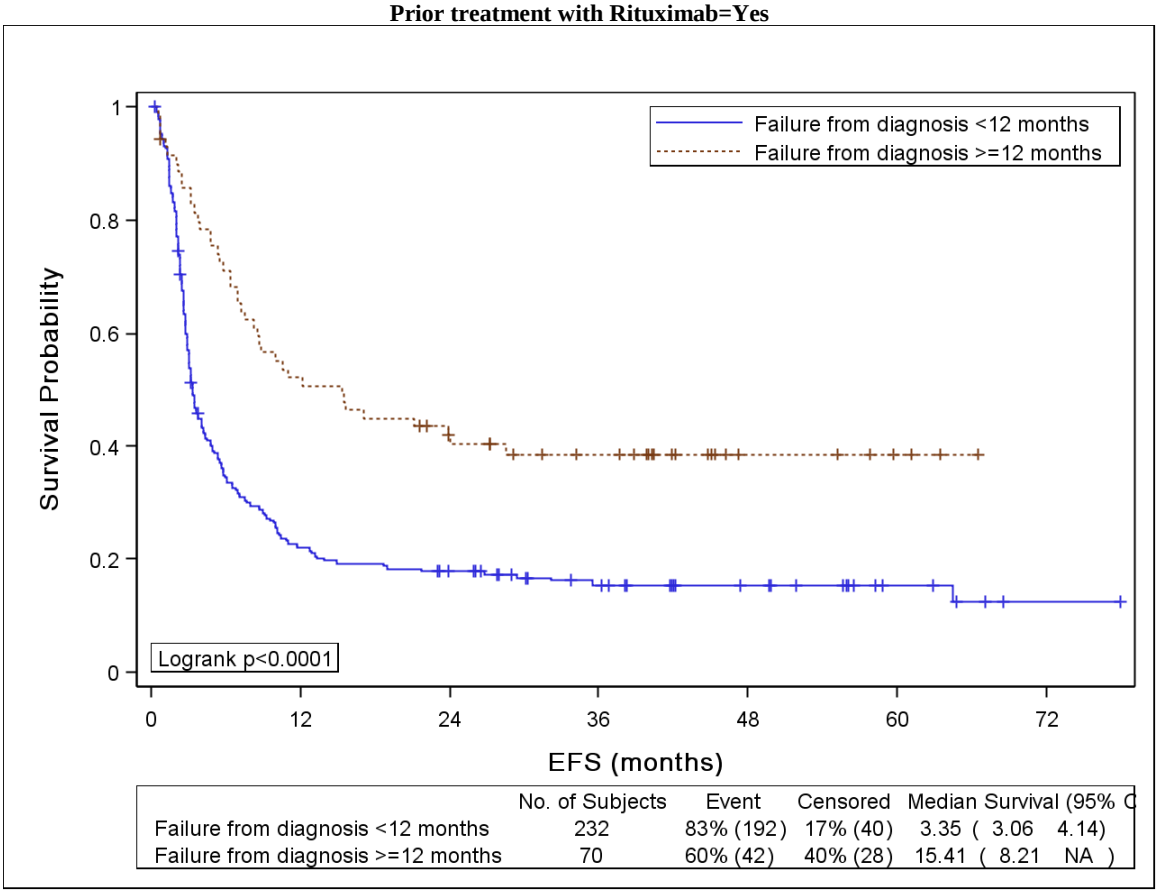
Failure from diagnosis = >= 12 months



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Prior rituximab: No	123	51% (63)	49% (60)	36.17 (25.56 65.54)
Prior rituximab: Yes	70	60% (42)	40% (28)	15.41 (8.21 NA)

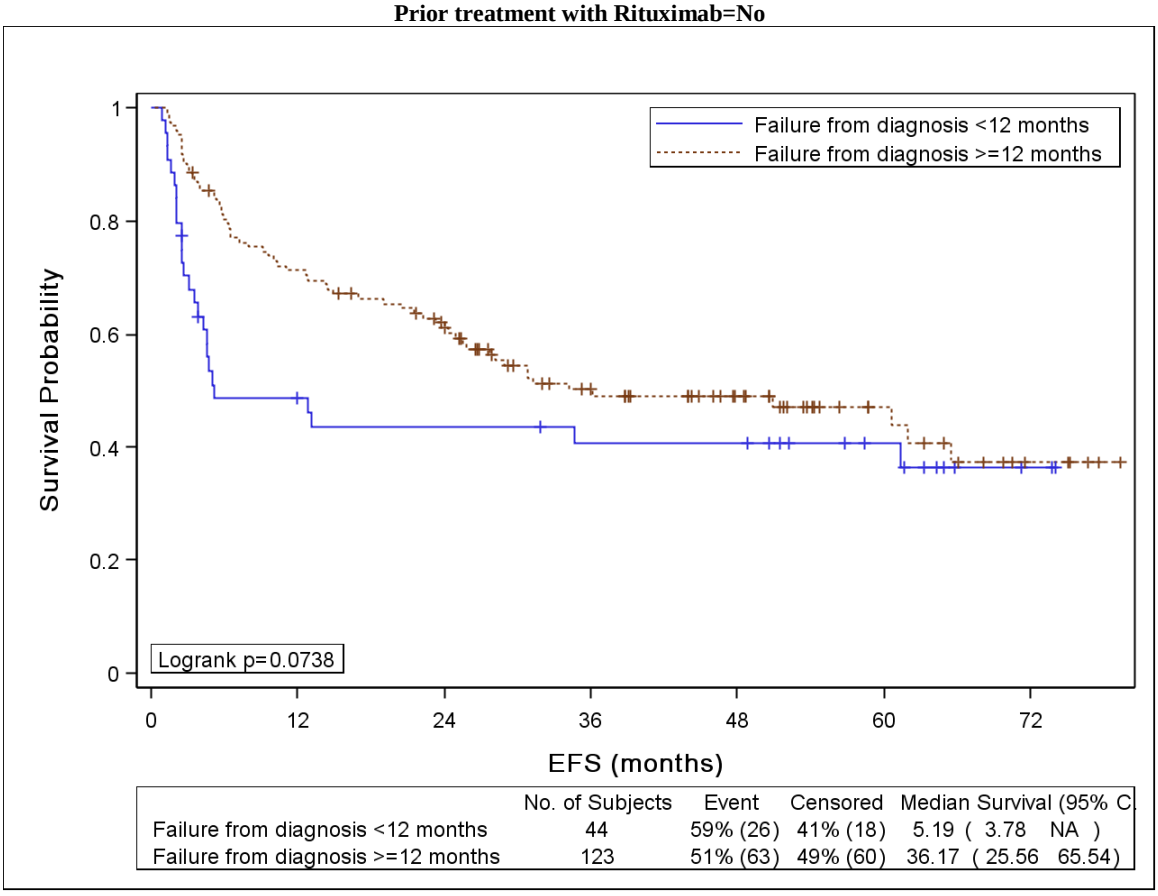
Figure 4.5-20 Exploratory analyses – Event-Free Survival according to failure from diagnosis by prior rituximab (induction ITT)

Prior treatment with Rituximab=Yes



	No. of Subjects	Event	Censored	Median Survival (95% C
Failure from diagnosis <12 months	232	83% (192)	17% (40)	3.35 (3.06 4.14)
Failure from diagnosis >=12 months	70	60% (42)	40% (28)	15.41 (8.21 NA)

Prior treatment with Rituximab=No



	No. of Subjects	Event	Censored	Median Survival (95% C
Failure from diagnosis <12 months	44	59% (26)	41% (18)	5.19 (3.78 NA)
Failure from diagnosis >=12 months	123	51% (63)	49% (60)	36.17 (25.56 65.54)

Table 4.5-92 Exploratory analyses – Duration of Event-Free Survival according to prior rituximab and failure from diagnosis (induction ITT)

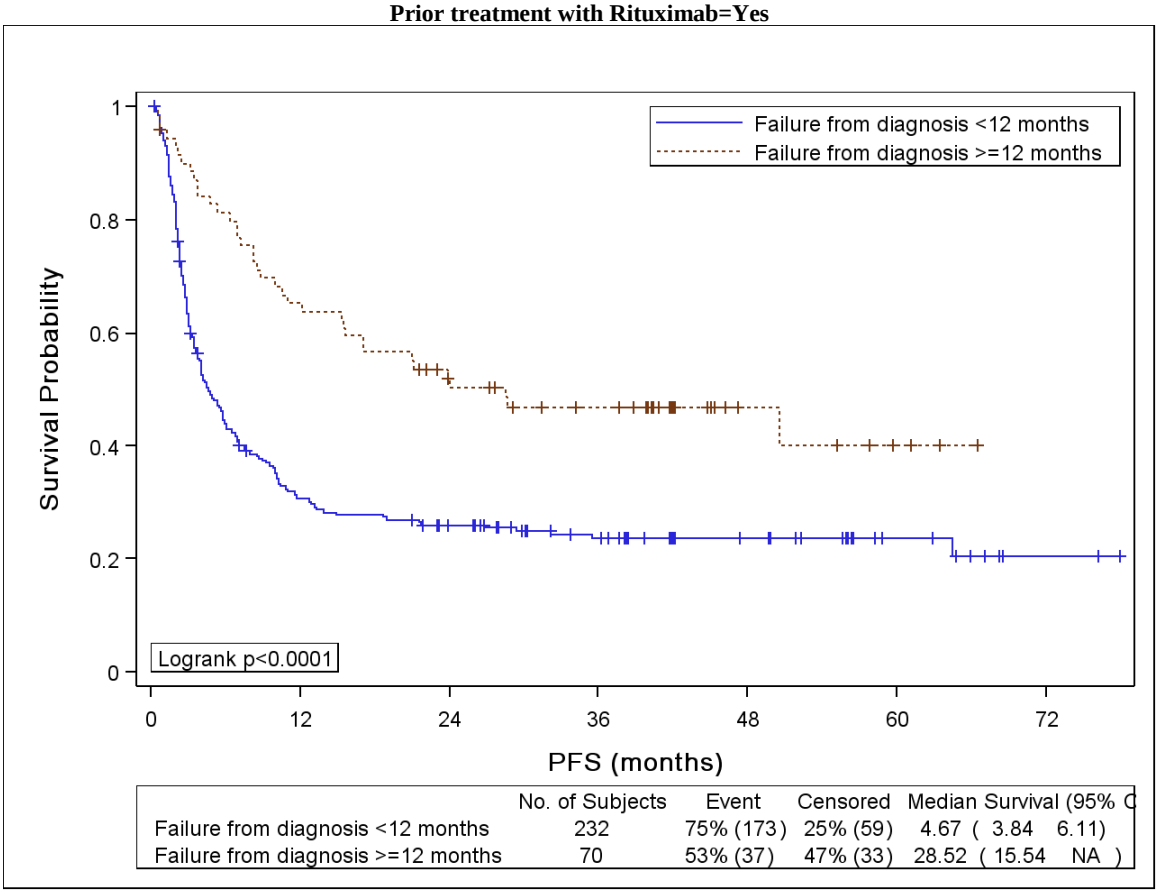
	Prior treatment with Rituximab	Failure from diagnosis (Randomization)	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	No	< 12 months	44	5	4	-	1	74
EFS (months)	No	>= 12 months	123	36	26	66	1	79
EFS (months)	Yes	< 12 months	232	3	3	4	0	78
EFS (months)	Yes	>= 12 months	70	15	8	-	1	66

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

Prior treatment with Rituximab	Failure from diagnosis	Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
No	< 12 months	12	48.6	33.0	62.6	19
No	< 12 months	24	43.5	28.3	57.7	17
No	< 12 months	36	40.8	25.9	55.2	15
No	< 12 months	48	40.8	25.9	55.2	15
No	< 12 months	60	40.8	25.9	55.2	9
No	< 12 months	72	36.3	21.1	51.6	2
No	>= 12 months	12	71.3	62.3	78.4	86
No	>= 12 months	24	62.0	52.7	70.0	70
No	>= 12 months	36	50.2	40.6	59.0	44
No	>= 12 months	48	49.1	39.5	58.0	31
No	>= 12 months	60	47.2	37.4	56.5	15
No	>= 12 months	72	37.2	24.8	49.6	5
Yes	< 12 months	12	21.9	16.7	27.5	49
Yes	< 12 months	24	17.8	13.2	23.1	37
Yes	< 12 months	36	15.5	11.0	20.7	24
Yes	< 12 months	48	15.5	11.0	20.7	15
Yes	< 12 months	60	15.5	11.0	20.7	6
Yes	< 12 months	72	12.4	6.7	19.9	1
Yes	>= 12 months	12	52.2	39.9	63.2	36
Yes	>= 12 months	24	42.0	30.2	53.2	26
Yes	>= 12 months	36	38.6	27.1	50.0	19
Yes	>= 12 months	48	38.6	27.1	50.0	6
Yes	>= 12 months	60	38.6	27.1	50.0	3
Yes	>= 12 months	72	38.6	27.1	50.0	0

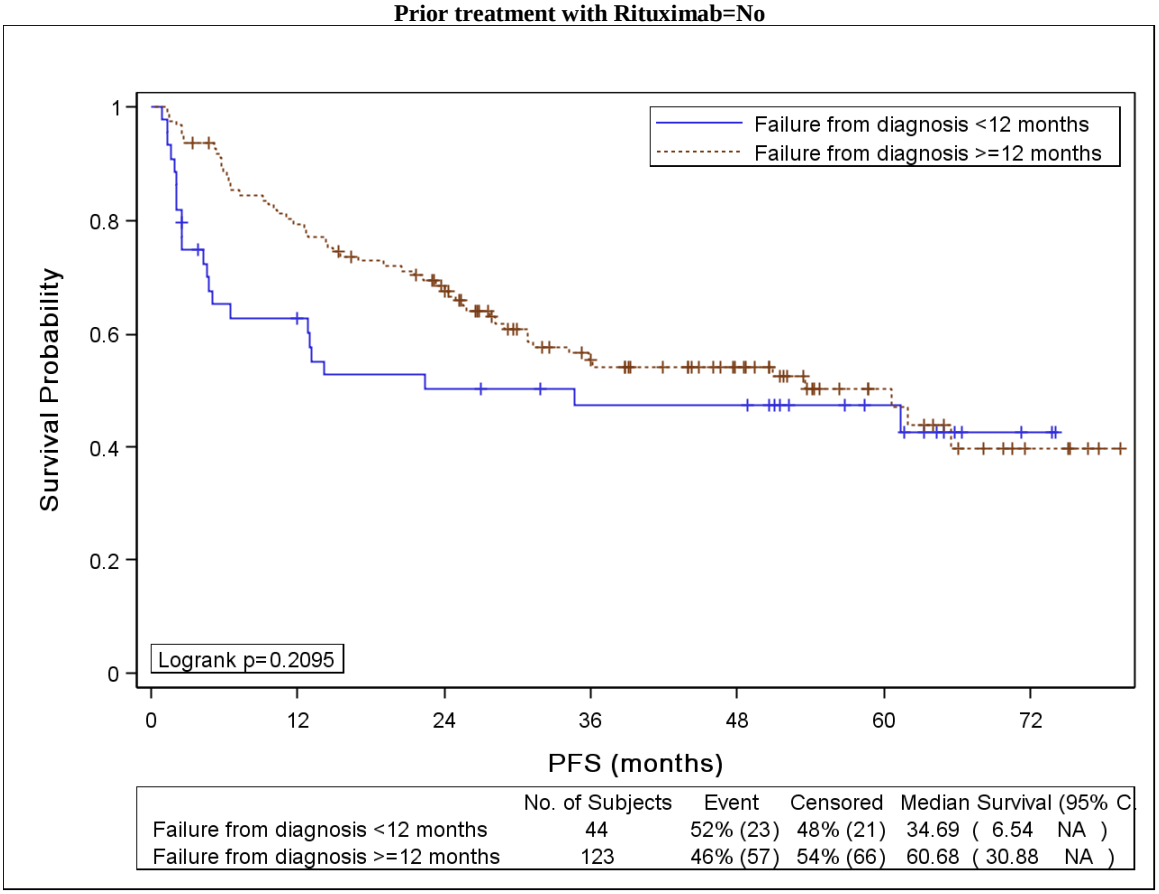
Figure 4.5-21 Exploratory analyses – Progression-Free Survival according to prior rituximab by failure from diagnosis (induction ITT)

Prior treatment with Rituximab=Yes



	No. of Subjects	Event	Censored	Median Survival (95% C
Failure from diagnosis <12 months	232	75% (173)	25% (59)	4.67 (3.84 6.11)
Failure from diagnosis >=12 months	70	53% (37)	47% (33)	28.52 (15.54 NA)

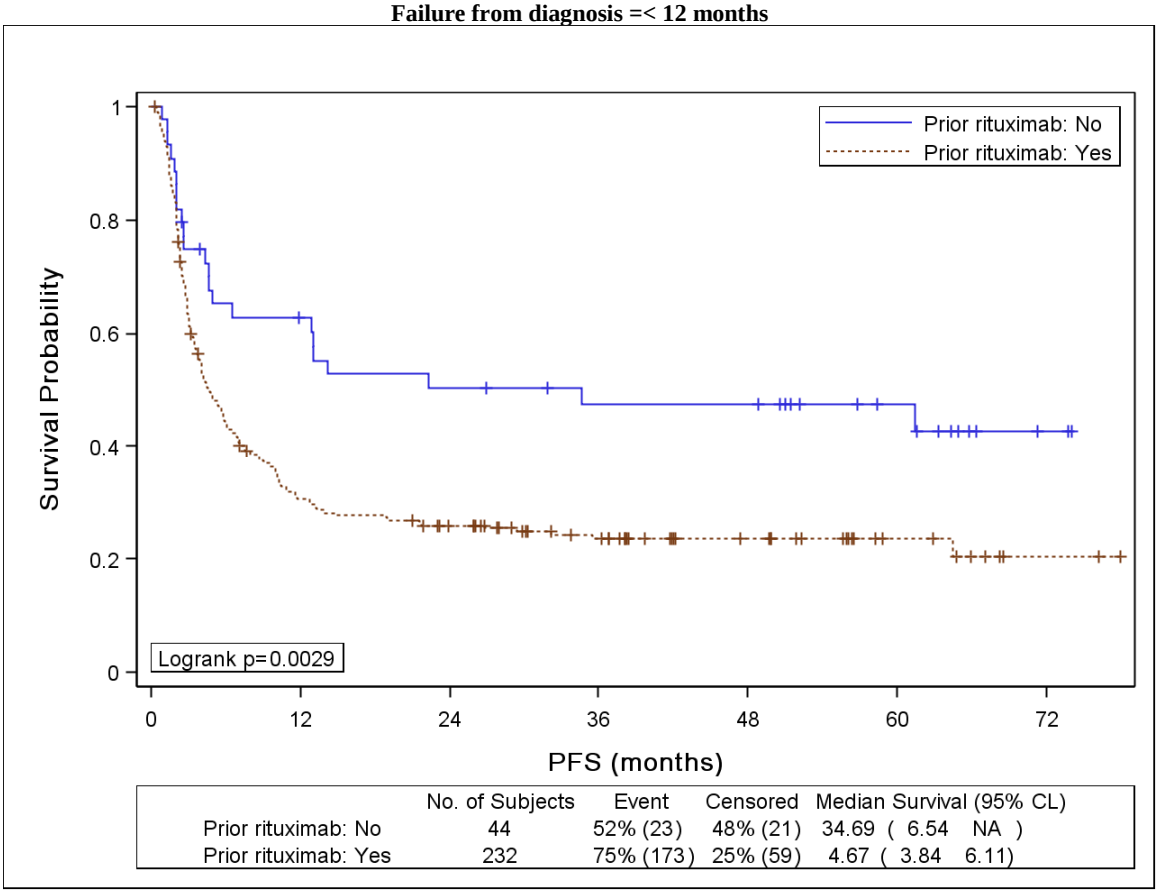
Prior treatment with Rituximab=No



	No. of Subjects	Event	Censored	Median Survival (95% C.
Failure from diagnosis <12 months	44	52% (23)	48% (21)	34.69 (6.54 NA)
Failure from diagnosis >=12 months	123	46% (57)	54% (66)	60.68 (30.88 NA)

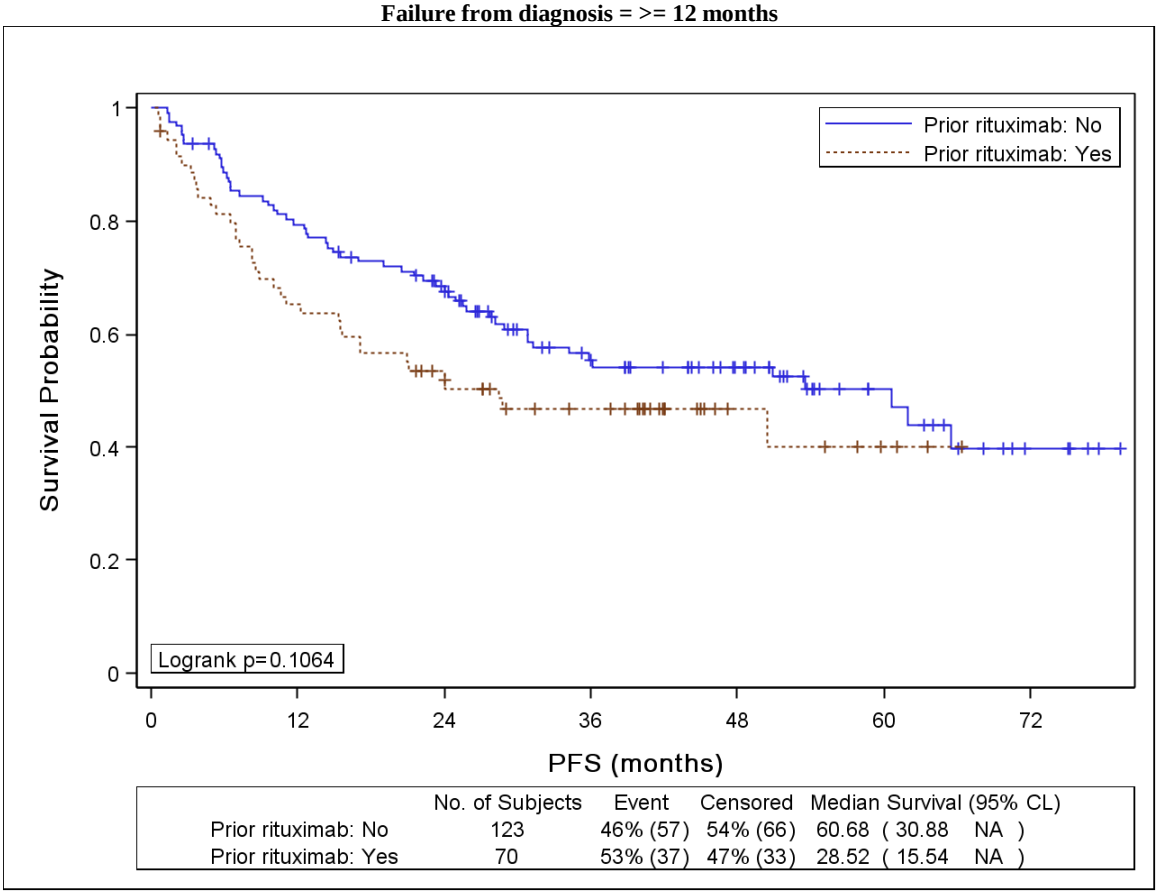
Figure 4.5-22 Exploratory analyses – Progression-Free Survival according to failure from diagnosis by prior rituximab (induction ITT)

Failure from diagnosis =< 12 months



	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



	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)

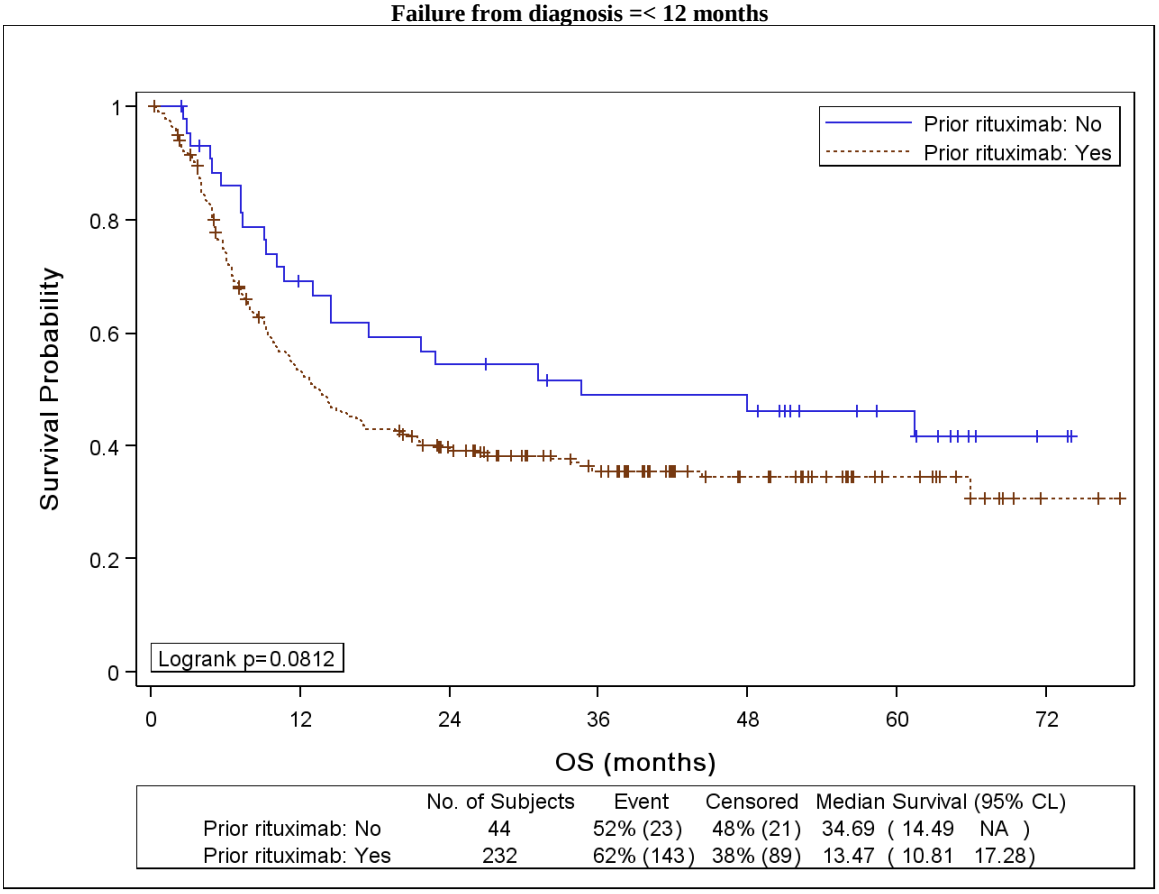
	Prior treatment with Rituximab	Failure from diagnosis (Randomization)	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	No	< 12 months	44	35	7	-	1	74
PFS (months)	No	>= 12 months	123	61	31	-	1	79
PFS (months)	Yes	< 12 months	232	5	4	6	0	78
PFS (months)	Yes	>= 12 months	70	29	16	-	1	66

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

Prior treatment with Rituximab	Failure from diagnosis	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
No	< 12 months	12	62.8	46.6	75.3	25
No	< 12 months	24	50.2	34.3	64.2	20
No	< 12 months	36	47.4	31.7	61.7	17
No	< 12 months	48	47.4	31.7	61.7	17
No	< 12 months	60	47.4	31.7	61.7	10
No	< 12 months	72	42.7	26.3	58.1	2
No	>= 12 months	12	79.4	71.1	85.6	96
No	>= 12 months	24	68.5	59.4	76.0	77
No	>= 12 months	36	55.4	45.7	64.2	48
No	>= 12 months	48	54.3	44.5	63.1	34
No	>= 12 months	60	50.2	39.6	59.9	16
No	>= 12 months	72	40.0	26.7	52.8	5
Yes	< 12 months	12	30.5	24.6	36.6	67
Yes	< 12 months	24	25.9	20.4	31.8	52
Yes	< 12 months	36	23.5	18.0	29.3	35
Yes	< 12 months	48	23.5	18.0	29.3	21
Yes	< 12 months	60	23.5	18.0	29.3	9
Yes	< 12 months	72	20.5	13.7	28.2	2
Yes	>= 12 months	12	65.3	52.8	75.2	45
Yes	>= 12 months	24	52.1	39.7	63.1	32
Yes	>= 12 months	36	46.8	34.5	58.2	23
Yes	>= 12 months	48	46.8	34.5	58.2	7
Yes	>= 12 months	60	40.2	24.4	55.4	3
Yes	>= 12 months	72	40.2	24.4	55.4	0

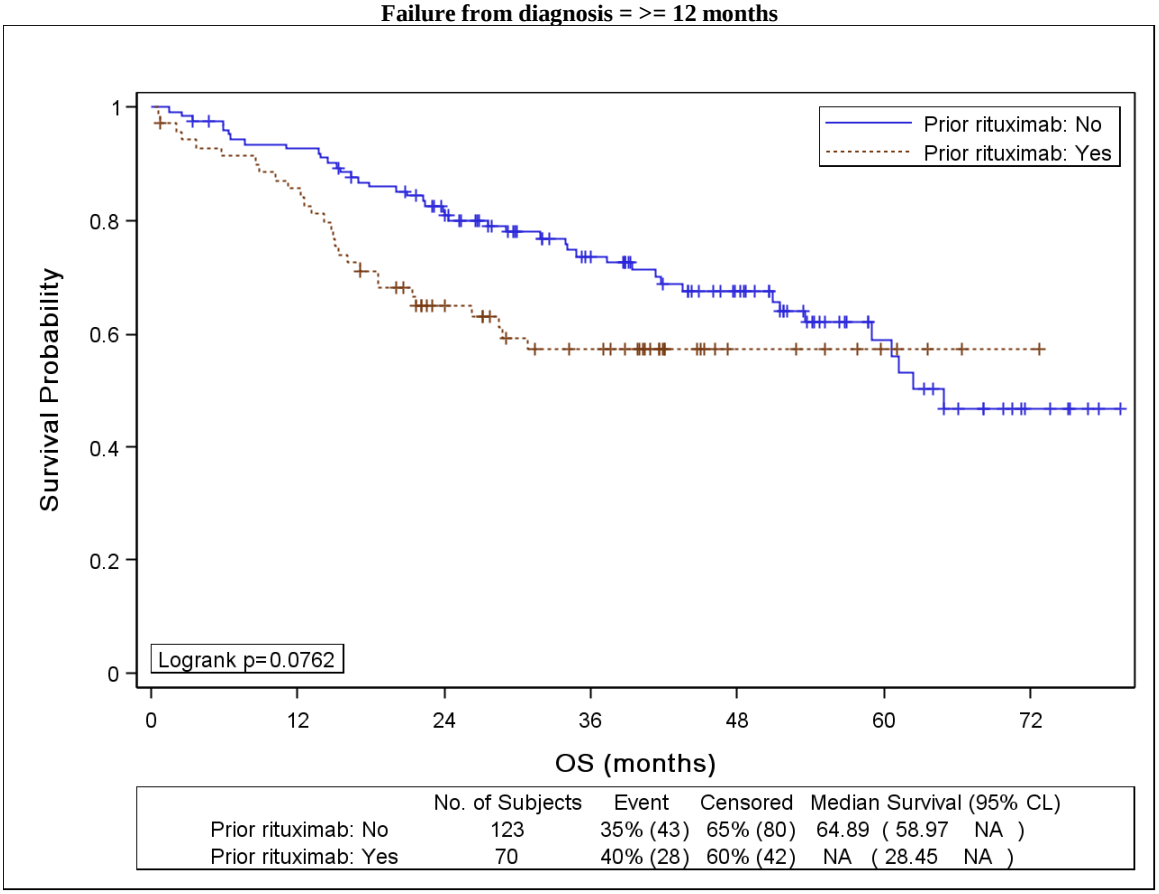
Figure 4.5-23 Exploratory analyses – Overall Survival according to prior rituximab by failure from diagnosis (induction ITT)

Failure from diagnosis =< 12 months



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Prior rituximab: No	44	52% (23)	48% (21)	34.69 (14.49 NA)
Prior rituximab: Yes	232	62% (143)	38% (89)	13.47 (10.81 17.28)

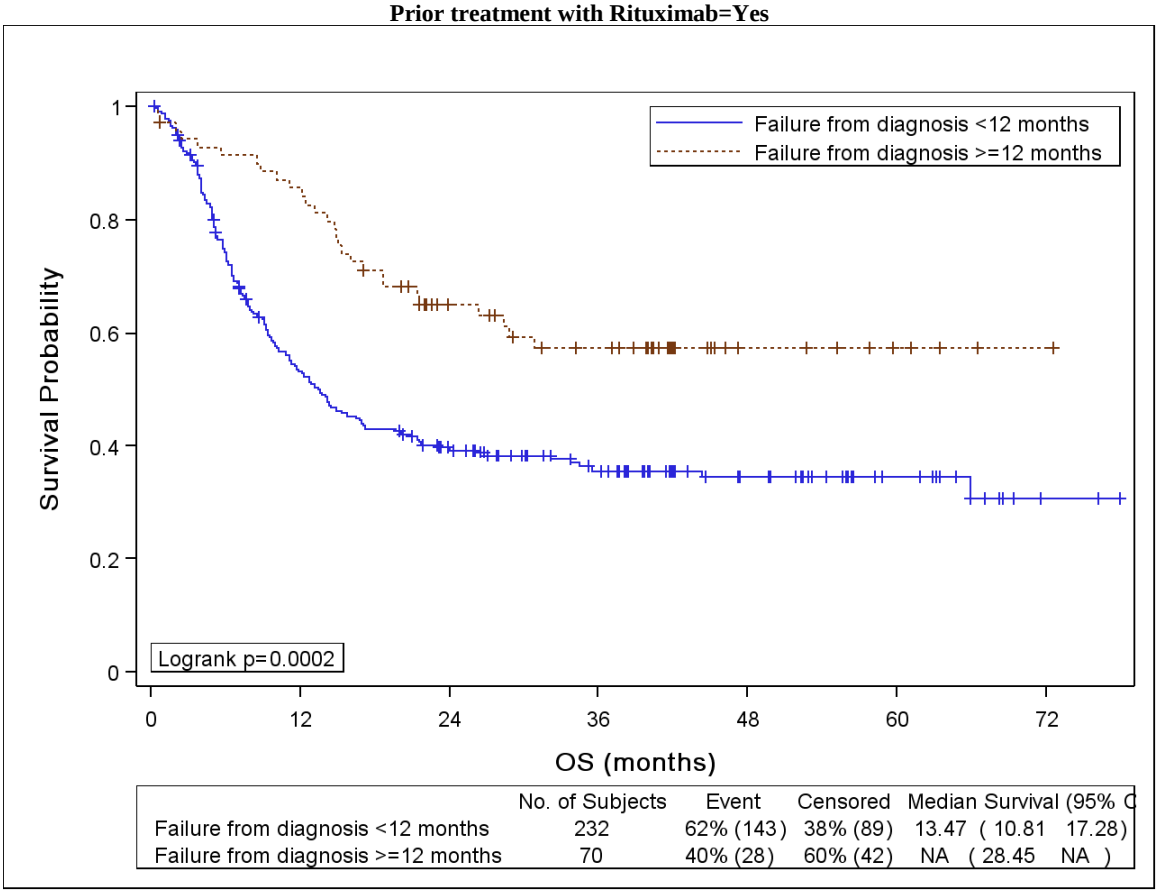
Failure from diagnosis = >= 12 months



	No. of Subjects	Event	Censored	Median Survival (95% CL)
Prior rituximab: No	123	35% (43)	65% (80)	64.89 (58.97 NA)
Prior rituximab: Yes	70	40% (28)	60% (42)	NA (28.45 NA)

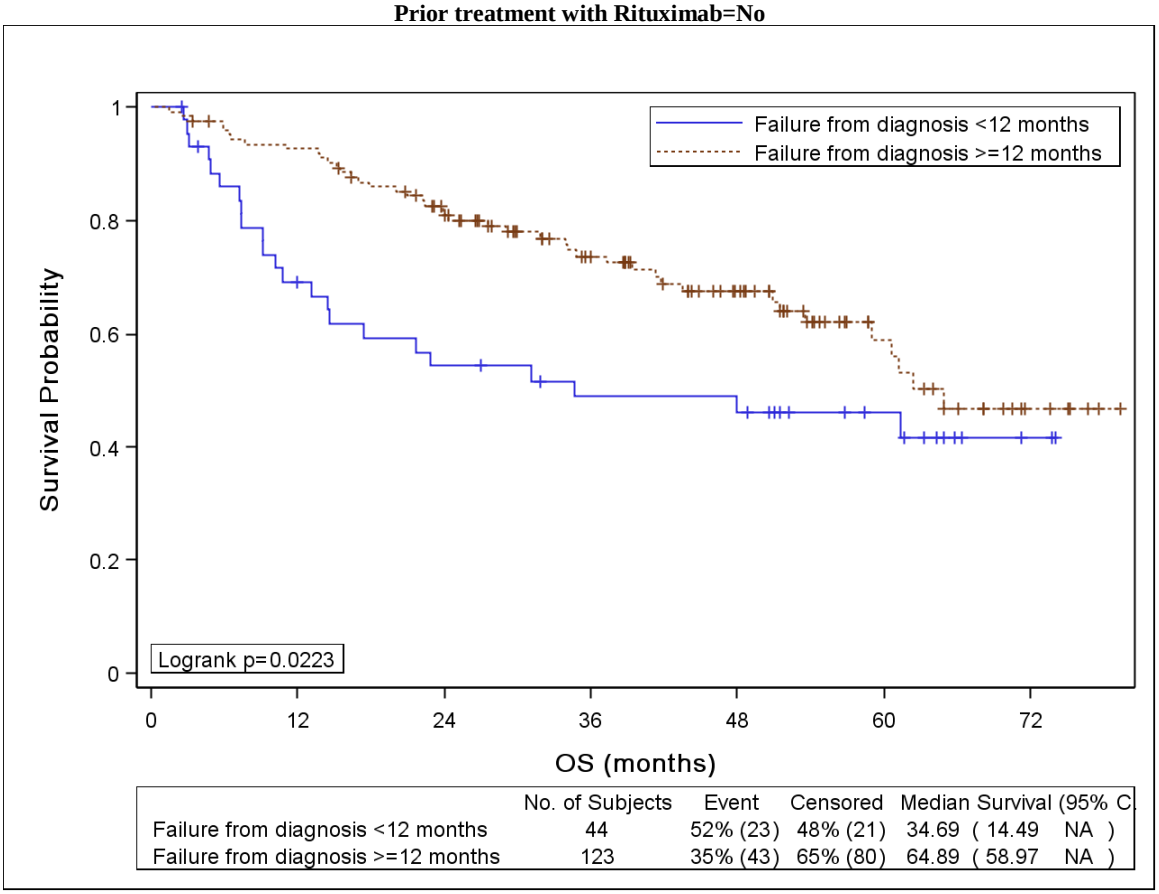
Figure 4.5-24 Exploratory analyses – Overall Survival according to failure from diagnosis by prior rituximab (induction ITT)

Prior treatment with Rituximab=Yes



	No. of Subjects	Event	Censored	Median Survival (95% C
Failure from diagnosis <12 months	232	62% (143)	38% (89)	13.47 (10.81 17.28)
Failure from diagnosis >=12 months	70	40% (28)	60% (42)	NA (28.45 NA)

Prior treatment with Rituximab=No



	No. of Subjects	Event	Censored	Median Survival (95% C.
Failure from diagnosis <12 months	44	52% (23)	48% (21)	34.69 (14.49 NA)
Failure from diagnosis >=12 months	123	35% (43)	65% (80)	64.89 (58.97 NA)

Table 4.5-96 Exploratory analyses – Duration of Overall Survival according to prior rituximab and failure from diagnosis (induction ITT)

	Prior treatment with Rituximab	Failure from diagnosis (Randomization)	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	No	< 12 months	44	35	14	-	3	74
OS (months)	No	>= 12 months	123	65	59	-	2	79
OS (months)	Yes	< 12 months	232	13	11	17	0	78
OS (months)	Yes	>= 12 months	70	-	28	-	1	73

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

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

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)

	Age-adjusted IPI			
	<2		>=2	
	N	%	N	%
Response after complete induction				
CR/CRu/PR	198	71	95	54
Other	80	29	82	46
Total	278	100	177	100

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

	Age-adjusted IPI			
	<2		>=2	
	N	%	N	%
Response after complete induction				
CR/CRu	119	43	52	29
Other	159	57	125	71
Total	278	100	177	100

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

	Age-adjusted IPI			
	<2		>=2	
	N	%	N	%
Mobilization adjusted overall response rate				
No	108	39	100	56
Yes	170	61	77	44
Total	278	100	177	100

Table 4.5-101 Exploratory analyses – Univariate analysis for response rates according to age adjusted IPI (induction ITT)

Age adjusted IPI 0-1	p-value (Wald Chi-2)	Odds ratio estimates	95% Wald confidence limits	
Response to induction CR/CRu/PR	0.0002	2.136	1.442	3.166
Response to induction CR/CRu	0.0041	1.799	1.204	2.687
Mobilization adjusted response rate	0.0003	0.489	0.334	0.717

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

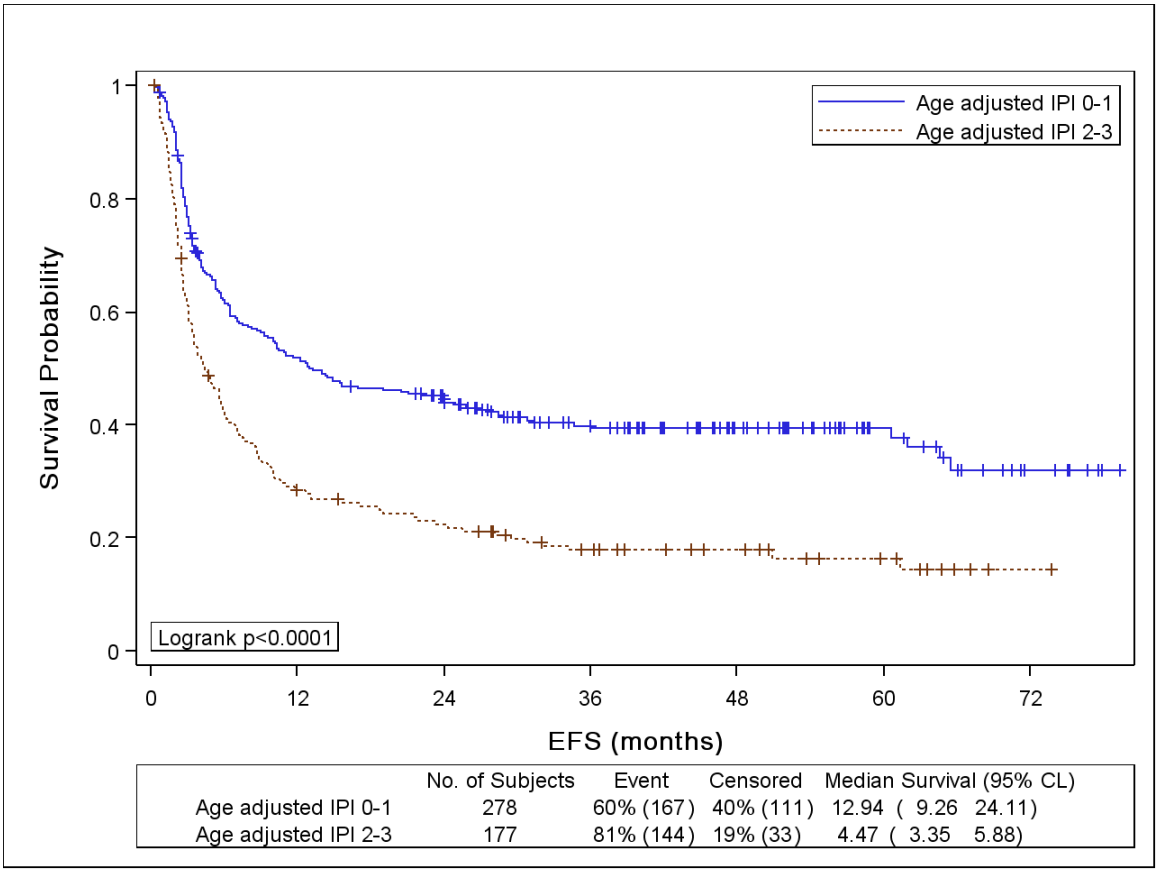


Table 4.5-102 Exploratory analyses – Duration of Event-Free Survival according to age adjusted IPI (induction ITT)

Age-adjusted IPI	N	Median	95% CI lower	95% CI Upper	Min	Max
0-1	278	13	9	24	0	79
2-3	177	4	3	6	0	74

Table 4.5-103 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to age adjusted IPI (induction ITT)

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

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age adjusted IPI 0-1	<.0001	0.538	0.430	0.673

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

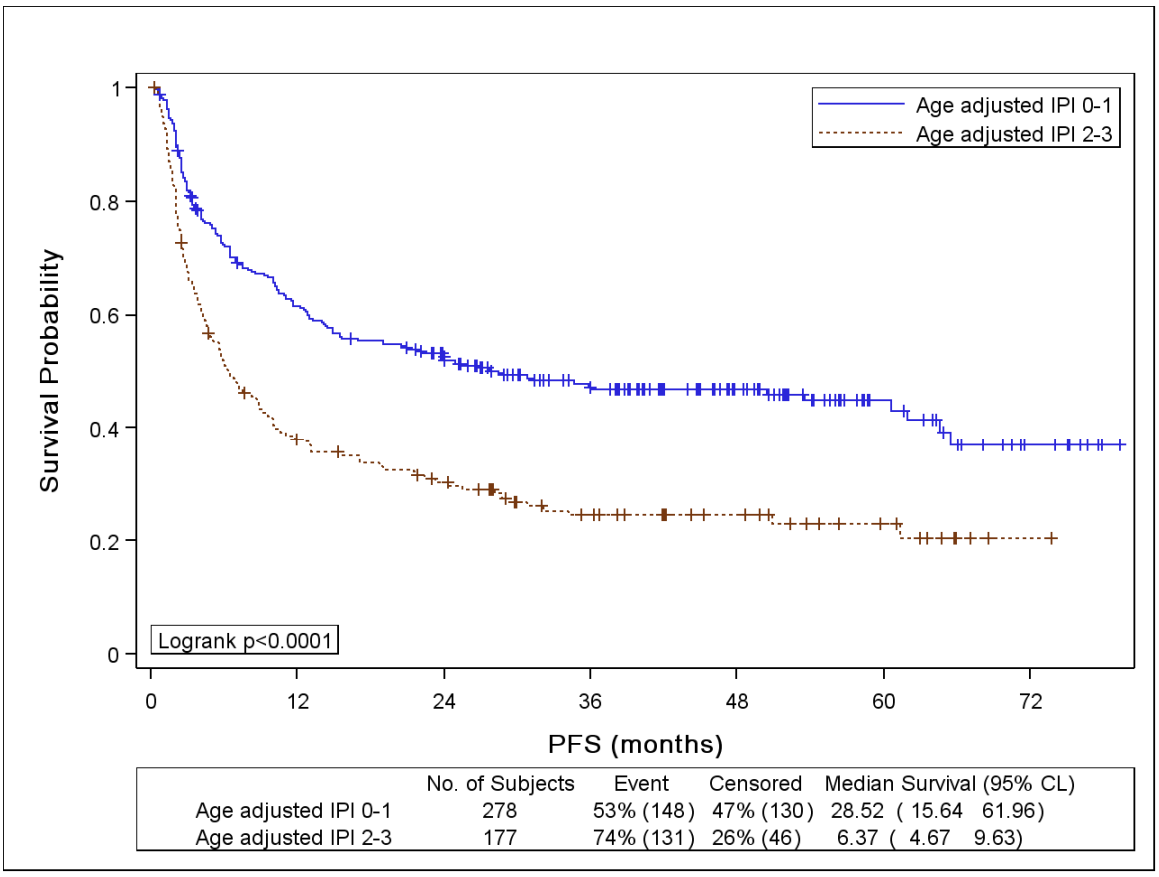


Table 4.5-105 Exploratory analyses – Duration of Progression-Free Survival according to age adjusted IPI (induction ITT)

Age-adjusted IPI	N	Median	95% CI lower	95% CI Upper	Min	Max
0-1	278	29	16	62	0	79
2-3	177	6	5	10	0	74

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

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

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

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age adjusted IPI 0-1	<.0001	0.532	0.420	0.674

Figure 4.5-27 Exploratory analyses – Overall Survival according to age adjusted IPI (induction ITT)

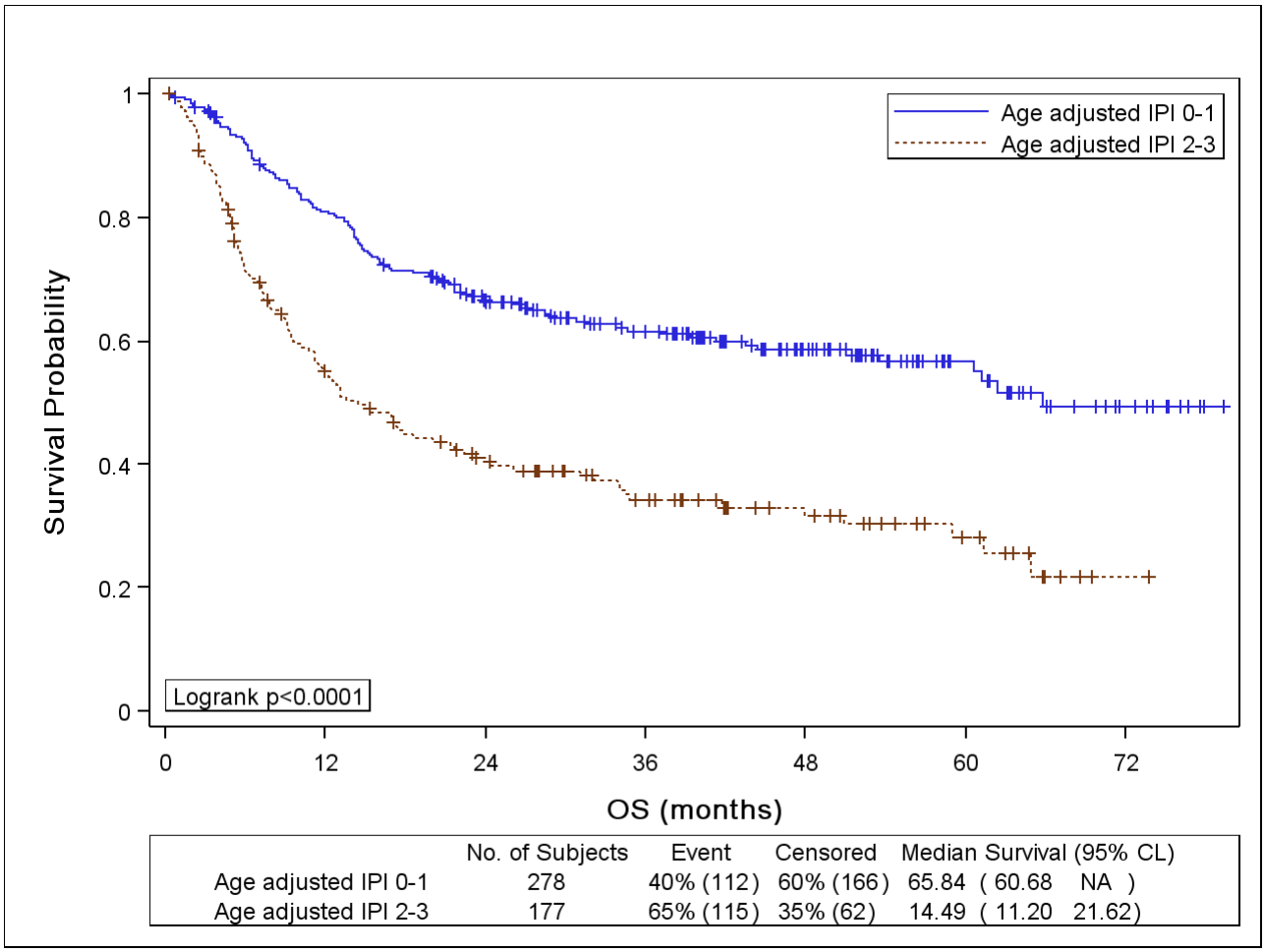


Table 4.5-108 Exploratory analyses – Duration of Overall Survival according to age adjusted IPI (induction ITT)

Age-adjusted IPI	N	Median	95% CI lower	95% CI Upper	Min	Max
0-1	278	66	61	-	0	79
2-3	177	14	11	22	0	74

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

Age-adjusted IPI	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
0-1	12	80.9	75.7	85.1	219
0-1	24	66.7	60.7	72.0	163
0-1	36	61.6	55.4	67.3	121
0-1	48	58.6	52.1	64.5	75
0-1	60	56.6	49.8	62.9	35
0-1	72	49.3	40.2	57.9	10
2-3	12	55.2	47.5	62.3	91
2-3	24	41.0	33.5	48.4	62
2-3	36	34.1	26.7	41.6	40
2-3	48	31.7	24.2	39.4	24

Age-adjusted IPI	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
2-3	60	28.0	20.0	36.5	12
2-3	72	21.8	12.7	32.6	1

Table 4.5-110 Exploratory analyses – Hazard ratio of age adjusted IPI for Overall Survival (induction ITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age adjusted IPI 0-1	<.0001	0.438	0.337	0.568

4.5.3.5. Multivariate models

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

Response to induction CR/CRu/PR	p-value (Wald Chi-2)	Odds ratio estimates	95% Wald confidence limits	
Prior rituximab: No	0.0386	1.744	1.030	2.953
Failure from diagnosis < 12 months	<.0001	0.204	0.121	0.345
Age adjusted IPI 0-1	0.0036	1.886	1.231	2.888
Treatment arm: R-ICE	0.9242	0.980	0.642	1.495

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

Response to induction CR/CRu	p-value (Wald Chi-2)	Odds ratio estimates	95% Wald confidence limits	
Prior rituximab: No	0.3718	1.236	0.776	1.970
Failure from diagnosis < 12 months	<.0001	0.298	0.189	0.470
Age adjusted IPI 0-1	0.0325	1.585	1.039	2.418
Treatment arm: R-ICE	0.8947	1.028	0.687	1.537

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

Mobilization adjusted response rate	p-value (Wald Chi-2)	Odds ratio estimates	95% Wald confidence limits	
Prior rituximab: No	0.0012	0.459	0.287	0.735
Failure from diagnosis < 12 months	<.0001	2.506	1.595	3.936
Age adjusted IPI 0-1	0.0042	0.553	0.369	0.830
Treatment arm: R-ICE	0.2848	1.242	0.835	1.847

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

Event-Free Survival	p-value	Hazard ratio	95% Hazard ratio confidence limits	
Prior rituximab: No	0.0011	0.627	0.475	0.829
Failure from diagnosis < 12 months	<.0001	1.911	1.465	2.493
Age adjusted IPI 0-1	<.0001	1.633	1.303	2.048
Treatment arm: R-ICE	0.3020	1.125	0.900	1.406

Table 4.5-115 Exploratory analyses – Multivariate Cox model for Progression-Free Survival (induction ITT)

Progression-Free Survival	p-value	Hazard ratio	95% Hazard ratio confidence limits	
Prior rituximab: No	0.0046	0.656	0.490	0.878
Failure from diagnosis < 12 months	<.0001	1.873	1.415	2.479
Age adjusted IPI 0-1	<.0001	1.677	1.322	2.128
Treatment arm: R-ICE	0.3554	1.117	0.883	1.414

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

Overall Survival	p-value	Hazard ratio	95% Hazard ratio confidence limits	
Prior rituximab: No	0.0765	0.746	0.539	1.032
Failure from diagnosis < 12 months	<.0001	2.011	1.461	2.768
Age adjusted IPI 0-1	<.0001	2.153	1.656	2.799
Treatment arm: R-ICE	0.2504	1.165	0.898	1.513

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)

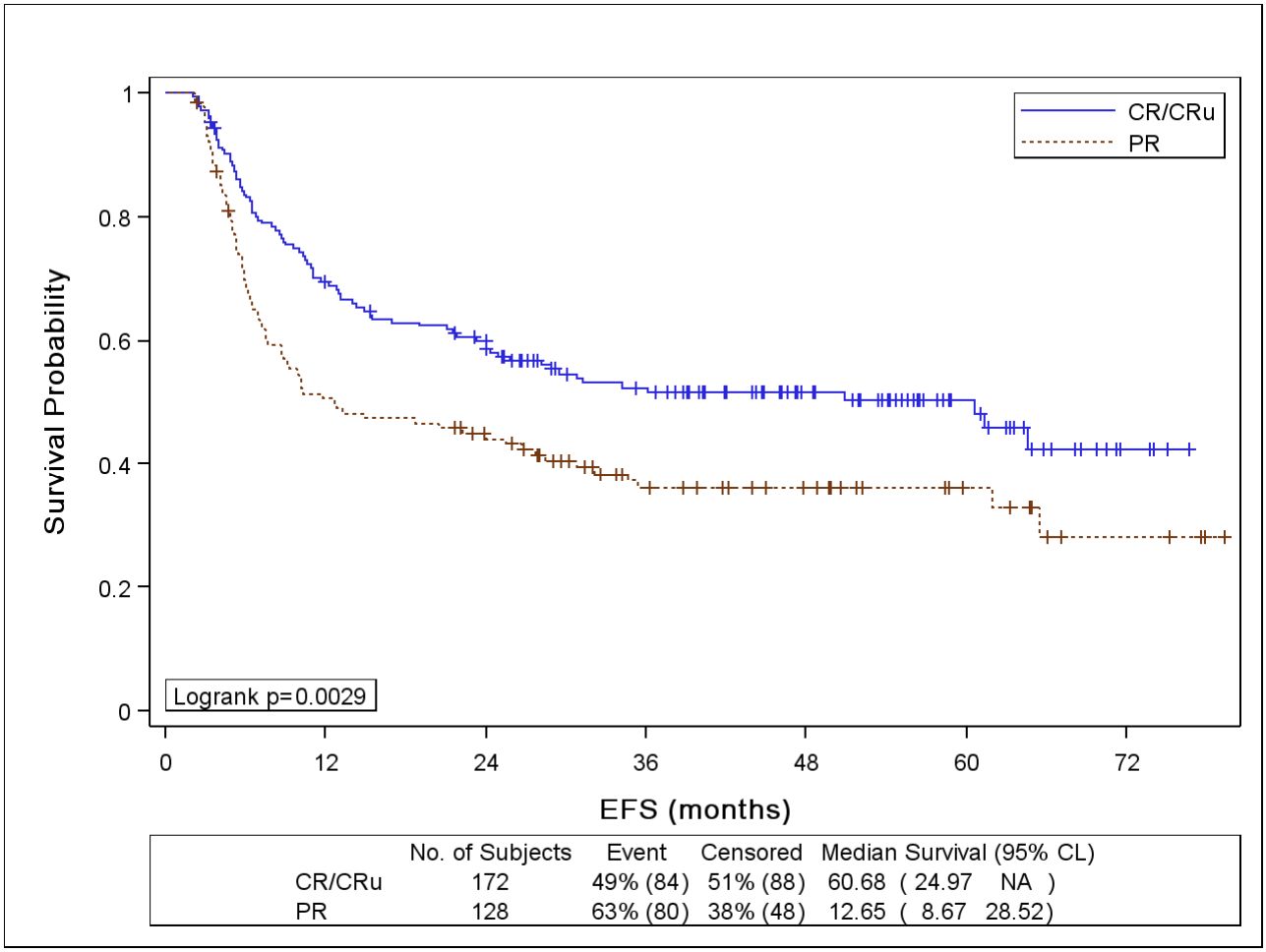


Table 4.5-117 Exploratory analyses – Duration of Event-Free Survival according to response to induction (induction ITT)

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

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

Response after complete induction (including deaths for all patients)	Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	69.5	61.9	75.8	117
CR/CRu	24	59.9	52.1	66.8	96
CR/CRu	36	52.4	44.4	59.7	70
CR/CRu	48	51.6	43.7	59.0	45
CR/CRu	60	50.4	42.3	58.0	22
CR/CRu	72	42.5	31.6	52.9	4
PR	12	50.6	41.5	58.9	63
PR	24	44.0	35.2	52.5	51
PR	36	36.1	27.4	44.8	31
PR	48	36.1	27.4	44.8	22
PR	60	36.1	27.4	44.8	11
PR	72	28.1	16.8	40.5	4

Figure 4.5-29 Exploratory analyses – Progression-Free Survival according to response to induction (induction ITT)

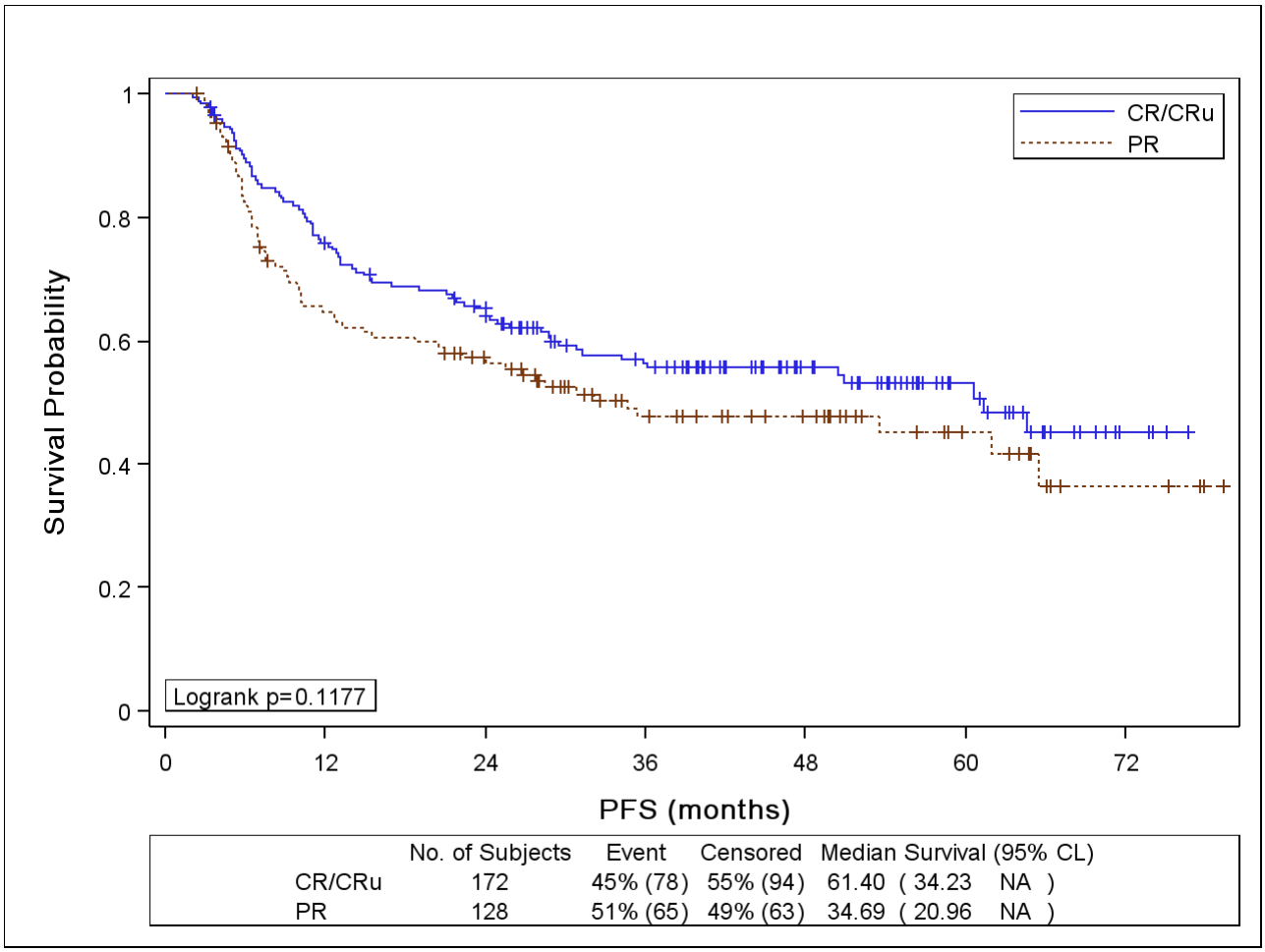


Table 4.5-119 Exploratory analyses – Duration of Progression-Free Survival according to response to induction (induction ITT)

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

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

Response after complete induction (including deaths for all patients)	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	75.9	68.7	81.6	128
CR/CRu	24	65.2	57.5	71.8	105
CR/CRu	36	56.3	48.3	63.6	77
CR/CRu	48	55.6	47.6	62.9	47
CR/CRu	60	53.1	44.7	60.8	23
CR/CRu	72	45.2	34.1	55.6	4
PR	12	64.7	55.6	72.4	79

Response after complete induction (including deaths for all patients)	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
PR	24	56.4	47.1	64.6	62
PR	36	47.8	38.3	56.7	39
PR	48	47.8	38.3	56.7	29
PR	60	45.2	34.9	54.9	13
PR	72	36.5	23.1	50.0	4

Figure 4.5-30 Exploratory analyses – Overall Survival according to response to induction (induction ITT)

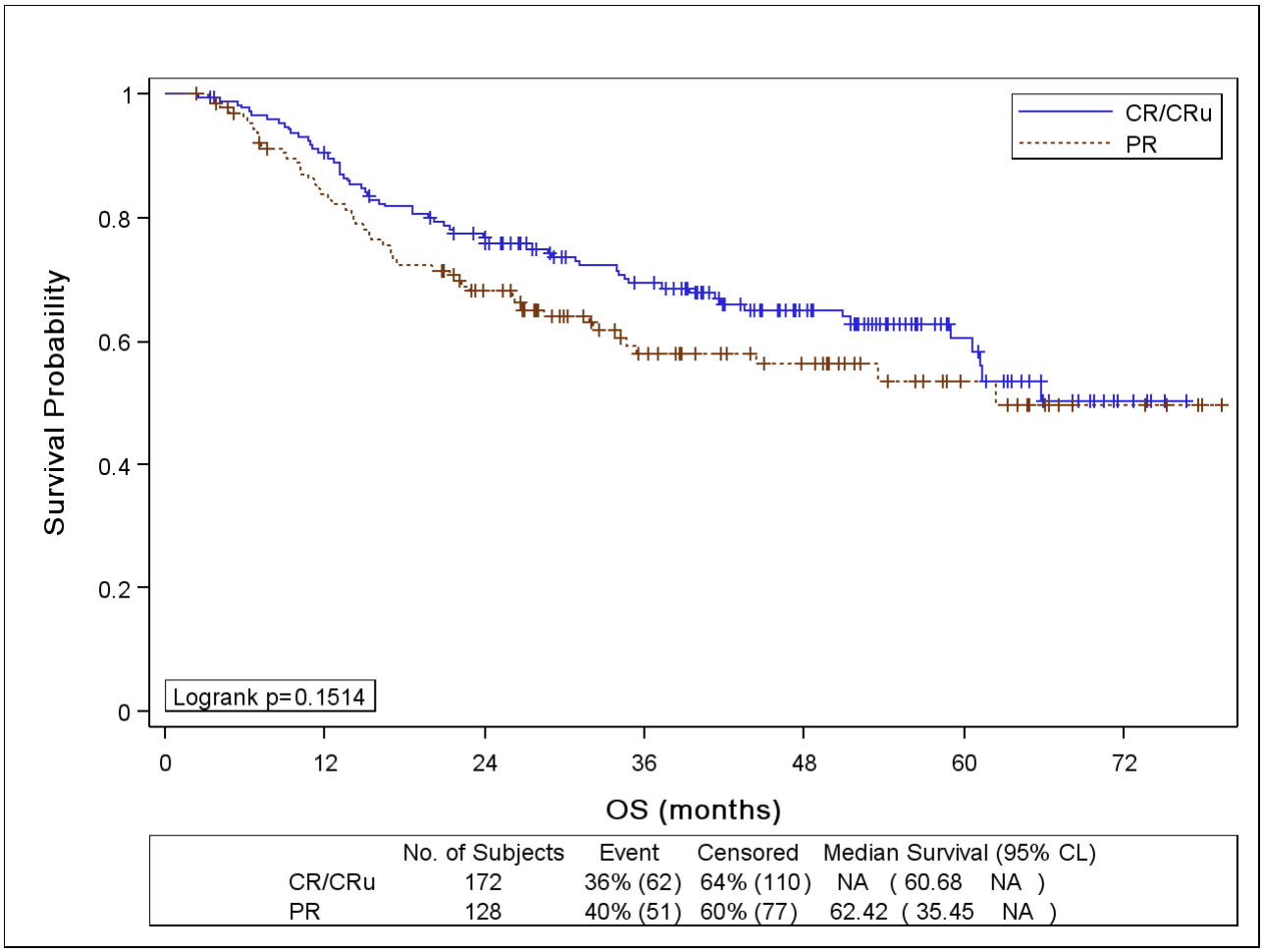


Table 4.5-121 Exploratory analyses – Duration of Overall Survival according to response to induction (induction ITT)

	Response after complete induction (including deaths for all patients)	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	CR/CRu	172	-	61	-	2	77
OS (months)	PR	128	62	35	-	2	79

Table 4.5-122 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to response to induction (induction ITT)

Response after complete induction (including deaths for all patients)	Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	90.6	85.1	94.1	153
CR/CRu	24	76.9	69.8	82.5	124
CR/CRu	36	69.3	61.5	75.8	96
CR/CRu	48	65.1	56.9	72.1	58
CR/CRu	60	60.5	51.1	68.7	27
CR/CRu	72	50.3	37.9	61.4	5
PR	12	83.8	76.0	89.2	102
PR	24	68.0	58.9	75.5	73
PR	36	58.0	48.1	66.7	45
PR	48	56.3	46.2	65.3	32
PR	60	53.7	42.6	63.5	14
PR	72	49.8	37.2	61.2	5

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)

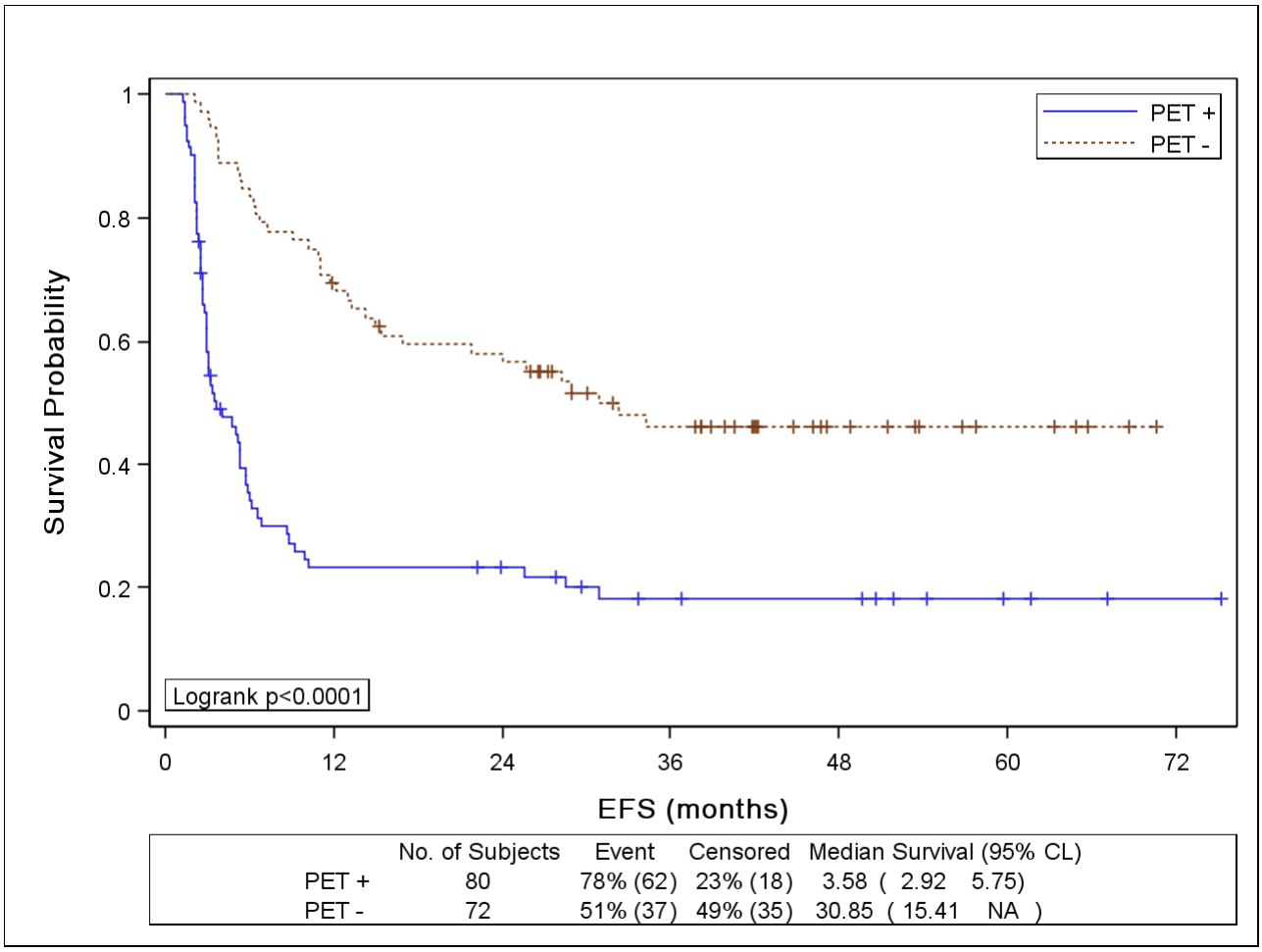


Table 4.5-123 Exploratory analyses – Duration of Event-Free Survival according to PET after induction (induction ITT)

	Pet scan after induction	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	PET -	72	31	15	-	2	71
EFS (months)	PET +	80	4	3	6	1	75

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

Pet scan after induction	Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
PET -	12	69.4	57.4	78.7	49
PET -	24	58.0	45.7	68.5	40
PET -	36	46.3	34.0	57.7	25
PET -	48	46.3	34.0	57.7	11
PET -	60	46.3	34.0	57.7	5
PET -	72	46.3	34.0	57.7	0
PET +	12	23.2	14.4	33.2	17
PET +	24	23.2	14.4	33.2	15
PET +	36	18.1	10.2	27.9	9

Pet scan after induction	Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
PET +	48	18.1	10.2	27.9	8
PET +	60	18.1	10.2	27.9	3
PET +	72	18.1	10.2	27.9	1

Figure 4.5-32 Exploratory analyses – Progression-Free Survival according to PET after induction (induction ITT)

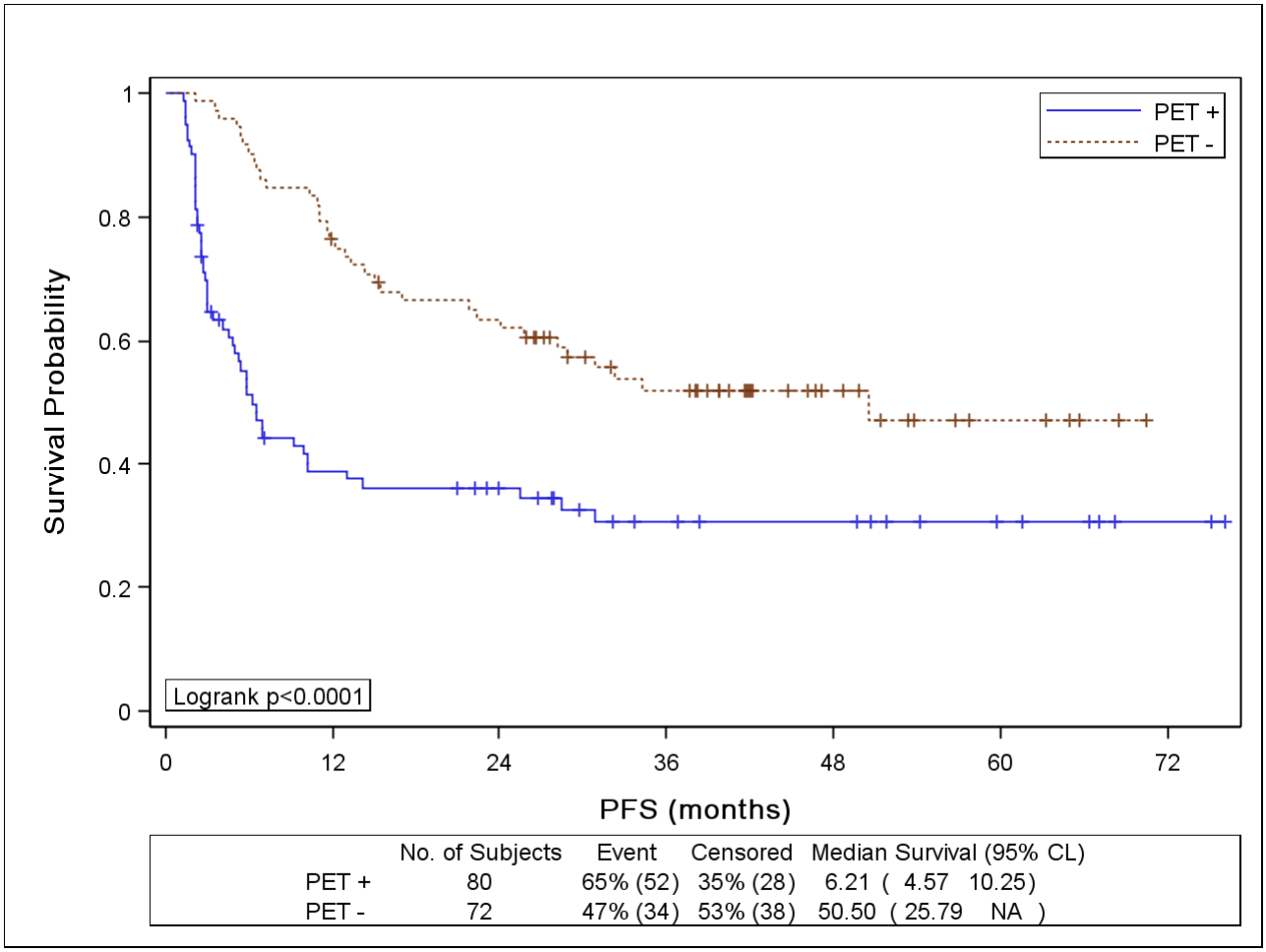


Table 4.5-125 Exploratory analyses – Duration of Progression-Free Survival according to PET after induction (induction ITT)

	Pet scan after induction	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	PET -	72	50	26	-	2	71
PFS (months)	PET +	80	6	5	10	1	76

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

Pet scan after induction	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
PET -	12	76.4	64.8	84.6	54
PET -	24	63.5	51.2	73.5	44
PET -	36	52.0	39.5	63.2	29
PET -	48	52.0	39.5	63.2	13

Pet scan after induction	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
PET -	60	47.3	32.9	60.5	5
PET -	72	47.3	32.9	60.5	0
PET +	12	38.9	28.0	49.7	28
PET +	24	36.1	25.4	46.9	22
PET +	36	30.5	20.1	41.5	13
PET +	48	30.5	20.1	41.5	11
PET +	60	30.5	20.1	41.5	6
PET +	72	30.5	20.1	41.5	2

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

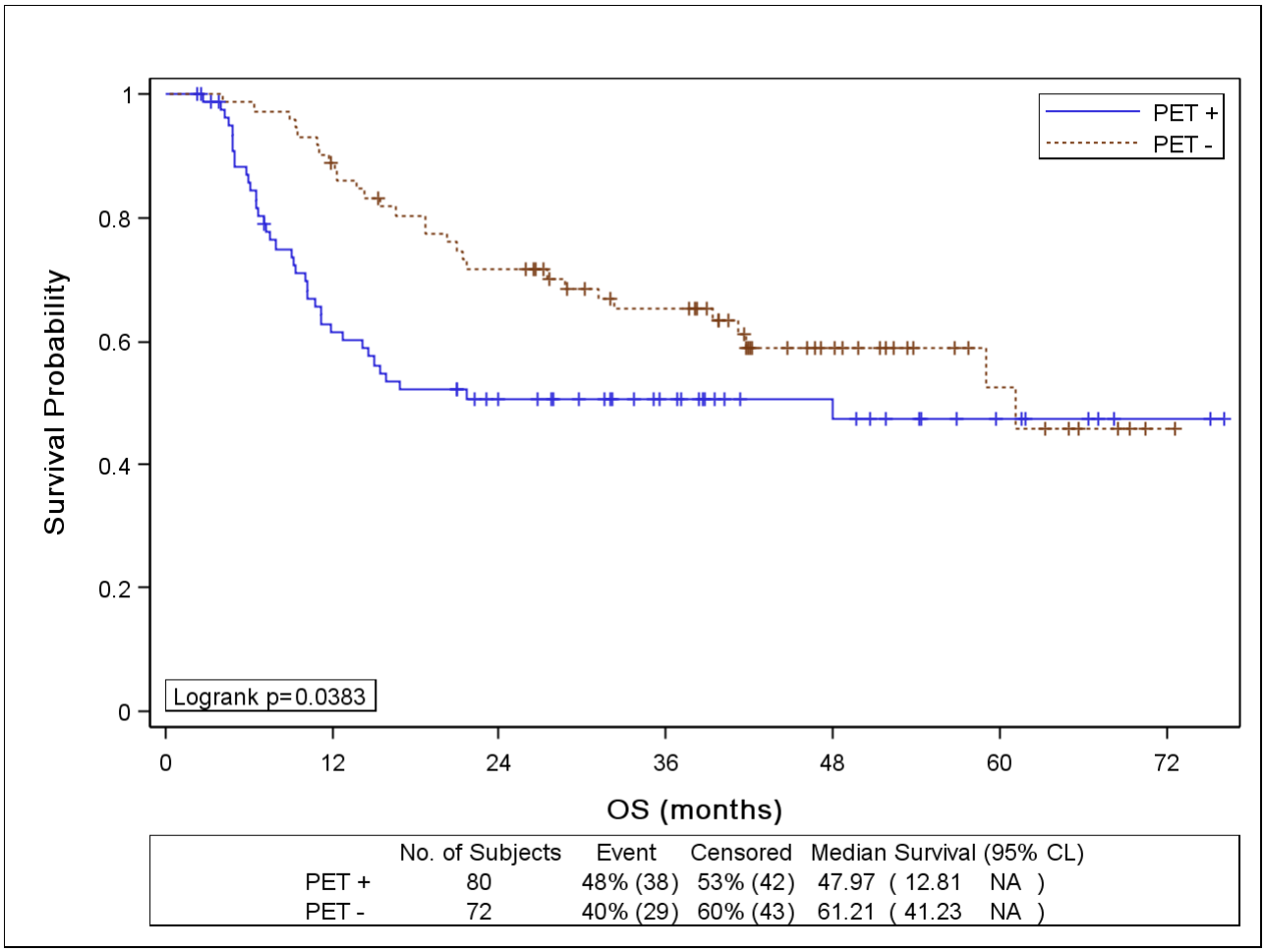


Table 4.5-127 Exploratory analyses – Duration of Overall Survival according to PET after induction (induction ITT)

	Pet scan after induction	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	PET -	72	61	41	-	4	73
OS (months)	PET +	80	48	13	-	2	76

Table 4.5-128 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to PET after induction (induction ITT)

Pet scan after induction	Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
PET -	12	88.9	79.0	94.3	63
PET -	24	71.8	59.7	80.8	50
PET -	36	65.2	52.6	75.2	38
PET -	48	59.0	45.7	70.1	19
PET -	60	52.4	35.2	67.1	8
PET -	72	45.9	26.9	63.0	1
PET +	12	61.6	49.6	71.5	46
PET +	24	50.8	39.0	61.4	33
PET +	36	50.8	39.0	61.4	23
PET +	48	47.4	34.7	59.1	14
PET +	60	47.4	34.7	59.1	7
PET +	72	47.4	34.7	59.1	2

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)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
New treatment out of progression				
Yes	36	15	31	13
No	203	85	199	87
Total	239	100	230	100

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Chemotherapy				
Yes	21	58	17	55
No	15	42	14	45
Radiotherapy				
No	29	81	20	65
Yes	7	19	11	35
Immunotherapy				
Yes	9	25	7	23
No	27	75	24	77
Transplantation				
No	16	44	16	52
Yes	20	56	15	48
Other treatment				
Yes	2	6	0	0
No	34	94	31	100
Total	36	100	31	100

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)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Progression/relapse n°1				
Yes	132	55	117	51
No	107	45	113	49
Progression/relapse n°2				
Yes	21	9	22	10
No	218	91	208	90
Progression/relapse n°3				
Yes	8	3	8	3
No	231	97	222	97
Progression/relapse n°4				
Yes	2	1	2	1
No	237	99	228	99
Progression/relapse n°5				
Yes	2	1	1	0
No	237	99	229	100
Total	239	100	230	100

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Period of Progression / Relapse				
TREATMENT PERIOD	64	48	63	54
FOLLOW UP PERIOD	66	50	54	46
Missing	2	2	0	0
Total	132	100	117	100

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Initial involvement				
Yes	92	70	90	77
No	40	30	27	23

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
New involvement				
Not Done	1	1	0	0
Yes	64	48	48	41
No	67	51	69	59
Nodal involvement				
Yes	95	72	76	65
No	37	28	41	35
Extra-nodal involvement				
Not Done	1	1	0	0
Yes	77	58	70	60
No	54	41	47	40
Total	132	100	117	100

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)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
LDH > Upper Limit				
Missing	2	2	2	2
Not Done	10	8	5	4
Yes	71	54	80	68
No	49	37	30	26
Stage III - IV				
Missing	1	1	2	2
Not Done	7	5	2	2
Yes	81	61	77	66
No	43	33	36	31
PS >= 2				
Missing	1	1	3	3
Not Done	7	5	4	3
Yes	39	30	38	32
No	85	64	72	62
Extra-nodal sites >= 2				
Missing	1	1	2	2
Not Done	3	2	1	1
Yes	35	27	28	24
No	93	70	86	74
Total	132	100	117	100

Table 4.5-135 Progression/relapse n°1 – Progression/relapse treatment (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Progression / Relapse treatment				
Missing	2	2	6	5
Yes	124	94	102	87
No	6	5	9	8
Total	132	100	117	100

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Chemotherapy				
Not Done	1	1	0	0
Yes	97	78	80	78
No	26	21	22	22
Radiotherapy				
Not Done	4	3	1	1
Yes	39	31	35	34
No	81	65	66	65
Immunotherapy				
Not Done	4	3	1	1
Yes	36	29	31	30
No	84	68	70	69
Transplantation				
Not Done	4	3	1	1
Yes	29	23	26	25
No	91	73	75	74
Other treatment				
Not Done	2	2	0	0
Yes	13	10	20	20
No	109	88	82	80
Total	124	100	102	100

Details of treatment are listed in section §6.6.4.

Table 4.5-137 Progression/relapse n°1 – Response after additional treatments (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Response after new treatment				
COMPLETE RESPONSE	16	13	19	19
UNCONFIRMED COMPLETE RESPONSE	7	6	2	2
PARTIAL RESPONSE	17	14	16	16
STABLE DISEASE	4	3	9	9
PROGRESSIVE DISEASE	67	54	47	46
NOT EVALUATED	12	10	8	8
Missing	1	1	1	1
Total	124	100	102	100

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 inductiontreatment 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 5.1-1 Induction treatment cycles received (induction safety population)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Cycle 1				
Yes	239	100	230	100
Cycle 2				
Yes	225	94	215	93
No	14	6	15	7
Cycle 3				
Yes	204	85	196	85
No	35	15	34	15
Total	239	100	230	100

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 5.1-2 Time between induction cycles (induction safety population)

		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
Time between cycles 1 and 2 (days)	**N**	225	214
	Mean	22.7	22.7
	Std	4.48	3.49
	Median	21.0	21.5
	Min	17	18
	Max	53	39
Time between cycles 2 and 3 (days)	**N**	204	195
	Mean	23.2	23.0
	Std	4.28	3.72
	Median	22.0	22.0
	Min	16	17
	Max	55	52

Table 5.1-3 Induction - Percentage of planned dose received by cycle for rituximab (induction safety population)

Dose received (% of planned dose)			Actual arm of induction	
			ARM A / R-ICE	ARM B / R-DHAP
Rituximab	**Cycle 1**	**N**	239	228
		Mean	95.0	94.6
		Std	15.29	15.83
		Median	100.0	100.0
		Min	37	0
		Max	113	110
	Cycle 2	**N**	225	212
		Mean	98.7	98.4
		Std	7.87	8.00
		Median	100.0	99.9
		Min	0	0
		Max	117	110
	Cycle 3	**N**	204	193
		Mean	98.7	99.0
		Std	8.06	4.09
		Median	100.0	99.9
		Min	0	83
		Max	117	116

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)

Dose received (% of planned dose)			Actual arm of induction ARM A / R-ICE
Etoposide	**Cycle 1**	**N**	239
		Mean	98.0
		Std	9.21
		Median	100.0
		Min	0
		Max	110
	Cycle 2	**N**	225
		Mean	97.9
		Std	7.79
		Median	100.0
		Min	33
		Max	111
	Cycle 3	**N**	204
		Mean	97.5
		Std	8.48
		Median	100.0
		Min	33
		Max	111
Carboplatine	**Cycle 1**	**N**	238
		Mean	99.0
		Std	16.76
		Median	99.0
		Min	0
		Max	149
	Cycle 2	**N**	224
		Mean	99.9
		Std	18.85
		Median	100.0
		Min	0
		Max	172
	Cycle 3	**N**	203
		Mean	98.7
		Std	15.64
		Median	99.5
		Min	47
		Max	150

Dose received (% of planned dose)			Actual arm of induction ARM A / R-ICE
Ifosfamide	**Cycle 1**	**N**	238
		Mean	98.1
		Std	8.60
		Median	100.0
		Min	0
		Max	104
	Cycle 2	**N**	224
		Mean	97.4
		Std	9.39
		Median	100.0
		Min	0
		Max	104
	Cycle 3	**N**	202
		Mean	97.1
		Std	10.50
		Median	100.0
		Min	0
		Max	105

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 2nd cycle (permanent stop but anyway withdrawn before C3 for progressive disease).
- ✓ One patient did not receive ifosfamide at 2nd and 3rd cycles due to CNS toxicity.

Table 5.1-5 Induction - Percentage of planned dose received by cycle for DHAP regimen (induction safety population)

Dose received (% of planned dose)			Actual arm of induction ARM B / R-DHAP
Dexamethasone	**Cycle 1**	**N**	229
		Mean	106.2
		Std	43.02
		Median	100.0
		Min	75
		Max	700
	Cycle 2	**N**	213
		Mean	103.3
		Std	18.65
		Median	100.0
		Min	25
		Max	200
	Cycle 3	**N**	196
		Mean	103.1
		Std	17.62
		Median	100.0
		Min	50
		Max	200
Cisplatine	**Cycle 1**	**N**	228
		Mean	97.8
		Std	7.49
		Median	100.0
		Min	28
		Max	106
	Cycle 2	**N**	212
		Mean	95.0
		Std	15.54
		Median	100.0
		Min	0
		Max	110
	Cycle 3	**N**	194
		Mean	91.0
		Std	27.03
		Median	100.0
		Min	0
		Max	253

Dose received (% of planned dose)			Actual arm of induction ARM B / R-DHAP
Cytarabine	**Cycle 1**	**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)

G-CSF		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Cycle 1	**No**	43	18	31	13
	Yes	194	81	195	85
	Not Done	2	1	2	1
	Missing	0	0	2	1
	Total	239	100	230	100
Cycle 2	**No**	25	10	17	7
	Yes	197	82	194	84
	Not Done	3	1	2	1
	Missing	14	6	17	7
	Total	239	100	230	100

G-CSF		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Cycle 3	No	9	4	15	7
	Yes	192	80	179	78
	Not Done	3	1	1	0
	Missing	35	15	35	15
	Total	239	100	230	100

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)

Dose received (% of planned dose)		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
BCNU	N	122	131
	Mean	98.5	97.2
	Std	8.47	9.22
	Median	100.0	99.8
	Min	69	49
	Max	167	129
Etoposide	N	122	131
	Mean	99.1	101.9
	Std	21.81	23.06
	Median	100.0	100.0
	Min	25	25
	Max	203	200
Cytarabine	N	122	131
	Mean	88.9	91.6
	Std	20.88	18.02
	Median	98.2	99.0
	Min	13	12
	Max	114	114
Melphalan	N	122	131
	Mean	97.9	97.1
	Std	6.81	8.86
	Median	99.9	99.5
	Min	50	30
	Max	108	111

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)

G-CSF	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
No	35	28	40	30
Yes	86	70	91	69
Missing	2	2	1	1
Total	123	100	132	100

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

G-CSF	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
G-CSF	83	97	88	97
OTHER	3	3	3	3
Total	86	100	91	100

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)

		Actual arm of induction																			
		ARM A / R-ICE										ARM B / R-DHAP									
		Grade										Grade									
		All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	5	>=3	NE	Total
Grade allergy	**N**	18	220	12	3	2	1	0	3	1	239	17	210	11	4	2	0	0	2	3	230
	%	8	92	5	1	1	0	0	1	0	100	7	91	5	2	1	0	0	1	1	100
Grade auditory	**N**	4	234	2	1	1	0	0	1	1	239	19	208	9	9	1	0	0	1	3	230
	%	2	98	1	0	0	0	0	0	0	100	8	90	4	4	0	0	0	0	1	100
Grade blood	**N**	219	18	5	28	49	137	0	186	2	239	214	13	3	13	29	169	0	198	3	230
	%	92	8	2	12	21	57	0	78	1	100	93	6	1	6	13	73	0	86	1	100
Grade cardiovascular	**N**	17	221	5	6	4	2	0	6	1	239	29	198	8	11	6	3	1	10	3	230
	%	7	92	2	3	2	1	0	3	0	100	13	86	3	5	3	1	0	4	1	100
Grade coagulation	**N**	11	224	5	3	1	2	0	3	4	239	12	214	7	2	0	3	0	3	4	230
	%	5	94	2	1	0	1	0	1	2	100	5	93	3	1	0	1	0	1	2	100
Grade skin	**N**	37	200	19	17	1	0	0	1	2	239	35	192	20	14	1	0	0	1	3	230
	%	15	84	8	7	0	0	0	0	1	100	15	83	9	6	0	0	0	0	1	100
Grade gastrointestinal	**N**	134	104	58	57	13	6	0	19	1	239	116	111	49	48	17	2	0	19	3	230
	%	56	44	24	24	5	3	0	8	0	100	50	48	21	21	7	1	0	8	1	100
Grade hepatic	**N**	42	196	20	16	4	2	0	6	1	239	39	188	18	16	5	0	0	5	3	230
	%	18	82	8	7	2	1	0	3	0	100	17	82	8	7	2	0	0	2	1	100
Grade infection with febrile neutropenia	**N**	47	191	2	4	30	8	3	41	1	239	47	180	0	8	33	4	2	39	3	230
	%	20	80	1	2	13	3	1	17	0	100	20	78	0	3	14	2	1	17	1	100

		Actual arm of induction																			
		ARM A / R-ICE										ARM B / R-DHAP									
		Grade										Grade									
		All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	5	>=3	NE	Total
Grade infection without febrile neutropenia	**N**	35	203	8	10	17	0	0	17	1	239	44	183	6	18	18	0	2	20	3	230
	%	15	85	3	4	7	0	0	7	0	100	19	80	3	8	8	0	1	9	1	100
Grade metabolic	**N**	39	199	17	12	7	3	0	10	1	239	63	163	23	17	13	10	0	23	4	230
	%	16	83	7	5	3	1	0	4	0	100	27	71	10	7	6	4	0	10	2	100
Grade neurology	**N**	32	206	18	6	5	3	0	8	1	239	33	194	14	10	6	3	0	9	3	230
	%	13	86	8	3	2	1	0	3	0	100	14	84	6	4	3	1	0	4	1	100
Grade pulmonary	**N**	22	216	9	4	5	4	0	9	1	239	34	193	20	8	4	1	1	6	3	230
	%	9	90	4	2	2	2	0	4	0	100	15	84	9	3	2	0	0	3	1	100
Grade renal	**N**	15	223	6	6	2	1	0	3	1	239	72	155	40	18	10	4	0	14	3	230
	%	6	93	3	3	1	0	0	1	0	100	31	67	17	8	4	2	0	6	1	100
Other toxicity	**N**	81	153	30	33	15	3	0	18	5	239	94	130	27	48	17	1	1	19	6	230
	%	34	64	13	14	6	1	0	8	2	100	41	57	12	21	7	0	0	8	3	100

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)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
At least one RBC transfusion				
No	25	10	62	27
Yes	119	50	104	45
Missing	95	40	64	28
At least one platelets transfusion				
No	52	22	32	14
Yes	92	38	134	58
Missing	95	40	64	28
Total	239	100	230	100

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)

		Actual arm of induction																			
		ARM A / R-ICE										ARM B / R-DHAP									
		Grade										Grade									
		All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	5	>=3	NE	Total
Grade Infection	**N**	90	32	9	13	60	6	2	68	1	123	107	25	4	21	77	4	1	82	0	132
	%	73	26	7	11	49	5	2	55	1	100	81	19	3	16	58	3	1	62	0	100
Grade Neurologic	**N**	2	120	1	1	0	0	0	0	1	123	13	118	5	5	1	2	0	3	1	132
	%	2	98	1	1	0	0	0	0	1	100	10	89	4	4	1	2	0	2	1	100
Grade Mucositis	**N**	81	41	21	39	15	6	0	21	1	123	101	31	18	41	31	11	0	42	0	132
	%	66	33	17	32	12	5	0	17	1	100	77	23	14	31	23	8	0	32	0	100
Grade Hepatic	**N**	20	102	12	4	4	0	0	4	1	123	28	103	13	9	6	0	0	6	1	132
	%	16	83	10	3	3	0	0	3	1	100	21	78	10	7	5	0	0	5	1	100
Grade Gastrointestinal	**N**	73	49	23	37	12	1	0	13	1	123	79	53	14	37	24	4	0	28	0	132
	%	59	40	19	30	10	1	0	11	1	100	60	40	11	28	18	3	0	21	0	100
Grade Renal	**N**	9	113	4	4	0	1	0	1	1	123	31	100	16	10	5	0	0	5	1	132
	%	7	92	3	3	0	1	0	1	1	100	23	76	12	8	4	0	0	4	1	100
Grade Cardiovascular	**N**	16	106	6	6	3	1	0	4	1	123	21	110	7	9	4	1	0	5	1	132
	%	13	86	5	5	2	1	0	3	1	100	16	83	5	7	3	1	0	4	1	100
Other toxicity	**N**	27	0	9	13	4	1	0	5	96	123	51	1	13	23	11	4	0	15	80	132
	%	22	0	7	11	3	1	0	4	78	100	39	1	10	17	8	3	0	11	61	100

NE = Not Evaluated

Other toxicities during consolidation are listed in section §6.7.2.

Table 5.2-4 Patients with RBC and platelets transfusions during consolidation (induction safety population)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
At least one RBC transfusion				
No	28	23	10	8
Yes	94	76	120	91
Missing	1	1	2	2
At least one platelets transfusion				
No	7	6	0	0
Yes	115	93	130	98
Missing	1	1	2	2
Total	123	100	132	100

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

		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
Neutrophils > 1 Giga/l (days after transplant)	**N**	117	124
	Mean	24.8	13.7
	Std	75.67	7.92
	Median	11.0	12.0
	Min	0	0
	Max	733	67
Neutrophils > 0.5 Giga/l (days after transplant)	**N**	116	125
	Mean	21.4	11.7
	Std	74.93	6.88
	Median	11.0	11.0
	Min	-22	-30
	Max	733	62
Platelets > 20 Giga/l (days after transplant)	**N**	119	126
	Mean	21.7	13.5
	Std	74.21	7.08
	Median	11.0	12.0
	Min	0	0
	Max	733	47

5.2.2. Description of adverse events

2 AEs were reported for patients who did not receive any study treatement. 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)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Patient with at least one AE				
Yes	154	64	172	75
No	85	36	58	25
Total	239	100	230	100

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)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Total number of AEs	347	100	552	100

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
System Organ Class					
INFECTIONS AND INFESTATIONS	Total number of AEs	135	39	166	30
	Preferred Term				
	INFECTION	27	8	22	4
	NEUTROPENIC INFECTION	11	3	13	2
	NEUTROPENIC SEPSIS	5	1	11	2
	HERPES ZOSTER	6	2	8	1
	PNEUMONIA	6	2	8	1
	CENTRAL LINE INFECTION	7	2	7	1
	LOWER RESPIRATORY TRACT INFECTION	2	1	10	2
	SEPSIS	7	2	4	1
	SEPTIC SHOCK	9	3	1	0
	BRONCHITIS	7	2	1	0
	STAPHYLOCOCCAL SEPSIS	0	0	6	1
	CATHETER RELATED INFECTION	3	1	3	1
	STAPHYLOCOCCAL INFECTION	0	0	5	1
	ORAL HERPES	1	0	3	1
	URINARY TRACT INFECTION	3	1	1	0
	FOLLICULITIS	2	1	2	0
	BRONCHOPNEUMONIA	2	1	2	0
	BACTERIAL SEPSIS	1	0	3	1
	UPPER RESPIRATORY TRACT INFECTION	1	0	3	1
	ESCHERICHIA SEPSIS	1	0	2	0
	SINUSITIS	1	0	2	0
	RESPIRATORY TRACT INFECTION	0	0	3	1
	ESCHERICHIA URINARY TRACT INFECTION	1	0	2	0
	CYTOMEGALOVIRUS INFECTION	0	0	3	1
	CLOSTRIDIUM DIFFICILE COLITIS	1	0	2	0
	CATHETER SEPSIS	1	0	2	0
	CANDIDIASIS	1	0	2	0
	PSEUDOMONAS INFECTION	0	0	2	0
	BRONCHOPULMONARY ASPERGILLOSIS	2	1	0	0
	ESCHERICHIA INFECTION	2	1	0	0
	ENTEROBACTER SEPSIS	0	0	2	0
	NASOPHARYNGITIS	2	1	0	0
	CLOSTRIDIAL INFECTION	0	0	2	0
	KLEBSIELLA INFECTION	2	1	0	0
	INFLUENZA	1	0	1	0
	HERPES VIRUS INFECTION	1	0	1	0
	HAEMOPHILUS INFECTION	0	0	2	0
	DIARRHOEA INFECTIOUS	1	0	1	0
	PSEUDOMONAL SEPSIS	0	0	2	0
	CELLULITIS	2	1	0	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
	CYSTITIS	0	0	2	0
	BRONCHITIS PNEUMOCOCCAL	1	0	0	0
	PERTUSSIS	1	0	0	0
	GASTROENTERITIS	0	0	1	0
	HERPES SIMPLEX	0	0	1	0
	ASPERGILLOSIS	1	0	0	0
	PNEUMONIA PNEUMOCOCCAL	0	0	1	0
	FUNGAL OESOPHAGITIS	0	0	1	0
	STREPTOCOCCAL SEPSIS	1	0	0	0
	VARICELLA	0	0	1	0
	MENINGITIS	1	0	0	0
	HELICOBACTER GASTRITIS	0	0	1	0
	ENTEROCOLITIS INFECTIOUS	0	0	1	0
	PNEUMOCYSTIS JIROVECI PNEUMONIA	0	0	1	0
	WEST NILE VIRAL INFECTION	0	0	1	0
	GASTROENTERITIS VIRAL	0	0	1	0
	PNEUMONIA STREPTOCOCCAL	1	0	0	0
	PNEUMONIA FUNGAL	1	0	0	0
	GASTROINTESTINAL INFECTION	0	0	1	0
	ENTEROCOCCAL INFECTION	0	0	1	0
	BACTERAEMIA	0	0	1	0
	BACTERIAL INFECTION	0	0	1	0
	CLOSTRIDIUM BACTERAEMIA	1	0	0	0
	TONSILLITIS STREPTOCOCCAL	1	0	0	0
	PNEUMONIA BACTERIAL	1	0	0	0
	VIRAL INFECTION	1	0	0	0
	CANDIDA SEPSIS	0	0	1	0
	TOOTH ABSCESS	1	0	0	0
	HEPATITIS C	0	0	1	0
	PNEUMONIA INFLUENZAL	1	0	0	0
	BRONCHIECTASIS	0	0	1	0
	KLEBSIELLA SEPSIS	0	0	1	0
	SKIN INFECTION	0	0	1	0
	HEPATITIS B	1	0	0	0
	GASTROINTESTINAL CANDIDIASIS	1	0	0	0
	LOCALISED INFECTION	1	0	0	0
	SINUSITIS ASPERGILLUS	0	0	1	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total number of AEs	64	18	116	21
	Preferred Term				
	FEBRILE NEUTROPENIA	36	10	60	11
	THROMBOCYTOPENIA	7	2	18	3
	NEUTROPENIA	8	2	14	3
	HAEMATOTOXICITY	4	1	5	1
	LEUKOPENIA	1	0	7	1
	FEBRILE BONE MARROW APLASIA	1	0	5	1
	ANAEMIA	0	0	4	1
	BICYTOPENIA	3	1	1	0
	LYMPHOPENIA	3	1	0	0
	PANCYTOPENIA	1	0	1	0
	THROMBOTIC THROMBOCYTOPENIC PURPURA	0	0	1	0
GASTROINTESTINAL DISORDERS	Total number of AEs	33	10	65	12
	Preferred Term				
	VOMITING	7	2	16	3
	DIARRHOEA	7	2	16	3
	NAUSEA	1	0	9	2
	GASTROINTESTINAL HAEMORRHAGE	2	1	4	1
	STOMATITIS	2	1	3	1
	GASTROINTESTINAL DISORDER	2	1	3	1
	ABDOMINAL PAIN	2	1	2	0
	SMALL INTESTINAL OBSTRUCTION	0	0	2	0
	CONSTIPATION	0	0	2	0
	HAEMATEMESIS	0	0	1	0
	GINGIVITIS	1	0	0	0
	DUODENAL ULCER	1	0	0	0
	OESOPHAGITIS	1	0	0	0
	GASTROINTESTINAL TOXICITY	0	0	1	0
	OESOPHAGEAL HAEMORRHAGE	1	0	0	0
	GASTROINTESTINAL ULCER HAEMORRHAGE	1	0	0	0
	INTESTINAL PERFORATION	0	0	1	0
	ENTEROCOLITIS HAEMORRHAGIC	0	0	1	0
	ILEUS	0	0	1	0
	FAECALOMA	0	0	1	0
	INTESTINAL OBSTRUCTION	1	0	0	0
	LARGE INTESTINE PERFORATION	1	0	0	0
	DENTAL CARIES	1	0	0	0
	NEUTROPENIC COLITIS	0	0	1	0
	GASTROINTESTINAL INFLAMMATION	1	0	0	0
	GINGIVAL PAIN	1	0	0	0
	MELAENA	0	0	1	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Total number of AEs	40	12	51	9
	Preferred Term				
	MUCOSAL INFLAMMATION	17	5	35	6
	PYREXIA	13	4	10	2
	FATIGUE	4	1	1	0
	ASTHENIA	1	0	1	0
	HYPERTHERMIA	2	1	0	0
	DISEASE PROGRESSION	0	0	2	0
	INFLAMMATION	0	0	1	0
	GENERAL PHYSICAL HEALTH DETERIORATION	1	0	0	0
	CATHETER SITE HAEMORRHAGE	0	0	1	0
	OEDEMA PERIPHERAL	1	0	0	0
	INJECTION SITE REACTION	1	0	0	0
METABOLISM AND NUTRITION DISORDERS	Total number of AEs	11	3	40	7
	Preferred Term				
	HYPOKALAEMIA	4	1	8	1
	HYPERGLYCAEMIA	0	0	9	2
	HYPONATRAEMIA	1	0	4	1
	METABOLIC DISORDER	1	0	4	1
	DEHYDRATION	2	1	3	1
	ANOREXIA	0	0	4	1
	HYPERURICAEMIA	0	0	3	1
	HYPOPHOSPHATAEMIA	1	0	1	0
	HYPOMAGNESAEMIA	0	0	2	0
	HYPOCALCAEMIA	0	0	1	0
	HYPERKALAEMIA	1	0	0	0
	FOOD INTOLERANCE	1	0	0	0
	HYPERMAGNESAEMIA	0	0	1	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
INVESTIGATIONS	Total number of AEs	12	3	17	3
	Preferred Term				
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	2	1	4	1
	BLOOD CREATININE INCREASED	0	0	3	1
	TRANSAMINASES INCREASED	0	0	2	0
	LIVER FUNCTION TEST ABNORMAL	2	1	0	0
	C-REACTIVE PROTEIN INCREASED	1	0	1	0
	INTERNATIONAL NORMALISED RATIO	2	1	0	0
	BLOOD ALKALINE PHOSPHATASE INCREASED	1	0	0	0
	ALANINE AMINOTRANSFERASE INCREASED	0	0	1	0
	CYTOMEGALOVIRUS TEST POSITIVE	1	0	0	0
	BLOOD FIBRINOGEN DECREASED	0	0	1	0
	RENAL FUNCTION TEST ABNORMAL	0	0	1	0
	GLOMERULAR FILTRATION RATE	0	0	1	0
	BLOOD PHOSPHORUS DECREASED	0	0	1	0
	BLOOD PHOSPHORUS ABNORMAL	1	0	0	0
	HEPATIC ENZYME INCREASED	0	0	1	0
	BLOOD LACTATE DEHYDROGENASE INCREASED	0	0	1	0
	PLATELET COUNT DECREASED	1	0	0	0
	GAMMA-GLUTAMYLTRANSFERASE ABNORMAL	1	0	0	0
NERVOUS SYSTEM DISORDERS	Total number of AEs	7	2	19	3
	Preferred Term				
	CEREBROVASCULAR ACCIDENT	1	0	3	1
	SYNCOPE	2	1	1	0
	SYNCOPE VASOVAGAL	0	0	2	0
	EPILEPSY	0	0	2	0
	PARESIS	1	0	1	0
	LEUKOENCEPHALOPATHY	1	0	1	0
	HEADACHE	0	0	2	0
	LOSS OF CONSCIOUSNESS	0	0	1	0
	APHASIA	0	0	1	0
	CEREBRAL ISCHAEMIA	0	0	1	0
	TRANSIENT ISCHAEMIC ATTACK	1	0	0	0
	NEUROTOXICITY	0	0	1	0
	EMBOLIC CEREBRAL INFARCTION	0	0	1	0
	TOXIC INDUCED ENCEPHALOPATHY	1	0	0	0
	PRESYNCOPE	0	0	1	0
	HYPOAESTHESIA	0	0	1	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
RENAL AND URINARY DISORDERS	Total number of AEs	2	1	21	4
	Preferred Term				
	RENAL FAILURE ACUTE	1	0	9	2
	RENAL FAILURE	0	0	9	2
	CYSTITIS HAEMORRHAGIC	0	0	1	0
	NEPHROPATHY TOXIC	0	0	1	0
	RENAL TUBULAR ACIDOSIS	0	0	1	0
	CALCULUS URINARY	1	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Total number of AEs	10	3	11	2
	Preferred Term				
	PULMONARY EMBOLISM	4	1	2	0
	DYSPNOEA	1	0	2	0
	BRONCHOPNEUMOPATHY	1	0	1	0
	LUNG DISORDER	2	1	0	0
	RESPIRATORY FAILURE	0	0	2	0
	EPISTAXIS	1	0	0	0
	INTERSTITIAL LUNG DISEASE	1	0	0	0
	LUNG INFILTRATION	0	0	1	0
	ACUTE PULMONARY OEDEMA	0	0	1	0
	RESPIRATORY DISORDER	0	0	1	0
	COUGH	0	0	1	0
CARDIAC DISORDERS	Total number of AEs	7	2	6	1
	Preferred Term				
	CARDIAC FAILURE	1	0	3	1
	ATRIAL FIBRILLATION	1	0	2	0
	CARDIAC ARREST	1	0	1	0
	MYOCARDIAL INFARCTION	1	0	0	0
	VENTRICULAR FIBRILLATION	1	0	0	0
	MYOCARDITIS	1	0	0	0
	MYOCARDIAL ISCHAEMIA	1	0	0	0
VASCULAR DISORDERS	Total number of AEs	6	2	7	1
	Preferred Term				
	THROMBOSIS	1	0	2	0
	JUGULAR VEIN THROMBOSIS	1	0	1	0
	HYPOTENSION	1	0	1	0
	HYPERTENSION	0	0	2	0
	CAPILLARY LEAK SYNDROME	1	0	0	0
	CIRCULATORY COLLAPSE	0	0	1	0
	VENOOCCLUSIVE DISEASE	1	0	0	0
	DEEP VEIN THROMBOSIS	1	0	0	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Total number of AEs	4	1	7	1
	Preferred Term				
	TUMOUR LYSIS SYNDROME	0	0	4	1
	OESOPHAGEAL CARCINOMA	1	0	0	0
	HEPATIC NEOPLASM MALIGNANT	0	0	1	0
	MALIGNANT MELANOMA	0	0	1	0
	ACUTE LEUKAEMIA	1	0	0	0
	HODGKIN'S DISEASE	1	0	0	0
	TRANSITIONAL CELL CARCINOMA	1	0	0	0
	MYELODYSPLASTIC SYNDROME	0	0	1	0
IMMUNE SYSTEM DISORDERS	Total number of AEs	4	1	5	1
	Preferred Term				
	HYPOGAMMAGLOBULINAEMIA	1	0	3	1
	DRUG HYPERSENSITIVITY	2	1	2	0
	ALLERGIC OEDEMA	1	0	0	0
HEPATOBILIARY DISORDERS	Total number of AEs	3	1	5	1
	Preferred Term				
	HEPATITIS	2	1	0	0
	CHOLESTASIS	0	0	2	0
	LIVER DISORDER	0	0	1	0
	BILE DUCT STONE	0	0	1	0
	HEPATOTOXICITY	0	0	1	0
	CHOLECYSTITIS ACUTE	1	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Total number of AEs	2	1	4	1
	Preferred Term				
	BONE PAIN	0	0	3	1
	BACK PAIN	0	0	1	0
	MUSCULOSKELETAL PAIN	1	0	0	0
	RHABDOMYOLYSIS	1	0	0	0
EAR AND LABYRINTH DISORDERS	Total number of AEs	2	1	4	1
	Preferred Term				
	DEAFNESS	1	0	1	0
	TINNITUS	0	0	2	0
	HEARING IMPAIRED	0	0	1	0
	DEAFNESS BILATERAL	1	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Total number of AEs	2	1	2	0
	Preferred Term				
	DRUG TOXICITY	0	0	1	0
	THROMBOSIS IN DEVICE	0	0	1	0
	SUBDURAL HAEMATOMA	1	0	0	0
	POST LUMBAR PUNCTURE SYNDROME	1	0	0	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
PSYCHIATRIC DISORDERS	**Total number of AEs**	1	0	3	1
	Preferred Term				
	CONFUSIONAL STATE	1	0	2	0
	DEPRESSION	0	0	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**Total number of AEs**	2	1	1	0
	Preferred Term				
	PURPURA	2	1	0	0
	SKIN REACTION	0	0	1	0
SOCIAL CIRCUMSTANCES	**Total number of AEs**	0	0	1	0
	Preferred Term				
	SOCIAL STAY HOSPITALISATION	0	0	1	0
SURGICAL AND MEDICAL PROCEDURES	**Total number of AEs**	0	0	1	0
	Preferred Term				
	HEPATECTOMY	0	0	1	0

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)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Non hematological toxicity grade				
NORMAL	3	1	9	2
MILD	11	3	18	3
MODERATE	62	18	99	18
SEVERE	196	56	313	57
LIFE THREATENING	36	10	61	11
DEATH	6	2	10	2
UNKNOWN	6	2	10	2
Missing	27	8	32	6
Hematological toxicity grade				
NORMAL	20	6	30	5
MILD	35	10	31	6
MODERATE	25	7	48	9
SEVERE	44	13	85	15
LIFE THREATENING	143	41	222	40
DEATH	3	1	5	1
UNKNOWN	13	4	12	2
Missing	64	18	119	22
Relation with study drugs				
No	174	50	264	48
Yes	172	50	286	52
Missing	1	0	2	0
Action taken with study drug				
No	305	88	475	86
Yes	41	12	73	13
Missing	1	0	4	1
Antibiotherapy				
No	132	38	250	45
Yes	199	57	272	49
Not Done	1	0	1	0
Missing	15	4	29	5
AE outcome				
RECOVERED	313	90	483	88
RECOVERED WITH SEQUELAE	11	3	30	5
ONGOING	2	1	12	2
FATAL	19	5	26	5
Missing	2	1	1	0
Total	347	100	552	100

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

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Specify action taken with study drug				
PERMANENT TREATMENT DISCONTINUATION	13	32	23	32
TEMPORARY TREATMENT DISCONTINUATION	23	56	31	42
DOSE REGIMEN ADAPTATION	5	12	19	26
Total	41	100	73	100

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)

	Actual arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Patients with corrective treatment				
No	23	15	31	18
Yes	131	85	141	82
Total	154	100	172	100

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)

	Actual arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
AEs with corrective treatment				
Yes	285	82	469	85
No	62	18	83	15
Total	347	100	552	100

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 treatement. 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 5.3-1 Patients with SAE (induction safety population)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Patient with at least one SAE				
Yes	66	28	84	37
No	173	72	146	63
Total	239	100	230	100

Table 5.3-2 Summary of serious adverse events by frequency of SOC and PT (induction safety population)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Total number of SAEs	106	100	151	100

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
System Organ Class					
INFECTIONS AND INFESTATIONS	Total number of SAEs	46	43	55	36
	Preferred Term				
	NEUTROPENIC SEPSIS	5	5	6	4
	PNEUMONIA	4	4	6	4
	SEPTIC SHOCK	7	7	1	1
	LOWER RESPIRATORY TRACT INFECTION	1	1	6	4
	SEPSIS	3	3	2	1
	NEUTROPENIC INFECTION	2	2	3	2
	HERPES ZOSTER	3	3	1	1
	STAPHYLOCOCCAL SEPSIS	0	0	3	2
	INFECTION	3	3	0	0
	BACTERIAL SEPSIS	1	1	2	1
	CENTRAL LINE INFECTION	3	3	0	0
	PSEUDOMONAS INFECTION	0	0	2	1
	BRONCHOPULMONARY ASPERGILLOSIS	2	2	0	0
	BRONCHOPNEUMONIA	1	1	1	1
	CELLULITIS	2	2	0	0
	CLOSTRIDIUM DIFFICILE COLITIS	0	0	2	1
	CYTOMEGALOVIRUS INFECTION	0	0	2	1
	BRONCHITIS PNEUMOCOCCAL	1	1	0	0
	ESCHERICHIA INFECTION	1	1	0	0
	ENTEROBACTER SEPSIS	0	0	1	1
	CLOSTRIDIAL INFECTION	0	0	1	1
	ASPERGILLOSIS	1	1	0	0
	HAEMOPHILUS INFECTION	0	0	1	1
	PNEUMONIA PNEUMOCOCCAL	0	0	1	1
	STREPTOCOCCAL SEPSIS	1	1	0	0
	VARICELLA	0	0	1	1
	URINARY TRACT INFECTION	0	0	1	1
	KLEBSIELLA INFECTION	1	1	0	0
	PNEUMOCYSTIS JIROVECI PNEUMONIA	0	0	1	1
	CATHETER RELATED INFECTION	0	0	1	1
	PNEUMONIA STREPTOCOCCAL	1	1	0	0
	DIARRHOEA INFECTIOUS	0	0	1	1
	PSEUDOMONAL SEPSIS	0	0	1	1
	BACTERAEMIA	0	0	1	1
	CATHETER SEPSIS	0	0	1	1
	PNEUMONIA BACTERIAL	1	1	0	0
	CANDIDA SEPSIS	0	0	1	1
	TOOTH ABSCESS	1	1	0	0
	UPPER RESPIRATORY TRACT INFECTION	0	0	1	1
	RESPIRATORY TRACT INFECTION	0	0	1	1

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
	HEPATITIS C	0	0	1	1
	KLEBSIELLA SEPSIS	0	0	1	1
	GASTROINTESTINAL CANDIDIASIS	1	1	0	0
	SINUSITIS ASPERGILLUS	0	0	1	1
GASTROINTESTINAL DISORDERS	Total number of SAEs	10	9	19	13
	Preferred Term				
	GASTROINTESTINAL HAEMORRHAGE	2	2	4	3
	VOMITING	0	0	5	3
	DIARRHOEA	3	3	2	1
	SMALL INTESTINAL OBSTRUCTION	0	0	2	1
	OESOPHAGEAL HAEMORRHAGE	1	1	0	0
	NAUSEA	0	0	1	1
	ABDOMINAL PAIN	0	0	1	1
	GASTROINTESTINAL ULCER HAEMORRHAGE	1	1	0	0
	GASTROINTESTINAL DISORDER	0	0	1	1
	INTESTINAL PERFORATION	0	0	1	1
	ENTEROCOLITIS HAEMORRHAGIC	0	0	1	1
	FAECALOMA	0	0	1	1
	INTESTINAL OBSTRUCTION	1	1	0	0
	LARGE INTESTINE PERFORATION	1	1	0	0
	DENTAL CARIES	1	1	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total number of SAEs	11	10	16	11
	Preferred Term				
	FEBRILE NEUTROPENIA	5	5	8	5
	NEUTROPENIA	2	2	3	2
	BICYTOPENIA	2	2	1	1
	THROMBOCYTOPENIA	1	1	2	1
	HAEMATOTOXICITY	0	0	1	1
	ANAEMIA	0	0	1	1
	PANCYTOPENIA	1	1	0	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
NERVOUS SYSTEM DISORDERS	Total number of SAEs	4	4	13	9
	Preferred Term				
	CEREBROVASCULAR ACCIDENT	1	1	3	2
	SYNCOPE VASOVAGAL	0	0	2	1
	LEUKOENCEPHALOPATHY	1	1	1	1
	LOSS OF CONSCIOUSNESS	0	0	1	1
	SYNCOPE	1	1	0	0
	APHASIA	0	0	1	1
	EPILEPSY	0	0	1	1
	PARESIS	0	0	1	1
	NEUROTOXICITY	0	0	1	1
	EMBOLIC CEREBRAL INFARCTION	0	0	1	1
	TOXIC INDUCED ENCEPHALOPATHY	1	1	0	0
	HYPOAESTHESIA	0	0	1	1
RENAL AND URINARY DISORDERS	Total number of SAEs	2	2	12	8
	Preferred Term				
	RENAL FAILURE ACUTE	1	1	8	5
	RENAL FAILURE	0	0	2	1
	NEPHROPATHY TOXIC	0	0	1	1
	RENAL TUBULAR ACIDOSIS	0	0	1	1
	CALCULUS URINARY	1	1	0	0
CARDIAC DISORDERS	Total number of SAEs	6	6	5	3
	Preferred Term				
	CARDIAC FAILURE	1	1	3	2
	ATRIAL FIBRILLATION	1	1	1	1
	CARDIAC ARREST	1	1	1	1
	MYOCARDIAL INFARCTION	1	1	0	0
	MYOCARDITIS	1	1	0	0
	MYOCARDIAL ISCHAEMIA	1	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Total number of SAEs	6	6	5	3
	Preferred Term				
	PULMONARY EMBOLISM	3	3	2	1
	RESPIRATORY FAILURE	0	0	2	1
	INTERSTITIAL LUNG DISEASE	1	1	0	0
	LUNG DISORDER	1	1	0	0
	LUNG INFILTRATION	0	0	1	1
	DYSPNOEA	1	1	0	0

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Total number of SAEs	5	5	6	4
	Preferred Term				
	PYREXIA	3	3	1	1
	MUCOSAL INFLAMMATION	0	0	3	2
	HYPERTHERMIA	1	1	0	0
	DISEASE PROGRESSION	0	0	1	1
	CATHETER SITE HAEMORRHAGE	0	0	1	1
	FATIGUE	1	1	0	0
METABOLISM AND NUTRITION DISORDERS	Total number of SAEs	2	2	6	4
	Preferred Term				
	DEHYDRATION	2	2	3	2
	HYPERGLYCAEMIA	0	0	2	1
	HYPONATRAEMIA	0	0	1	1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Total number of SAEs	4	4	3	2
	Preferred Term				
	OESOPHAGEAL CARCINOMA	1	1	0	0
	HEPATIC NEOPLASM MALIGNANT	0	0	1	1
	MALIGNANT MELANOMA	0	0	1	1
	ACUTE LEUKAEMIA	1	1	0	0
	HODGKIN'S DISEASE	1	1	0	0
	TRANSITIONAL CELL CARCINOMA	1	1	0	0
	MYELODYSPLASTIC SYNDROME	0	0	1	1
VASCULAR DISORDERS	Total number of SAEs	2	2	2	1
	Preferred Term				
	THROMBOSIS	0	0	1	1
	CIRCULATORY COLLAPSE	0	0	1	1
	HYPOTENSION	1	1	0	0
	VENOOCCLUSIVE DISEASE	1	1	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Total number of SAEs	1	1	2	1
	Preferred Term				
	BACK PAIN	0	0	1	1
	RHABDOMYOLYSIS	1	1	0	0
	BONE PAIN	0	0	1	1
HEPATOBILIARY DISORDERS	Total number of SAEs	3	3	0	0
	Preferred Term				
	HEPATITIS	2	2	0	0
	CHOLECYSTITIS ACUTE	1	1	0	0
EAR AND LABYRINTH DISORDERS	Total number of SAEs	1	1	1	1
	Preferred Term				
	DEAFNESS	1	1	0	0
	TINNITUS	0	0	1	1

		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
PSYCHIATRIC DISORDERS	Total number of SAEs	1	1	1	1
	Preferred Term				
	CONFUSIONAL STATE	1	1	0	0
	DEPRESSION	0	0	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Total number of SAEs	2	2	0	0
	Preferred Term				
	SUBDURAL HAEMATOMA	1	1	0	0
	POST LUMBAR PUNCTURE SYNDROME	1	1	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Total number of SAEs	0	0	1	1
	Preferred Term				
	SKIN REACTION	0	0	1	1
IMMUNE SYSTEM DISORDERS	Total number of SAEs	0	0	1	1
	Preferred Term				
	DRUG HYPERSENSITIVITY	0	0	1	1
SOCIAL CIRCUMSTANCES	Total number of SAEs	0	0	1	1
	Preferred Term				
	SOCIAL STAY HOSPITALISATION	0	0	1	1
INVESTIGATIONS	Total number of SAEs	0	0	1	1
	Preferred Term				
	BLOOD CREATININE INCREASED	0	0	1	1
SURGICAL AND MEDICAL PROCEDURES	Total number of SAEs	0	0	1	1
	Preferred Term				
	HEPATECTOMY	0	0	1	1

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)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Resulting of death				
Missing	0	0	4	3
No	97	92	132	87
Yes	9	8	15	10
Congenital anomaly				
Missing	0	0	4	3
No	106	100	147	97
Life threatening				
Missing	0	0	4	3
No	87	82	124	82
Yes	19	18	23	15
Medically sign. event				
Missing	0	0	4	3
No	95	90	126	83
Yes	11	10	21	14
Persistent				
Missing	0	0	4	3
No	97	92	143	95
Yes	9	8	4	3
Hospitalization				
Missing	0	0	4	3
No	17	16	18	12
Yes	89	84	129	85
Total	106	100	151	100

Table 5.3-4 Characteristics of SAEs (induction safety population)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Non hematological toxicity grade				
MILD	3	3	8	5
MODERATE	9	8	18	12
SEVERE	52	49	76	50
LIFE THREATENING	26	25	29	19
DEATH	6	6	10	7
UNKNOWN	2	2	3	2
Missing	8	8	7	5

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Hematological toxicity grade				
NORMAL	13	12	10	7
MILD	15	14	9	6
MODERATE	7	7	19	13
SEVERE	9	8	27	18
LIFE THREATENING	35	33	47	31
DEATH	3	3	5	3
UNKNOWN	5	5	3	2
Missing	19	18	31	21
Relation with study drugs				
No	51	48	68	45
Yes	55	52	82	54
Missing	0	0	1	1
Action taken with study drug				
No	76	72	110	73
Yes	29	27	38	25
Missing	1	1	3	2
Antibiotherapy				
No	39	37	60	40
Yes	60	57	84	56
Missing	7	7	7	5
Corrective treatment				
No	18	17	15	10
Yes	88	83	136	90
AE outcome				
RECOVERED	86	81	111	74
RECOVERED WITH SEQUELAE	6	6	17	11
ONGOING	2	2	2	1
FATAL	12	11	21	14
Total	106	100	151	100

Table 5.3-5 Action taken with study drugs due to SAE (induction safety population)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Specify action taken with study drug				
PERMANENT TREATMENT DISCONTINUATION	11	38	20	53
TEMPORARY TREATMENT DISCONTINUATION	18	62	13	34
DOSE REGIMEN ADAPTATION	0	0	5	13
Total	29	100	38	100

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)

	Actual arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Patients with corrective treatment				
No	11	17	9	11
Yes	55	83	75	89
Total	66	100	84	100

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)

	Actual arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
AEs with corrective treatment				
Yes	88	83	136	90
No	18	17	15	10
Total	106	100	151	100

5.3.2. Deaths

4 deaths were reported for patients who did not receive any study treatement. 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)

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Deaths				
Yes	126	53	112	49
No	113	47	118	51
Total	239	100	230	100

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

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Reason for death				
LYMPHOMA	98	78	81	72
TOXICITY OF STUDY TREATMENT	7	6	9	8
CONCURRENT ILLNESS	2	2	2	2
OTHER CANCER	3	2	3	3
TOXICITY OF ADDITIONNAL TREATMENT	7	6	15	13
OTHER REASON	6	5	2	2
UNKNOWN	3	2	0	0
Total	126	100	112	100

See details of deaths in the following list:

Listing 5.3-1 Deaths (induction safety population)

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003101021008	ARM A / R-ICE	12/05/2004	NOT APPLICABLE	-	-	FEMALE	20	22/10/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003101021027	ARM A / R-ICE	01/06/2005	NOT APPLICABLE	-	-	MALE	33	26/10/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101021605	ARM A / R-ICE	04/11/2003	OBSERVATION	04/02/2004	03/02/2004	MALE	58	20/06/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101031001	ARM A / R-ICE	24/07/2003	RITUXIMAB	21/10/2003	22/10/2003	MALE	65	06/05/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003101051004	ARM A / R-ICE	26/11/2003	NOT APPLICABLE	-	-	FEMALE	49	04/06/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003101051075	ARM A / R-ICE	19/02/2008	NOT APPLICABLE	-	-	MALE	63	21/09/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101051603	ARM A / R-ICE	27/10/2003	NOT APPLICABLE	-	-	FEMALE	56	09/02/2005	OTHER CANCER	MAIL PROVIDED : OESOPHAGUS CARCINOMA	COMPLETE RESPONSE
5003101071020	ARM A / R-ICE	15/03/2005	NOT APPLICABLE	-	-	FEMALE	63	08/01/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101071059	ARM A / R-ICE	22/12/2006	NOT APPLICABLE	-	-	FEMALE	59	16/04/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101091602	ARM A / R-ICE	16/10/2003	NOT APPLICABLE	-	-	MALE	45	27/10/2005	LYMPHOMA	MAJOR RESPIRATORY DISTRESS	PROGRESSIVE DISEASE
5003101131030	ARM A / R-ICE	16/06/2005	NOT APPLICABLE	-	-	FEMALE	48	16/08/2005	TOXICITY OF STUDY TREATMENT		NOT EVALUATED
5003101131062	ARM A / R-ICE	20/02/2007	NOT APPLICABLE	-	-	FEMALE	30	02/06/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101131409	ARM A / R-ICE	07/03/2006	RITUXIMAB	16/06/2006	14/06/2006	MALE	55	09/06/2007	UNKNOWN		NOT EVALUATED
5003101141065	ARM A / R-ICE	24/04/2007	NOT APPLICABLE	-	-	MALE	40	20/09/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101141406	ARM A / R-ICE	13/09/2005	NOT APPLICABLE	-	-	FEMALE	48	06/12/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101161407	ARM A / R-ICE	25/11/2005	OBSERVATION	17/03/2006	28/02/2006	MALE	60	20/06/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101211023	ARM A / R-ICE	25/04/2005	NOT APPLICABLE	-	-	MALE	29	03/10/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003101221043	ARM A / R-ICE	27/02/2006	NOT APPLICABLE	-	-	MALE	51	17/06/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101281017	ARM A / R-ICE	18/11/2004	NOT APPLICABLE	-	-	MALE	60	12/01/2005	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003101281033	ARM A / R-ICE	15/07/2005	RITUXIMAB	15/11/2005	04/10/2005	MALE	61	16/02/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101281208	ARM A / R-ICE	09/02/2006	NOT APPLICABLE	-	-	FEMALE	56	19/09/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101331077	ARM A / R-ICE	18/03/2008	NOT APPLICABLE	-	-	MALE	38	24/01/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003101351040	ARM A / R-ICE	21/12/2005	NOT APPLICABLE	-	-	MALE	47	30/06/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101391039	ARM A / R-ICE	02/11/2005	NOT APPLICABLE	-	-	MALE	43	13/08/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101391201	ARM A / R-ICE	24/09/2003	NOT APPLICABLE	-	-	MALE	35	08/12/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003101431622	ARM A / R-ICE	26/04/2005	RITUXIMAB	13/07/2005	18/07/2005	MALE	49	18/10/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101441036	ARM A / R-ICE	02/08/2005	NOT APPLICABLE	-	-	MALE	57	10/05/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101441074	ARM A / R-ICE	12/11/2007	NOT APPLICABLE	-	-	MALE	57	28/01/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003101491042	ARM A / R-ICE	14/02/2006	RITUXIMAB	09/05/2006	18/05/2006	MALE	46	05/02/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101601404	ARM A / R-ICE	04/07/2005	NOT APPLICABLE	-	-	FEMALE	65	05/09/2005	TOXICITY OF STUDY TREATMENT	PROBABLE INFECTION, PATIENT REFUSED HOSPITALIZATION	NOT EVALUATED
5003101621026	ARM A / R-ICE	31/05/2005	OBSERVATION	14/09/2005	06/09/2005	MALE	64	09/02/2009	OTHER REASON	MESENTERIC INFARCTUS	COMPLETE RESPONSE
5003101621609	ARM A / R-ICE	16/02/2004	OBSERVATION	19/05/2004	10/05/2004	FEMALE	64	26/03/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101621615	ARM A / R-ICE	10/06/2004	OBSERVATION	16/09/2004	21/09/2004	MALE	64	09/03/2006	LYMPHOMA	RELAPSE N° 3 : 3/02/2006	PROGRESSIVE DISEASE
5003101641618	ARM A / R-ICE	19/08/2004	OBSERVATION	19/11/2004	16/11/2004	FEMALE	49	29/11/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003102161078	ARM A / R-ICE	21/05/2008	NOT APPLICABLE	-	-	MALE	46	06/08/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003102161413	ARM A / R-ICE	18/10/2006	NOT APPLICABLE	-	-	MALE	48	05/11/2006	TOXICITY OF STUDY TREATMENT		NOT EVALUATED
5003102321024	ARM A / R-ICE	29/04/2005	NOT APPLICABLE	-	-	FEMALE	62	31/08/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003102341049	ARM A / R-ICE	11/07/2006	NOT APPLICABLE	-	-	MALE	33	19/09/2007	OTHER REASON	AUTOLYSIS	NOT EVALUATED
5003102341416	ARM A / R-ICE	20/12/2006	NOT APPLICABLE	-	-	MALE	59	25/02/2008	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003102491619	ARM A / R-ICE	28/09/2004	RITUXIMAB	27/12/2004	03/01/2005	MALE	60	04/11/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003102541052	ARM A / R-ICE	26/07/2006	OBSERVATION	12/10/2006	05/11/2006	MALE	29	07/05/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003601201041	ARM A / R-ICE	28/11/2006	NOT APPLICABLE	-	-	MALE	31	16/07/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003601401002	ARM A / R-ICE	15/04/2004	RITUXIMAB	22/07/2004	06/07/2004	MALE	56	09/07/2006	CONCURRENT ILLNESS	ACUTE NON LYMPHOCYTIC LEUKEMIA	UNCONFIRMED COMPLETE RESPONSE
5003601401003	ARM A / R-ICE	15/06/2005	NOT APPLICABLE	-	-	FEMALE	54	11/10/2006	LYMPHOMA		NOT EVALUATED
5003601401006	ARM A / R-ICE	18/04/2007	OBSERVATION	11/07/2007	03/07/2007	FEMALE	62	14/09/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003601401401	ARM A / R-ICE	04/03/2004	NOT APPLICABLE	-	-	FEMALE	62	18/07/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003601401602	ARM A / R-ICE	04/08/2004	RITUXIMAB	27/10/2004	01/11/2004	MALE	41	06/08/2006	OTHER REASON	PERIMYOCARDITE	COMPLETE RESPONSE
5003601401603	ARM A / R-ICE	27/10/2005	OBSERVATION	12/01/2006	05/01/2006	MALE	59	26/08/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003601601002	ARM A / R-ICE	02/01/2007	NOT APPLICABLE	-	-	MALE	46	07/06/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003601601003	ARM A / R-ICE	07/03/2007	OBSERVATION	08/06/2007	29/05/2007	MALE	27	23/04/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003601601005	ARM A / R-ICE	15/01/2008	OBSERVATION	16/04/2008	08/04/2008	FEMALE	53	15/10/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003601881401	ARM A / R-ICE	19/07/2006	RITUXIMAB	07/11/2006	10/11/2006	MALE	63	06/02/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003602301001	ARM A / R-ICE	12/02/2004	NOT APPLICABLE	-	-	FEMALE	55	29/08/2004	OTHER REASON	INTERSTITIAL PNEUMONIA	PROGRESSIVE DISEASE
5003602401005	ARM A / R-ICE	29/11/2006	NOT APPLICABLE	-	-	MALE	61	04/04/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003602801001	ARM A / R-ICE	01/12/2003	NOT APPLICABLE	-	-	MALE	60	27/12/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003602801011	ARM A / R-ICE	14/09/2006	OBSERVATION	22/12/2006	06/12/2006	MALE	48	09/08/2007	TOXICITY OF ADDITIONNAL TREATMENT	SEPTIC SHOCK AFTER SALVAGE CHEMOTHERAPY	PROGRESSIVE DISEASE
5003602801403	ARM A / R-ICE	20/03/2007	RITUXIMAB	31/05/2007	20/06/2007	MALE	64	29/05/2009	TOXICITY OF ADDITIONNAL TREATMENT	BILATERAL PNEUMONIA, SEPTIC SHOCK	PARTIAL RESPONSE
5003602801605	ARM A / R-ICE	20/07/2006	RITUXIMAB	08/11/2006	12/10/2006	FEMALE	58	26/12/2009	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003602901002	ARM A / R-ICE	24/01/2005	NOT APPLICABLE	-	-	MALE	64	04/04/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003602901201	ARM A / R-ICE	03/03/2004	NOT APPLICABLE	-	-	FEMALE	31	08/06/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003602901401	ARM A / R-ICE	12/11/2004	NOT APPLICABLE	-	-	MALE	60	11/05/2006	LYMPHOMA		NOT EVALUATED
5003602901601	ARM A / R-ICE	08/09/2004	OBSERVATION	27/12/2004	21/03/2005	MALE	63	04/09/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003603201038	ARM A / R-ICE	09/10/2006	OBSERVATION	17/01/2007	29/12/2006	FEMALE	50	20/09/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003603201213	ARM A / R-ICE	23/02/2007	OBSERVATION	29/05/2007	23/05/2007	MALE	54	28/03/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003603201628	ARM A / R-ICE	18/05/2007	RITUXIMAB	17/08/2007	22/08/2007	MALE	48	20/01/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003603701004	ARM A / R-ICE	12/08/2005	NOT APPLICABLE	-	-	MALE	64	01/09/2005	TOXICITY OF STUDY TREATMENT	PULMONAL INFECT STARTED IN AGRANULOCYTOSIS, TRANSFER TO INTENSIV CARE UNIT, ARTIFICIAL RESPIRATION, DEVELOPMENT OF A SEPTIC SHOCK	NOT EVALUATED
5003603701006	ARM A / R-ICE	14/10/2005	OBSERVATION	30/01/2006	09/01/2006	MALE	54	12/05/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003603701010	ARM A / R-ICE	03/07/2006	NOT APPLICABLE	-	-	MALE	54	29/11/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003603801002	ARM A / R-ICE	24/09/2004	OBSERVATION	22/12/2004	09/12/2004	FEMALE	49	21/03/2010	LYMPHOMA	DIED AFTER 1 CYCLE OF SALVAGE CHEMO FOR GENERALISED RELAPSE. IMMEDIATE REASON FOR DEATH SEPIC SHOCK	NOT EVALUATED
5003603801015	ARM A / R-ICE	11/04/2007	NOT APPLICABLE	-	-	FEMALE	20	25/10/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003603801202	ARM A / R-ICE	18/11/2004	NOT APPLICABLE	-	-	MALE	60	17/11/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003603801203	ARM A / R-ICE	01/12/2004	RITUXIMAB	14/03/2005	01/03/2005	FEMALE	53	25/10/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003603801406	ARM A / R-ICE	15/02/2008	RITUXIMAB	15/05/2008	13/05/2008	MALE	31	01/03/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003603801602	ARM A / R-ICE	12/10/2004	OBSERVATION	01/02/2005	18/01/2005	MALE	54	14/08/2007	TOXICITY OF ADDITIONNAL TREATMENT	GVHD + INFECTION POST ALLOGENEIC PBCT FROM SIBLING DONOR	COMPLETE RESPONSE
5003603801608	ARM A / R-ICE	09/04/2008	OBSERVATION	03/07/2008	01/07/2008	MALE	26	03/06/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003604201204	ARM A / R-ICE	08/07/2004	NOT APPLICABLE	-	-	MALE	60	16/02/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003604801014	ARM A / R-ICE	15/02/2007	NOT APPLICABLE	-	-	MALE	62	09/07/2007	LYMPHOMA		NOT EVALUATED

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003604801205	ARM A / R-ICE	29/03/2006	RITUXIMAB	11/07/2006	21/06/2006	MALE	34	19/01/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003604901005	ARM A / R-ICE	05/01/2006	RITUXIMAB	09/05/2006	24/04/2006	FEMALE	62	11/01/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003605201006	ARM A / R-ICE	10/11/2004	NOT APPLICABLE	-	-	FEMALE	63	16/04/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003605301010	ARM A / R-ICE	16/08/2007	NOT APPLICABLE	-	-	MALE	55	18/12/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003605301601	ARM A / R-ICE	05/04/2004	NOT APPLICABLE	-	-	MALE	61	20/06/2004	CONCURRENT ILLNESS	SUDDEN DEATH, PRESUMED MYOCARDIAL EVENT. KNOWN MODERATE AORTIC STENOSIS	UNCONFIRMED COMPLETE RESPONSE
5003606201605	ARM A / R-ICE	17/05/2004	RITUXIMAB	29/10/2004	08/10/2004	MALE	42	17/10/2006	TOXICITY OF ADDITIONNAL TREATMENT	SEPTIC MULTIPLE ORGAN FAILURE AFTER AUTOL. TX 07/06 AND UNREL. ALLO TX 08/06 / EXTENSIVE GVHD SKIN + GUT - INTERSTITIAL PNEUMONIA HEMORRHAGIC CYSTITIS	NOT EVALUATED
5003606301207	ARM A / R-ICE	27/08/2004	OBSERVATION	02/12/2004	23/11/2004	MALE	37	09/10/2009	OTHER CANCER	METASTATIC CARCINOMA OF THE BLADDER	COMPLETE RESPONSE
5003606301612	ARM A / R-ICE	15/02/2005	NOT APPLICABLE	-	-	FEMALE	58	30/05/2009	OTHER REASON	PULMONARY HAEMORRHAGE	PARTIAL RESPONSE
5003607201016	ARM A / R-ICE	09/05/2005	OBSERVATION	11/08/2005	01/08/2005	FEMALE	54	07/03/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003607201032	ARM A / R-ICE	01/06/2006	NOT APPLICABLE	-	-	MALE	59	18/10/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003607201045	ARM A / R-ICE	09/05/2007	NOT APPLICABLE	-	09/08/2007	MALE	48	18/08/2007	TOXICITY OF STUDY TREATMENT		NOT EVALUATED
5003607501403	ARM A / R-ICE	16/10/2006	OBSERVATION	07/02/2007	02/02/2007	MALE	56	23/10/2007	LYMPHOMA		NOT EVALUATED
5003607701007	ARM A / R-ICE	06/12/2005	RITUXIMAB	09/03/2006	14/03/2006	MALE	56	01/06/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003607701009	ARM A / R-ICE	18/04/2006	NOT APPLICABLE	-	-	MALE	56	19/09/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003609301608	ARM A / R-ICE	02/11/2004	NOT APPLICABLE	-	-	MALE	43	21/04/2009	OTHER CANCER	AML TRANSFORMED FROM MDS	STABLE DISEASE
5003610201206	ARM A / R-ICE	13/04/2005	RITUXIMAB	16/06/2005	24/06/2005	MALE	40	12/03/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003610201611	ARM A / R-ICE	05/04/2005	RITUXIMAB	22/06/2005	28/06/2005	FEMALE	61	13/02/2007	OTHER REASON	ORGANIC BRAIN SYNDROME	COMPLETE RESPONSE
5003610201612	ARM A / R-ICE	12/04/2005	NOT APPLICABLE	-	-	FEMALE	56	23/07/2005	TOXICITY OF ADDITIONNAL TREATMENT	PNEUMONIA (ASPERGILLUS)	STABLE DISEASE
5003610301208	ARM A / R-ICE	27/08/2004	NOT APPLICABLE	-	-	FEMALE	47	11/04/2005	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003610301617	ARM A / R-ICE	31/01/2006	NOT APPLICABLE	-	-	MALE	41	01/08/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003610501031	ARM A / R-ICE	20/03/2008	OBSERVATION	08/07/2008	11/06/2008	MALE	54	01/09/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003611201057	ARM A / R-ICE	30/04/2008	NOT APPLICABLE	-	-	MALE	52	25/09/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003612501015	ARM A / R-ICE	22/05/2007	NOT APPLICABLE	-	-	MALE	55	04/11/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003614501002	ARM A / R-ICE	12/09/2006	NOT APPLICABLE	-	-	MALE	27	06/01/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003615301004	ARM A / R-ICE	17/08/2005	NOT APPLICABLE	-	-	FEMALE	64	03/03/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003615501014	ARM A / R-ICE	02/05/2007	RITUXIMAB	14/08/2007	09/08/2007	MALE	53	04/05/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003615501018	ARM A / R-ICE	08/08/2007	NOT APPLICABLE	-	-	FEMALE	49	22/10/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003615501028	ARM A / R-ICE	10/01/2008	NOT APPLICABLE	-	-	MALE	59	18/08/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003615501201	ARM A / R-ICE	12/09/2006	NOT APPLICABLE	-	-	MALE	56	15/05/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003615501404	ARM A / R-ICE	19/03/2007	NOT APPLICABLE	-	-	FEMALE	60	04/12/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003616301615	ARM A / R-ICE	29/09/2005	RITUXIMAB	22/12/2005	21/12/2005	MALE	63	01/09/2006	TOXICITY OF STUDY TREATMENT	PNEUMONIA	COMPLETE RESPONSE
5003616501005	ARM A / R-ICE	27/10/2006	NOT APPLICABLE	-	14/02/2007	FEMALE	59	21/02/2007	TOXICITY OF STUDY TREATMENT	SEPSIS : MULTIPLE ORGAN FAILURE WITH INTESTINAL, MARROW, CARDIAC + RENAL FAILURE	PARTIAL RESPONSE
5003617201004	ARM A / R-ICE	23/08/2004	NOT APPLICABLE	-	-	MALE	58	23/01/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003617201042	ARM A / R-ICE	06/12/2006	NOT APPLICABLE	-	-	MALE	64	10/06/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003617501024	ARM A / R-ICE	04/12/2007	NOT APPLICABLE	-	-	FEMALE	61	02/05/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003618501008	ARM A / R-ICE	16/01/2007	OBSERVATION	18/05/2007	01/05/2007	MALE	65	30/12/2009	LYMPHOMA	ACUTE GASTROINTESTINAL TRACT HAEMORRHAGE	PARTIAL RESPONSE
5003620301011	ARM A / R-ICE	14/09/2007	NOT APPLICABLE	-	-	MALE	41	07/07/2008	LYMPHOMA		NOT EVALUATED
5003621201020	ARM A / R-ICE	28/07/2005	OBSERVATION	07/12/2005	17/11/2005	FEMALE	59	14/07/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003621201023	ARM A / R-ICE	22/11/2005	NOT APPLICABLE	-	-	MALE	53	13/06/2006	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003621201026	ARM A / R-ICE	25/01/2006	NOT APPLICABLE	-	-	FEMALE	63	10/04/2006	TOXICITY OF ADDITIONNAL TREATMENT		PROGRESSIVE DISEASE
5003621301014	ARM A / R-ICE	29/10/2007	NOT APPLICABLE	-	-	FEMALE	58	03/12/2007	TOXICITY OF ADDITIONNAL TREATMENT	SEPSIC AFTER CHEMO OFF THE CORAL PROTOCOL (ICE)	NOT EVALUATED
5003622201022	ARM A / R-ICE	04/11/2005	NOT APPLICABLE	-	-	MALE	60	19/06/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003622201403	ARM A / R-ICE	24/11/2005	NOT APPLICABLE	-	-	FEMALE	58	08/03/2007	UNKNOWN	DEATH DUE TO LYMPHOMA COULD BE SUSPECTED BUT NOT PROVEN SINCE WE HAVE NO INFO ABOUT THE DEATH REASON	PROGRESSIVE DISEASE
5003628201003	ARM A / R-ICE	30/07/2004	NOT APPLICABLE	-	-	MALE	54	24/01/2005	LYMPHOMA	BONE MARROW INFILTRATION, PANCYTOPENIA, INFECTION	PROGRESSIVE DISEASE
5003628201052	ARM A / R-ICE	10/09/2007	NOT APPLICABLE	-	-	MALE	48	-	UNKNOWN	PATIENT DID NOT PRESENT TO HOSPITAL OR HIS GP / WE WERE INFORMED THE HE DIED SHORTLY AFTER *	NOT EVALUATED
5003631201035	ARM A / R-ICE	28/08/2006	NOT APPLICABLE	-	19/12/2006	FEMALE	45	14/07/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003633201036	ARM A / R-ICE	15/09/2006	NOT APPLICABLE	-	-	MALE	51	23/08/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003642501030	ARM A / R-ICE	19/03/2008	NOT APPLICABLE	-	-	MALE	37	23/01/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003643501202	ARM A / R-ICE	19/03/2008	NOT APPLICABLE	-	-	MALE	62	14/11/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101021038	ARM B / R-DHAP	06/10/2005	OBSERVATION	02/02/2006	09/01/2006	MALE	52	30/05/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101031019	ARM B / R-DHAP	30/12/2004	NOT APPLICABLE	-	-	FEMALE	58	24/04/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003101031067	ARM B / R-DHAP	22/05/2007	NOT APPLICABLE	-	-	FEMALE	21	18/09/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101031401	ARM B / R-DHAP	31/08/2004	RITUXIMAB	25/11/2004	26/11/2004	MALE	60	30/11/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003101051050	ARM B / R-DHAP	13/07/2006	RITUXIMAB	16/10/2006	11/10/2006	MALE	62	19/02/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101051063	ARM B / R-DHAP	26/03/2007	NOT APPLICABLE	-	-	FEMALE	61	12/08/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101071002	ARM B / R-DHAP	16/10/2003	NOT APPLICABLE	-	-	MALE	64	21/11/2003	TOXICITY OF STUDY TREATMENT		NOT EVALUATED
5003101071051	ARM B / R-DHAP	25/07/2006	NOT APPLICABLE	-	-	FEMALE	61	01/12/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101071073	ARM B / R-DHAP	19/10/2007	NOT APPLICABLE	-	-	MALE	47	09/01/2008	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003101071408	ARM B / R-DHAP	14/12/2005	RITUXIMAB	25/04/2006	03/04/2006	FEMALE	57	03/10/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101071417	ARM B / R-DHAP	16/03/2007	RITUXIMAB	17/07/2007	06/07/2007	FEMALE	56	03/10/2008	LYMPHOMA		NOT EVALUATED
5003101071607	ARM B / R-DHAP	07/01/2004	NOT APPLICABLE	-	-	MALE	59	04/06/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003101071643	ARM B / R-DHAP	29/10/2007	OBSERVATION	20/03/2008	27/02/2008	FEMALE	58	15/05/2008	TOXICITY OF STUDY TREATMENT	SEPTICEMIA STAPHYLOCOCCUS EPIDERMIDIS PNEUMOPATHY	COMPLETE RESPONSE
5003101091022	ARM B / R-DHAP	31/03/2005	NOT APPLICABLE	-	-	FEMALE	63	05/09/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003101091025	ARM B / R-DHAP	04/05/2005	NOT APPLICABLE	-	-	FEMALE	61	20/08/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003101091626	ARM B / R-DHAP	01/09/2005	NOT APPLICABLE	-	-	MALE	53	15/07/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101141402	ARM B / R-DHAP	06/04/2005	NOT APPLICABLE	-	-	MALE	63	13/03/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101141624	ARM B / R-DHAP	19/05/2005	OBSERVATION	26/10/2005	10/10/2005	FEMALE	64	18/04/2010	LYMPHOMA		PROGRESSIVE DISEASE
5003101221070	ARM B / R-DHAP	17/09/2007	NOT APPLICABLE	-	-	MALE	49	21/11/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101251035	ARM B / R-DHAP	26/07/2005	RITUXIMAB	16/11/2005	14/11/2005	MALE	55	10/05/2007	LYMPHOMA		NOT EVALUATED
5003101251044	ARM B / R-DHAP	28/03/2006	NOT APPLICABLE	-	-	FEMALE	64	26/09/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101391032	ARM B / R-DHAP	12/07/2005	NOT APPLICABLE	-	-	MALE	54	15/01/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101391048	ARM B / R-DHAP	15/06/2006	NOT APPLICABLE	-	-	MALE	61	17/12/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101391613	ARM B / R-DHAP	22/04/2004	NOT APPLICABLE	-	-	MALE	56	05/07/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003101431204	ARM B / R-DHAP	25/11/2003	NOT APPLICABLE	-	-	MALE	56	30/06/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101431608	ARM B / R-DHAP	23/01/2004	RITUXIMAB	23/04/2004	13/04/2004	MALE	64	19/04/2008	OTHER CANCER		UNCONFIRMED COMPLETE RESPONSE
5003101481614	ARM B / R-DHAP	07/05/2004	RITUXIMAB	17/09/2004	07/09/2004	MALE	58	20/07/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003101601066	ARM B / R-DHAP	18/05/2007	NOT APPLICABLE	-	-	MALE	55	18/09/2007	TOXICITY OF ADDITIONNAL TREATMENT	STOMACH HAEMORRHAGE	STABLE DISEASE
5003101601076	ARM B / R-DHAP	05/03/2008	NOT APPLICABLE	-	-	MALE	52	14/07/2008	LYMPHOMA		PROGRESSIVE DISEASE

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5003101601610	ARM B / R-DHAP	16/02/2004	NOT APPLICABLE	17/05/2004	24/05/2004	MALE	49	12/08/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003101641018	ARM B / R-DHAP	28/12/2004	NOT APPLICABLE	-	-	MALE	61	20/07/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003101641047	ARM B / R-DHAP	25/04/2006	NOT APPLICABLE	-	-	MALE	45	14/02/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101641079	ARM B / R-DHAP	27/06/2008	NOT APPLICABLE	-	-	MALE	27	24/11/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003102181031	ARM B / R-DHAP	24/06/2005	NOT APPLICABLE	-	-	MALE	63	16/12/2005	LYMPHOMA		STABLE DISEASE
5003102341003	ARM B / R-DHAP	07/11/2003	NOT APPLICABLE	-	-	MALE	27	02/11/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003102361203	ARM B / R-DHAP	21/11/2003	NOT APPLICABLE	19/02/2004	18/02/2004	MALE	38	12/10/2006	LYMPHOMA	NOT DATA ARE AVAILABLE BUT IT IS PROBABLE TO STATE THAT DEATH IS DUE TO LYMPHOMA	NOT EVALUATED
5003102411069	ARM B / R-DHAP	05/07/2007	OBSERVATION	24/10/2007	04/10/2007	MALE	63	16/10/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003102541016	ARM B / R-DHAP	21/09/2004	NOT APPLICABLE	-	-	MALE	54	19/05/2005	TOXICITY OF ADDITIONNAL TREATMENT		PROGRESSIVE DISEASE
5003601201018	ARM B / R-DHAP	14/06/2005	NOT APPLICABLE	-	-	FEMALE	43	08/08/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003601401004	ARM B / R-DHAP	27/09/2006	RITUXIMAB	19/12/2006	15/12/2006	FEMALE	62	26/08/2007	TOXICITY OF STUDY TREATMENT		COMPLETE RESPONSE
5003601401402	ARM B / R-DHAP	17/02/2005	RITUXIMAB	04/05/2005	10/05/2005	MALE	63	14/11/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003601601402	ARM B / R-DHAP	29/10/2004	NOT APPLICABLE	-	-	FEMALE	65	13/01/2005	CONCURRENT ILLNESS	PLEASE SEE AUTOPSY - PROVISIONAL. COMPLETE REPORT TO FOLLOW WHEN AVAILABLE.	COMPLETE RESPONSE
5003601801003	ARM B / R-DHAP	08/11/2004	NOT APPLICABLE	-	-	MALE	63	03/12/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003602801016	ARM B / R-DHAP	21/08/2007	NOT APPLICABLE	-	-	FEMALE	39	31/10/2007	TOXICITY OF ADDITIONNAL TREATMENT	PATIENT DIED IN PROLONGED NEUTROPENIA AFTER NEW TREATMENT (R-G/FOX)	STABLE DISEASE
5003602801204	ARM B / R-DHAP	22/12/2004	NOT APPLICABLE	-	-	MALE	61	22/03/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003603201001	ARM B / R-DHAP	11/03/2004	NOT APPLICABLE	-	-	MALE	50	13/05/2004	TOXICITY OF STUDY TREATMENT		STABLE DISEASE
5003603201034	ARM B / R-DHAP	14/08/2006	NOT APPLICABLE	-	-	MALE	33	11/04/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003603201050	ARM B / R-DHAP	06/08/2007	NOT APPLICABLE	-	-	MALE	61	01/11/2008	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003603201211	ARM B / R-DHAP	21/02/2006	NOT APPLICABLE	-	-	MALE	61	16/07/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003603801007	ARM B / R-DHAP	08/03/2006	NOT APPLICABLE	-	-	FEMALE	34	11/02/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003603801009	ARM B / R-DHAP	31/05/2006	OBSERVATION	07/09/2006	05/09/2006	MALE	49	31/03/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003603801010	ARM B / R-DHAP	23/08/2006	NOT APPLICABLE	-	-	FEMALE	62	21/11/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003603801013	ARM B / R-DHAP	20/12/2006	NOT APPLICABLE	-	-	FEMALE	60	24/04/2007	TOXICITY OF ADDITIONNAL TREATMENT	SEPTIC SHOCK AFTER HIGH DOSE CHEMOTHERAPY WITH ASCT	PARTIAL RESPONSE
5003603901001	ARM B / R-DHAP	06/10/2004	NOT APPLICABLE	-	-	MALE	54	19/11/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003604201028	ARM B / R-DHAP	02/02/2006	NOT APPLICABLE	-	-	MALE	65	15/04/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003604701012	ARM B / R-DHAP	19/04/2007	NOT APPLICABLE	-	-	MALE	62	04/05/2007	TOXICITY OF STUDY TREATMENT		NOT EVALUATED
5003604801006	ARM B / R-DHAP	18/10/2005	RITUXIMAB	09/03/2006	13/02/2006	MALE	53	10/11/2006	LYMPHOMA		NOT EVALUATED
5003604801201	ARM B / R-DHAP	08/09/2004	NOT APPLICABLE	-	-	FEMALE	40	29/11/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003604801405	ARM B / R-DHAP	30/05/2007	NOT APPLICABLE	-	-	FEMALE	55	29/09/2008	LYMPHOMA	PROGRESSION NODAL INVOLVEMENT WITH THROMBOSIS IN VENA CAVA INFERIOR / SEPSIS	PROGRESSIVE DISEASE
5003604901004	ARM B / R-DHAP	22/11/2005	RITUXIMAB	09/03/2006	25/05/2006	FEMALE	52	30/07/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003604901603	ARM B / R-DHAP	03/03/2008	RITUXIMAB	19/06/2008	18/06/2008	FEMALE	62	13/09/2008	TOXICITY OF STUDY TREATMENT	POST-MORTEM PATHOLOGICAL ANALYSIS WAS PERFORMED TODAY (14/09/2008)	COMPLETE RESPONSE
5003605201603	ARM B / R-DHAP	14/04/2004	NOT APPLICABLE	-	-	MALE	54	22/07/2005	TOXICITY OF ADDITIONNAL TREATMENT	PNEUMOCYSTIS CAVINII PNEUMONIA	NOT EVALUATED
5003605301203	ARM B / R-DHAP	23/03/2004	NOT APPLICABLE	-	-	FEMALE	30	11/09/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003605301610	ARM B / R-DHAP	18/11/2004	RITUXIMAB	02/05/2005	23/02/2005	MALE	60	14/07/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003605701404	ARM B / R-DHAP	30/01/2008	NOT APPLICABLE	-	-	MALE	52	13/11/2009	TOXICITY OF ADDITIONNAL TREATMENT	PAT DIED OF GRAFT VS HOST DISEASE AFTER ALLOGENE ENGRAFTMENT	COMPLETE RESPONSE
5003606201033	ARM B / R-DHAP	02/06/2006	NOT APPLICABLE	-	-	MALE	56	08/08/2007	TOXICITY OF ADDITIONNAL TREATMENT	CMV-PNEUMONIA AFTER ALLOGENEIC TRANSPLANT	NOT EVALUATED

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5003606201407	ARM B / R-DHAP	06/06/2006	RITUXIMAB	21/09/2006	13/09/2006	MALE	54	10/04/2007	TOXICITY OF ADDITIONNAL TREATMENT	CMV-PNEUMONIA, RENAL FAILURE, MULTIPLE ORGAN FAILURE AFTER AUTOLOGOUS TRANSPLANT ON 19/03/2007	PARTIAL RESPONSE
5003606301012	ARM B / R-DHAP	11/10/2007	NOT APPLICABLE	-	15/01/2008	FEMALE	63	12/02/2008	TOXICITY OF STUDY TREATMENT	1) CANDIDA GUILLIERMONDII SEPTICEMIA 2) CMV ENTEROCOLITIS (SEVERE)	PARTIAL RESPONSE
5003606301604	ARM B / R-DHAP	01/06/2004	OBSERVATION	22/09/2004	21/09/2004	MALE	61	22/06/2009	OTHER CANCER	MYELODYSPLASTIC SYNDROME	COMPLETE RESPONSE
5003606301606	ARM B / R-DHAP	07/07/2004	NOT APPLICABLE	-	-	FEMALE	40	03/09/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003607301603	ARM B / R-DHAP	01/06/2004	OBSERVATION	15/09/2004	10/09/2004	MALE	64	27/04/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003607301622	ARM B / R-DHAP	11/12/2006	NOT APPLICABLE	-	-	FEMALE	65	26/01/2007	TOXICITY OF STUDY TREATMENT	GRAM NEGATIVE SEPTICAEMIA	NOT EVALUATED
5003607501401	ARM B / R-DHAP	19/07/2006	RITUXIMAB	30/10/2006	18/10/2006	MALE	54	25/08/2007	LYMPHOMA	BRONCHOPNEUMONIA	PROGRESSIVE DISEASE
5003608701008	ARM B / R-DHAP	09/02/2006	OBSERVATION	19/05/2006	01/05/2006	MALE	57	14/10/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003610201008	ARM B / R-DHAP	15/11/2004	NOT APPLICABLE	-	-	MALE	39	01/08/2005	TOXICITY OF ADDITIONNAL TREATMENT	SEPSIS, INFECTION NODE ALLO = GENER TRANSPLANTATION	COMPLETE RESPONSE
5003610201212	ARM B / R-DHAP	13/04/2006	NOT APPLICABLE	-	-	MALE	23	29/01/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003610301613	ARM B / R-DHAP	01/03/2005	OBSERVATION	23/05/2005	31/05/2005	MALE	53	29/07/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003610501402	ARM B / R-DHAP	21/09/2006	RITUXIMAB	28/12/2006	20/12/2006	MALE	58	13/02/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003610701014	ARM B / R-DHAP	24/09/2007	RITUXIMAB	07/01/2008	14/01/2008	MALE	57	01/06/2010	OTHER CANCER	HODGKIN LYMPHOMA	PROGRESSIVE DISEASE
5003611301002	ARM B / R-DHAP	14/09/2004	NOT APPLICABLE	-	-	MALE	61	13/03/2005	LYMPHOMA	CENTRAL NERVOUS SYSTEM LYMPHOMA AND SYSTEMIC DISEASE AND MARROW INVOLVEMENT	PROGRESSIVE DISEASE
5003611301003	ARM B / R-DHAP	02/05/2005	NOT APPLICABLE	-	-	MALE	60	12/05/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003612301623	ARM B / R-DHAP	13/12/2006	RITUXIMAB	16/04/2007	30/03/2007	MALE	56	23/04/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003612501019	ARM B / R-DHAP	03/09/2007	NOT APPLICABLE	-	-	FEMALE	51	12/01/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003614501013	ARM B / R-DHAP	20/04/2007	NOT APPLICABLE	-	-	MALE	35	21/07/2007	OTHER REASON	AMPHOTERICIN TOXICITY	PROGRESSIVE DISEASE
5003615501004	ARM B / R-DHAP	05/10/2006	NOT APPLICABLE	-	-	FEMALE	64	11/07/2007	LYMPHOMA		PROGRESSIVE DISEASE

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5003615501007	ARM B / R-DHAP	20/12/2006	NOT APPLICABLE	-	-	FEMALE	52	25/05/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003616201413	ARM B / R-DHAP	29/04/2008	NOT APPLICABLE	-	-	MALE	62	20/08/2008	TOXICITY OF ADDITIONNAL TREATMENT		NOT EVALUATED
5003616301212	ARM B / R-DHAP	21/04/2006	NOT APPLICABLE	-	-	FEMALE	65	23/01/2007	TOXICITY OF ADDITIONNAL TREATMENT		PARTIAL RESPONSE
5003616501003	ARM B / R-DHAP	14/09/2006	RITUXIMAB	20/12/2006	05/12/2006	MALE	30	21/08/2008	CONCURRENT ILLNESS	PNEUMONIA, DEVIC'S DISEASE	NOT EVALUATED
5003616501411	ARM B / R-DHAP	26/06/2008	NOT APPLICABLE	-	-	MALE	63	28/11/2009	TOXICITY OF ADDITIONNAL TREATMENT	MOTOR NEURONE DISEASE AND CJ VIRUS.	STABLE DISEASE
5003617201021	ARM B / R-DHAP	17/10/2005	OBSERVATION	14/02/2006	01/02/2006	FEMALE	50	22/12/2007	OTHER REASON	RESPIRATORY INSUFFICIENCY	COMPLETE RESPONSE
5003617201024	ARM B / R-DHAP	07/12/2005	NOT APPLICABLE	-	-	MALE	58	12/09/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003617201031	ARM B / R-DHAP	26/05/2006	NOT APPLICABLE	-	-	FEMALE	56	05/03/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003617201043	ARM B / R-DHAP	25/01/2007	RITUXIMAB	16/04/2007	19/04/2007	MALE	42	28/06/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003617201049	ARM B / R-DHAP	10/07/2007	NOT APPLICABLE	-	-	FEMALE	49	29/04/2009	TOXICITY OF ADDITIONNAL TREATMENT		COMPLETE RESPONSE
5003617301619	ARM B / R-DHAP	06/02/2006	OBSERVATION	27/04/2006	05/05/2006	FEMALE	19	24/05/2008	TOXICITY OF ADDITIONNAL TREATMENT	MULTI-ORGAN FAILURE SECONDARY TO GRAFT VERSUS HOST DISEASE FOLLOWING ALLOGENEIC BONE MARROW TRANSPLANT	COMPLETE RESPONSE
5003617501006	ARM B / R-DHAP	01/12/2006	NOT APPLICABLE	-	-	MALE	61	04/02/2007	LYMPHOMA	PATIENT ADMITTED WITH SHORTNESS OF BREATH AND DIED WITHIN 4 HOURS THEREFORE GONE TO CORONER. WILL UPDATE WHEN INFORMATION OBTAINED.	PROGRESSIVE DISEASE
5003617501026	ARM B / R-DHAP	06/12/2007	NOT APPLICABLE	-	-	FEMALE	59	24/01/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003618301005	ARM B / R-DHAP	01/02/2006	OBSERVATION	19/05/2006	03/05/2006	MALE	27	07/12/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003618501025	ARM B / R-DHAP	05/12/2007	OBSERVATION	29/04/2008	10/04/2008	MALE	59	08/01/2009	LYMPHOMA	CAUSE OF DEATH DUE TO LYMPHOMA FOUND ON POST-MORTEM	PROGRESSIVE DISEASE
5003619301016	ARM B / R-DHAP	22/01/2008	NOT APPLICABLE	-	-	MALE	38	20/06/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003619501010	ARM B / R-DHAP	14/02/2007	NOT APPLICABLE	-	-	FEMALE	45	06/04/2007	TOXICITY OF STUDY TREATMENT	RESPIRATORY FAILURE DUE TO SEPSIS	NOT EVALUATED

Randomization Number	Actual arm of induction	First Randomization Date	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003620201017	ARM B / R-DHAP	09/05/2005	NOT APPLICABLE	-	-	FEMALE	58	24/11/2005	TOXICITY OF ADDITIONNAL TREATMENT	SEPSIS	PARTIAL RESPONSE
5003623501405	ARM B / R-DHAP	05/07/2007	NOT APPLICABLE	-	-	MALE	58	26/07/2007	LYMPHOMA		NOT EVALUATED
5003625501020	ARM B / R-DHAP	14/09/2007	NOT APPLICABLE	-	-	MALE	60	24/05/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003628201046	ARM B / R-DHAP	21/06/2007	NOT APPLICABLE	-	-	FEMALE	48	17/03/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003630201040	ARM B / R-DHAP	06/11/2006	RITUXIMAB	09/03/2007	13/02/2007	MALE	65	21/12/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003631201011	ARM B / R-DHAP	03/12/2004	NOT APPLICABLE	-	-	FEMALE	61	29/12/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003631201012	ARM B / R-DHAP	15/12/2004	NOT APPLICABLE	-	-	FEMALE	58	25/05/2006	LYMPHOMA	CHEMOREFRACTORY DISEASE	PROGRESSIVE DISEASE
5003631201619	ARM B / R-DHAP	24/02/2006	NOT APPLICABLE	14/06/2006	29/05/2006	MALE	37	14/10/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003632201015	ARM B / R-DHAP	01/04/2005	NOT APPLICABLE	-	-	MALE	51	04/06/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003635201411	ARM B / R-DHAP	11/05/2007	NOT APPLICABLE	-	-	FEMALE	61	01/11/2007	LYMPHOMA	06-07/07 3X R-ICE : PROGRESSIVE DISEASE / 09/07 RITUX. / GEMCITABIN / OXALIPLATIN : PD	PROGRESSIVE DISEASE
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)

		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
Lymphocytes (G/L)	**N**	226	224
	Mean	1.138	1.102
	Std	0.6287	0.7269
	Median	0.997	0.967
	Min	0.11	0.01
	Max	4.65	4.61
Lymphoma cells (G/L)	**N**	181	182
	Mean	0.0	0.0
	Std	0.22	0.10
	Median	0.0	0.0
	Min	0	0
	Max	2	1
ASAT (UI/L)	**N**	220	210
	Mean	31.6	29.0
	Std	39.23	20.73
	Median	25.0	23.0
	Min	9	8
	Max	566	209
ALAT (UI/L)	**N**	229	219
	Mean	35.9	33.2
	Std	61.26	34.26
	Median	23.0	24.0
	Min	4	7
	Max	861	384
beta 2 microglobulin (mg/l)	**N**	160	156
	Mean	2.815	2.381
	Std	5.2793	1.1310
	Median	2.000	2.100
	Min	0.20	0.90
	Max	67.00	8.30
Aaline phosphatase (UI/L)	**N**	232	224
	Mean	113.1	126.0
	Std	89.67	131.10
	Median	85.0	88.5
	Min	35	41
	Max	788	1285

		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
Total bilirubin (µmol/l)	**N**	232	225
	Mean	10.430	11.732
	Std	8.9383	22.6876
	Median	8.800	8.550
	Min	0.40	0.60
	Max	90.00	333.00
Creatinin (µmol/l)	**N**	238	229
	Mean	78.6	77.9
	Std	18.64	19.95
	Median	77.9	77.0
	Min	35	1
	Max	155	174
Calcium (mmol/l)	**N**	218	214
	Mean	2.376	2.386
	Std	0.5149	0.3347
	Median	2.355	2.360
	Min	1.03	1.83
	Max	9.50	5.25
Sodium (mmol/l)	**N**	233	227
	Mean	139.8	139.4
	Std	3.27	3.13
	Median	140.0	139.0
	Min	129	126
	Max	150	146
Potassium (mmol/l)	**N**	234	223
	Mean	4.149	4.121
	Std	0.4220	0.4563
	Median	4.100	4.100
	Min	3.30	2.50
	Max	5.80	5.60

Table 5.4-2 Serum electrophoresis values at relapse diagnosis (induction safety population)

		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
Total protein (G/L)	**N**	206	203
	Mean	68.43	68.17
	Std	10.560	8.668
	Median	69.00	69.00
	Min	6.6	5.4
	Max	90	84
Albumin (G/L)	**N**	202	207
	Mean	40.52	40.27
	Std	6.606	6.693
	Median	41.00	41.00
	Min	2.9	22.0
	Max	62	66
Monoclonal component value (G/L)	**N**	4	9
	Mean	5.25	9.79
	Std	7.182	15.683
	Median	2.00	5.00
	Min	1.0	1.6
	Max	16	51

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)

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003101021008	ARM A / R-ICE	12/05/2004	NOT APPLICABLE	-	06/07/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101021014	ARM A / R-ICE	20/08/2004	NOT APPLICABLE	-	20/10/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		UNCONFIRMED COMPLETE RESPONSE	-	3	-
5003101021027	ARM A / R-ICE	01/06/2005	NOT APPLICABLE	-	26/07/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003101021605	ARM A / R-ICE	04/11/2003	OBSERVATION	04/02/2004	29/04/2004	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	03/02/2004	3	4
5003101021631	ARM A / R-ICE	07/02/2006	RITUXIMAB	01/06/2006	09/05/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	22/05/2006	3	5
5003101031001	ARM A / R-ICE	24/07/2003	RITUXIMAB	21/10/2003	18/11/2003	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	22/10/2003	3	1
5003101031007	ARM A / R-ICE	26/01/2004	NOT APPLICABLE	-	20/04/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101041606	ARM A / R-ICE	03/12/2003	NOT APPLICABLE	-	05/12/2003	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION		NOT EVALUATED	-	-	-
5003101051004	ARM A / R-ICE	26/11/2003	NOT APPLICABLE	-	29/01/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003101051068	ARM A / R-ICE	04/07/2007	NOT APPLICABLE	-	24/09/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101051075	ARM A / R-ICE	19/02/2008	NOT APPLICABLE	-	02/06/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101051603	ARM A / R-ICE	27/10/2003	NOT APPLICABLE	-	29/12/2003	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-
5003101071020	ARM A / R-ICE	15/03/2005	NOT APPLICABLE	-	20/07/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101071029	ARM A / R-ICE	09/06/2005	NOT APPLICABLE	-	05/12/2005	CONSOLIDATION PHASE	OTHER	FORGOT 2NDE RANDOMIZATION	COMPLETE RESPONSE	10/10/2005	3	-
5003101071059	ARM A / R-ICE	22/12/2006	NOT APPLICABLE	-	26/01/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003101071647	ARM A / R-ICE	11/04/2008	NOT APPLICABLE	-	01/05/2008	INDUCTION PHASE	OTHER	TREATMENT OUT OF RADIOTHERAPY BETWEEN CYCLE 1 AND 2	COMPLETE RESPONSE	-	1	-
5003101091602	ARM A / R-ICE	16/10/2003	NOT APPLICABLE	-	22/12/2003	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101131030	ARM A / R-ICE	16/06/2005	NOT APPLICABLE	-	16/08/2005	INDUCTION PHASE	DEATH		NOT EVALUATED	-	2	-
5003101131062	ARM A / R-ICE	20/02/2007	NOT APPLICABLE	-	02/05/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101131072	ARM A / R-ICE	27/09/2007	OBSERVATION	26/12/2007	18/01/2008	FOLLOW UP PERIOD	OTHER	PATIENT RETURN IN ROUMANIA	UNCONFIRMED COMPLETE RESPONSE	24/12/2007	3	1
5003101131409	ARM A / R-ICE	07/03/2006	RITUXIMAB	16/06/2006	23/11/2006	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	14/06/2006	3	1
5003101141065	ARM A / R-ICE	24/04/2007	NOT APPLICABLE	-	12/07/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101141406	ARM A / R-ICE	13/09/2005	NOT APPLICABLE	-	20/12/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101211023	ARM A / R-ICE	25/04/2005	NOT APPLICABLE	-	06/07/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101221043	ARM A / R-ICE	27/02/2006	NOT APPLICABLE	-	29/03/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003101281017	ARM A / R-ICE	18/11/2004	NOT APPLICABLE	-	10/12/2004	INDUCTION PHASE	TREATMENT TOXICITY		PROGRESSIVE DISEASE	-	1	-
5003101281033	ARM A / R-ICE	15/07/2005	RITUXIMAB	15/11/2005	10/01/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	04/10/2005	3	1
5003101281208	ARM A / R-ICE	09/02/2006	NOT APPLICABLE	-	21/03/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003101331077	ARM A / R-ICE	18/03/2008	NOT APPLICABLE	-	26/06/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101351040	ARM A / R-ICE	21/12/2005	NOT APPLICABLE	-	10/03/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101391039	ARM A / R-ICE	02/11/2005	NOT APPLICABLE	-	03/01/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003101391201	ARM A / R-ICE	24/09/2003	NOT APPLICABLE	-	12/12/2003	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101391638	ARM A / R-ICE	26/01/2007	NOT APPLICABLE	-	26/02/2007	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		NOT EVALUATED	-	1	-
5003101431010	ARM A / R-ICE	11/06/2004	NOT APPLICABLE	-	18/08/2004	INDUCTION PHASE	OTHER	THE SECOND RANDOMIZATION COULD NOT BE PERFORMED DUE TO THE DELAY TO GET THE PATHOLOGICAL EVALUATION	STABLE DISEASE	-	3	-
5003101431046	ARM A / R-ICE	19/04/2006	NOT APPLICABLE	-	13/06/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003101431622	ARM A / R-ICE	26/04/2005	RITUXIMAB	13/07/2005	12/10/2005	FOLLOW UP PERIOD	TREATMENT TOXICITY		COMPLETE RESPONSE	18/07/2005	3	1
5003101441036	ARM A / R-ICE	02/08/2005	NOT APPLICABLE	-	17/10/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101441074	ARM A / R-ICE	12/11/2007	NOT APPLICABLE	-	31/01/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101481403	ARM A / R-ICE	21/06/2005	NOT APPLICABLE	-	01/09/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		UNCONFIRMED COMPLETE RESPONSE	-	3	-
5003101491042	ARM A / R-ICE	14/02/2006	RITUXIMAB	09/05/2006	31/07/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	18/05/2006	3	1
5003101601404	ARM A / R-ICE	04/07/2005	NOT APPLICABLE	-	21/08/2005	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	-	2	-
5003101621026	ARM A / R-ICE	31/05/2005	OBSERVATION	14/09/2005	22/03/2006	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	06/09/2005	3	3
5003101621615	ARM A / R-ICE	10/06/2004	OBSERVATION	16/09/2004	19/04/2005	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	21/09/2004	3	4
5003102161078	ARM A / R-ICE	21/05/2008	NOT APPLICABLE	-	03/09/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003102161413	ARM A / R-ICE	18/10/2006	NOT APPLICABLE	-	05/11/2006	INDUCTION PHASE	DEATH		NOT EVALUATED	-	1	-
5003102321024	ARM A / R-ICE	29/04/2005	NOT APPLICABLE	-	17/08/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003102341045	ARM A / R-ICE	30/03/2006	OBSERVATION	03/07/2006	09/09/2006	FOLLOW UP PERIOD	OTHER	RADIOTHERAPY TREATMENT	PARTIAL RESPONSE	21/06/2006	3	3

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003102341049	ARM A / R-ICE	11/07/2006	NOT APPLICABLE	-	11/10/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003102341061	ARM A / R-ICE	31/01/2007	RITUXIMAB	04/05/2007	03/12/2007	FOLLOW UP PERIOD	OTHER	POST TRANSPLANTATION RELAPSE	PROGRESSIVE DISEASE	02/05/2007	3	4
5003102341416	ARM A / R-ICE	20/12/2006	NOT APPLICABLE	-	31/01/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003102491616	ARM A / R-ICE	29/06/2004	NOT APPLICABLE	-	27/09/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003102541052	ARM A / R-ICE	26/07/2006	OBSERVATION	12/10/2006	04/01/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	05/11/2006	3	1
5003102541625	ARM A / R-ICE	13/06/2005	NOT APPLICABLE	-	18/08/2005	INDUCTION PHASE	MAJOR PROTOCOL VIOLATION		PARTIAL RESPONSE	-	3	-
5003601201041	ARM A / R-ICE	28/11/2006	NOT APPLICABLE	-	02/02/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003601201602	ARM A / R-ICE	16/03/2004	NOT APPLICABLE	-	23/05/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		UNCONFIRMED COMPLETE RESPONSE	-	3	-
5003601401003	ARM A / R-ICE	15/06/2005	NOT APPLICABLE	-	12/08/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003601401006	ARM A / R-ICE	18/04/2007	OBSERVATION	11/07/2007	25/02/2008	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	03/07/2007	3	4
5003601401401	ARM A / R-ICE	04/03/2004	NOT APPLICABLE	-	04/05/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003601401605	ARM A / R-ICE	21/09/2006	NOT APPLICABLE	-	24/11/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003601601002	ARM A / R-ICE	02/01/2007	NOT APPLICABLE	-	06/03/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003601601003	ARM A / R-ICE	07/03/2007	OBSERVATION	08/06/2007	31/08/2007	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	29/05/2007	3	6
5003601601005	ARM A / R-ICE	15/01/2008	OBSERVATION	16/04/2008	03/07/2008	FOLLOW UP PERIOD	OTHER	PROGRESSION OF DISEASE	PROGRESSIVE DISEASE	08/04/2008	3	2
5003601601401	ARM A / R-ICE	26/03/2004	NOT APPLICABLE	-	13/06/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003601881401	ARM A / R-ICE	19/07/2006	RITUXIMAB	07/11/2006	26/07/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	10/11/2006	3	4
5003602301001	ARM A / R-ICE	12/02/2004	NOT APPLICABLE	-	16/04/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003602401005	ARM A / R-ICE	29/11/2006	NOT APPLICABLE	-	30/01/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003602501001	ARM A / R-ICE	05/09/2006	NOT APPLICABLE	-	18/10/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003602801001	ARM A / R-ICE	01/12/2003	NOT APPLICABLE	-	25/02/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003602801011	ARM A / R-ICE	14/09/2006	OBSERVATION	22/12/2006	13/07/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	06/12/2006	3	3
5003602901002	ARM A / R-ICE	24/01/2005	NOT APPLICABLE	-	29/03/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003602901201	ARM A / R-ICE	03/03/2004	NOT APPLICABLE	-	29/04/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003602901401	ARM A / R-ICE	12/11/2004	NOT APPLICABLE	-	01/02/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003602901601	ARM A / R-ICE	08/09/2004	OBSERVATION	27/12/2004	06/10/2005	FOLLOW UP PERIOD	OTHER	RELAPS	PROGRESSIVE DISEASE	21/03/2005	3	6
5003603201025	ARM A / R-ICE	12/01/2006	NOT APPLICABLE	-	20/04/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003603201038	ARM A / R-ICE	09/10/2006	OBSERVATION	17/01/2007	11/04/2007	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	29/12/2006	3	5
5003603201213	ARM A / R-ICE	23/02/2007	OBSERVATION	29/05/2007	28/03/2008	FOLLOW UP PERIOD	DEATH		PROGRESSIVE DISEASE	23/05/2007	3	3
5003603201406	ARM A / R-ICE	04/05/2006	NOT APPLICABLE	-	01/08/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		UNCONFIRMED COMPLETE RESPONSE	-	3	-
5003603201409	ARM A / R-ICE	25/01/2007	NOT APPLICABLE	-	16/02/2007	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		NOT EVALUATED	-	1	-
5003603201627	ARM A / R-ICE	28/03/2007	NOT APPLICABLE	-	03/04/2007	BEFORE TREATMENT	DEATH		PROGRESSIVE DISEASE	-	-	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003603201628	ARM A / R-ICE	18/05/2007	RITUXIMAB	17/08/2007	20/03/2008	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	22/08/2007	3	4
5003603301201	ARM A / R-ICE	11/03/2004	NOT APPLICABLE	-	23/07/2004	CONSOLIDATION PHASE	OTHER	POSITIVE PET RESULT AFTER CONSOLIDATION: REQUIRED RADIOTHERAPY (INVESTIGATOR'S DECISION)	PARTIAL RESPONSE	25/06/2004	3	-
5003603701004	ARM A / R-ICE	12/08/2005	NOT APPLICABLE	-	01/09/2005	INDUCTION PHASE	DEATH		NOT EVALUATED	-	1	-
5003603701006	ARM A / R-ICE	14/10/2005	OBSERVATION	30/01/2006	13/03/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	09/01/2006	3	1
5003603701010	ARM A / R-ICE	03/07/2006	NOT APPLICABLE	-	16/08/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003603801015	ARM A / R-ICE	11/04/2007	NOT APPLICABLE	-	20/06/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003603801202	ARM A / R-ICE	18/11/2004	NOT APPLICABLE	-	07/02/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003603801203	ARM A / R-ICE	01/12/2004	RITUXIMAB	14/03/2005	02/05/2005	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	01/03/2005	3	1
5003603801406	ARM A / R-ICE	15/02/2008	RITUXIMAB	15/05/2008	05/08/2008	FOLLOW UP PERIOD	OTHER	PR ; START OF NEW TREATMENT	PARTIAL RESPONSE	13/05/2008	3	1
5003603801608	ARM A / R-ICE	09/04/2008	OBSERVATION	03/07/2008	24/10/2008	FOLLOW UP PERIOD	OTHER	EARLY RELAPSE AFTER TRANSPLANTATION	PROGRESSIVE DISEASE	01/07/2008	3	2
5003604201204	ARM A / R-ICE	08/07/2004	NOT APPLICABLE	-	19/08/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003604301618	ARM A / R-ICE	02/02/2006	NOT APPLICABLE	-	03/05/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003604801014	ARM A / R-ICE	15/02/2007	NOT APPLICABLE	-	26/02/2007	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	-	1	-
5003604801205	ARM A / R-ICE	29/03/2006	RITUXIMAB	11/07/2006	07/08/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	21/06/2006	3	1
5003604901005	ARM A / R-ICE	05/01/2006	RITUXIMAB	09/05/2006	27/07/2006	FOLLOW UP PERIOD	OTHER	BONE MARROW INVOLVEMENT	PROGRESSIVE DISEASE	24/04/2006	3	1
5003604901006	ARM A / R-ICE	20/06/2006	NOT APPLICABLE	-	25/09/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003605201006	ARM A / R-ICE	10/11/2004	NOT APPLICABLE	-	05/01/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003605301010	ARM A / R-ICE	16/08/2007	NOT APPLICABLE	-	24/09/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003605301601	ARM A / R-ICE	05/04/2004	NOT APPLICABLE	-	20/06/2004	INDUCTION PHASE	DEATH		UNCONFIRMED COMPLETE RESPONSE	-	3	-
5003605701401	ARM A / R-ICE	11/10/2006	RITUXIMAB	30/01/2007	28/11/2007	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL		COMPLETE RESPONSE	12/01/2007	3	5
5003605901003	ARM A / R-ICE	15/02/2005	NOT APPLICABLE	-	28/06/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003606301612	ARM A / R-ICE	15/02/2005	NOT APPLICABLE	-	25/05/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		UNCONFIRMED COMPLETE RESPONSE	-	3	-
5003606701003	ARM A / R-ICE	10/03/2005	OBSERVATION	07/06/2005	13/01/2006	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	08/06/2005	3	6
5003607201016	ARM A / R-ICE	09/05/2005	OBSERVATION	11/08/2005	16/12/2005	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	01/08/2005	3	3
5003607201032	ARM A / R-ICE	01/06/2006	NOT APPLICABLE	-	14/07/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003607201045	ARM A / R-ICE	09/05/2007	NOT APPLICABLE	-	18/08/2007	CONSOLIDATION PHASE	DEATH		PARTIAL RESPONSE	09/08/2007	3	-
5003607501403	ARM A / R-ICE	16/10/2006	OBSERVATION	07/02/2007	11/07/2007	FOLLOW UP PERIOD	OTHER	RELAPSE DISEASE	PROGRESSIVE DISEASE	02/02/2007	3	4
5003607701007	ARM A / R-ICE	06/12/2005	RITUXIMAB	09/03/2006	21/04/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	14/03/2006	3	1
5003607701009	ARM A / R-ICE	18/04/2006	NOT APPLICABLE	-	24/07/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003608301605	ARM A / R-ICE	03/06/2004	RITUXIMAB	25/08/2004	13/09/2004	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL		COMPLETE RESPONSE	25/08/2004	3	-
5003608701016	ARM A / R-ICE	04/04/2008	NOT APPLICABLE	-	23/06/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003609201013	ARM A / R-ICE	14/03/2005	NOT APPLICABLE	-	14/03/2005	BEFORE TREATMENT	OTHER	MEET NOT INCLUSION CRITERIAS	NOT EVALUATED	-	-	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003609201058	ARM A / R-ICE	02/06/2008	NOT APPLICABLE	-	05/08/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003609301608	ARM A / R-ICE	02/11/2004	NOT APPLICABLE	-	25/01/2005	INDUCTION PHASE	OTHER	INVESTIGATOR'S DECISION (REQUIRES 4TH CYCLE OF INDUCTION)	PARTIAL RESPONSE	-	3	-
5003610201007	ARM A / R-ICE	12/11/2004	NOT APPLICABLE	-	14/01/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003610201612	ARM A / R-ICE	12/04/2005	NOT APPLICABLE	-	16/06/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003610301208	ARM A / R-ICE	27/08/2004	NOT APPLICABLE	-	23/09/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003610301617	ARM A / R-ICE	31/01/2006	NOT APPLICABLE	-	24/04/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003610501031	ARM A / R-ICE	20/03/2008	OBSERVATION	08/07/2008	28/07/2008	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	11/06/2008	3	1
5003611201057	ARM A / R-ICE	30/04/2008	NOT APPLICABLE	-	25/07/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003612501012	ARM A / R-ICE	19/03/2007	NOT APPLICABLE	-	13/06/2007	INDUCTION PHASE	TREATMENT TOXICITY		PARTIAL RESPONSE	-	2	-
5003612501015	ARM A / R-ICE	22/05/2007	NOT APPLICABLE	-	16/08/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003612501021	ARM A / R-ICE	19/09/2007	NOT APPLICABLE	-	29/11/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003613301210	ARM A / R-ICE	16/05/2005	NOT APPLICABLE	-	01/08/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003614301614	ARM A / R-ICE	16/06/2005	NOT APPLICABLE	-	17/06/2005	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION		NOT EVALUATED	-	-	-
5003614501002	ARM A / R-ICE	12/09/2006	NOT APPLICABLE	-	24/11/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003615301004	ARM A / R-ICE	17/08/2005	NOT APPLICABLE	-	14/11/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003615501014	ARM A / R-ICE	02/05/2007	RITUXIMAB	14/08/2007	04/02/2008	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	09/08/2007	3	2

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003615501018	ARM A / R-ICE	08/08/2007	NOT APPLICABLE	-	01/10/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003615501028	ARM A / R-ICE	10/01/2008	NOT APPLICABLE	-	18/03/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003615501201	ARM A / R-ICE	12/09/2006	NOT APPLICABLE	-	23/11/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003615501404	ARM A / R-ICE	19/03/2007	NOT APPLICABLE	-	21/05/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		UNCONFIRMED COMPLETE RESPONSE	-	3	-
5003616301615	ARM A / R-ICE	29/09/2005	RITUXIMAB	22/12/2005	01/09/2006	FOLLOW UP PERIOD	DEATH		COMPLETE RESPONSE	21/12/2005	3	4
5003616501005	ARM A / R-ICE	27/10/2006	NOT APPLICABLE	-	21/02/2007	CONSOLIDATION PHASE	DEATH		PARTIAL RESPONSE	14/02/2007	3	-
5003617201004	ARM A / R-ICE	23/08/2004	NOT APPLICABLE	-	24/11/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003617201010	ARM A / R-ICE	30/11/2004	NOT APPLICABLE	-	24/02/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003617201039	ARM A / R-ICE	20/10/2006	NOT APPLICABLE	-	16/01/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003617201042	ARM A / R-ICE	06/12/2006	NOT APPLICABLE	-	06/03/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003617201048	ARM A / R-ICE	06/07/2007	NOT APPLICABLE	-	26/09/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003617501024	ARM A / R-ICE	04/12/2007	NOT APPLICABLE	-	20/02/2008	INDUCTION PHASE	OTHER	PATIENT REFUSED TO CONTINUE THE STUDY TREATMENT	PARTIAL RESPONSE	-	3	-
5003617501606	ARM A / R-ICE	19/11/2007	NOT APPLICABLE	-	15/02/2008	INDUCTION PHASE	OTHER	TRANSPLANT CENTRE WOULD NOT TRANSPLANT PATIENT AS PATIENT WAS PET POSITIVE	PARTIAL RESPONSE	-	3	-
5003619301008	ARM A / R-ICE	17/11/2006	NOT APPLICABLE	-	04/01/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003619301621	ARM A / R-ICE	01/12/2006	OBSERVATION	19/03/2007	18/10/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	08/03/2007	3	2

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003620301011	ARM A / R-ICE	14/09/2007	NOT APPLICABLE	-	29/10/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003620301017	ARM A / R-ICE	13/03/2008	NOT APPLICABLE	-	19/05/2008	INDUCTION PHASE	OTHER	USE OF DIFFERENT CONSOLIDATION TREATMENT THAN SPECIFIED IN PROTOCOL	STABLE DISEASE	-	3	-
5003621201020	ARM A / R-ICE	28/07/2005	OBSERVATION	07/12/2005	26/04/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	17/11/2005	3	3
5003621201023	ARM A / R-ICE	22/11/2005	NOT APPLICABLE	-	08/02/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003621201026	ARM A / R-ICE	25/01/2006	NOT APPLICABLE	-	13/02/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003621301014	ARM A / R-ICE	29/10/2007	NOT APPLICABLE	-	11/11/2007	INDUCTION PHASE	TREATMENT TOXICITY		STABLE DISEASE	-	1	-
5003621501603	ARM A / R-ICE	10/04/2007	NOT APPLICABLE	-	28/08/2007	CONSOLIDATION PHASE	OTHER	FAILURE TO RANDOMISE	UNCONFIRMED COMPLETE RESPONSE	08/08/2007	3	-
5003622201022	ARM A / R-ICE	04/11/2005	NOT APPLICABLE	-	21/02/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003622201210	ARM A / R-ICE	20/02/2006	NOT APPLICABLE	-	27/03/2006	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	-	1	-
5003622201403	ARM A / R-ICE	24/11/2005	NOT APPLICABLE	-	24/01/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		NOT EVALUATED	-	3	-
5003624501017	ARM A / R-ICE	31/07/2007	NOT APPLICABLE	-	07/11/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003628201003	ARM A / R-ICE	30/07/2004	NOT APPLICABLE	-	08/10/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003628201009	ARM A / R-ICE	26/11/2004	NOT APPLICABLE	-	31/01/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003628201052	ARM A / R-ICE	10/09/2007	NOT APPLICABLE	-	-	INDUCTION PHASE	-		-	-	1	-
5003628201624	ARM A / R-ICE	06/12/2006	NOT APPLICABLE	-	06/03/2007	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		COMPLETE RESPONSE	-	3	-
5003630201055	ARM A / R-ICE	09/04/2008	NOT APPLICABLE	-	24/07/2008	INDUCTION PHASE	TREATMENT TOXICITY		COMPLETE RESPONSE	-	2	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003631201035	ARM A / R-ICE	28/08/2006	NOT APPLICABLE	-	12/02/2007	CONSOLIDATION PHASE	OTHER	THE PATIENT WAS ALLOGRAFTED BECAUSE OF HIGH RISK OF RELAPSE ON 01/06/2007	COMPLETE RESPONSE	19/12/2006	3	-
5003632201054	ARM A / R-ICE	07/02/2008	NOT APPLICABLE	-	08/07/2008	CONSOLIDATION PHASE	OTHER	PATIENT REFUSES SECOND RANDOMIZATION	COMPLETE RESPONSE	05/05/2008	3	-
5003633201036	ARM A / R-ICE	15/09/2006	NOT APPLICABLE	-	07/12/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003635201051	ARM A / R-ICE	17/08/2007	NOT APPLICABLE	-	03/10/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003642501030	ARM A / R-ICE	19/03/2008	NOT APPLICABLE	-	02/05/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003642501410	ARM A / R-ICE	08/02/2008	NOT APPLICABLE	-	29/05/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003643501202	ARM A / R-ICE	19/03/2008	NOT APPLICABLE	-	02/06/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003649501033	ARM A / R-ICE	05/06/2008	NOT APPLICABLE	-	03/09/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101021038	ARM B / R-DHAP	06/10/2005	OBSERVATION	02/02/2006	05/12/2006	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	09/01/2006	3	5
5003101031006	ARM B / R-DHAP	17/12/2003	NOT APPLICABLE	-	19/02/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101031019	ARM B / R-DHAP	30/12/2004	NOT APPLICABLE	-	21/01/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003101031067	ARM B / R-DHAP	22/05/2007	NOT APPLICABLE	-	14/06/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003101031401	ARM B / R-DHAP	31/08/2004	RITUXIMAB	25/11/2004	30/03/2005	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	26/11/2004	3	2
5003101031411	ARM B / R-DHAP	26/09/2006	NOT APPLICABLE	-	06/12/2006	INDUCTION PHASE	OTHER	COLLECTION FAILURE	COMPLETE RESPONSE	-	3	-
5003101051050	ARM B / R-DHAP	13/07/2006	RITUXIMAB	16/10/2006	13/01/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	11/10/2006	3	2
5003101051063	ARM B / R-DHAP	26/03/2007	NOT APPLICABLE	-	25/06/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003101071002	ARM B / R-DHAP	16/10/2003	NOT APPLICABLE	-	21/11/2003	INDUCTION PHASE	DEATH		NOT EVALUATED	-	1	-
5003101071051	ARM B / R-DHAP	25/07/2006	NOT APPLICABLE	-	19/09/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003101071073	ARM B / R-DHAP	19/10/2007	NOT APPLICABLE	-	28/11/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003101071408	ARM B / R-DHAP	14/12/2005	RITUXIMAB	25/04/2006	14/11/2006	FOLLOW UP PERIOD	OTHER	FAILURE TREATMENT	PROGRESSIVE DISEASE	03/04/2006	3	4
5003101071414	ARM B / R-DHAP	16/11/2006	NOT APPLICABLE	-	16/02/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-
5003101071607	ARM B / R-DHAP	07/01/2004	NOT APPLICABLE	-	16/01/2004	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	-	1	-
5003101071620	ARM B / R-DHAP	29/10/2004	NOT APPLICABLE	-	29/10/2004	BEFORE TREATMENT	PATIENT VOLONTARY WITHDRAWAL		NOT EVALUATED	-	-	-
5003101071643	ARM B / R-DHAP	29/10/2007	OBSERVATION	20/03/2008	15/05/2008	FOLLOW UP PERIOD	DEATH		DEATH WITHOUT PROGRESSION	27/02/2008	3	2
5003101091022	ARM B / R-DHAP	31/03/2005	NOT APPLICABLE	-	14/06/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101091025	ARM B / R-DHAP	04/05/2005	NOT APPLICABLE	-	12/07/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101091626	ARM B / R-DHAP	01/09/2005	NOT APPLICABLE	-	17/10/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003101131060	ARM B / R-DHAP	25/01/2007	NOT APPLICABLE	-	06/04/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101141402	ARM B / R-DHAP	06/04/2005	NOT APPLICABLE	-	21/06/2005	INDUCTION PHASE	TREATMENT TOXICITY		PROGRESSIVE DISEASE	-	3	-
5003101161028	ARM B / R-DHAP	08/06/2005	NOT APPLICABLE	-	22/08/2005	INDUCTION PHASE	TREATMENT TOXICITY		COMPLETE RESPONSE	-	3	-
5003101221057	ARM B / R-DHAP	29/11/2006	NOT APPLICABLE	-	25/01/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101221070	ARM B / R-DHAP	17/09/2007	NOT APPLICABLE	-	13/12/2007	INDUCTION PHASE	OTHER	INVESTIGATOR DECISION	PARTIAL RESPONSE	-	3	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003101221639	ARM B / R-DHAP	01/02/2007	NOT APPLICABLE	-	19/04/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101251015	ARM B / R-DHAP	15/09/2004	NOT APPLICABLE	-	01/12/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101251035	ARM B / R-DHAP	26/07/2005	RITUXIMAB	16/11/2005	31/05/2006	FOLLOW UP PERIOD	OTHER	RELAPSE NHL	PROGRESSIVE DISEASE	14/11/2005	3	4
5003101251044	ARM B / R-DHAP	28/03/2006	NOT APPLICABLE	-	12/05/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003101391032	ARM B / R-DHAP	12/07/2005	NOT APPLICABLE	-	02/08/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003101391048	ARM B / R-DHAP	15/06/2006	NOT APPLICABLE	-	12/09/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101391207	ARM B / R-DHAP	30/01/2006	NOT APPLICABLE	-	05/06/2006	CONSOLIDATION PHASE	OTHER	MEDICAL DECISION TO TREAT WITH RADIOTHERAPY ON SINUS BECAUSE OF RESIDUAL MASS	UNCONFIRMED COMPLETE RESPONSE	04/05/2006	3	-
5003101391613	ARM B / R-DHAP	22/04/2004	NOT APPLICABLE	-	02/07/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003101431204	ARM B / R-DHAP	25/11/2003	NOT APPLICABLE	-	13/02/2004	INDUCTION PHASE	TREATMENT TOXICITY		UNCONFIRMED COMPLETE RESPONSE	-	3	-
5003101601066	ARM B / R-DHAP	18/05/2007	NOT APPLICABLE	-	24/07/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101601076	ARM B / R-DHAP	05/03/2008	NOT APPLICABLE	-	25/04/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101601610	ARM B / R-DHAP	16/02/2004	OBSERVATION	17/05/2004	11/08/2004	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	24/05/2004	3	-
5003101641018	ARM B / R-DHAP	28/12/2004	NOT APPLICABLE	-	31/03/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101641047	ARM B / R-DHAP	25/04/2006	NOT APPLICABLE	-	29/06/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003101641079	ARM B / R-DHAP	27/06/2008	NOT APPLICABLE	-	12/08/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003102181031	ARM B / R-DHAP	24/06/2005	NOT APPLICABLE	-	20/08/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003102341003	ARM B / R-DHAP	07/11/2003	NOT APPLICABLE	-	12/01/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003102361203	ARM B / R-DHAP	21/11/2003	OBSERVATION	19/02/2004	13/03/2004	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL		NOT EVALUATED	18/02/2004	3	-
5003102411054	ARM B / R-DHAP	27/09/2006	OBSERVATION	08/01/2007	28/08/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	28/12/2006	3	6
5003102411069	ARM B / R-DHAP	05/07/2007	OBSERVATION	24/10/2007	21/01/2008	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	04/10/2007	3	3
5003102541016	ARM B / R-DHAP	21/09/2004	NOT APPLICABLE	-	20/10/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003102541640	ARM B / R-DHAP	02/04/2007	RITUXIMAB	27/07/2007	11/09/2007	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	26/07/2007	3	1
5003104621053	ARM B / R-DHAP	02/08/2006	OBSERVATION	15/11/2006	22/01/2007	FOLLOW UP PERIOD	OTHER	INDUCTION RESPONSE WAS SD AND NOT RESOLVED AFTER TRANSPLANT	STABLE DISEASE	22/11/2006	3	2
5003601201018	ARM B / R-DHAP	14/06/2005	NOT APPLICABLE	-	04/08/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003601201201	ARM B / R-DHAP	26/03/2004	NOT APPLICABLE	-	15/06/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003601301015	ARM B / R-DHAP	21/11/2007	RITUXIMAB	08/02/2008	18/03/2008	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL		PARTIAL RESPONSE	14/02/2008	3	-
5003601401001	ARM B / R-DHAP	13/11/2003	NOT APPLICABLE	-	02/01/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003601401004	ARM B / R-DHAP	27/09/2006	RITUXIMAB	19/12/2006	26/06/2007	FOLLOW UP PERIOD	TREATMENT TOXICITY		COMPLETE RESPONSE	15/12/2006	3	3
5003601401402	ARM B / R-DHAP	17/02/2005	RITUXIMAB	04/05/2005	16/09/2005	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	10/05/2005	3	2
5003601601001	ARM B / R-DHAP	05/04/2006	NOT APPLICABLE	-	16/06/2006	INDUCTION PHASE	OTHER	WEST NILE VIRUS	NOT EVALUATED	-	3	-
5003601601004	ARM B / R-DHAP	02/11/2007	NOT APPLICABLE	-	04/11/2007	BEFORE TREATMENT	PATIENT VOLONTARY WITHDRAWAL		NOT EVALUATED	-	-	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003601601402	ARM B / R-DHAP	29/10/2004	NOT APPLICABLE	-	03/01/2005	INDUCTION PHASE	TREATMENT TOXICITY		COMPLETE RESPONSE	-	3	-
5003601601602	ARM B / R-DHAP	05/12/2007	OBSERVATION	13/03/2008	23/05/2008	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	27/02/2008	3	2
5003601801003	ARM B / R-DHAP	08/11/2004	NOT APPLICABLE	-	13/01/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003601801603	ARM B / R-DHAP	15/12/2004	NOT APPLICABLE	-	09/03/2005	INDUCTION PHASE	TREATMENT TOXICITY		PARTIAL RESPONSE	-	3	-
5003602801016	ARM B / R-DHAP	21/08/2007	NOT APPLICABLE	-	04/10/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003602801204	ARM B / R-DHAP	22/12/2004	NOT APPLICABLE	-	08/02/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003603201001	ARM B / R-DHAP	11/03/2004	NOT APPLICABLE	-	03/05/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003603201005	ARM B / R-DHAP	08/10/2004	NOT APPLICABLE	-	12/10/2004	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION		NOT EVALUATED	-	-	-
5003603201027	ARM B / R-DHAP	26/01/2006	NOT APPLICABLE	-	26/01/2006	BEFORE TREATMENT	DEATH		NOT EVALUATED	-	-	-
5003603201034	ARM B / R-DHAP	14/08/2006	NOT APPLICABLE	-	12/10/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003603201050	ARM B / R-DHAP	06/08/2007	NOT APPLICABLE	-	08/11/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003603201211	ARM B / R-DHAP	21/02/2006	NOT APPLICABLE	-	26/04/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003603301401	ARM B / R-DHAP	06/09/2004	NOT APPLICABLE	-	30/04/2005	CONSOLIDATION PHASE	OTHER	IT WAS DECIDED BY GELA THAT THE PATIENT COULD NOT BE RANDOMIZED AS IT WAS 5 MONTH BETWEEN TRANSPLANT AND MAINTENANCE AND THEREFORE PATIENT HAS COME OFF PROTOCOL	UNCONFIRMED COMPLETE RESPONSE	10/12/2004	3	-
5003603801007	ARM B / R-DHAP	08/03/2006	NOT APPLICABLE	-	17/05/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003603801009	ARM B / R-DHAP	31/05/2006	OBSERVATION	07/09/2006	10/11/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	05/09/2006	3	2

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003603801010	ARM B / R-DHAP	23/08/2006	NOT APPLICABLE	-	07/11/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003603801013	ARM B / R-DHAP	20/12/2006	NOT APPLICABLE	-	15/02/2007	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	-	2	-
5003603901001	ARM B / R-DHAP	06/10/2004	NOT APPLICABLE	-	14/11/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003604201028	ARM B / R-DHAP	02/02/2006	NOT APPLICABLE	-	27/03/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003604201056	ARM B / R-DHAP	22/04/2008	OBSERVATION	22/08/2008	15/04/2009	FOLLOW UP PERIOD	OTHER	PD	PROGRESSIVE DISEASE	12/08/2008	3	3
5003604301607	ARM B / R-DHAP	12/08/2004	NOT APPLICABLE	-	27/10/2004	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		PARTIAL RESPONSE	-	3	-
5003604701002	ARM B / R-DHAP	25/02/2005	RITUXIMAB	19/05/2005	26/10/2005	FOLLOW UP PERIOD	OTHER	PROGRESSION UNDER MAINTENANCE THERAPIE	PROGRESSIVE DISEASE	17/05/2005	3	3
5003604701012	ARM B / R-DHAP	19/04/2007	NOT APPLICABLE	-	04/05/2007	INDUCTION PHASE	DEATH		NOT EVALUATED	-	1	-
5003604701015	ARM B / R-DHAP	26/09/2007	RITUXIMAB	12/12/2007	18/04/2008	FOLLOW UP PERIOD	OTHER	PATIENT REFUSED THE TREATMENT. HE COULD NOT FOLLOW THE PROTOCOL	NOT EVALUATED	19/12/2007	3	1
5003604801006	ARM B / R-DHAP	18/10/2005	RITUXIMAB	09/03/2006	16/05/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	13/02/2006	3	1
5003604801201	ARM B / R-DHAP	08/09/2004	NOT APPLICABLE	-	14/11/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003604801405	ARM B / R-DHAP	30/05/2007	NOT APPLICABLE	-	09/08/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-
5003604901004	ARM B / R-DHAP	22/11/2005	RITUXIMAB	09/03/2006	21/12/2006	FOLLOW UP PERIOD	OTHER	RELAPSE	PROGRESSIVE DISEASE	25/05/2006	3	2
5003604901007	ARM B / R-DHAP	15/01/2008	OBSERVATION	18/06/2008	05/10/2008	FOLLOW UP PERIOD	OTHER	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 UPTATE DUE TO PET-CT RESULTS, THE TREATING PHYSICIAN SUSPECTED THAT *	PARTIAL RESPONSE	19/05/2008	3	2
5003604901602	ARM B / R-DHAP	02/02/2005	RITUXIMAB	02/05/2005	28/06/2005	FOLLOW UP PERIOD	OTHER	LOST TO FOLLOW-UP AFTER BMT	NOT EVALUATED	16/06/2005	3	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003604901603	ARM B / R-DHAP	03/03/2008	RITUXIMAB	19/06/2008	13/09/2008	FOLLOW UP PERIOD	DEATH		COMPLETE RESPONSE	18/06/2008	3	1
5003605201603	ARM B / R-DHAP	14/04/2004	NOT APPLICABLE	-	29/06/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-
5003605301203	ARM B / R-DHAP	23/03/2004	NOT APPLICABLE	-	25/05/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003605301610	ARM B / R-DHAP	18/11/2004	RITUXIMAB	02/05/2005	08/12/2005	FOLLOW UP PERIOD	OTHER	PROGRESSION- NEW LESION VERVICAL LYMPH NODE	PROGRESSIVE DISEASE	23/02/2005	3	4
5003605701404	ARM B / R-DHAP	30/01/2008	NOT APPLICABLE	-	04/04/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003606201033	ARM B / R-DHAP	02/06/2006	NOT APPLICABLE	-	22/08/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003606201407	ARM B / R-DHAP	06/06/2006	RITUXIMAB	21/09/2006	16/11/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	13/09/2006	3	1
5003606201410	ARM B / R-DHAP	09/05/2007	NOT APPLICABLE	-	31/05/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003606201622	ARM B / R-DHAP	21/07/2006	NOT APPLICABLE	-	25/09/2006	INDUCTION PHASE	OTHER	NO STEM CELL MOBILIZATION POSSIBLE	PARTIAL RESPONSE	-	3	-
5003606201626	ARM B / R-DHAP	22/02/2007	NOT APPLICABLE	-	18/06/2007	CONSOLIDATION PHASE	OTHER	NO SECOND RANDOMISATION DONE	COMPLETE RESPONSE	21/05/2007	3	-
5003606301012	ARM B / R-DHAP	11/10/2007	NOT APPLICABLE	-	12/02/2008	CONSOLIDATION PHASE	DEATH		PARTIAL RESPONSE	15/01/2008	3	-
5003606301606	ARM B / R-DHAP	07/07/2004	NOT APPLICABLE	-	13/09/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-
5003606701005	ARM B / R-DHAP	22/09/2005	NOT APPLICABLE	-	05/02/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-
5003607201408	ARM B / R-DHAP	14/12/2006	NOT APPLICABLE	-	10/05/2007	CONSOLIDATION PHASE	OTHER	NO SECOND RANDOMIZATION DUE TO PROLONGED THROMBOCYTOPENIA AND LEUCOCYTOPENIA	COMPLETE RESPONSE	15/03/2007	3	-
5003607301622	ARM B / R-DHAP	11/12/2006	NOT APPLICABLE	-	26/01/2007	INDUCTION PHASE	DEATH		NOT EVALUATED	-	2	-
5003607501401	ARM B / R-DHAP	19/07/2006	RITUXIMAB	30/10/2006	06/06/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	18/10/2006	3	4

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003608301205	ARM B / R-DHAP	25/06/2004	RITUXIMAB	01/10/2004	15/06/2005	FOLLOW UP PERIOD	OTHER	INADVERTENTLY STOPPED RITUXIMAB	UNCONFIRMED COMPLETE RESPONSE	29/09/2004	3	4
5003608701008	ARM B / R-DHAP	09/02/2006	OBSERVATION	19/05/2006	13/06/2006	FOLLOW UP PERIOD	OTHER	PROGRESSED AFTER STABLE DISEASE	PROGRESSIVE DISEASE	01/05/2006	3	3
5003610201008	ARM B / R-DHAP	15/11/2004	NOT APPLICABLE	-	11/01/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003610201212	ARM B / R-DHAP	13/04/2006	NOT APPLICABLE	-	17/05/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003610301209	ARM B / R-DHAP	17/03/2005	OBSERVATION	21/06/2005	14/03/2006	FOLLOW UP PERIOD	OTHER	PATIENT WITHDRAWN BY INVESTIGATOR AS IS NON COMPLIANT WITH ATTENDING FOR REVIEW	UNCONFIRMED COMPLETE RESPONSE	27/06/2005	3	2
5003610301613	ARM B / R-DHAP	01/03/2005	OBSERVATION	23/05/2005	07/09/2005	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	31/05/2005	3	4
5003610701014	ARM B / R-DHAP	24/09/2007	RITUXIMAB	07/01/2008	14/04/2008	FOLLOW UP PERIOD	OTHER	PD	COMPLETE RESPONSE	14/01/2008	3	2
5003610701403	ARM B / R-DHAP	06/12/2007	OBSERVATION	28/03/2008	06/10/2008	FOLLOW UP PERIOD	OTHER	RECCURENT IN FU-PHASE 6 MONTHS AFTER TRANSPLANT	PROGRESSIVE DISEASE	03/03/2008	3	4
5003611301002	ARM B / R-DHAP	14/09/2004	NOT APPLICABLE	-	30/10/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003611301003	ARM B / R-DHAP	02/05/2005	NOT APPLICABLE	-	19/07/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	-	3	-
5003612201401	ARM B / R-DHAP	09/05/2005	RITUXIMAB	29/09/2005	12/10/2005	FOLLOW UP PERIOD	OTHER	THE PATIENT WAS RANDOMIZED AT RITUXIMAB BUT IT WAS NOT GIVEN BECAUSE OF INCORRECTED COMMUNICATION BETWEEN US AND THE PRIVATE PRAXIS	COMPLETE RESPONSE	25/08/2005	3	6
5003612301623	ARM B / R-DHAP	13/12/2006	RITUXIMAB	16/04/2007	31/07/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	30/03/2007	3	2
5003612501016	ARM B / R-DHAP	29/06/2007	NOT APPLICABLE	-	12/09/2007	INDUCTION PHASE	OTHER	RESPONSE NOT ENOUGH, THERE IS STILL BULKY DISEASE	PARTIAL RESPONSE	-	3	-
5003612501019	ARM B / R-DHAP	03/09/2007	NOT APPLICABLE	-	20/11/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003614301407	ARM B / R-DHAP	06/03/2008	OBSERVATION	21/07/2008	18/09/2008	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	20/06/2008	3	2
5003614501013	ARM B / R-DHAP	20/04/2007	NOT APPLICABLE	-	21/07/2007	INDUCTION PHASE	DEATH		PROGRESSIVE DISEASE	-	3	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003615501004	ARM B / R-DHAP	05/10/2006	NOT APPLICABLE	-	18/12/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003615501007	ARM B / R-DHAP	20/12/2006	NOT APPLICABLE	-	23/02/2007	INDUCTION PHASE	OTHER	CVA	NOT EVALUATED	-	1	-
5003615501029	ARM B / R-DHAP	27/02/2008	NOT APPLICABLE	-	02/05/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003616201413	ARM B / R-DHAP	29/04/2008	NOT APPLICABLE	-	03/06/2008	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	-	1	-
5003616301212	ARM B / R-DHAP	21/04/2006	NOT APPLICABLE	-	05/07/2006	INDUCTION PHASE	OTHER	FAILURE TO MOBILIZE	PARTIAL RESPONSE	-	3	-
5003616501411	ARM B / R-DHAP	26/06/2008	NOT APPLICABLE	-	22/09/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003617201021	ARM B / R-DHAP	17/10/2005	RITUXIMAB	14/02/2006	17/03/2006	FOLLOW UP PERIOD	OTHER	ACTIVE HEPATITIS C INFECTION AFTER APHERESIS, BAD CONDITION AFTER TRANSPLANTATION / DECISION NOT TO TREAT PATIENT WITH RITUXIMAB FURTHER AS RANDOMIZED IN STUDY	UNCONFIRMED COMPLETE RESPONSE	01/02/2006	3	6
5003617201024	ARM B / R-DHAP	07/12/2005	NOT APPLICABLE	-	02/01/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003617201031	ARM B / R-DHAP	26/05/2006	NOT APPLICABLE	-	13/07/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
5003617201043	ARM B / R-DHAP	25/01/2007	RITUXIMAB	16/04/2007	13/09/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	19/04/2007	3	2
5003617201049	ARM B / R-DHAP	10/07/2007	NOT APPLICABLE	-	24/09/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003617201616	ARM B / R-DHAP	28/07/2005	NOT APPLICABLE	-	14/10/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		NOT EVALUATED	-	3	-
5003617501006	ARM B / R-DHAP	01/12/2006	NOT APPLICABLE	-	12/01/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003617501026	ARM B / R-DHAP	06/12/2007	NOT APPLICABLE	-	07/01/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	1	-
5003618301005	ARM B / R-DHAP	01/02/2006	OBSERVATION	19/05/2006	23/06/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	03/05/2006	3	4

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003618501025	ARM B / R-DHAP	05/12/2007	OBSERVATION	29/04/2008	08/01/2009	FOLLOW UP PERIOD	OTHER	PROGRESSION DURING MAINTENANCE	PROGRESSIVE DISEASE	10/04/2008	3	3
5003619301006	ARM B / R-DHAP	26/05/2006	NOT APPLICABLE	-	21/09/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003619301016	ARM B / R-DHAP	22/01/2008	NOT APPLICABLE	-	26/03/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003619501009	ARM B / R-DHAP	17/01/2007	NOT APPLICABLE	-	06/06/2007	CONSOLIDATION PHASE	OTHER	CLINICIAN DECISION TO PLAN AND GIVE RADIOTHERAPY POST TRANSPLANT	PARTIAL RESPONSE	15/05/2007	3	-
5003619501010	ARM B / R-DHAP	14/02/2007	NOT APPLICABLE	-	06/04/2007	INDUCTION PHASE	DEATH		NOT EVALUATED	-	2	-
5003620201017	ARM B / R-DHAP	09/05/2005	NOT APPLICABLE	-	10/08/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		-	-	3	-
5003622201037	ARM B / R-DHAP	28/09/2006	NOT APPLICABLE	-	14/12/2006	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003623501405	ARM B / R-DHAP	05/07/2007	NOT APPLICABLE	-	26/07/2007	INDUCTION PHASE	DEATH		DEATH WITHOUT PROGRESSION	-	1	-
5003623501408	ARM B / R-DHAP	18/10/2007	OBSERVATION	25/01/2008	28/04/2008	FOLLOW UP PERIOD	OTHER	COMMENCING RADIOTHERAPY, CONSIDERED A NEW TREATMENT, PATIENT IS IN PARTIAL RESPONSE	PARTIAL RESPONSE	18/01/2008	3	2
5003625501020	ARM B / R-DHAP	14/09/2007	NOT APPLICABLE	-	30/11/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003626501605	ARM B / R-DHAP	14/09/2007	RITUXIMAB	19/12/2007	28/04/2008	FOLLOW UP PERIOD	TREATMENT TOXICITY		PARTIAL RESPONSE	09/01/2008	3	1
5003628201002	ARM B / R-DHAP	15/07/2004	NOT APPLICABLE	-	28/09/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PARTIAL RESPONSE	-	3	-
5003628201046	ARM B / R-DHAP	21/06/2007	NOT APPLICABLE	-	04/09/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	3	-
5003628201404	ARM B / R-DHAP	13/02/2006	NOT APPLICABLE	-	07/06/2006	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		STABLE DISEASE	-	3	-
5003630201040	ARM B / R-DHAP	06/11/2006	RITUXIMAB	09/03/2007	22/05/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	13/02/2007	3	2
5003631201011	ARM B / R-DHAP	03/12/2004	NOT APPLICABLE	-	25/12/2004	INDUCTION PHASE	TREATMENT TOXICITY		PROGRESSIVE DISEASE	-	1	-

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of cycles received	Nb of maintenance visits
5003631201012	ARM B / R-DHAP	15/12/2004	NOT APPLICABLE	-	01/03/2005	INDUCTION PHASE	TREATMENT TOXICITY		STABLE DISEASE	-	3	-
5003632201015	ARM B / R-DHAP	01/04/2005	NOT APPLICABLE	-	01/07/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	3	-
5003635201411	ARM B / R-DHAP	11/05/2007	NOT APPLICABLE	-	04/06/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		STABLE DISEASE	-	2	-
5003636201047	ARM B / R-DHAP	29/06/2007	NOT APPLICABLE	-	14/08/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	-	2	-
N = 318												

6.2. Initial treatment

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

Randomization Number	Arm of treatment	Number of cycles of chemotherapy	Chemotherapy regimen	Specify other Chemotherapy regimen
5003603801601	ARM A / R-ICE	4	OTHER	B ALL GERMAN : PEDIATRIC PROTOCOL NHL-BFM95
5003603801608	ARM A / R-ICE	6	OTHER	NHL-BFM 95 PROTOCOL FOR RISK GROUP 3
5003607201016	ARM A / R-ICE	6	OTHER	B ALL GERMAN : HOELZER PROTO (BLOCK A1, B1, C1, A2, B2, C2) + INTRATHECAL MTX + ARAC + DEXAMETHASONE
5003609201058	ARM A / R-ICE	6	OTHER	GMALL B-NHL
5003617201209	ARM A / R-ICE	8	OTHER	BEACOPP ESC.
5003631201035	ARM A / R-ICE	2	OTHER	B-NHL PROTOCOL
5003642501030	ARM A / R-ICE	8	OTHER	R-CHOP (R-CHOP 14 VS 21 STUDY)
5003601201201	ARM B / R-DHAP	6	OTHER	VM26 / ARA-C / VINCRISTIN / HD-MTX / IFOSFAMID / DEXAMETHASON
5003604201028	ARM B / R-DHAP	6	OTHER	B-ALL GERMAN / B-NHL ELDERLY : MTX, VINCR, ADRIA, CYCLOPHO, DEXA, RITUX, IFOSF, VM-26, ARA-C, GEMCI
5003616201413	ARM B / R-DHAP	8	OTHER	CHOEP-14
5003617201616	ARM B / R-DHAP	3	OTHER	B ALL GERMAN / NHL 2002 PROTOCOL (>55 YEARS)
N = 11				

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

Randomization Number	Arm of treatment	Radiotherapy	Specify dose of radiotherapy (Gy)
5003101071013	ARM A / R-ICE	LOCAL	36
5003101071647	ARM A / R-ICE	LOCAL	40
5003101131058	ARM A / R-ICE	LOCAL	30
5003101131062	ARM A / R-ICE	LOCAL	36
5003101281033	ARM A / R-ICE	LOCAL	36
5003101391201	ARM A / R-ICE	LOCAL	40
5003101441036	ARM A / R-ICE	LOCAL	40
5003101621609	ARM A / R-ICE	LOCAL	40
5003101621615	ARM A / R-ICE	LOCAL	40
5003102161413	ARM A / R-ICE	LOCAL	20
5003102341641	ARM A / R-ICE	LOCAL	40
5003102491619	ARM A / R-ICE	LOCAL	30
5003102541052	ARM A / R-ICE	LOCAL	36
5003601401605	ARM A / R-ICE	LOCAL	40
5003601601005	ARM A / R-ICE	LOCAL	45
5003601801017	ARM A / R-ICE	LOCAL	16
5003601881401	ARM A / R-ICE	-	48
5003602201601	ARM A / R-ICE	LOCAL	36
5003602801605	ARM A / R-ICE	LOCAL	40
5003602901402	ARM A / R-ICE	LOCAL	45
5003603201213	ARM A / R-ICE	LOCAL	40
5003603201608	ARM A / R-ICE	LOCAL	36
5003603701004	ARM A / R-ICE	LOCAL	30.6
5003603801002	ARM A / R-ICE	LOCAL	36
5003603801203	ARM A / R-ICE	LOCAL	6

Randomization Number	Arm of treatment	Radiotherapy	Specify dose of radiotherapy (Gy)
5003603801406	ARM A / R-ICE	LOCAL	40
5003603801601	ARM A / R-ICE	LOCAL	36
5003604301013	ARM A / R-ICE	LOCAL	36
5003604301602	ARM A / R-ICE	LOCAL	40
5003604301618	ARM A / R-ICE	LOCAL	40
5003604801014	ARM A / R-ICE	LOCAL	30
5003604801205	ARM A / R-ICE	LOCAL	40
5003605301010	ARM A / R-ICE	LOCAL	40
5003606201029	ARM A / R-ICE	LOCAL	38
5003606201605	ARM A / R-ICE	LOCAL	36
5003606301204	ARM A / R-ICE	LOCAL	30
5003606301612	ARM A / R-ICE	LOCAL	30
5003607201016	ARM A / R-ICE	LOCAL	59
5003607201045	ARM A / R-ICE	LOCAL	20
5003607701007	ARM A / R-ICE	LOCAL	36
5003607701405	ARM A / R-ICE	LOCAL	39.6
5003608301605	ARM A / R-ICE	OTHER	40
5003608701016	ARM A / R-ICE	LOCAL	36
5003610201612	ARM A / R-ICE	LOCAL	36
5003610201615	ARM A / R-ICE	LOCAL	39.6
5003612501015	ARM A / R-ICE	LOCAL	30
5003616301403	ARM A / R-ICE	LOCAL	36
5003616501005	ARM A / R-ICE	OTHER	35
5003617201209	ARM A / R-ICE	LOCAL	30
5003620301017	ARM A / R-ICE	LOCAL	45
5003622201022	ARM A / R-ICE	LOCAL	36
5003622201210	ARM A / R-ICE	LOCAL	36
5003622201403	ARM A / R-ICE	LOCAL	36
5003626501607	ARM A / R-ICE	LOCAL	40
5003628201618	ARM A / R-ICE	LOCAL	36
5003628201624	ARM A / R-ICE	LOCAL	36
5003630201055	ARM A / R-ICE	LOCAL	35
5003632201054	ARM A / R-ICE	LOCAL	24
5003632201614	ARM A / R-ICE	LOCAL	40
5003642501410	ARM A / R-ICE	LOCAL	20
5003643501202	ARM A / R-ICE	LOCAL	30
5003101061617	ARM B / R-DHAP	LOCAL	40
5003101071607	ARM B / R-DHAP	LOCAL	50
5003101071620	ARM B / R-DHAP	LOCAL	50
5003101071643	ARM B / R-DHAP	LOCAL	50
5003101141624	ARM B / R-DHAP	LOCAL	27
5003101251009	ARM B / R-DHAP	LOCAL	36
5003101251021	ARM B / R-DHAP	LOCAL	40
5003101251035	ARM B / R-DHAP	LOCAL	40
5003101391613	ARM B / R-DHAP	LOCAL	40

Randomization Number	Arm of treatment	Radiotherapy	Specify dose of radiotherapy (Gy)
5003101391646	ARM B / R-DHAP	LOCAL	40
5003101431627	ARM B / R-DHAP	LOCAL	40
5003101481614	ARM B / R-DHAP	LOCAL	40
5003102341003	ARM B / R-DHAP	OTHER	40
5003102541636	ARM B / R-DHAP	LOCAL	7.6
5003102541640	ARM B / R-DHAP	LOCAL	36
5003601201201	ARM B / R-DHAP	LOCAL	36
5003601201604	ARM B / R-DHAP	LOCAL	40
5003601301015	ARM B / R-DHAP	LOCAL	30
5003601401601	ARM B / R-DHAP	LOCAL	44
5003601401604	ARM B / R-DHAP	LOCAL	40
5003601601601	ARM B / R-DHAP	LOCAL	30
5003601801607	ARM B / R-DHAP	LOCAL	40
5003601881601	ARM B / R-DHAP	LOCAL	36
5003603201001	ARM B / R-DHAP	LOCAL	36
5003603701001	ARM B / R-DHAP	LOCAL	30.6
5003603801013	ARM B / R-DHAP	LOCAL	38
5003604701011	ARM B / R-DHAP	LOCAL	36
5003604801004	ARM B / R-DHAP	LOCAL	40
5003604901602	ARM B / R-DHAP	LOCAL	4
5003605301203	ARM B / R-DHAP	LOCAL	30
5003606301604	ARM B / R-DHAP	LOCAL	30
5003606501601	ARM B / R-DHAP	LOCAL	39.6
5003606701005	ARM B / R-DHAP	LOCAL	39.6
5003607201623	ARM B / R-DHAP	LOCAL	36
5003607501401	ARM B / R-DHAP	LOCAL	30
5003608701008	ARM B / R-DHAP	LOCAL	36
5003610201008	ARM B / R-DHAP	LOCAL	39.6
5003610201212	ARM B / R-DHAP	LOCAL	36
5003612301623	ARM B / R-DHAP	LOCAL	40
5003616501411	ARM B / R-DHAP	LOCAL	35
5003617201031	ARM B / R-DHAP	LOCAL	9
5003617201616	ARM B / R-DHAP	LOCAL	36
5003617201629	ARM B / R-DHAP	LOCAL	36
5003617301616	ARM B / R-DHAP	LOCAL	30
5003623501405	ARM B / R-DHAP	LOCAL	40
5003628201046	ARM B / R-DHAP	LOCAL	36
5003630201040	ARM B / R-DHAP	LOCAL	36
5003632201015	ARM B / R-DHAP	LOCAL	20
5003632201606	ARM B / R-DHAP	LOCAL	36
N = 110			

6.3. Progression/relapse diagnosis

Table 6.3-1 Nodal involvement (FAS)

	Arm of treatment					
	ARM A / R-ICE		ARM B / R-DHAP		All	
	N	%	N	%	N	%
Cervical right						
Normal	185	76	171	73	356	75
Involved	49	20	54	23	103	22
Not evaluated	8	3	9	4	17	4
.	1	0	0	0	1	0
Cervical left						
Normal	170	70	173	74	343	72
Involved	64	26	53	23	117	25
Not evaluated	8	3	8	3	16	3
.	1	0	0	0	1	0
Supraclavicular right						
Normal	219	90	193	82	412	86
Involved	18	7	33	14	51	11
Not evaluated	5	2	8	3	13	3
.	1	0	0	0	1	0
Supraclavicular left						
Normal	202	83	196	84	398	83
Involved	35	14	30	13	65	14
Not evaluated	5	2	8	3	13	3
.	1	0	0	0	1	0
Axillary right						
Normal	205	84	196	84	401	84
Involved	34	14	36	15	70	15
Not evaluated	3	1	2	1	5	1
.	1	0	0	0	1	0
Axillary left						
Normal	191	79	195	83	386	81
Involved	49	20	35	15	84	18
Not evaluated	3	1	4	2	7	1
Inguinal right						
Normal	199	82	201	86	400	84
Involved	39	16	26	11	65	14
Not evaluated	4	2	7	3	11	2
.	1	0	0	0	1	0
Inguinal left						
Normal	201	83	197	84	398	83
Involved	37	15	31	13	68	14
Not evaluated	4	2	6	3	10	2

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
.	1	0	0	0	1	0
Mediastinal						
Normal	135	56	158	68	293	61
Involved	105	43	71	30	176	37
Not evaluated	2	1	5	2	7	1
.	1	0	0	0	1	0
Pulmonary hilar						
Normal	204	84	197	84	401	84
Involved	35	14	31	13	66	14
Not evaluated	3	1	6	3	9	2
.	1	0	0	0	1	0
Para-aortic						
Normal	132	54	140	60	272	57
Involved	109	45	90	38	199	42
Not evaluated	1	0	4	2	5	1
.	1	0	0	0	1	0
Mesenteric						
Normal	155	64	151	65	306	64
Involved	84	35	79	34	163	34
Not evaluated	2	1	4	2	6	1
.	2	1	0	0	2	0
Iliac right						
Normal	204	84	195	83	399	84
Involved	37	15	32	14	69	14
Not evaluated	1	0	7	3	8	2
.	1	0	0	0	1	0
Iliac left						
Normal	203	84	184	79	387	81
Involved	38	16	43	18	81	17
Not evaluated	1	0	7	3	8	2
.	1	0	0	0	1	0
Splenic Hilar						
Normal	221	91	202	86	423	89
Involved	18	7	23	10	41	9
Not evaluated	3	1	7	3	10	2
.	1	0	2	1	3	1
Other nodal involvement						
No	218	90	209	89	427	90
Yes	17	7	22	9	39	8

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
.	8	3	3	1	11	2
TOTAL	243	100	234	100	477	100

Listing 6.3-1 Other nodal involvement localizations (FAS)

Randomization Number	Arm of treatment	Other nodal involvement	Other nodal involvement - localization
5003101051648	ARM A / R-ICE	Yes	INTERBRONCHIAL
5003101161407	ARM A / R-ICE	Yes	RIGHT-LATERO AND RETRO CAVA
5003101431622	ARM A / R-ICE	Yes	SUBCAPSULAR HEPATIC LESION
5003102541625	ARM A / R-ICE	Yes	PARA VERTEBRAL LEFT
5003603201627	ARM A / R-ICE	Yes	RETROPERITONEAL
5003603201628	ARM A / R-ICE	Yes	RETROCRURAL BOTH SIDES
5003603701010	ARM A / R-ICE	Yes	HEAD AND TAIL OF PANCREAS (LYMPHNODES)
5003604301013	ARM A / R-ICE	Yes	LEFT LOWER LEG
5003606501409	ARM A / R-ICE	Yes	SUBCUTANEOUS LYMPH NODES BEHIND MASTOID
5003607701007	ARM A / R-ICE	Yes	HEPATIC
5003610501031	ARM A / R-ICE	Yes	OMENTUM
5003613301210	ARM A / R-ICE	Yes	SOFT TISSUE OF RIGHT SUPERIOR BUTTOCK
5003614501002	ARM A / R-ICE	Yes	LIVER
5003622201022	ARM A / R-ICE	Yes	LEFT GROIN TO LEFT UPPER LEG
5003626501607	ARM A / R-ICE	Yes	PORLA LYMPH NODE
5003630201055	ARM A / R-ICE	Yes	LIVER HILAR
5003649501033	ARM A / R-ICE	Yes	PORTA HEPATIS
5003101031006	ARM B / R-DHAP	Yes	PERIGASTRIC CHAIN
5003101031401	ARM B / R-DHAP	Yes	LEFT POPLITEAL NODE
5003101031411	ARM B / R-DHAP	Yes	PERI GASTRIC
5003101051050	ARM B / R-DHAP	Yes	RIGHT MAMMAR NODE
5003101051405	ARM B / R-DHAP	Yes	LEFT EPITROCHLEEN NODE
5003103161206	ARM B / R-DHAP	Yes	EPIGASTRIC LODGE
5003601601001	ARM B / R-DHAP	Yes	RIGHT PARATRACHEAL NODAL MASS
5003601601601	ARM B / R-DHAP	Yes	CELIAC
5003603301401	ARM B / R-DHAP	Yes	LEFT POPLITEAL FOSSA
5003604301607	ARM B / R-DHAP	Yes	Retrocrural node
5003604901603	ARM B / R-DHAP	Yes	OMENTUM
5003605701404	ARM B / R-DHAP	Yes	RETROMANDIBULAR LEFT
5003606201033	ARM B / R-DHAP	Yes	PELVIS
5003610201008	ARM B / R-DHAP	Yes	PELVIS
5003614501032	ARM B / R-DHAP	Yes	COELIAC AXIS
5003615501007	ARM B / R-DHAP	Yes	SUBCARINAL
5003616501411	ARM B / R-DHAP	Yes	LEFT SIDE RETROCRURAL

Randomization Number	Arm of treatment	Other nodal involvement	Other nodal involvement - localization
5003617201021	ARM B / R-DHAP	Yes	SUBCUTANEOUS LYMPH NODES
5003620201017	ARM B / R-DHAP	Yes	PLEURAL RIGHT
5003621501412	ARM B / R-DHAP	Yes	RIGHT INTERNAL MAMMARY
5003622201037	ARM B / R-DHAP	Yes	TUMOR IN THE SMALL PELVIS
5003623501408	ARM B / R-DHAP	Yes	SPLENOMEGALY
N = 39			

Table 6.3-2 Extra-nodal involvement (FAS)

	Arm of treatment					
	ARM A / R-ICE		ARM B / R-DHAP		All	
	N	%	N	%	N	%
Liver						
Normal	215	88	201	86	416	87
Involved	22	9	29	12	51	11
Not evaluated	5	2	4	2	9	2
.	1	0	0	0	1	0
Ascites						
Normal	229	94	222	95	451	95
Involved	6	2	4	2	10	2
Not evaluated	7	3	8	3	15	3
.	1	0	0	0	1	0
Pleural effusion						
Normal	222	91	211	90	433	91
Involved	13	5	15	6	28	6
Not evaluated	7	3	7	3	14	3
.	1	0	1	0	2	0
Lung						
Normal	202	83	193	82	395	83
Involved	34	14	38	16	72	15
Not evaluated	6	2	3	1	9	2
.	1	0	0	0	1	0
Spleen						
Normal	202	83	191	82	393	82
Involved	33	14	39	17	72	15
Not evaluated	7	3	4	2	11	2
.	1	0	0	0	1	0
Pericardium						
Normal	233	96	220	94	453	95
Involved	2	1	5	2	7	1
Not evaluated	7	3	9	4	16	3
.	1	0	0	0	1	0

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Breast						
Normal	229	94	212	91	441	92
Involved	3	1	4	2	7	1
Not evaluated	10	4	18	8	28	6
.	1	0	0	0	1	0
Gonadal						
Normal	222	91	207	88	429	90
Involved	7	3	5	2	12	3
Not evaluated	13	5	22	9	35	7
.	1	0	0	0	1	0
Kidney						
Normal	226	93	215	92	441	92
Involved	10	4	14	6	24	5
Not evaluated	6	2	5	2	11	2
.	1	0	0	0	1	0
Adrenal						
Normal	227	93	221	94	448	94
Involved	8	3	5	2	13	3
Not evaluated	7	3	8	3	15	3
.	1	0	0	0	1	0
Thyroid						
Normal	225	93	215	92	440	92
Involved	2	1	3	1	5	1
Not evaluated	15	6	16	7	31	6
.	1	0	0	0	1	0
Skin						
Normal	223	92	217	93	440	92
Involved	8	3	11	5	19	4
Not evaluated	11	5	6	3	17	4
.	1	0	0	0	1	0
Bone						
Normal	209	86	202	86	411	86
Involved	24	10	19	8	43	9
Not evaluated	9	4	13	6	22	5
.	1	0	0	0	1	0
Tonsil						
Normal	202	83	190	81	392	82
Involved	15	6	9	4	24	5
Not evaluated	25	10	34	15	59	12
.	1	0	1	0	2	0

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Cavum						
Normal	210	86	187	80	397	83
Involved	3	1	6	3	9	2
Not evaluated	29	12	40	17	69	14
.	1	0	1	0	2	0
Parotid						
Normal	212	87	194	83	406	85
Involved	1	0	1	0	2	0
Not evaluated	29	12	38	16	67	14
.	1	0	1	0	2	0
Orbit						
Normal	209	86	186	79	395	83
Involved	0	0	3	1	3	1
Not evaluated	33	14	44	19	77	16
.	1	0	1	0	2	0
Sinus						
Normal	209	86	181	77	390	82
Involved	0	0	5	2	5	1
Not evaluated	33	14	47	20	80	17
.	1	0	1	0	2	0
Oesophagus						
Normal	197	81	183	78	380	80
Involved	2	1	0	0	2	0
Not evaluated	43	18	50	21	93	19
.	1	0	1	0	2	0
Stomach						
Normal	190	78	173	74	363	76
Involved	11	5	11	5	22	5
Not evaluated	42	17	49	21	91	19
.	0	0	1	0	1	0
Duodenum						
Normal	193	79	178	76	371	78
Involved	8	3	5	2	13	3
Not evaluated	41	17	50	21	91	19
.	1	0	1	0	2	0
Colon						
Normal	191	79	175	75	366	77
Involved	6	2	9	4	15	3
Not evaluated	45	19	49	21	94	20
.	1	0	1	0	2	0

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Caecum						
Normal	193	79	176	75	369	77
Involved	3	1	7	3	10	2
Not evaluated	46	19	50	21	96	20
.	1	0	1	0	2	0
Rectum						
Normal	196	81	185	79	381	80
Not evaluated	46	19	48	21	94	20
.	1	0	1	0	2	0
Other extra nodal involvement						
No	214	88	201	86	415	87
Yes	28	12	33	14	61	13
.	1	0	0	0	1	0
TOTAL	243	100	234	100	477	100

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

Randomization Number	Arm of treatment	Other extra nodal involvement	Other extra nodal involvement - localization
5003101031001	ARM A / R-ICE	Yes	LEFT SHOULDER MUSCLE
5003101431010	ARM A / R-ICE	Yes	SOFT TISSUE
5003101441036	ARM A / R-ICE	Yes	SOFT TISSUE
5003102491619	ARM A / R-ICE	Yes	LARGE TUMORAL MASS (INCLUDING PROSTATE AND BLADDER)
5003601601003	ARM A / R-ICE	Yes	
5003601881401	ARM A / R-ICE	Yes	ANTERIOR TIBIAL MUSCLE
5003603201627	ARM A / R-ICE	Yes	JEJUNUM
5003603801008	ARM A / R-ICE	Yes	NERVUS ULNARIS L. SINISTRI
5003603801404	ARM A / R-ICE	Yes	INFILTRATION OF MUSC. ILIACUS L. SIN
5003605301010	ARM A / R-ICE	Yes	SOFT TISSUE (LEFT) L2/L3 NEURAL FORAMEN
5003607201045	ARM A / R-ICE	Yes	M. PSOAS LEFT
5003607501403	ARM A / R-ICE	Yes	ANTERIOR ABDOMINAL WALL INVASION RIGHT RECTUS MUSCLE
5003607701009	ARM A / R-ICE	Yes	UNPROVED APICAL RIGHT PLEURAL (POSITIVE PET EXAM)
5003608701016	ARM A / R-ICE	Yes	PLEURAL
5003610301208	ARM A / R-ICE	Yes	SOFT TISSUE MASS INFILTRATING STERNO MASTOID SCALENE MUSCLES
5003611201057	ARM A / R-ICE	Yes	OMENTUM MAJUS
5003612501021	ARM A / R-ICE	Yes	
5003613301210	ARM A / R-ICE	Yes	SOFT TISSUE - RIGHT SUPERIOR BUTTOCK
5003616501005	ARM A / R-ICE	Yes	RIGHT QUADRICEPS MUSCLE GROUP
5003617201042	ARM A / R-ICE	Yes	PANCREAS
5003617501024	ARM A / R-ICE	Yes	PELVIS (RIGHT ILIAC CREST)
5003620301011	ARM A / R-ICE	Yes	CENTRAL ABDOMINAL MASS
5003620301017	ARM A / R-ICE	Yes	POSTERIOR PANCREATIC PARENCHYMA

Randomization Number	Arm of treatment	Other extra nodal involvement	Other extra nodal involvement - localization
5003620501027	ARM A / R-ICE	Yes	LEFT CHEST / ABDOMINAL WALL MASS
5003621201023	ARM A / R-ICE	Yes	PSOAS LEFT 3 CM
5003621201026	ARM A / R-ICE	Yes	PANCREAS
5003622201022	ARM A / R-ICE	Yes	DORSAL LEFT UPPER FEMORAL
5003631201035	ARM A / R-ICE	Yes	RIGHT RECTUS FEMORIS MUSCLE
5003101051050	ARM B / R-DHAP	Yes	PANCREAS
5003101141624	ARM B / R-DHAP	Yes	PSOAS
5003101221057	ARM B / R-DHAP	Yes	PANCREAS
5003101431627	ARM B / R-DHAP	Yes	RIGHT THIGH
5003101601610	ARM B / R-DHAP	Yes	Abdominal mass
5003601401402	ARM B / R-DHAP	Yes	
5003601601004	ARM B / R-DHAP	Yes	SOFT TISSUE NODULE (SUBCUTANEOUS) RIGHT UPPER BACK
5003601601602	ARM B / R-DHAP	Yes	LEFT UPPER QUADRANT SMALL BOWEL
5003601881602	ARM B / R-DHAP	Yes	MUSCLE
5003603201211	ARM B / R-DHAP	Yes	DIAPHRAGM LEFT SIDE
5003603301401	ARM B / R-DHAP	Yes	LEFT THIGH
5003603701001	ARM B / R-DHAP	Yes	MUSCLE HUMERUS PROX LEFT 7.5 X 6 CM
5003603801009	ARM B / R-DHAP	Yes	SOFT TISSUE - RIGHT ARM
5003603801010	ARM B / R-DHAP	Yes	PANCREAS
5003603801013	ARM B / R-DHAP	Yes	CHEST WALL PARASTERNAL LEFT
5003604301202	ARM B / R-DHAP	Yes	RIGHT FLANK MASS
5003604701602	ARM B / R-DHAP	Yes	PLEURA RIGHT
5003604801201	ARM B / R-DHAP	Yes	OMENTUM
5003604901602	ARM B / R-DHAP	Yes	PANCREAS
5003605301203	ARM B / R-DHAP	Yes	pancreas
5003605301610	ARM B / R-DHAP	Yes	
5003606201033	ARM B / R-DHAP	Yes	VESICULA URINARIA
5003606201410	ARM B / R-DHAP	Yes	RIGHT LEG AND CALF
5003607201408	ARM B / R-DHAP	Yes	NASOPHARYNX
5003607201623	ARM B / R-DHAP	Yes	FOSSA INFRASPINATA
5003610201212	ARM B / R-DHAP	Yes	ILIAC RIGHT, PSOAS MUSCLE
5003610501402	ARM B / R-DHAP	Yes	LEFT INFRA TEMPERAL FOSSA SOFT TISSUE MASS
5003615501004	ARM B / R-DHAP	Yes	UPPER THIGH - RIGHT
5003617501026	ARM B / R-DHAP	Yes	BLADDER
5003620201017	ARM B / R-DHAP	Yes	
5003622201014	ARM B / R-DHAP	Yes	RIGHT UPPER LEG MEDIAL
5003622201037	ARM B / R-DHAP	Yes	TUMOR IN THE SMALL PELVIS 50 X 54 MM WITH INFILTRATION OF MUSCULUS LEVATOR ANI (RIGHT) AND MUSCULUS OBTURATORIUS INTERNUS (RIGHT)
5003631201619	ARM B / R-DHAP	Yes	
N = 61			

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

	Arm of treatment					
	ARM A / R-ICE		ARM B / R-DHAP		All	
	N	%	N	%	N	%
Lesion Codification						
Para-aortic / Portal	101	17	70	13	171	15
Mediastinal / Paratracheal	87	14	66	12	153	13
Celiac / Mesenteric	61	10	56	10	117	10
Cervical / Post_cervical / Upper cervical / Pre_auricular : Left	46	8	33	6	79	7
Cervical / Post_cervical / Upper cervical / Pre_auricular : Right	28	5	35	7	63	6
Axillary : Left	34	6	21	4	55	5
Axillary : Right	20	3	20	4	40	3
Inguinal / Femoral / Retrocrural : Left	21	3	19	4	40	3
External iliac / Iliac : Left	20	3	20	4	40	3
Inguinal / Femoral / Retrocrural : Right	19	3	18	3	37	3
Lung	20	3	17	3	37	3
Liver	18	3	17	3	35	3
Spleen	12	2	21	4	33	3
External iliac / Iliac : Right	20	3	9	2	29	3
Soft Tissues	13	2	13	2	26	2
Skin	7	1	14	3	21	2
Pulmonary hilar	8	1	8	1	16	1
Infraclavicular / Supraclavicular : Right	6	1	8	1	14	1
Infraclavicular / Supraclavicular : Left	10	2	4	1	14	1
Kidney	5	1	8	1	13	1
Tonsil / Waldeyer's ring	10	2	3	1	13	1
Epitrochlear Right or Left / Other	4	1	7	1	11	1
Adrenal	6	1	3	1	9	1
Bone	5	1	4	1	9	1
Other extra-nodal involvement	2	0	7	1	9	1
Stomach	6	1	2	0	8	1
Splenic hilar	3	0	4	1	7	1
Pleura	3	0	2	0	5	0
Gonadal	2	0	3	1	5	0
Colon	1	0	4	1	5	0
Breast	1	0	3	1	4	0
Cavum	0	0	4	1	4	0
Sinus	0	0	4	1	4	0
Caecum	0	0	4	1	4	0
Duodenum	0	0	3	1	3	0
Thyroid	1	0	1	0	2	0
Parotid	2	0	0	0	2	0
Ileon	1	0	1	0	2	0

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Urinary Tract	2	0	0	0	2	0
Ascites	1	0	0	0	1	0
Pericardium	0	0	1	0	1	0
Oesophagus	1	0	0	0	1	0
TOTAL	607	100	537	100	1144	100

6.4. Evaluation after complete induction treatment

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

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Lesion Codification						
Para-aortic / Portal	95	17	74	14	169	15
Mediastinal / Paratracheal	82	14	59	11	141	13
Celiac / Mesenteric	57	10	55	10	112	10
Cervical / Post_cervical / Upper cervical / Pre_auricular : Left	42	7	32	6	74	7
Cervical / Post_cervical / Upper cervical / Pre_auricular : Right	27	5	34	6	61	6
Axillary : Left	33	6	21	4	54	5
External iliac / Iliac : Left	20	3	20	4	40	4
Inguinal / Femoral / Retrocrural : Left	21	4	19	4	40	4
Axillary : Right	19	3	19	4	38	3
Lung	20	3	16	3	36	3
Inguinal / Femoral / Retrocrural : Right	18	3	17	3	35	3
Spleen	12	2	21	4	33	3
External iliac / Iliac : Right	20	3	9	2	29	3
Liver	13	2	16	3	29	3
Soft Tissues	11	2	12	2	23	2
Skin	7	1	14	3	21	2
Pulmonary hilar	7	1	8	2	15	1
Tonsil / Waldeyer's ring	10	2	3	1	13	1
Kidney	5	1	8	2	13	1
Infraclavicular / Supraclavicular : Left	9	2	3	1	12	1
Infraclavicular / Supraclavicular : Right	6	1	6	1	12	1
Epitrochlear Right or Left / Other	4	1	7	1	11	1
Bone	5	1	4	1	9	1
Adrenal	6	1	3	1	9	1
Stomach	6	1	2	0	8	1
Other extra-nodal involvement	1	0	7	1	8	1
Splenic hilar	3	1	4	1	7	1
Not coded	3	1	3	1	6	1

	Arm of treatment				All	
	ARM A / R-ICE		ARM B / R-DHAP			
	N	%	N	%	N	%
Pleura	3	1	2	0	5	0
Breast	1	0	3	1	4	0
Gonadal	1	0	3	1	4	0
Colon	0	0	4	1	4	0
Caecum	0	0	4	1	4	0
Sinus	0	0	4	1	4	0
Duodenum	0	0	3	1	3	0
Cavum	0	0	3	1	3	0
Ileon	1	0	1	0	2	0
Urinary Tract	2	0	0	0	2	0
Thyroid	1	0	1	0	2	0
Parotid	2	0	0	0	2	0
Ascites	1	0	0	0	1	0
Oesophagus	1	0	0	0	1	0
Pericardium	0	0	1	0	1	0
Total	575	100	525	100	1100	100

6.5. Follow-up

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

Randomization Number	Arm of treatment	Date of last contact
5003101131072	ARM A / R-ICE	18/01/2008
5003102341045	ARM A / R-ICE	09/06/2009
5003102491616	ARM A / R-ICE	01/06/2006
5003601201602	ARM A / R-ICE	15/01/2008
5003601401605	ARM A / R-ICE	17/06/2008
5003602501001	ARM A / R-ICE	15/05/2008
5003603201409	ARM A / R-ICE	16/02/2007
5003604301013	ARM A / R-ICE	17/06/2009
5003605901003	ARM A / R-ICE	15/07/2009
5003606301204	ARM A / R-ICE	23/06/2008
5003608301605	ARM A / R-ICE	13/09/2004
5003612501012	ARM A / R-ICE	06/11/2007
5003612501021	ARM A / R-ICE	29/11/2007
5003613301210	ARM A / R-ICE	01/08/2005
5003613301611	ARM A / R-ICE	25/05/2006
5003617201010	ARM A / R-ICE	22/08/2005
5003619301008	ARM A / R-ICE	16/07/2009
5003620301017	ARM A / R-ICE	19/05/2008
5003621501603	ARM A / R-ICE	20/08/2008
5003622201210	ARM A / R-ICE	21/05/2008
5003624501017	ARM A / R-ICE	07/11/2007

Randomization Number	Arm of treatment	Date of last contact
5003628201009	ARM A / R-ICE	07/04/2009
5003628201052	ARM A / R-ICE	19/09/2007
5003628201402	ARM A / R-ICE	22/04/2009
5003628201618	ARM A / R-ICE	03/06/2009
5003628201624	ARM A / R-ICE	12/05/2009
5003630201055	ARM A / R-ICE	10/11/2008
5003632201614	ARM A / R-ICE	24/05/2007
5003635201051	ARM A / R-ICE	12/06/2009
5003649501033	ARM A / R-ICE	05/11/2008
5003101031006	ARM B / R-DHAP	05/02/2007
5003601301015	ARM B / R-DHAP	18/03/2008
5003601401001	ARM B / R-DHAP	06/12/2006
5003603301401	ARM B / R-DHAP	28/08/2009
5003604701011	ARM B / R-DHAP	18/05/2009
5003604701602	ARM B / R-DHAP	21/08/2008
5003604901602	ARM B / R-DHAP	28/06/2005
5003606201410	ARM B / R-DHAP	27/01/2009
5003606201620	ARM B / R-DHAP	11/07/2008
5003606701005	ARM B / R-DHAP	30/04/2009
5003607201623	ARM B / R-DHAP	29/07/2009
5003610301209	ARM B / R-DHAP	14/03/2006
5003612501016	ARM B / R-DHAP	01/02/2008
5003615501029	ARM B / R-DHAP	04/08/2008
5003617201616	ARM B / R-DHAP	07/05/2009
5003619301006	ARM B / R-DHAP	30/04/2009
5003619501009	ARM B / R-DHAP	16/10/2008
5003622201037	ARM B / R-DHAP	23/03/2009
5003622201607	ARM B / R-DHAP	04/01/2007
5003628201002	ARM B / R-DHAP	25/03/2009
5003628201044	ARM B / R-DHAP	12/06/2009
5003628201404	ARM B / R-DHAP	20/07/2007
N = 52		

6.6. Efficacy results

6.6.1. Primary criterion

Listing 6.6-1 Induction - Patients with missing or not evaluated response after induction (induction ITT)

Randomization Number	Arm of treatment	Response after complete induction	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Date of death	Response at death	Nb of cycles received
5003101071647	ARM A / R-ICE	NOT EVALUATED	01/05/2008	INDUCTION PHASE	OTHER	TREATMENT OUT OF RADIOTHERAPY BETWEEN CYCLE 1 AND 2	COMPLETE RESPONSE	-	-	1
5003101131030	ARM A / R-ICE	NOT EVALUATED	16/08/2005	INDUCTION PHASE	DEATH		NOT EVALUATED	16/08/2005	NOT EVALUATED	2
5003101391638	ARM A / R-ICE	NOT EVALUATED	26/02/2007	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		NOT EVALUATED	-	-	1
5003101601404	ARM A / R-ICE	NOT EVALUATED	21/08/2005	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	05/09/2005	NOT EVALUATED	2
5003102161413	ARM A / R-ICE	-	05/11/2006	INDUCTION PHASE	DEATH		NOT EVALUATED	05/11/2006	NOT EVALUATED	1
5003603201409	ARM A / R-ICE	NOT EVALUATED	16/02/2007	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		NOT EVALUATED	-	-	1
5003603701004	ARM A / R-ICE	NOT EVALUATED	01/09/2005	INDUCTION PHASE	DEATH		NOT EVALUATED	01/09/2005	NOT EVALUATED	1
5003620301017	ARM A / R-ICE	-	19/05/2008	INDUCTION PHASE	OTHER	USE OF DIFFERENT CONSOLIDATION TREATMENT THAN SPECIFIED IN PROTOCOL	STABLE DISEASE	-	-	3
5003621301014	ARM A / R-ICE	-	11/11/2007	INDUCTION PHASE	TREATMENT TOXICITY		STABLE DISEASE	03/12/2007	NOT EVALUATED	1
5003621501603	ARM A / R-ICE	-	28/08/2007	CONSOLIDATION PHASE	OTHER	FAILURE TO RANDOMISE	UNCONFIRMED COMPLETE RESPONSE	-	-	3
5003622201210	ARM A / R-ICE	NOT EVALUATED	27/03/2006	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	-	-	1
5003628201052	ARM A / R-ICE	NOT EVALUATED	-	INDUCTION PHASE	-		-	-	NOT EVALUATED	1
5003630201055	ARM A / R-ICE	-	24/07/2008	INDUCTION PHASE	TREATMENT TOXICITY		COMPLETE RESPONSE	-	-	2
5003101071002	ARM B / R-DHAP	NOT EVALUATED	21/11/2003	INDUCTION PHASE	DEATH		NOT EVALUATED	21/11/2003	NOT EVALUATED	1

Randomization Number	Arm of treatment	Response after complete induction	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Date of death	Response at death	Nb of cycles received
5003101071607	ARM B / R-DHAP	NOT EVALUATED	16/01/2004	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	04/06/2009	PROGRESSIVE DISEASE	1
5003603801013	ARM B / R-DHAP	NOT EVALUATED	15/02/2007	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	24/04/2007	PARTIAL RESPONSE	2
5003604701012	ARM B / R-DHAP	-	04/05/2007	INDUCTION PHASE	DEATH		NOT EVALUATED	04/05/2007	NOT EVALUATED	1
5003607301622	ARM B / R-DHAP	-	26/01/2007	INDUCTION PHASE	DEATH		NOT EVALUATED	26/01/2007	NOT EVALUATED	2
5003610701403	ARM B / R-DHAP	-	06/10/2008	FOLLOW UP PERIOD	OTHER	RECCURENT IN FU-PHASE 6 MONTHS AFTER TRANSPLANT	PROGRESSIVE DISEASE	-	-	3
5003615501007	ARM B / R-DHAP	NOT EVALUATED	23/02/2007	INDUCTION PHASE	OTHER	CVA	NOT EVALUATED	25/05/2007	PROGRESSIVE DISEASE	1
5003616201413	ARM B / R-DHAP	-	03/06/2008	INDUCTION PHASE	TREATMENT TOXICITY		NOT EVALUATED	20/08/2008	NOT EVALUATED	1
5003617201616	ARM B / R-DHAP	NOT EVALUATED	14/10/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		NOT EVALUATED	-	-	3
5003619501010	ARM B / R-DHAP	NOT EVALUATED	06/04/2007	INDUCTION PHASE	DEATH		NOT EVALUATED	06/04/2007	NOT EVALUATED	2
5003623501405	ARM B / R-DHAP	NOT EVALUATED	26/07/2007	INDUCTION PHASE	DEATH		DEATH WITHOUT PROGRESSION	26/07/2007	NOT EVALUATED	1
N = 24										

Table 6.6-1 Primary criterion – Overall response rate by arm according to prior rituximab (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Prior treatment with Rituximab	Response after complete induction				
No	CR/CRu/PR	66	78	71	87
	Other	19	22	11	13
Yes	CR/CRu/PR	87	56	77	52
	Other	67	44	71	48
Total		239	100	230	100

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

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Failure from diagnosis	Response after complete induction				
< 12 months	CR/CRu/PR	71	49	64	49
	Other	74	51	67	51
>= 12 months	CR/CRu/PR	82	87	84	85
	Other	12	13	15	15
Total		239	100	230	100

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

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Country	Response after complete induction				
Gela	CR/CRu/PR	50	65	50	65
	Other	27	35	27	35
	Total	77	100	77	100
Germany	Response after complete induction				
	CR/CRu/PR	29	55	30	56
	Other	24	45	24	44
	Total	53	100	54	100
Australia	Response after complete induction				
	CR/CRu/PR	18	64	24	83
	Other	10	36	5	17
	Total	28	100	29	100
Total		158	100	160	100

Table 6.6-4 Primary criterion – Overall response rate by arm according age adjusted IPI (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Age-adjusted IPI	Response after complete induction				
<2	CR/CRu/PR	98	70	100	73
	Other	43	30	37	27
	Total	141	100	137	100
>=2	Response after complete induction				
	CR/CRu/PR	50	55	45	52
	Other	41	45	41	48
	Total	91	100	86	100
Total		232	100	223	100

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

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Prior treatment with Rituximab	Response after complete induction				
No	CR/CRu	41	48	43	52
	Other	44	52	39	48
Yes	CR/CRu	47	31	42	28
	Other	107	69	106	72
Total		239	100	230	100

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

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Failure from diagnosis	Response after complete induction				
< 12 months	CR/CRu	35	24	31	24
	Other	110	76	100	76
>= 12 months	CR/CRu	53	56	54	55
	Other	41	44	45	45
Total		239	100	230	100

Table 6.6-7 Primary criterion – Complete response rate by arm according to country (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Country	Response after complete induction				
Gela	CR/CRu	32	42	28	36
	Other	45	58	49	64
	Total	77	100	77	100
Germany	Response after complete induction				
	CR/CRu	15	28	19	35
	Other	38	72	35	65
	Total	53	100	54	100
Australia	Response after complete induction				
	CR/CRu	11	39	11	38
	Other	17	61	18	62
	Total	28	100	29	100
Total		158	100	160	100

Table 6.6-8 Primary criterion – Complete response rate by arm according to age adjusted IPI (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Age-adjusted IPI	Response after complete induction				
<2	CR/CRu	60	43	59	43
	Other	81	57	78	57
	Total	141	100	137	100
>=2	Response after complete induction				
	CR/CRu	27	30	25	29
	Other	64	70	61	71
	Total	91	100	86	100
Total		232	100	223	100

Listing 6.6-2 Induction - Patients who died during treatment phase (induction ITT)

Randomization Number	Arm of treatment	First Randomization Date	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Date of death	Reason for death	Response at death	Response after complete induction (raw data from CRF)	Nb of cycles received
5003101071002	ARM B / R-DHAP	16/10/2003	21/11/2003	INDUCTION PHASE	DEATH	21/11/2003	TOXICITY OF STUDY TREATMENT	NOT EVALUATED	NOT EVALUATED	1
5003101131030	ARM A / R-ICE	16/06/2005	16/08/2005	INDUCTION PHASE	DEATH	16/08/2005	TOXICITY OF STUDY TREATMENT	NOT EVALUATED	NOT EVALUATED	2
5003101281017	ARM A / R-ICE	18/11/2004	10/12/2004	INDUCTION PHASE	TREATMENT TOXICITY	12/01/2005	LYMPHOMA	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	1
5003101601404	ARM A / R-ICE	04/07/2005	21/08/2005	INDUCTION PHASE	TREATMENT TOXICITY	05/09/2005	TOXICITY OF STUDY TREATMENT	NOT EVALUATED	NOT EVALUATED	2
5003102161413	ARM A / R-ICE	18/10/2006	05/11/2006	INDUCTION PHASE	DEATH	05/11/2006	TOXICITY OF STUDY TREATMENT	NOT EVALUATED	-	1
5003603201001	ARM B / R-DHAP	11/03/2004	03/05/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE	13/05/2004	TOXICITY OF STUDY TREATMENT	STABLE DISEASE	STABLE DISEASE	3
5003603701004	ARM A / R-ICE	12/08/2005	01/09/2005	INDUCTION PHASE	DEATH	01/09/2005	TOXICITY OF STUDY TREATMENT	NOT EVALUATED	NOT EVALUATED	1
5003603901001	ARM B / R-DHAP	06/10/2004	14/11/2004	INDUCTION PHASE	INDUCTION TREATMENT FAILURE	19/11/2004	LYMPHOMA	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	1
5003604701012	ARM B / R-DHAP	19/04/2007	04/05/2007	INDUCTION PHASE	DEATH	04/05/2007	TOXICITY OF STUDY TREATMENT	NOT EVALUATED	-	1
5003605301601	ARM A / R-ICE	05/04/2004	20/06/2004	INDUCTION PHASE	DEATH	20/06/2004	CONCURRENT ILLNESS	UNCONFIRMED COMPLETE RESPONSE	UNCONFIRMED COMPLETE RESPONSE	3
5003607301622	ARM B / R-DHAP	11/12/2006	26/01/2007	INDUCTION PHASE	DEATH	26/01/2007	TOXICITY OF STUDY TREATMENT	NOT EVALUATED	-	2
5003614501013	ARM B / R-DHAP	20/04/2007	21/07/2007	INDUCTION PHASE	DEATH	21/07/2007	OTHER REASON	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	3
5003617501006	ARM B / R-DHAP	01/12/2006	12/01/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE	04/02/2007	LYMPHOMA	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	1
5003617501026	ARM B / R-DHAP	06/12/2007	07/01/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE	24/01/2008	LYMPHOMA	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	1
5003619501010	ARM B / R-DHAP	14/02/2007	06/04/2007	INDUCTION PHASE	DEATH	06/04/2007	TOXICITY OF STUDY TREATMENT	NOT EVALUATED	NOT EVALUATED	2

Randomization Number	Arm of treatment	First Randomization Date	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Date of death	Reason for death	Response at death	Response after complete induction (raw data from CRF)	Nb of cycles received
5003621301014	ARM A / R-ICE	29/10/2007	11/11/2007	INDUCTION PHASE	TREATMENT TOXICITY	03/12/2007	TOXICITY OF ADDITIONNAL TREATMENT	NOT EVALUATED	-	1
5003623501405	ARM B / R-DHAP	05/07/2007	26/07/2007	INDUCTION PHASE	DEATH	26/07/2007	LYMPHOMA	NOT EVALUATED	NOT EVALUATED	1
5003631201011	ARM B / R-DHAP	03/12/2004	25/12/2004	INDUCTION PHASE	TREATMENT TOXICITY	29/12/2004	LYMPHOMA	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	1
N = 18										

Table 6.6-9 Primary criterion – Overall response rate (including all deaths) by arm according to prior rituximab (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Prior treatment with Rituximab	Response after complete induction (including deaths for all patients)				
No	CR/CRu/PR	65	76	71	87
	Other	20	24	11	13
Yes	CR/CRu/PR	87	56	77	52
	Other	67	44	71	48
Total		239	100	230	100

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

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Failure from diagnosis	Response after complete induction (including deaths for all patients)				
< 12 months	CR/CRu/PR	71	49	64	49
	Other	74	51	67	51
>= 12 months	CR/CRu/PR	81	86	84	85
	Other	13	14	15	15
Total		239	100	230	100

Table 6.6-11 Primary criterion – Overall response rate (including all deaths) by arm according country (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Country	Response after complete induction (including deaths for all patients)				
Gela	CR/CRu/PR	50	65	50	65
	Other	27	35	27	35
	Total	77	100	77	100
Germany	Response after complete induction (including deaths for all patients)				
	CR/CRu/PR	29	55	30	56
	Other	24	45	24	44
	Total	53	100	54	100
Australia	Response after complete induction (including deaths for all patients)				
	CR/CRu/PR	17	61	24	83
	Other	11	39	5	17
	Total	28	100	29	100
Total		158	100	160	100

Table 6.6-12 Primary criterion – Overall response rate (including all deaths) by arm according to age adjusted IPI (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Age-adjusted IPI	Response after complete induction (including deaths for all patients)				
<2	CR/CRu/PR	98	70	100	73
	Other	43	30	37	27
	Total	141	100	137	100
>=2	Response after complete induction (including deaths for all patients)				
	CR/CRu/PR	49	54	45	52
	Other	42	46	41	48
	Total	91	100	86	100
Total		232	100	223	100

Table 6.6-13 Primary criterion – Complete response rate (including all deaths) by arm according to prior rituximab (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Prior treatment with Rituximab	Response after complete induction (including deaths for all patients)				
No	CR/CRu	40	47	43	52
	Other	45	53	39	48
Yes	CR/CRu	47	31	42	28
	Other	107	69	106	72
Total		239	100	230	100

Table 6.6-14 Primary criterion – Complete response rate (including all deaths) by arm according to failure from diagnosis (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Failure from diagnosis	Response after complete induction (including deaths for all patients)				
< 12 months	CR/CRu	35	24	31	24
	Other	110	76	100	76
>= 12 months	CR/CRu	52	55	54	55
	Other	42	45	45	45
Total		239	100	230	100

Table 6.6-15 Primary criterion – Complete response rate (including all deaths) by arm according to country (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Country	Response after complete induction (including deaths for all patients)				
Gela	CR/CRu	32	42	28	36
	Other	45	58	49	64
	Total	77	100	77	100
Germany	Response after complete induction (including deaths for all patients)				
	CR/CRu	15	28	19	35
	Other	38	72	35	65
	Total	53	100	54	100
Australia	Response after complete induction (including deaths for all patients)				
	CR/CRu	10	36	11	38
	Other	18	64	18	62
	Total	28	100	29	100
Total		158	100	160	100

Table 6.6-16 Primary criterion – Complete response rate (including all deaths) by arm according to age adjusted IPI (induction ITT)

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Age-adjusted IPI	Response after complete induction (including deaths for all patients)				
<2	CR/CRu	60	43	59	43
	Other	81	57	78	57
	Total	141	100	137	100
>=2	Response after complete induction (including deaths for all patients)				
	CR/CRu	26	29	25	29
	Other	65	71	61	71
	Total	91	100	86	100
Total		232	100	223	100

Listing 6.6-3 Primary criterion – Other cause of collection failure (induction ITT)

Randomization Number	Arm of treatment	Response after complete induction (raw data from CRF)	first collection date	Collected Cells	Collection failure	Specify other cause for collection failure
5003101141065	ARM A / R-ICE	STABLE DISEASE	ND	-	Yes	NO COLLECTION DURING THE STUDY AS COLLECTION HAD BEEN DONE BEFORE
5003101171644	ARM A / R-ICE	COMPLETE RESPONSE	06/04/2008	3.08	Yes	CELL VIABILITY ISSUE
5003101541415	ARM B / R-DHAP	PARTIAL RESPONSE	21/06/2005	5.1	Yes	NO COLLECTION DURING THE STUDY : ALREADY HARVESTED IN MAY 2005 (5.1 10^6 CD34/KG) ENOUGH CELLS
5003102541052	ARM A / R-ICE	COMPLETE RESPONSE	09/01/2006	15.09	Yes	COLLECTION DONE BEFORE INCLUSION
5003601501407	ARM A / R-ICE	PARTIAL RESPONSE	ND	-	Yes	COLLECTION ALREADY ON 23/08/2005
5003601601001	ARM B / R-DHAP	PARTIAL RESPONSE	05/06/2006	6.1	Yes	WEST NILE VIRUS DISCOVERED DURING COLLECTION
5003601601402	ARM B / R-DHAP	COMPLETE RESPONSE	31/12/2004	0.9	Yes	ADVERSE REACTION, PATIENT EXPIRED
5003604801402	ARM B / R-DHAP	COMPLETE RESPONSE	19/11/2003	9.42	Yes	1ST COLLECTION DATE : BACK-UP !
5003617501024	ARM A / R-ICE	PARTIAL RESPONSE	15/02/2008	0	Yes	INCORRECT DOSE OF G-CSF PRESCRIBED
5003621201023	ARM A / R-ICE	PARTIAL RESPONSE	10/01/2006	-	Yes	NO STEM CELL LEACHATE INTO THE PERIPHERAL BLOOD
N = 10						

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

		Arm of treatment			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Response after complete induction	**Collection failure**				
CR/CRu	**No**	76	32	75	33
	Yes	11	5	10	4
	Missing	1	0	0	0
Other	**No**	83	35	92	40
	Yes	26	11	14	6
	Missing	42	18	39	17
Total		239	100	230	100

Table 6.6-18 Mobilization Adjusted Complete Response Rate (induction ITT)

Arm of treatment	Nb patients	Nb responders with successful mobilization	MARR (%)	95% CI lower	95% CI upper
ARM A / R-ICE	239	163	68.2	61.9	74.1
ARM B / R-DHAP	230	155	67.4	60.9	73.4

Table 6.6-19 Difference between Mobilization Adjusted Complete Response Rates (induction ITT)

	Difference between MARR (%)	95% CI lower	95% CI upper	p-value
R-ICE vs R-DHAP	0.8	-7.6	9.3	0.8512

6.6.2. Secondary criteria

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

Randomization Number	Arm of treatment	Response after complete induction	Collection failure	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Nb of cycles received
5003101071020	ARM A / R-ICE	PARTIAL RESPONSE	No	20/07/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	3
5003101071414	ARM B / R-DHAP	COMPLETE RESPONSE	No	16/02/2007	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		COMPLETE RESPONSE	3
5003101141406	ARM A / R-ICE	UNCONFIRMED COMPLETE RESPONSE	No	20/12/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	3
5003101161028	ARM B / R-DHAP	COMPLETE RESPONSE	No	22/08/2005	INDUCTION PHASE	TREATMENT TOXICITY		COMPLETE RESPONSE	3
5003101431204	ARM B / R-DHAP	UNCONFIRMED COMPLETE RESPONSE	No	13/02/2004	INDUCTION PHASE	TREATMENT TOXICITY		UNCONFIRMED COMPLETE RESPONSE	3
5003102321024	ARM A / R-ICE	UNCONFIRMED COMPLETE RESPONSE	No	17/08/2005	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	3
5003601801603	ARM B / R-DHAP	PARTIAL RESPONSE	No	09/03/2005	INDUCTION PHASE	TREATMENT TOXICITY		PARTIAL RESPONSE	3
5003604301607	ARM B / R-DHAP	PARTIAL RESPONSE	No	27/10/2004	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		PARTIAL RESPONSE	3
5003605301601	ARM A / R-ICE	UNCONFIRMED COMPLETE RESPONSE	No	20/06/2004	INDUCTION PHASE	DEATH		UNCONFIRMED COMPLETE RESPONSE	3
5003605701404	ARM B / R-DHAP	COMPLETE RESPONSE	No	04/04/2008	INDUCTION PHASE	INDUCTION TREATMENT FAILURE		PROGRESSIVE DISEASE	3
5003609301608	ARM A / R-ICE	PARTIAL RESPONSE	No	25/01/2005	INDUCTION PHASE	OTHER	INVESTIGATOR'S DECISION (REQUIRES 4TH CYCLE OF INDUCTION)	PARTIAL RESPONSE	3
5003612501016	ARM B / R-DHAP	PARTIAL RESPONSE	No	12/09/2007	INDUCTION PHASE	OTHER	RESPONSE NOT ENOUGH, THERE IS STILL BULKY DISEASE	PARTIAL RESPONSE	3
5003617501606	ARM A / R-ICE	PARTIAL RESPONSE	No	15/02/2008	INDUCTION PHASE	OTHER	TRANSPLANT CENTRE WOULD NOT TRANSPLANT PATIENT AS PATIENT WAS PET POSITIVE	PARTIAL RESPONSE	3
5003628201624	ARM A / R-ICE	COMPLETE RESPONSE	No	06/03/2007	INDUCTION PHASE	PATIENT VOLONTARY WITHDRAWAL		COMPLETE RESPONSE	3
N = 14									

Listing 6.6-5 Consolidation – Non responder patients presenting with ASCT (induction ITT)

Randomization Number	Arm of treatment	Response after complete induction	BEAM - date of first administration	Transplantation date	Date of 2nd randomization	Nb of cycles received
5003605701601	ARM A / R-ICE	STABLE DISEASE	03/06/2005	09/06/2005	25/05/2005	3
5003621501603	ARM A / R-ICE	.	01/08/2007	08/08/2007	.	3
5003104621053	ARM B / R-DHAP	STABLE DISEASE	16/11/2006	22/11/2006	15/11/2006	3
5003604701002	ARM B / R-DHAP	STABLE DISEASE	10/05/2005	17/05/2005	19/05/2005	3
5003608701008	ARM B / R-DHAP	STABLE DISEASE	24/04/2006	01/05/2006	19/05/2006	3
5003608701603	ARM B / R-DHAP	STABLE DISEASE	15/05/2008	21/05/2008	28/05/2008	3
5003610701403	ARM B / R-DHAP	.	03/03/2008	03/03/2008	28/03/2008	3
5003616501003	ARM B / R-DHAP	STABLE DISEASE	29/11/2006	05/12/2006	20/12/2006	3
5003621501412	ARM B / R-DHAP	STABLE DISEASE	08/10/2008	14/10/2008	01/10/2008	3
N = 9						

6.6.3. Non study or new treatment out of progression

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

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003101021014	ARM A / R-ICE	Yes	30/11/2004	ENDOXAN (1 CYCLE) + ICE (1 CYCLE ON 14122004)	2
5003101031007	ARM A / R-ICE	Yes	20/04/2004	DHAX	4
5003101051068	ARM A / R-ICE	Yes	02/10/2007	DHAP + 1 ETOPOSIDE IFOSFAMIDE	2
5003101051603	ARM A / R-ICE	Yes	11/02/2004	R-ICE	3
5003101071647	ARM A / R-ICE	Yes	03/07/2008	ICE	-
5003101141065	ARM A / R-ICE	Yes	27/07/2007	DHAOX (OXALOPLATINE, CYTARABINE, DEXAMETHASONE)	2
5003101331077	ARM A / R-ICE	Yes	26/06/2008	DHAP	2
5003101481403	ARM A / R-ICE	Yes	07/12/2005	R-CHOP	1
5003601601002	ARM A / R-ICE	Yes	13/03/2007	EPOCH	2
5003603201406	ARM A / R-ICE	Yes	-	DEXA-BEAM	-
5003603801406	ARM A / R-ICE	Yes	12/08/2008	R-GFOX	4
5003609301608	ARM A / R-ICE	Yes	05/02/2005	ICE	1
5003612501012	ARM A / R-ICE	Yes	06/11/2007	VINBLASTINE, METHOTREXATE, BLEOMYCIN, LOMUSTINE, CHLORAMBUCIL	3
5003615501201	ARM A / R-ICE	Yes	04/12/2006	GDCVP	3
5003617201042	ARM A / R-ICE	Yes	22/03/2007	R-DHAP	1
5003617501606	ARM A / R-ICE	Yes	02/03/2008	MINI BEAM	1
5003621201023	ARM A / R-ICE	Yes	13/02/2006	DEXA-BEAM	1
5003621301014	ARM A / R-ICE	Yes	21/11/2007	ICE	1
5003622201210	ARM A / R-ICE	Yes	29/03/2006	R-DHAP	2
5003632201054	ARM A / R-ICE	Yes	08/07/2008	RITUXIMAB	2
5003635201051	ARM A / R-ICE	Yes	-	2 X R-DHAP + 2 X R-GEM OX	4
5003101031006	ARM B / R-DHAP	Yes	28/03/2004	MIV	2
5003101031411	ARM B / R-DHAP	Yes	11/12/2006	DHAP N°4	1
5003101051063	ARM B / R-DHAP	Yes	03/07/2007	R-DHAP	3
5003101221070	ARM B / R-DHAP	Yes	01/01/2008	DHAP	1
5003101391613	ARM B / R-DHAP	Yes	10/07/2004	2 COPADEM + 3 VAD (16/04/2005)	5

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003101431204	ARM B / R-DHAP	Yes	19/03/2004	R-ICE (FROM 19 TO 21/03/2004)	1
5003602801016	ARM B / R-DHAP	Yes	04/10/2007	R-GIFOX	1
5003603801013	ARM B / R-DHAP	Yes	15/02/2007	R-ICE	1
5003605201603	ARM B / R-DHAP	Yes	-	DHAP	3
5003610201008	ARM B / R-DHAP	Yes	20/01/2005	IMMUNO-CHEMOTHERAPY (B-ALL PROTOCOL) VINCRISTINE, MTX, CYCLOPHOSPHAMIDE, DOXORUBICINE, DEXAMETHASONE	2
5003610201212	ARM B / R-DHAP	Yes	-	RITUXIMAB, VINCRISTIN, METHOTREXATE, IFOSFAMID, CYTARABIN, ETOPOSID (GMALL-B-ALL-PROTOCOL)	2
5003612501016	ARM B / R-DHAP	Yes	07/09/2007	HIGH DOSE METHOTREXATE	4
5003616201413	ARM B / R-DHAP	Yes	04/06/2008	CYCLOPHOSPHAMID	1
5003616301212	ARM B / R-DHAP	Yes	08/08/2006	IFOSFAMIDE & ETOPOSIDE	3
5003617201049	ARM B / R-DHAP	Yes	26/09/2007	DEXA BEAM	1
5003628201046	ARM B / R-DHAP	Yes	06/09/2007	ICE	2
5003635201411	ARM B / R-DHAP	Yes	-	R-ICE	3
N = 38					

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

Randomization Number	Arm of treatment	Radiotherapy	Date of radiotherapy	Site of radiotherapy	Dose of radiotherapy (Gy)
5003101071647	ARM A / R-ICE	Yes	-	CERVICAL RIGHT	-
5003101441074	ARM A / R-ICE	Yes	16/06/2008	INGUINAL	8
5003102341045	ARM A / R-ICE	Yes	09/09/2006	MEDIASTINAL	40
5003601601401	ARM A / R-ICE	Yes	21/07/2004	UPPER NECK + OROPHARYNX AND LOWER ANTERIOR NECK FIELD FOR DLBCL INSTEAD OF TRANSPLANT	72
5003603301201	ARM A / R-ICE	Yes	16/08/2004	RIGHT ADRENAL GLAND	30
5003617201048	ARM A / R-ICE	Yes	11/10/2007	MEDIASTINUM	46
5003628201009	ARM A / R-ICE	Yes	05/08/2005	ABDOMINAL RESIDUAL MASS	-
5003101391207	ARM B / R-DHAP	Yes	19/06/2006	LEFT NASAL FOSSA	40
5003101391613	ARM B / R-DHAP	Yes	12/11/2004	COELIOMESENTERIC	40
5003104621053	ARM B / R-DHAP	Yes	22/01/2007	MEDIASTINUM	40
5003601401001	ARM B / R-DHAP	Yes	02/05/2004	LEFT PART OF ABDOMEN	50
5003601601001	ARM B / R-DHAP	Yes	07/07/2006	PARATRACHEAL REGION	31
5003601801603	ARM B / R-DHAP	Yes	24/03/2005	NECK	40
5003604901007	ARM B / R-DHAP	Yes	05/10/2008	MEDIASTINUM	40
5003617201049	ARM B / R-DHAP	Yes	14/11/2007	ABDOMINAL LN	36
5003619501009	ARM B / R-DHAP	Yes	20/07/2007	RIGHT PERINEPHRIC MASS : PET POSITIVE 17/APR/2007	40
5003622201037	ARM B / R-DHAP	Yes	-	RESIDUAL FINDINGS IN SMALL PELVIS	36
5003623501408	ARM B / R-DHAP	Yes	02/06/2008	LEFT GROIN	-
N = 18					

Listing 6.6-8 New treatment out of progression - Immunotherapy (induction ITT)

Randomization Number	Arm of treatment	Immunotherapy	Date of immunotherapy	Specify immunotherapy
5003101021014	ARM A / R-ICE	Yes	14/12/2004	RITUXIMAB WITH ICE
5003101051068	ARM A / R-ICE	Yes	02/10/2007	RITUXIMAB ON 02/10/2007 AND 25/10/2007 AND 05/12/2007
5003101071647	ARM A / R-ICE	Yes	03/07/2008	RITUXIMAB
5003101331077	ARM A / R-ICE	Yes	26/06/2008	RITUXIMAB
5003609301608	ARM A / R-ICE	Yes	05/02/2005	RITUXIMAB
5003617201042	ARM A / R-ICE	Yes	24/04/2007	RITUXIMAB
5003621201023	ARM A / R-ICE	Yes	13/02/2006	RITUXIMAB 1 CYCLE
5003622201210	ARM A / R-ICE	Yes	11/07/2006	RITUXIMAB
5003635201051	ARM A / R-ICE	Yes	-	RITUXIMAB IN COMBINATION WITH CHEMOTHERAPY (SEE ABOVE)
5003101031411	ARM B / R-DHAP	Yes	11/12/2006	RITUXIMAB N°4 X 1
5003101221070	ARM B / R-DHAP	Yes	01/01/2008	RITUXIMAB
5003601601001	ARM B / R-DHAP	Yes	07/11/2006	RITUXIMAB WEEKLY 4 CYCLES
5003610201008	ARM B / R-DHAP	Yes	19/01/2005	RITUXIMAB
5003616501411	ARM B / R-DHAP	Yes	09/01/2009	RITUXIMAB MAINTENANCE 700 MG GIVEN ON 09/01/2009 AND 03/04/2009
5003622201037	ARM B / R-DHAP	Yes	23/04/2007	RITUXIMAB
5003635201411	ARM B / R-DHAP	Yes	-	IN COMBINATION WITH CHEMOTHERAPY (SEE ABOVE)
N = 16				

Listing 6.6-9 New treatment out of progression - Tranplant (induction ITT)

Randomization Number	Arm of treatment	Transplantation	Date of transplantation	Conditioning Regimen
5003101031007	ARM A / R-ICE	Yes	-	BEAM
5003101051068	ARM A / R-ICE	Yes	09/01/2008	BEAM
5003101071647	ARM A / R-ICE	Yes	06/09/2008	BEAM
5003101431010	ARM A / R-ICE	Yes	13/09/2004	BEAM ON 07/09/2004
5003101441074	ARM A / R-ICE	Yes	13/02/2008	BEAM + ALLO TRANSPLANTATION ON 27/06/2008
5003101481403	ARM A / R-ICE	Yes	13/01/2006	BEAM
5003102491616	ARM A / R-ICE	Yes	25/10/2004	BEAM STARTED ON 19/10/2004
5003601401401	ARM A / R-ICE	Yes	21/09/2004	BEAC
5003603801202	ARM A / R-ICE	Yes	15/02/2005	BEAM ON 08/02/2005
5003604301618	ARM A / R-ICE	Yes	07/06/2006	BEAM STARTED 01/06/2006 : 557 MG BCNU, 1520 MG ETOPOSIDE, 2960 MG CYTARABINE, 260 MG MELPHALAN
5003604901006	ARM A / R-ICE	Yes	29/03/2007	FLUDARABINE 50 MG DAYS -6 TO -2 / MELPHALAN 80 MG DAYS -3 TO -2
5003606301612	ARM A / R-ICE	Yes	21/06/2005	BEAM ON 15062005
5003609301608	ARM A / R-ICE	Yes	23/03/2005	BEAM
5003617201042	ARM A / R-ICE	Yes	26/04/2007	DEXA BEAM + STEM CELL RETRANSFUSION (NO HD TREATMENT)
5003617201048	ARM A / R-ICE	Yes	04/01/2008	IBRITUMOMAB TIUXETAN, ALEMTUZUMAB, FLU, MEL
5003617501606	ARM A / R-ICE	Yes	16/05/2008	BEAM BCNU 552 MG, ETOPOSIDE 1840 MG, CYTARABINE 1840, MG MELPHALAN 258 MG. CD34 = 5.89 10^6/KG
5003622201210	ARM A / R-ICE	Yes	24/05/2006	BEAM STARTED ON 17/05/2006
5003628201003	ARM A / R-ICE	Yes	22/10/2004	BEAM
5003628201009	ARM A / R-ICE	Yes	04/03/2005	BEAM
5003642501410	ARM A / R-ICE	Yes	-	BEAM

Randomization Number	Arm of treatment	Transplantation	Date of transplantation	Conditioning Regimen
5003101031411	ARM B / R-DHAP	Yes	31/01/2007	BEAM (24/01/2007)
5003101071414	ARM B / R-DHAP	Yes	18/04/2007	BEAM ON 12/04/2007
5003101221070	ARM B / R-DHAP	Yes	06/02/2008	BEAM
5003101391613	ARM B / R-DHAP	Yes	09/09/2004	BEAM
5003101431204	ARM B / R-DHAP	Yes	28/04/2004	CBV NOVANTRONE FROM 20 TO 24/04/2004
5003601601001	ARM B / R-DHAP	Yes	19/09/2006	BEAM ON 13/09/2006
5003603201034	ARM B / R-DHAP	Yes	07/11/2006	BEAM STARTED ON 31/10/2006
5003603801013	ARM B / R-DHAP	Yes	17/04/2007	BEAM REDUCED 40%
5003606201622	ARM B / R-DHAP	Yes	19/03/2007	BONE MARROW TRANSPLANT AFTER COND. BEAM
5003610201008	ARM B / R-DHAP	Yes	-	BEAM
5003610201212	ARM B / R-DHAP	Yes	-	BEAM
5003612501016	ARM B / R-DHAP	Yes	01/02/2008	BEAM CHEMOTHERAPY
5003616501411	ARM B / R-DHAP	Yes	07/10/2008	BEAM
5003622201037	ARM B / R-DHAP	Yes	22/12/2006	BEAM ON 15/12/2006
5003628201002	ARM B / R-DHAP	Yes	24/11/2004	BEAM
N = 35				

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

Randomization Number	Arm of treatment	Other treatment	Date of other treatment	Specify other treatment
5003101021014	ARM A / R-ICE	Yes	17/02/2005	ZEVALIN
5003101441074	ARM A / R-ICE	Yes	25/08/2008	DLI
N = 2				

6.6.4. Progression/relapse

Table 6.6-20 Progression/relapse n°1 – Extra-nodal involvement (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Bone marrow				
Missing	0	0	1	1
Not Done	24	31	37	53
Yes	12	16	6	9
No	41	53	26	37
Blood				
Missing	0	0	1	1
Not Done	6	8	7	10
Yes	8	10	3	4
No	63	82	59	84
Bone				
Missing	1	1	1	1
Not Done	11	14	7	10
Yes	13	17	12	17
No	52	68	50	71
Skin				
Missing	0	0	1	1
Not Done	5	6	2	3
Yes	8	10	10	14
No	64	83	57	81
Liver				
Missing	0	0	1	1
Not Done	5	6	3	4
Yes	16	21	16	23
No	56	73	50	71
Ascite				
Missing	1	1	1	1
Not Done	5	6	4	6
Yes	3	4	3	4
No	68	88	62	89
Pleural effusion				
Not Done	5	6	5	7
Yes	15	19	8	11
No	57	74	57	81
Lung				
Not Done	4	5	3	4
Yes	19	25	20	29

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
No	54	70	47	67
Spleen				
Missing	1	1	1	1
Not Done	3	4	2	3
Yes	11	14	10	14
No	62	81	57	81
Pericardium				
Missing	0	0	1	1
Not Done	6	8	5	7
Yes	3	4	1	1
No	68	88	63	90
Breast				
Missing	0	0	1	1
Not Done	8	10	6	9
Yes	1	1	2	3
No	68	88	61	87
Gonadal				
Missing	0	0	1	1
Not Done	10	13	7	10
Yes	7	9	3	4
No	60	78	59	84
Kidney				
Missing	1	1	2	3
Not Done	6	8	2	3
Yes	5	6	6	9
No	65	84	60	86
Adrenal				
Missing	0	0	1	1
Not Done	6	8	6	9
Yes	3	4	2	3
No	68	88	61	87
Thyroid				
Missing	0	0	1	1
Not Done	12	16	8	11
Yes	1	1	1	1
No	64	83	60	86
ORL area				
Missing	0	0	1	1
Not Done	12	16	9	13
Yes	3	4	4	6

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
No	62	81	56	80
Digestive area				
Missing	0	0	1	1
Not Done	13	17	8	11
Yes	11	14	11	16
No	53	69	50	71
CNS				
Missing	0	0	1	1
Not Done	17	22	14	20
Yes	4	5	5	7
No	56	73	50	71
Total	77	100	70	100

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Cervical right				
Normal	18	19	14	18
Involved	3	3	4	5
Not evaluated	2	2	4	5
Missing	72	76	54	71
Cervical left				
Normal	15	16	14	18
Involved	6	6	4	5
Not evaluated	2	2	4	5
Missing	72	76	54	71
Supraclavicular right				
Normal	18	19	18	24
Involved	2	2	1	1
Not evaluated	3	3	3	4
Missing	72	76	54	71
Supraclavicular left				
Normal	19	20	16	21
Involved	2	2	3	4
Not evaluated	2	2	3	4
Missing	72	76	54	71
Axillary right				
Normal	16	17	17	22
Involved	6	6	1	1

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Not evaluated	1	1	3	4
Missing	72	76	55	72
Axillary left				
Normal	16	17	14	18
Involved	7	7	5	7
Not evaluated	1	1	3	4
Missing	71	75	54	71
Inguinal right				
Normal	20	21	16	21
Involved	3	3	6	8
Not evaluated	0	0	1	1
Missing	72	76	53	70
Inguinal left				
Normal	21	22	18	24
Involved	2	2	4	5
Not evaluated	0	0	1	1
Missing	72	76	53	70
Mediastinal				
Normal	13	14	15	20
Involved	9	9	3	4
Not evaluated	1	1	3	4
Missing	72	76	55	72
Pulmonary hilar				
Normal	18	19	16	21
Involved	3	3	3	4
Not evaluated	1	1	3	4
Missing	73	77	54	71
Para-ortic				
Normal	11	12	11	14
Involved	11	12	10	13
Not evaluated	1	1	2	3
Missing	72	76	53	70
Mesenteric				
Normal	17	18	15	20
Involved	5	5	7	9
Not evaluated	1	1	1	1
Missing	72	76	53	70
Iliac right				
Normal	17	18	16	21
Involved	5	5	5	7

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Not evaluated	1	1	2	3
Missing	72	76	53	70
Iliac left				
Normal	19	20	14	18
Involved	3	3	7	9
Not evaluated	1	1	2	3
Missing	72	76	53	70
Splenic Hilar				
Normal	21	22	20	26
Involved	1	1	1	1
Not evaluated	1	1	2	3
Missing	72	76	53	70
Other nodal involvement				
No	16	17	18	24
Yes	5	5	4	5
Missing	74	78	54	71
TOTAL	95	100	76	100

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

Randomization Number	Arm of treatment	Other nodal involvement	Other nodal involvement - localization
5003101161407	ARM A / R-ICE	Yes	RIGHT CRURAL
5003101621609	ARM A / R-ICE	Yes	SUB CLAVICULAR LEFT
5003605701601	ARM A / R-ICE	Yes	KIDNEY HILUS LEFT
5003606201605	ARM A / R-ICE	Yes	INTERAORTOCAVAL
5003649501033	ARM A / R-ICE	Yes	PORTA HEPATIS
5003603201211	ARM B / R-DHAP	Yes	PREHEPATIC
5003604301607	ARM B / R-DHAP	Yes	PARAVERTEBRAL
5003617301619	ARM B / R-DHAP	Yes	SUBMANDIBULAR RIGHT
5003635201411	ARM B / R-DHAP	Yes	LIVER HILUS
N = 9			

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Liver				
Normal	14	18	14	20
Involved	3	4	3	4
Not evaluated	0	0	2	3
Missing	60	78	51	73

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Ascites				
Normal	17	22	17	24
Not evaluated	0	0	3	4
Missing	60	78	50	71
Pleural effusion				
Normal	13	17	15	21
Involved	3	4	1	1
Not evaluated	1	1	4	6
Missing	60	78	50	71
Lung				
Normal	9	12	10	14
Involved	7	9	7	10
Not evaluated	1	1	4	6
Missing	60	78	49	70
Spleen				
Normal	16	21	15	21
Involved	1	1	3	4
Not evaluated	0	0	2	3
Missing	60	78	50	71
Pericardium				
Normal	16	21	15	21
Not evaluated	1	1	5	7
Missing	60	78	50	71
Breast				
Normal	16	21	13	19
Involved	0	0	1	1
Not evaluated	1	1	6	9
Missing	60	78	50	71
Gonadal				
Normal	16	21	15	21
Not evaluated	1	1	5	7
Missing	60	78	50	71
Kidney				
Normal	15	19	17	24
Involved	2	3	1	1
Not evaluated	0	0	2	3
Missing	60	78	50	71
Adrenal				
Normal	16	21	17	24
Involved	1	1	0	0

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Not evaluated	0	0	3	4
Missing	60	78	50	71
Thyroid				
Normal	14	18	15	21
Not evaluated	3	4	5	7
Missing	60	78	50	71
Skin				
Normal	13	17	16	23
Involved	3	4	2	3
Not evaluated	1	1	2	3
Missing	60	78	50	71
Bone				
Normal	13	17	12	17
Involved	2	3	5	7
Not evaluated	2	3	4	6
Missing	60	78	49	70
Tonsil				
Normal	10	13	12	17
Not evaluated	6	8	7	10
Missing	61	79	51	73
Cavum				
Normal	10	13	12	17
Not evaluated	6	8	7	10
Missing	61	79	51	73
Parotid				
Normal	10	13	12	17
Not evaluated	6	8	7	10
Missing	61	79	51	73
Orbit				
Normal	10	13	12	17
Not evaluated	6	8	7	10
Missing	61	79	51	73
Sinus				
Normal	10	13	11	16
Involved	0	0	1	1
Not evaluated	6	8	7	10
Missing	61	79	51	73
Oesophagus				
Normal	14	18	13	19
Not evaluated	2	3	6	9

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Missing	61	79	51	73
Stomach				
Normal	14	18	13	19
Not evaluated	2	3	6	9
Missing	61	79	51	73
Duodenum				
Normal	13	17	13	19
Involved	1	1	0	0
Not evaluated	2	3	6	9
Missing	61	79	51	73
Colon				
Normal	14	18	12	17
Involved	0	0	1	1
Not evaluated	2	3	6	9
Missing	61	79	51	73
Caecum				
Normal	14	18	12	17
Involved	0	0	1	1
Not evaluated	2	3	6	9
Missing	61	79	51	73
Rectum				
Normal	13	17	13	19
Involved	1	1	0	0
Not evaluated	2	3	6	9
Missing	61	79	51	73
Other extra-nodal involvement				
Yes	7	9	8	11
No	9	12	12	17
Missing	61	79	50	71
TOTAL	77	100	70	100

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

Randomization Number	Arm of treatment	Progression/relapse number	Other extra-nodal involvement - localization
5003101491042	ARM A / R-ICE	1	BLADDER
5003101641618	ARM A / R-ICE	1	ENDOMETRIUM
5003611201057	ARM A / R-ICE	1	ABDOMINAL MUSCLES
5003620301011	ARM A / R-ICE	1	CENTRAL ABDOMINAL MASS
5003603201211	ARM B / R-DHAP	1	DIAPHRAGM
5003606201410	ARM B / R-DHAP	1	RIGHT KNEE AND CALF
5003606301606	ARM B / R-DHAP	1	OMENTUM

Randomization Number	Arm of treatment	Progression/relapse number	Other extra-nodal involvement - localization
5003610201212	ARM B / R-DHAP	1	ILIAC
5003628201044	ARM B / R-DHAP	1	STERNOCLEIDOMASTOID MUSCLE (INFILTRATION)
N = 9			

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Histological documentation				
Not Done	1	1	0	0
Yes	46	35	30	26
No	85	64	87	74
Cytological documentation				
Missing	2	2	0	0
Not Done	2	2	1	1
Yes	26	20	21	18
No	102	77	95	81
Total	132	100	117	100

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

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003101021008	ARM A / R-ICE	Yes	13/07/2004	DEXAMETHASONE-GEMOX	1
5003101021027	ARM A / R-ICE	Yes	28/07/2005	DHAOX	2
5003101021605	ARM A / R-ICE	Yes	28/05/2004	R-GEMOX	8
5003101021631	ARM A / R-ICE	Yes	14/06/2007	R-GEMOX	8
5003101031001	ARM A / R-ICE	Yes	11/03/2004	ONCOVIN + CELLTOP	-
5003101051004	ARM A / R-ICE	Yes	22/04/2004	VEPESIDE + CHLORAMINOPHENE	2
5003101051075	ARM A / R-ICE	Yes	25/06/2008	REVLIMID / DEXAMETHASONE	2
5003101071029	ARM A / R-ICE	Yes	16/06/2006	GEMOX	4
5003101071059	ARM A / R-ICE	Yes	21/02/2007	DHAOX	2
5003101091602	ARM A / R-ICE	Yes	10/01/2005	DHAP	3
5003101131062	ARM A / R-ICE	Yes	06/05/2007	DHAP	1
5003101141406	ARM A / R-ICE	Yes	04/01/2006	3 DHAOX + 4 CHOP	7
5003101161407	ARM A / R-ICE	Yes	28/03/2007	DHAP (1 CYCLE) THEN DEXAMETHASONE + CYTARABINE + ETOPOSIDE (1 CYCLE) THEN CYCLOPHOSPHAMIDE + MITOXANTRONE + VINCRISTINE + DEXAMETHASONE	3
5003101221043	ARM A / R-ICE	Yes	08/04/2006	DHAP DOXORUBICINE	1
5003101281017	ARM A / R-ICE	Yes	13/12/2004	DHAP	-
5003101281033	ARM A / R-ICE	Yes	12/01/2006	DHAP	2
5003101281208	ARM A / R-ICE	Yes	29/03/2006	DHAP	-
5003101351040	ARM A / R-ICE	Yes	11/03/2006	HYPER C-VAD	2
5003101391039	ARM A / R-ICE	Yes	04/04/2006	CYCLOPHOSPHAMIDE HIGH DOSE AND VINBLASTIN	2
5003101391201	ARM A / R-ICE	Yes	23/12/2003	DHAP + COPADEM	5

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003101431046	ARM A / R-ICE	Yes	13/06/2006	DHAP	3
5003101431622	ARM A / R-ICE	Yes	03/04/2008	COP (1 CYCLE) DHAP (3 CYCLES) CARBO DHAP (1 CYCLE) GEMOX (1 CYCLE)	6
5003101441036	ARM A / R-ICE	Yes	12/01/2006	CISPLATINE + ARAC + RITUXIMAB / UNTIL 29/3/06	3
5003101491042	ARM A / R-ICE	Yes	04/08/2006	LOW DOSE CYCLOPHOSPHAMIDE, 18/09/06 : HOELZER BLOK A, 30/10/06 : HOELZER BLOK D, GEMCITABINE 15/01/07 AND 26/01/07	-
5003101621026	ARM A / R-ICE	Yes	12/03/2007	RITUXIMAB - DEXAMETHASONE CISPLATINE CYTARABINE	6
5003101621609	ARM A / R-ICE	Yes	13/11/2006	R CHOP	6
5003101621615	ARM A / R-ICE	Yes	04/05/2005	DHAP	4
5003101641618	ARM A / R-ICE	Yes	25/01/2007	GEMCITABINE - OXALIPLATIN	8
5003102161078	ARM A / R-ICE	Yes	14/08/2008	EPOCH THEN METHOTREXATE + CYTARABINE HD	2
5003102321024	ARM A / R-ICE	Yes	17/08/2005	METHOTREXATE INTRATHECAL	-
5003102341049	ARM A / R-ICE	Yes	08/09/2007	CYTARABINE - ETOPOSIDE - MITOXANTRONE - IFOSFAMIDE - MITOGUAZONE	1
5003102341061	ARM A / R-ICE	Yes	10/01/2008	CYTARABINE, ETOPOSIDE, MITOXANTRONE, IFOSFAMIDE, METHOTREXATE	3
5003102341416	ARM A / R-ICE	Yes	08/02/2007	VIM - CYTARABIN	3
5003102341641	ARM A / R-ICE	Yes	12/11/2009	CHOP	3
5003102541052	ARM A / R-ICE	Yes	10/01/2007	DHAP	1
5003102541625	ARM A / R-ICE	Yes	01/02/2008	ESAP	4
5003601201041	ARM A / R-ICE	Yes	-	GEMOX -> GEMCITABINE / OXILIPLATIN	2
5003601401003	ARM A / R-ICE	Yes	26/06/2006	TROPHOSPHAMID 100 MG X 1 CONTINUOUSLY TO 16/07/2006	-
5003601401006	ARM A / R-ICE	Yes	05/03/2008	CYCLOPHOSPHAMIDE PER ORAL CONTINUOUS TREATEMENT TOGETHER WITH METHOTREXATE 2 DAYS / WEEK	-
5003601401401	ARM A / R-ICE	Yes	15/12/2005	VINCRISTINE, DOXORUBICIN, DEXAMETHASON	4
5003601401603	ARM A / R-ICE	Yes	28/11/2007	DOXORUBICIN (LIPOSOMAL) + GEMCITABIN TO 3/4-08 + ISOFOSFAMIDE 100 MG PO DAILY DOSE	6
5003601401605	ARM A / R-ICE	Yes	17/06/2008	MITOGUAZONE, IFOSFAMIDE, ETOPOSID, METHOTREXATE	4
5003601601003	ARM A / R-ICE	Yes	16/11/2007	PALLIATIVE CYCLOPHOSPHAMIDE	3
5003601601005	ARM A / R-ICE	Yes	11/09/2008	ORAL CYCLOPHOSPHAMIDE / ETOPOSIDE X 7 DAYS	1
5003601881401	ARM A / R-ICE	Yes	11/08/2007	DEXAMETHASONE / CYTARABINE / PLATINE	4
5003602201601	ARM A / R-ICE	Yes	01/04/2006	DHAP DOSE REDUCED	2
5003602801001	ARM A / R-ICE	Yes	25/03/2004	HYPER C-VAD / HD-MTX-ARA-C + RITUXIMAB	2
5003602801011	ARM A / R-ICE	Yes	15/07/2007	HIGH DOSE MTX + ARA-C	1
5003602801403	ARM A / R-ICE	Yes	24/03/2009	R-ESAP	1
5003602801605	ARM A / R-ICE	Yes	24/09/2008	R-GDP	5
5003602901201	ARM A / R-ICE	Yes	-	GEMSAR	1
5003602901401	ARM A / R-ICE	Yes	-	GEMSAR	2
5003603201038	ARM A / R-ICE	Yes	-	SEE COPY	-
5003603201628	ARM A / R-ICE	Yes	-	CHOP	5
5003603701010	ARM A / R-ICE	Yes	16/08/2006	ARM A, R-DHAP	1
5003603801002	ARM A / R-ICE	Yes	05/03/2010	R-MINE	1
5003603801203	ARM A / R-ICE	Yes	17/08/2005	ESHAP	1
5003603801406	ARM A / R-ICE	Yes	13/11/2008	P.O. ETOPOSIDE	3
5003603801602	ARM A / R-ICE	Yes	13/10/2006	R-FND	4
5003603801608	ARM A / R-ICE	Yes	03/11/2008	R-MEGA CHOP	3
5003604201204	ARM A / R-ICE	Yes	25/08/2004	Gemcitabin	4

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003604301602	ARM A / R-ICE	Yes	17/08/2006	2 CYCLES OF FLUDARABINE + 6 CYCLES OF CEOP	8
5003604801014	ARM A / R-ICE	Yes	21/04/2007	DHAP	1
5003604801205	ARM A / R-ICE	Yes	10/08/2006	R-DHAP	4
5003605201006	ARM A / R-ICE	Yes	18/01/2005	DHAP	1
5003606201605	ARM A / R-ICE	Yes	05/01/2006	GEMCITABINE / OXALIPLATIN	5
5003606301612	ARM A / R-ICE	Yes	27/02/2008	RDHAP THEN RICE	2
5003607201032	ARM A / R-ICE	Yes	25/07/2006	GMALL-PROTOCOL	1
5003607501403	ARM A / R-ICE	Yes	13/07/2007	GEMCYTABINE CISPLATIN	3
5003607701007	ARM A / R-ICE	Yes	29/04/2006	DHAP	1
5003607701009	ARM A / R-ICE	Yes	28/07/2006	ARA-C HIGH DOSE	1
5003609201058	ARM A / R-ICE	Yes	18/09/2008	DEXA-BEAM	1
5003610201007	ARM A / R-ICE	Yes	-	2 X B ALL PROTOCOL	2
5003610201206	ARM A / R-ICE	Yes	21/06/2006	DHAP	2
5003610201612	ARM A / R-ICE	Yes	19/06/2005	HD-MTX, IFOSFAMIDE, CYTARABIN, TENIPOSIDE, DEXAMETHASONE	1
5003610301208	ARM A / R-ICE	Yes	24/09/2004	GEMCITABINE / VINORELBINE	1
5003610501031	ARM A / R-ICE	Yes	30/07/2008	GEMCITABINE, VINORELBINE	1
5003611201057	ARM A / R-ICE	Yes	27/07/2008	GEMCITABINE + OXALIPLATINE	1
5003612501015	ARM A / R-ICE	Yes	-	LOW DOSE CHEMOTHERAPY (SHAMASH REGIMEN)	4
5003615501018	ARM A / R-ICE	Yes	15/10/2007	GEMCITABINE DACARBAZINE CYCLOPHOSPHAMIDE VINCRISTINE PREDNISOLONE	1
5003615501028	ARM A / R-ICE	Yes	02/05/2008	GEMCITABINE, DACARBAZINE, CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISOLONE	3
5003615501404	ARM A / R-ICE	Yes	20/08/2007	GDCVP (GEMCITABINE, DACARBAZINE, CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISOLONE)	2
5003617201004	ARM A / R-ICE	Yes	26/11/2004	1 CYCLE CYTARABINE / MITOXANTRONE 12/04 + 1 CYCLE R-GEMOX 01/05	2
5003617201010	ARM A / R-ICE	Yes	25/02/2005	DEXA-BEAM + VINCRISTIN	2
5003617201039	ARM A / R-ICE	Yes	23/01/2007	DEXA-BEAM	1
5003619301621	ARM A / R-ICE	Yes	24/10/2007	R-VGF	4
5003620301011	ARM A / R-ICE	Yes	03/01/2008	GEMCITABINE / VINORELBINE	3
5003621201020	ARM A / R-ICE	Yes	28/04/2006	DEXAMETHASONE / CYTARABINE / METHOTREXATE	2
5003621201026	ARM A / R-ICE	Yes	17/02/2006	DEXA - BEAM	1
5003622201022	ARM A / R-ICE	Yes	24/02/2006	R-DHAP / HIGH-DOSE MTX NB CYCLES 1	2
5003622201403	ARM A / R-ICE	Yes	10/07/2006	FLUDARABIN / CYCLOPHOSPHAMID	2
5003631201035	ARM A / R-ICE	Yes	-	DHAP	5
5003632201054	ARM A / R-ICE	Yes	29/09/2008	GEMCITABINE	3
5003633201036	ARM A / R-ICE	Yes	07/12/2006	DEXA-BEAM	-
5003642501030	ARM A / R-ICE	Yes	06/05/2008	GEMCITABINE / DHAP	3
5003643501202	ARM A / R-ICE	Yes	11/06/2008	MINI BEAM	1
5003649501033	ARM A / R-ICE	Yes	10/09/2008	OXALIPLATIN + GEMCITABINE	-
5003101021038	ARM B / R-DHAP	Yes	19/12/2006	GEMOX	4
5003101031019	ARM B / R-DHAP	Yes	02/02/2005	MIV	3
5003101031067	ARM B / R-DHAP	Yes	14/06/2007	MIV X 2 THEN GEMCITABINE - VINORELBINE X 1, ESHAP X 1	4
5003101031401	ARM B / R-DHAP	Yes	14/04/2005	MIV	2
5003101051050	ARM B / R-DHAP	Yes	15/01/2007	CYCLOPHOSPHAMIDE + ETOPOSIDE	1
5003101051063	ARM B / R-DHAP	Yes	31/03/2008	R-GEMOX	4

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003101071051	ARM B / R-DHAP	Yes	19/09/2006	1 ICE + 1 GEMOX	1
5003101071073	ARM B / R-DHAP	Yes	28/11/2007	ICE	1
5003101071408	ARM B / R-DHAP	Yes	29/11/2006	GEMOX	4
5003101071417	ARM B / R-DHAP	Yes	09/08/2008	GEMOX	1
5003101071607	ARM B / R-DHAP	Yes	17/03/2004	HOLOXAN- VP16	6
5003101091022	ARM B / R-DHAP	Yes	05/07/2005	VEPESIDE / CARBOPLATINE / IFOSFAMIDE (ICE)	1
5003101091025	ARM B / R-DHAP	Yes	01/08/2005	CYTARABINE / DEXAMETHASONE	1
5003101091626	ARM B / R-DHAP	Yes	17/10/2005	(R)ICE	3
5003101141402	ARM B / R-DHAP	Yes	01/09/2005	IFOSFAMIDE ETOPOSIDE MESNA	4
5003101141624	ARM B / R-DHAP	Yes	10/06/2009	ENDOXAN AND SOLUMEDROL FOLLOWING BY CHOP 1 CYCLE AND CVP	1
5003101221057	ARM B / R-DHAP	Yes	08/02/2007	MIME DOXORUBICINE	2
5003101221070	ARM B / R-DHAP	Yes	07/05/2008	MINE : FAILURE, THEN DOXORUBICINE + BLEOMYCINE 11/09/2008	2
5003101221639	ARM B / R-DHAP	Yes	27/04/2007	MIME	3
5003101251015	ARM B / R-DHAP	Yes	26/12/2004	IVAM X 1 / IVA X 2	3
5003101251035	ARM B / R-DHAP	Yes	17/07/2006	IVAM + 3 ETOPOSIDE/CYCLOPHOSPHAMIDE	5
5003101251044	ARM B / R-DHAP	Yes	18/05/2006	IVAM	1
5003101391032	ARM B / R-DHAP	Yes	03/08/2005	R-ICE	1
5003101391048	ARM B / R-DHAP	Yes	25/09/2006	APLIDINE	2
5003101391613	ARM B / R-DHAP	Yes	16/04/2005	2 VAD + 1 MTX	2
5003101431204	ARM B / R-DHAP	Yes	04/11/2005	CARYOLYSINE ONCOVIN NATULAN / ADRIA-VELBE-BLEOMYCINE	-
5003101601066	ARM B / R-DHAP	Yes	27/07/2007	ICE	2
5003101601076	ARM B / R-DHAP	Yes	25/04/2008	R-DHAP X2 + BOD X1 + VIM X1	4
5003101641018	ARM B / R-DHAP	Yes	06/04/2005	ICE	2
5003101641047	ARM B / R-DHAP	Yes	04/07/2006	ICE	2
5003101641079	ARM B / R-DHAP	Yes	13/08/2008	COPADEM	2
5003102181031	ARM B / R-DHAP	Yes	08/09/2005	RICE	2
5003102341003	ARM B / R-DHAP	Yes	05/02/2004	HCVAD : ENDOXAN, DEXAMETHASONE, DOXORUBICINE (INDUCTION)	2
5003102411054	ARM B / R-DHAP	Yes	04/09/2007	RITUXIMAB + ETOPOSIDE + IFOSFAMIDE	2
5003102541016	ARM B / R-DHAP	Yes	22/11/2004	IFOSFAMIDE, GEMCITABINE	3
5003102541640	ARM B / R-DHAP	Yes	11/09/2007	RACVBP	3
5003103161041	ARM B / R-DHAP	Yes	20/04/2007	ETOPOSIDE + IFOSFAMIDE	4
5003601201018	ARM B / R-DHAP	Yes	07/10/2005	ICE	2
5003601401402	ARM B / R-DHAP	Yes	19/09/2005	CHOR / CYTOSAR	4
5003601601602	ARM B / R-DHAP	Yes	14/08/2008	GEMATABINE W/ RITUXIMAB + DACETUZUMAB (INVESTIGATIONAL)	5
5003601801003	ARM B / R-DHAP	Yes	26/01/2005	RICE	2
5003602801204	ARM B / R-DHAP	Yes	10/03/2005	VIN-BLEO (VINCRISTIN, BLEOMYCIN, PREDNISON)	1
5003603801007	ARM B / R-DHAP	Yes	22/05/2006	MINIDEXA BEAM	1
5003603801010	ARM B / R-DHAP	Yes	07/11/2006	ICE	1
5003604201056	ARM B / R-DHAP	Yes	18/06/2009	B-ALL	-
5003604301607	ARM B / R-DHAP	Yes	04/03/2010	ETOPOSIDE	-
5003604801006	ARM B / R-DHAP	Yes	07/06/2006	R-ICE	2
5003605201603	ARM B / R-DHAP	Yes	12/05/2005	CHOP	3
5003605301203	ARM B / R-DHAP	Yes	16/06/2004	VINCRISTINE AND BLEOMYCIN	2

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003605701404	ARM B / R-DHAP	Yes	29/04/2008	METHOTREXATE (MTX)	3
5003606201033	ARM B / R-DHAP	Yes	24/08/2006	3 X ICE (NO RESPONSE), 2 X GEMCITABIN / IRINOTECAN : MR	3
5003606201407	ARM B / R-DHAP	Yes	23/11/2006	GEMCITABINE / IRINOTECAN	2
5003606201410	ARM B / R-DHAP	Yes	01/06/2007	DEXABEAM	2
5003606201609	ARM B / R-DHAP	Yes	-	ICE	3
5003606301606	ARM B / R-DHAP	Yes	18/01/2005	GEMCITABINE, VINORELBINE COMBINATION	4
5003606701005	ARM B / R-DHAP	Yes	24/05/2006	VINORELBINE - GEMCITABINE	2
5003607201408	ARM B / R-DHAP	Yes	22/10/2008	R-GEMOX	2
5003607301603	ARM B / R-DHAP	Yes	27/06/2006	VINCRISTINE 2 MG EVERY 2 OR 3 WEEKS / DEXAMETHASONE 40 MG DAILY FOR FOUR DAYS EVEREY THREE WEEKS	6
5003607501401	ARM B / R-DHAP	Yes	19/06/2007	GEMCITABINE + CISPLATIN DEXAMETHASONE	2
5003609301620	ARM B / R-DHAP	Yes	26/11/2007	R-ICE	6
5003610701403	ARM B / R-DHAP	Yes	20/11/2008	R-ICE	2
5003611301003	ARM B / R-DHAP	Yes	23/01/2006	FLUDARABINE / MITOZONTRONE / DEXAMETHASONE	2
5003612501019	ARM B / R-DHAP	Yes	29/11/2007	METHOTREXATE	2
5003614301407	ARM B / R-DHAP	Yes	24/06/2009	ICE	6
5003615501004	ARM B / R-DHAP	Yes	08/01/2007	ESHAP	1
5003615501029	ARM B / R-DHAP	Yes	30/05/2008	GEMCITABINE, DACARBAZINE, CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISOLONE	1
5003617201021	ARM B / R-DHAP	Yes	30/05/2007	R-BENDAMUSTIN	5
5003617201024	ARM B / R-DHAP	Yes	03/01/2006	DEXA-BEAM	1
5003617201043	ARM B / R-DHAP	Yes	24/09/2007	2 G VINCRISTIN FOLLOWED BY 6EM DEX OX	1
5003617301619	ARM B / R-DHAP	Yes	09/05/2007	GEMCITABINE ; IFOSFAMIDE ; PREDNISOLONE	4
5003618301005	ARM B / R-DHAP	Yes	05/07/2006	GEMCITABINE VINORELBINE	2
5003619301016	ARM B / R-DHAP	Yes	04/04/2008	VGIF-R	1
5003620201017	ARM B / R-DHAP	Yes	18/08/2005	R-DEXA BEAM	2
5003628201044	ARM B / R-DHAP	Yes	05/08/2008	R-ICE, R-CHOP, GEMCITABINE / VINORELBINE	3
5003628201046	ARM B / R-DHAP	Yes	10/10/2007	GEMCITABINE / ENZASTAURIN / OXALIPLATIN / RITUXIMAB : SD	6
5003630201040	ARM B / R-DHAP	Yes	16/06/2007	RITUXIMAB - GEMCITABINE - OXALIPLATIN	2
5003631201012	ARM B / R-DHAP	Yes	13/01/2006	PREPHASE CYCLOPHOSPHAMIDE / DOSE REDUCED ICE 3 X FOLLOWED BY BENDAMUSTINE DEXAMETHASONE / FOLLOWED BY GEMCITABINE VINORELBINE	5
5003631201619	ARM B / R-DHAP	Yes	13/09/2006	ICE C IFOSFAMIDE 50%	1
5003635201411	ARM B / R-DHAP	Yes	-	R-GEMOX	1
5003636201047	ARM B / R-DHAP	Yes	17/08/2007	R-ICE	2
N = 177					

Listing 6.6-14 Progression/relapse n°1 - Radiotherapy (induction ITT)

Randomization Number	Arm of treatment	Radiotherapy	Date of radiotherapy	Site of radiotherapy	Dose of radiotherapy (Gy)
5003101021027	ARM A / R-ICE	Yes	07/11/2005	MEDIASTINAL	46
5003101031001	ARM A / R-ICE	Yes	16/01/2004	LEFT ARM	47
5003101071020	ARM A / R-ICE	Yes	05/09/2005	TONSIL RIGHT AND CERVICAL RIGHT	40
5003101071029	ARM A / R-ICE	Yes	-	EXTERNAL BEAM RADIATION (AXILLAR, SUSCLAVICULAR RIGHT, MEDIASTINAL)	20
5003101071059	ARM A / R-ICE	Yes	26/01/2007	SHOULDER LEFT AND LEFT AXILLAR	30
5003101161407	ARM A / R-ICE	Yes	-	RIGHT LEG	36

Randomization Number	Arm of treatment	Radiotherapy	Date of radiotherapy	Site of radiotherapy	Dose of radiotherapy (Gy)
5003101211023	ARM A / R-ICE	Yes	19/07/2005	MEDDIASTINAL AND LEFT SUPRACLAVICULATR	40
5003101351040	ARM A / R-ICE	Yes	23/05/2006	MEDIASTINUM	-
5003101431046	ARM A / R-ICE	Yes	16/10/2006	MESENTERIC (RESIDUAL MASS)	40
5003101491042	ARM A / R-ICE	Yes	18/08/2006	BLADDER (TILL 01/09/2006) + 13/12/2006 - 02/01/2007, SITE : LATERAL LUMBAL FIELD, 30 GY	30
5003601201041	ARM A / R-ICE	Yes	-	MEDIASTINAL LYMPH NODES	-
5003601601005	ARM A / R-ICE	Yes	29/07/2008	LEFT PELVIC WALL	37
5003601601401	ARM A / R-ICE	Yes	28/07/2008	RADIOTHERAPY : LEFT CHEST WALL, ENFACE FOR LOW GRADE FOLLICULAR LYMPHOMA	36
5003602901601	ARM A / R-ICE	Yes	-	RIGHT ADRENAL	-
5003603201025	ARM A / R-ICE	Yes	-	MEDIASTINAL	40
5003603201038	ARM A / R-ICE	Yes	10/09/2007	TOTAL BODY	4
5003603701006	ARM A / R-ICE	Yes	07/04/2006	THORAX WOUND	42
5003603701010	ARM A / R-ICE	Yes	13/09/2006	LESSER PELVIS, INGUINAL RIGHT	30
5003603801015	ARM A / R-ICE	Yes	25/06/2007	MEDIASTINUM	40
5003603801202	ARM A / R-ICE	Yes	20/02/2006	BONE LESIONS	30
5003603801203	ARM A / R-ICE	Yes	16/05/2005	RIGHT INGUINA AND RIGHT ILIAC REGION	40
5003604201204	ARM A / R-ICE	Yes	19/11/2004	cervical right : 40 Gy, paraaortic: 40 Gy, cervical left : 32 Gy, frontal right : 24 Gy	40
5003604301013	ARM A / R-ICE	Yes	17/06/2009	RIGHT FOREARM	20
5003604901005	ARM A / R-ICE	Yes	17/07/2006	ILIAC BONE	36
5003605201006	ARM A / R-ICE	Yes	-	BULKY LYMPHOMA HYPOGASTRIUM	-
5003605901003	ARM A / R-ICE	Yes	10/10/2007	LEFT UPPER NECK	25
5003606701003	ARM A / R-ICE	Yes	09/03/2006	MESENTERIC MASS	40
5003607201032	ARM A / R-ICE	Yes	22/08/2006	CERVICAL LEFT	65
5003609201058	ARM A / R-ICE	Yes	14/08/2008	MEDIASTINUM	2
5003610301617	ARM A / R-ICE	Yes	-	RIGHT INGUINAL REGION	-
5003615301004	ARM A / R-ICE	Yes	20/12/2005	ABDOMEN	40
5003615501201	ARM A / R-ICE	Yes	09/02/2007	ABDOMEN	29
5003617201010	ARM A / R-ICE	Yes	22/08/2005		36
5003617201039	ARM A / R-ICE	Yes	03/04/2007	PARA-AORTIC	45
5003621201020	ARM A / R-ICE	Yes	27/06/2006	TONSILLA RIGHT, ZONA LEG LEFT	8
5003621201026	ARM A / R-ICE	Yes	-	ABDOMINAL	9
5003628201003	ARM A / R-ICE	Yes	06/12/2004	ABDOMINAL MASSES	48
5003632201054	ARM A / R-ICE	Yes	16/10/2008	LEFT SHANK	30
5003642501030	ARM A / R-ICE	Yes	22/10/2008	MEDIASTINUM	30
5003101031067	ARM B / R-DHAP	Yes	28/08/2007	MEDIASTINUM	40
5003101031401	ARM B / R-DHAP	Yes	-	ENCEPHALON	45
5003101091626	ARM B / R-DHAP	Yes	16/01/2006	RIGHT AXILLARY	40
5003101131060	ARM B / R-DHAP	Yes	12/06/2007	CARINA LESION AND MEDIASTINUM	44
5003101251015	ARM B / R-DHAP	Yes	14/06/2005	MESENTERIC MASS	36
5003101251044	ARM B / R-DHAP	Yes	22/06/2006	CERVICAL	42
5003101391032	ARM B / R-DHAP	Yes	29/08/2005	ND	-
5003102411054	ARM B / R-DHAP	Yes	16/10/2007	LEFT ILIAC + LEFT INGUINAL	40
5003102411069	ARM B / R-DHAP	Yes	20/02/2008	CERVICO SUB CLAVICULAR GANGLION + WALDEYER RING	36
5003102541016	ARM B / R-DHAP	Yes	26/01/2005	ABDOMINAL	40

Randomization Number	Arm of treatment	Radiotherapy	Date of radiotherapy	Site of radiotherapy	Dose of radiotherapy (Gy)
5003601201201	ARM B / R-DHAP	Yes	24/06/2004	LUNG RIGHT SIDE, CERVICAL BOTH SIDES	36
5003601801003	ARM B / R-DHAP	Yes	17/05/2005	INGUINAL + ILIAC	39
5003602801204	ARM B / R-DHAP	Yes	05/03/2005	RIGHT SHOULDER, MEDIASTINUM	30
5003603801007	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
5003604801006	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	07/01/2010	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
N = 74					

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

Randomization Number	Arm of treatment	Immunotherapy	Date of immunotherapy	Specify immunotherapy
5003101021027	ARM A / R-ICE	Yes	28/07/2005	RITUXIMAB
5003101021631	ARM A / R-ICE	Yes	14/06/2007	RITUXIMAB
5003101051075	ARM A / R-ICE	Yes	03/06/2008	RITUXIMAB
5003101071020	ARM A / R-ICE	Yes	05/03/2006	MABTHERA AND ZEVALIN (THE 09.03.06)
5003101091602	ARM A / R-ICE	Yes	13/01/2005	RITUXIMAB
5003101131062	ARM A / R-ICE	Yes	06/05/2007	RITUXIMAB
5003101141406	ARM A / R-ICE	Yes	04/01/2006	RITUXIMAB
5003101161407	ARM A / R-ICE	Yes	28/03/2007	RITUXIMAB THEN ANTI CD20
5003101281017	ARM A / R-ICE	Yes	13/12/2004	RITUXIMAB
5003101281033	ARM A / R-ICE	Yes	12/01/2006	RITUXIMAB
5003101281208	ARM A / R-ICE	Yes	29/03/2006	RITUXIMAB
5003101351040	ARM A / R-ICE	Yes	03/05/2006	MABTHERA
5003101431046	ARM A / R-ICE	Yes	13/06/2006	RITUXIMAB
5003101431622	ARM A / R-ICE	Yes	09/04/2008	RITUXIMAB

Randomization Number	Arm of treatment	Immunotherapy	Date of immunotherapy	Specify immunotherapy
5003101481403	ARM A / R-ICE	Yes	04/02/2008	RITUXIMAB
5003101621615	ARM A / R-ICE	Yes	27/08/2005	RITUXIMAB 8 CURES
5003101641618	ARM A / R-ICE	Yes	25/01/2007	RITUXIMAB
5003102161078	ARM A / R-ICE	Yes	14/08/2008	RITUXIMAB
5003102341641	ARM A / R-ICE	Yes	12/11/2009	RITUXIMAB
5003102541625	ARM A / R-ICE	Yes	01/02/2008	RITUXIMAB
5003602901601	ARM A / R-ICE	Yes	17/01/2006	MABTHERA
5003603701010	ARM A / R-ICE	Yes	16/08/2006	RITUXIMAB
5003603801602	ARM A / R-ICE	Yes	13/10/2006	RITUXIMAB IN COMBINATION WITH FND
5003604801205	ARM A / R-ICE	Yes	10/08/2006	RITUXIMAB
5003605701601	ARM A / R-ICE	Yes	28/07/2006	RITUXIMAB (STOP : 04.08.2006)
5003606301612	ARM A / R-ICE	Yes	27/02/2008	RITUXIMAB
5003609201058	ARM A / R-ICE	Yes	06/11/2008	RITUXIMAB (2 RITUXIMAB 750 MG ON 25/08/2008 + 17/09/2008)
5003611201057	ARM A / R-ICE	Yes	26/07/2008	RITUXIMAB
5003615501014	ARM A / R-ICE	Yes	12/03/2008	OFATUMOMAB
5003617201010	ARM A / R-ICE	Yes	07/04/2005	ZEVALIN + RITUXIMAB
5003617201039	ARM A / R-ICE	Yes	19/01/2007	RITUXIMAB
5003621201020	ARM A / R-ICE	Yes	08/05/2006	MABTHERA 2 CYCLES
5003621201023	ARM A / R-ICE	Yes	30/05/2006	RITUXIMAB 1 CYCLE
5003621201026	ARM A / R-ICE	Yes	16/02/2006	RITUXIMAB
5003622201022	ARM A / R-ICE	Yes	03/06/2006	RITUXIMAB / CYCLOSPORIN (DATE NK)
5003649501033	ARM A / R-ICE	Yes	09/09/2008	RITUXIMAB
5003101021038	ARM B / R-DHAP	Yes	18/12/2006	RITUXIMAB (4 CYCLES)
5003101031019	ARM B / R-DHAP	Yes	02/02/2005	RITUXIMAB
5003101031067	ARM B / R-DHAP	Yes	14/06/2007	R X 3
5003101071051	ARM B / R-DHAP	Yes	19/09/2006	RITUXIMAB
5003101071073	ARM B / R-DHAP	Yes	28/11/2007	RITUXIMAB
5003101071408	ARM B / R-DHAP	Yes	05/04/2007	IBRITUMOMAB TIUXETAN + RITUXIMAB
5003101071607	ARM B / R-DHAP	Yes	17/03/2004	MABTHERA
5003101091022	ARM B / R-DHAP	Yes	05/07/2005	RITUXIMAB
5003101091626	ARM B / R-DHAP	Yes	17/10/2005	RITUXIMAB
5003101141624	ARM B / R-DHAP	Yes	10/06/2009	RITUXIMAB
5003101221070	ARM B / R-DHAP	Yes	05/08/2008	OFATUMUMAB
5003101251015	ARM B / R-DHAP	Yes	26/12/2004	RITUXIMAB X 3
5003101251035	ARM B / R-DHAP	Yes	17/07/2006	RITUXIMAB
5003101251044	ARM B / R-DHAP	Yes	18/05/2006	RITUXIMAB
5003101601066	ARM B / R-DHAP	Yes	27/07/2007	RITUXIMAB
5003101641018	ARM B / R-DHAP	Yes	06/04/2005	RITUXIMAB
5003101641047	ARM B / R-DHAP	Yes	04/07/2006	RITUXIMAB
5003101641079	ARM B / R-DHAP	Yes	13/08/2008	RITUXIMAB
5003102341003	ARM B / R-DHAP	Yes	05/02/2004	MABTHERA
5003601201018	ARM B / R-DHAP	Yes	05/10/2005	RITUXIMAB 2X
5003601601602	ARM B / R-DHAP	Yes	14/08/2008	RITUXIMAB W/GEMCITABINE AND DACETUZUMAB (INVESTIGATIONAL)
5003601801003	ARM B / R-DHAP	Yes	26/01/2005	RITUXIMAB

Randomization Number	Arm of treatment	Immunotherapy	Date of immunotherapy	Specify immunotherapy
5003605201603	ARM B / R-DHAP	Yes	12/05/2005	RITUXIMAB
5003606201410	ARM B / R-DHAP	Yes	01/06/2007	RITUXIMAB
5003606201609	ARM B / R-DHAP	Yes	-	RITUXIMAB EVERY 3 MONTHS
5003606301606	ARM B / R-DHAP	Yes	30/06/2005	RITUXIMAB
5003606701005	ARM B / R-DHAP	Yes	17/07/2006	17/07 TO 05/09/06 RITUXIMAB (1X/MONTH / 5 CYCLES) + 03/10 AND 01/11/06, 30/11/06, 24/01 AND 21/03/07
5003609301620	ARM B / R-DHAP	Yes	26/11/2007	RITUXIMAB (IN CONJUNCTION WITH CHEMOTHERAPY)
5003611301003	ARM B / R-DHAP	Yes	24/01/2006	RITUXIMAB
5003617201043	ARM B / R-DHAP	Yes	26/09/2007	RITUXIMAB
5003618301005	ARM B / R-DHAP	Yes	-	RITUXIMAB
N = 67				

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

Randomization Number	Arm of treatment	Transplantation	Date of transplantation	Conditioning Regimen
5003101141406	ARM A / R-ICE	Yes	30/05/2006	BEAM
5003101351040	ARM A / R-ICE	Yes	16/05/2006	BEAM
5003101431046	ARM A / R-ICE	Yes	05/09/2006	BEAM
5003101441036	ARM A / R-ICE	Yes	10/11/2005	BEAM ON 03/11/2005
5003102341061	ARM A / R-ICE	Yes	26/05/2008	FLUDARABINE, ENDOXAN, IRRADIATION
5003102341416	ARM A / R-ICE	Yes	09/05/2007	BEAM
5003102341641	ARM A / R-ICE	Yes	18/02/2010	IBRITUMOMAB TIUXETAN (ETUDE ZEVALLO)
5003102491619	ARM A / R-ICE	Yes	06/09/2007	FLUDARABINE BUSULFAN AND ATG
5003102541625	ARM A / R-ICE	Yes	02/06/2008	BEAM
5003601881401	ARM A / R-ICE	Yes	11/12/2007	FLUDARABINE / BUSULFAN / SAL
5003602201601	ARM A / R-ICE	Yes	28/06/2006	FLUDARABIN / BUSULFAN / CYCLOPHOSPHAMID / ATG: ACC. DSHNHL-2004-R3 PROTOCOL (ARM B, WITHOUT RITUXIMAB)
5003602301001	ARM A / R-ICE	Yes	28/04/2004	BEAM
5003602501001	ARM A / R-ICE	Yes	03/01/2007	BEAM STARTED ON 28122006
5003602801001	ARM A / R-ICE	Yes	31/07/2004	BEAM
5003602801605	ARM A / R-ICE	Yes	16/04/2009	FLUDARABIN, BUSULFAN, ANTITHYMOCYTE GLOBULIN
5003602901201	ARM A / R-ICE	Yes	19/05/2004	FLUDARABIN ATG RADIATION
5003603201025	ARM A / R-ICE	Yes	27/04/2006	BEAM ON 21/04/2006
5003603201038	ARM A / R-ICE	Yes	19/09/2007	MELPHALAN + FLUDARABIN
5003603801602	ARM A / R-ICE	Yes	08/03/2007	TBI + ALEMTUZUMAB + CYCLOPHOSPHAMIDE
5003603801608	ARM A / R-ICE	Yes	28/01/2009	FLAMSA + TBI
5003604801205	ARM A / R-ICE	Yes	22/12/2006	BU-CY
5003608701016	ARM A / R-ICE	Yes	12/08/2008	ZBEAM / 3.45 (CD34 X 10^6/KG)
5003609201058	ARM A / R-ICE	Yes	19/11/2008	IBRITUMOMAB IUXETAN + RITUXIMAB 06/11/2008 BEAM 13/11-17/11/2008
5003610201007	ARM A / R-ICE	Yes	11/03/2005	FLUDARABIN, BUSULFAN CYCLOPHOSPHAMID
5003610201612	ARM A / R-ICE	Yes	15/07/2005	BEAM
5003617201010	ARM A / R-ICE	Yes	21/04/2005	BEAM
5003622201022	ARM A / R-ICE	Yes	05/05/2006	FLUDARABIN / BCNU / MELPHALAN / RITUXIMAB
5003633201036	ARM A / R-ICE	Yes	05/04/2007	BEAM
5003649501033	ARM A / R-ICE	Yes	05/11/2008	BEAM : CARMUSTINE, ETOPOSIDE, CYTABINE, MELPHALAN, STARTED 30/10/2008

Randomization Number	Arm of treatment	Transplantation	Date of transplantation	Conditioning Regimen
5003101131060	ARM B / R-DHAP	Yes	02/05/2007	TRANSPLANTATION OF CELLS INFUSED CD34+
5003101221057	ARM B / R-DHAP	Yes	11/04/2007	CBV AUTOGRAFT N°1 (CSH) + 2ND AUTOGRAFT CSH 14/06/07 CBV
5003101221639	ARM B / R-DHAP	Yes	10/08/2007	Z-BEAM
5003101601066	ARM B / R-DHAP	Yes	10/09/2007	BEAM
5003101641047	ARM B / R-DHAP	Yes	08/09/2006	BEAM
5003102341003	ARM B / R-DHAP	Yes	07/07/2004	BEAM SANS ARACYTINE
5003102541640	ARM B / R-DHAP	Yes	21/04/2008	CPA, FLUDA, ATG, MPD, CYCLO
5003601201018	ARM B / R-DHAP	Yes	19/12/2005	BEAM
5003601201201	ARM B / R-DHAP	Yes	13/08/2004	BEAM
5003601601602	ARM B / R-DHAP	Yes	14/01/2009	CYCLOPHOSPHAMIDE, FLUDARABINE, METHOTREXATE
5003601801003	ARM B / R-DHAP	Yes	05/04/2005	BEAM
5003603201050	ARM B / R-DHAP	Yes	17/01/2008	BEAM ON 11/01/2008
5003603801007	ARM B / R-DHAP	Yes	04/08/2006	BEAM
5003604701002	ARM B / R-DHAP	Yes	30/12/2005	POMP
5003606201033	ARM B / R-DHAP	Yes	29/12/2006	CARMUSTINE, CYTARABIN, ETOPOSID, MELPHALAN, RITUXIMAB
5003606201407	ARM B / R-DHAP	Yes	19/03/2007	HD MELPHALAN
5003606201410	ARM B / R-DHAP	Yes	08/08/2007	BEAM
5003610201212	ARM B / R-DHAP	Yes	-	BYLDYLFAN, FLUDARABIN, CYCLOPHOSPHAMID, ALLOG TX TAMILIENOPENDER
5003611301002	ARM B / R-DHAP	Yes	10/11/2004	BEAM
5003617201021	ARM B / R-DHAP	Yes	13/11/2007	FLUDARABIN, BUSULFAN, CYCLOPHOSPHAMIDE, ATG
5003617201024	ARM B / R-DHAP	Yes	20/04/2006	IBRITUMOMAB TIUXETAN, FLUDARABINE, MELPHALAN, ALEMTUZUMAB
5003619301006	ARM B / R-DHAP	Yes	05/10/2006	BEAM
5003625501020	ARM B / R-DHAP	Yes	30/01/2008	BEAM STARTED ON 22/01/2008
5003628201046	ARM B / R-DHAP	Yes	25/02/2008	ALLO TRANSPLANTATION (AFTER CEPHALIN / FLUDARABIN / MELPHALAN)
5003632201015	ARM B / R-DHAP	Yes	18/08/2005	BEAM
5003636201047	ARM B / R-DHAP	Yes	12/10/2007	BEAM BONU
N = 55				

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

Randomization Number	Arm of treatment	Other treatment	Date of other treatment	Specify other treatment
5003101021631	ARM A / R-ICE	Yes	07/02/2008	IBRITUMOMAB TIUXETAN
5003101031001	ARM A / R-ICE	Yes	23/12/2003	CORTICOIDES
5003101131062	ARM A / R-ICE	Yes	14/05/2007	METHOTREXATE INTRATHECAL
5003101141065	ARM A / R-ICE	Yes	-	PALLIATIVE TREATMENT (WITH CORTICOIDS)
5003101351040	ARM A / R-ICE	Yes	03/05/2006	DHAP
5003603801202	ARM A / R-ICE	Yes	19/01/2006	CORTICOSTEROIDS - DEXAMETHASONE
5003605701601	ARM A / R-ICE	Yes	28/07/2006	IBRITUMOMAB TIUXETAN (STOP : 04.08.2006)
5003606301612	ARM A / R-ICE	Yes	21/05/2008	RITUXIMAB THREE MONTHLY PLANNED X 8 TREATMENTS
5003613701402	ARM A / R-ICE	Yes	01/12/2010	MABTHERA
5003617201010	ARM A / R-ICE	Yes	-	RELAPSE INTRAABDOMINAL, PULMONIC / 1 CYCLE R-GEM-OX-DEXA / 11/05 DEXAMETHASONE / CYCLOPHOSPHAMIDE : PALLIATIVE INTENTION
5003621201020	ARM A / R-ICE	Yes	09/05/2006	MTX HIGH DOSE 2 CYCLES

Randomization Number	Arm of treatment	Other treatment	Date of other treatment	Specify other treatment
5003621201023	ARM A / R-ICE	Yes	31/05/2006	STUDY DRUG CMC 544 1 CYCLE
5003633201036	ARM A / R-ICE	Yes	03/07/2007	GMALL-B-ALL-PROTOCOL
5003101071051	ARM B / R-DHAP	Yes	28/10/2006	DEXAMETHASONE
5003101071073	ARM B / R-DHAP	Yes	18/12/2007	GEMZAR NAVELBINE
5003101251035	ARM B / R-DHAP	Yes	05/03/2007	MERCAPTOPURINE METHOTREXATE
5003101351012	ARM B / R-DHAP	Yes	10/08/2006	CORTICOIDS
5003101391032	ARM B / R-DHAP	Yes	10/11/2005	CHEMOTHERAPY PROCARBAZINE DEXAMETHAZONE
5003101391048	ARM B / R-DHAP	Yes	04/12/2006	PROCARBAZINE DEXAMETHASONE
5003101601076	ARM B / R-DHAP	Yes	25/04/2008	IT METHOTREXATE - CYTOSAR - DEPOCYTE
5003102341003	ARM B / R-DHAP	Yes	19/05/2004	METHOTREXATE (HD), DEXAMETHASONE (CONSOLIDATION)
5003102411069	ARM B / R-DHAP	Yes	01/02/2008	CORTICOTHERAPY
5003102541016	ARM B / R-DHAP	Yes	19/03/2005	DEXAMETHASONE, BCNU, ETOPOSIDE, ARAC, MELPHALAN
5003102541640	ARM B / R-DHAP	Yes	-	RADIOIMMUNOTHERAPY : IBRITUMOMAB TIUXETAN
5003103161041	ARM B / R-DHAP	Yes	10/05/2007	HUMAN IMMUNOGLOBULIN
5003604701002	ARM B / R-DHAP	Yes	08/06/2006	THORACOTOMY WITH RESECTION OF TUMOR - HISTOLOGY SHOWED NO VISIBLE LYMPHOMA ANYMORE
5003606201033	ARM B / R-DHAP	Yes	27/02/2007	UNRELATED STEM CELL TRANSPLANT AFTER CONDITIONING WITH FLU BU CY
5003610301613	ARM B / R-DHAP	Yes	18/10/2005	SPLENECTOMY
5003615501029	ARM B / R-DHAP	Yes	20/06/2008	ETOPOSIDE, CYTARABINE, CISPLATIN, METHYLPREDNISOLONE
5003616301212	ARM B / R-DHAP	Yes	03/01/2007	HYPER CVAD A
5003617501006	ARM B / R-DHAP	Yes	12/01/2007	PALLIATIVE TREATMENT
5003625501020	ARM B / R-DHAP	Yes	20/12/2007	RESIDUAL LEFT LOWER LUNG MASS EXCISED SURGICALLY
5003630201040	ARM B / R-DHAP	Yes	20/08/2007	RITUXIMAB - BENDAMUSTIN
N = 33				

Table 6.6-24 Progression/relapse n°2 – Period (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Period of Progression / Relapse				
TREATMENT PERIOD	2	10	2	9
FOLLOW UP PERIOD	19	90	19	86
Missing	0	0	1	5
Total	21	100	22	100

Table 6.6-25 Progression/relapse n°2 – Involvement (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Initial involvement				
Missing	0	0	2	9
Yes	15	71	13	59
No	6	29	7	32

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
New involvement				
Missing	0	0	2	9
Yes	13	62	9	41
No	8	38	11	50
Nodal involvement				
Missing	0	0	2	9
Yes	13	62	12	55
No	8	38	8	36
Extra-nodal involvement				
Missing	0	0	1	5
Yes	14	67	14	64
No	7	33	7	32
Total	21	100	22	100

Table 6.6-26 Progression/relapse n°2 – Extra-nodal involvement (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Bone marrow				
Missing	0	0	2	14
Not Done	6	43	7	50
Yes	0	0	1	7
No	8	57	4	29
Blood				
Missing	0	0	2	14
Not Done	2	14	1	7
Yes	0	0	1	7
No	12	86	10	71
Bone				
Missing	0	0	2	14
Not Done	4	29	2	14
Yes	1	7	2	14
No	9	64	8	57
Skin				
Missing	0	0	1	7
Not Done	3	21	1	7
Yes	3	21	5	36
No	8	57	7	50
Liver				
Missing	0	0	2	14

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Not Done	2	14	0	0
Yes	2	14	5	36
No	10	71	7	50
Ascite				
Missing	0	0	2	14
Not Done	3	21	1	7
No	11	79	11	79
Pleural effusion				
Missing	0	0	1	7
Not Done	1	7	2	14
Yes	2	14	2	14
No	11	79	9	64
Lung				
Missing	0	0	1	7
Not Done	0	0	2	14
Yes	3	21	1	7
No	11	79	10	71
Spleen				
Missing	0	0	2	14
Not Done	1	7	1	7
Yes	0	0	2	14
No	13	93	9	64
Pericardium				
Missing	0	0	2	14
Not Done	3	21	2	14
No	11	79	10	71
Breast				
Missing	0	0	2	14
Not Done	3	21	2	14
No	11	79	10	71
Gonadal				
Missing	0	0	2	14
Not Done	4	29	3	21
Yes	1	7	0	0
No	9	64	9	64
Kidney				
Missing	0	0	2	14
Not Done	2	14	4	29
Yes	1	7	0	0
No	11	79	8	57

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Adrenal				
Missing	0	0	2	14
Not Done	3	21	4	29
Yes	1	7	0	0
No	10	71	8	57
Thyroid				
Missing	0	0	2	14
Not Done	4	29	3	21
No	10	71	9	64
ORL area				
Missing	0	0	2	14
Not Done	4	29	2	14
Yes	0	0	1	7
No	10	71	9	64
Digestive area				
Missing	0	0	2	14
Not Done	3	21	4	29
Yes	2	14	1	7
No	9	64	7	50
CNS				
Missing	0	0	2	14
Not Done	3	21	3	21
Yes	1	7	1	7
No	10	71	8	57
Total	14	100	14	100

Table 6.6-27 Progression/relapse n°2 – Nodal involvement (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Cervical right				
Normal	10	77	6	50
Involved	1	8	2	17
Not evaluated	2	15	0	0
Missing	0	0	4	33
Cervical left				
Normal	10	77	7	58
Involved	1	8	1	8
Not evaluated	2	15	0	0
Missing	0	0	4	33

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Supraclavicular right				
Normal	11	85	8	67
Involved	0	0	1	8
Not evaluated	2	15	0	0
Missing	0	0	3	25
Supraclavicular left				
Normal	11	85	8	67
Involved	0	0	1	8
Not evaluated	2	15	0	0
Missing	0	0	3	25
Axillary right				
Normal	11	85	8	67
Not evaluated	2	15	0	0
Missing	0	0	4	33
Axillary left				
Normal	10	77	8	67
Involved	1	8	0	0
Not evaluated	2	15	0	0
Missing	0	0	4	33
Inguinal right				
Normal	12	92	8	67
Not evaluated	1	8	0	0
Missing	0	0	4	33
Inguinal left				
Normal	11	85	7	58
Involved	2	15	1	8
Missing	0	0	4	33
Mediastinal				
Normal	9	69	4	33
Involved	4	31	2	17
Not evaluated	0	0	3	25
Missing	0	0	3	25
Pulmonary hilar				
Normal	12	92	5	42
Not evaluated	1	8	3	25
Missing	0	0	4	33
Para-ortic				
Normal	8	62	4	33
Involved	4	31	0	0
Not evaluated	1	8	4	33

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Missing	0	0	4	33
Mesenteric				
Normal	10	77	2	17
Involved	2	15	2	17
Not evaluated	1	8	4	33
Missing	0	0	4	33
Iliac right				
Normal	11	85	4	33
Involved	1	8	1	8
Not evaluated	1	8	3	25
Missing	0	0	4	33
Iliac left				
Normal	11	85	3	25
Involved	1	8	1	8
Not evaluated	1	8	4	33
Missing	0	0	4	33
Splenic Hilar				
Normal	10	77	4	33
Involved	2	15	0	0
Not evaluated	1	8	4	33
Missing	0	0	4	33
Other nodal involvement				
No	10	77	7	58
Yes	3	23	1	8
Missing	0	0	4	33
TOTAL	13	100	12	100

Listing 6.6-18 Progression/relapse n°2 – Other nodal involvement (induction ITT)

Randomization Number	Arm of treatment	Other nodal involvement	Other nodal involvement - localization	Other nodal involvement
5003101021027	ARM A / R-ICE	Yes	PRECARDIAC NODE	-
5003101491042	ARM A / R-ICE	Yes	RETROPERITONEAL	-
5003605701601	ARM A / R-ICE	Yes	KIDNEY HILUS LEFT	-
5003615501029	ARM B / R-DHAP	Yes	COELIAC	-
N = 4				

Table 6.6-28 Progression/relapse n°2 – Extra-nodal involvement bis (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Liver				
Normal	10	71	2	14
Involved	2	14	3	21
Not evaluated	1	7	1	7
Missing	1	7	8	57
Ascites				
Normal	10	71	3	21
Not evaluated	3	21	3	21
Missing	1	7	8	57
Pleural effusion				
Normal	10	71	2	14
Involved	2	14	2	14
Not evaluated	1	7	2	14
Missing	1	7	8	57
Lung				
Normal	10	71	3	21
Involved	3	21	1	7
Not evaluated	0	0	2	14
Missing	1	7	8	57
Spleen				
Normal	13	93	3	21
Involved	0	0	1	7
Not evaluated	0	0	2	14
Missing	1	7	8	57
Pericardium				
Normal	10	71	4	29
Not evaluated	3	21	2	14
Missing	1	7	8	57
Breast				
Normal	10	71	3	21
Not evaluated	3	21	2	14
Missing	1	7	9	64
Gonadal				
Normal	9	64	2	14
Involved	1	7	0	0
Not evaluated	3	21	3	21
Missing	1	7	9	64
Kidney				
Normal	10	71	2	14

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Involved	1	7	0	0
Not evaluated	2	14	3	21
Missing	1	7	9	64
Adrenal				
Normal	10	71	2	14
Not evaluated	3	21	3	21
Missing	1	7	9	64
Thyroid				
Normal	9	64	2	14
Not evaluated	4	29	3	21
Missing	1	7	9	64
Skin				
Normal	8	57	3	21
Involved	2	14	1	7
Not evaluated	3	21	2	14
Missing	1	7	8	57
Bone				
Normal	8	57	3	21
Involved	1	7	2	14
Not evaluated	4	29	1	7
Missing	1	7	8	57
Tonsil				
Normal	7	50	4	29
Not evaluated	6	43	2	14
Missing	1	7	8	57
Cavum				
Normal	6	43	4	29
Not evaluated	7	50	2	14
Missing	1	7	8	57
Parotid				
Normal	7	50	4	29
Not evaluated	6	43	2	14
Missing	1	7	8	57
Orbit				
Normal	7	50	4	29
Not evaluated	6	43	2	14
Missing	1	7	8	57
Sinus				
Normal	6	43	4	29
Involved	0	0	1	7

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Not evaluated	7	50	1	7
Missing	1	7	8	57
Oesophagus				
Normal	7	50	2	14
Not evaluated	6	43	4	29
Missing	1	7	8	57
Stomach				
Normal	6	43	2	14
Involved	1	7	0	0
Not evaluated	6	43	4	29
Missing	1	7	8	57
Duodenum				
Normal	7	50	2	14
Not evaluated	6	43	4	29
Missing	1	7	8	57
Colon				
Normal	7	50	2	14
Not evaluated	6	43	4	29
Missing	1	7	8	57
Caecum				
Normal	7	50	2	14
Not evaluated	6	43	4	29
Missing	1	7	8	57
Rectum				
Normal	7	50	2	14
Not evaluated	6	43	4	29
Missing	1	7	8	57
Other extra-nodal involvement				
Yes	5	36	0	0
No	7	50	6	43
Missing	2	14	8	57
TOTAL	14	100	14	100

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

Randomization Number	Arm of treatment	Progression/relapse number	Other extra-nodal involvement 1 - localization
5003101491042	ARM A / R-ICE	2	BLADDER
5003101641618	ARM A / R-ICE	2	UTERUS
5003602801001	ARM A / R-ICE	2	CNS
5003605701601	ARM A / R-ICE	2	INFILTRATION WALL ILEUM
5003615501028	ARM A / R-ICE	2	PERICARDIAL EFFUSION

Randomization Number	Arm of treatment	Progression/relapse number	Other extra-nodal involvement 1 - localization
N = 5			

Table 6.6-29 Progression/relapse n°2 – Documentation (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Histological documentation				
Missing	0	0	2	9
Yes	5	24	8	36
No	16	76	12	55
Cytological documentation				
Missing	0	0	2	9
Yes	4	19	6	27
No	17	81	14	64
Total	21	100	22	100

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
LDH > Upper Limit				
Missing	0	0	3	14
Not Done	3	14	3	14
Yes	9	43	12	55
No	9	43	4	18
Stage III - IV				
Missing	0	0	3	14
Not Done	1	5	0	0
Yes	8	38	13	59
No	12	57	6	27
PS >= 2				
Missing	0	0	2	9
Not Done	1	5	0	0
Yes	6	29	10	45
No	14	67	10	45
Extra-nodal sites >= 2				
Missing	0	0	2	9
Not Done	1	5	0	0
Yes	3	14	7	32
No	17	81	13	59
Total	21	100	22	100

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Progression / Relapse treatment				
Missing	1	5	2	9
Yes	19	90	17	77
No	1	5	3	14
Total	21	100	22	100

Table 6.6-32 Progression/relapse n°2 – Type of treatment (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Chemotherapy				
Yes	16	84	12	71
No	3	16	5	29
Radiotherapy				
Missing	5	26	2	12
Yes	7	37	5	29
No	7	37	10	59
Immunotherapy				
Missing	3	16	1	6
Yes	8	42	7	41
No	8	42	9	53
Transplantation				
Missing	5	26	3	18
Yes	1	5	1	6
No	13	68	13	76
Other treatment				
Missing	5	26	3	18
Yes	1	5	2	12
No	13	68	12	71
Total	19	100	17	100

Listing 6.6-20 Progression/relapse n°2 - Chemotherapy (induction ITT)

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003101021027	ARM A / R-ICE	Yes	30/01/2006	GEMOX	3
5003101021605	ARM A / R-ICE	Yes	11/04/2006	TAXOL - TOPOTECAN	6
5003101021631	ARM A / R-ICE	Yes	28/05/2008	DHAOX	4
5003101071020	ARM A / R-ICE	Yes	30/06/2006	GEMOX	4
5003101131409	ARM A / R-ICE	Yes	09/05/2007	R-GEMOX	1
5003101161407	ARM A / R-ICE	Yes	-	CYTARABINE-ETOPOSIDE-DEXAMETHASONE	-

Randomization Number	Arm of treatment	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003101431622	ARM A / R-ICE	Yes	05/08/2008	CHOP	3
5003101491042	ARM A / R-ICE	Yes	15/01/2007	GEMCITABINE	-
5003101641618	ARM A / R-ICE	Yes	03/08/2007	DHAP	3
5003102341061	ARM A / R-ICE	Yes	17/02/2010	DHAP	-
5003102341416	ARM A / R-ICE	Yes	04/12/2007	ANTIBODIES ANTI CD20 - PROTOCOL ROCHE	3
5003102491619	ARM A / R-ICE	Yes	04/08/2008	IFOSFAMIDE + ETOPOSIDE	-
5003602901601	ARM A / R-ICE	Yes	12/07/2006	VINCRISTIN AND BLEOMYCIN	1
5003604801205	ARM A / R-ICE	Yes	09/08/2007	IVE	1
5003605701601	ARM A / R-ICE	Yes	27/11/2006	CVP (= COP) + RITUXIMAB (STOP 18/12/2006)	2
5003615501014	ARM A / R-ICE	Yes	29/08/2008	GCVP (GEMCITABINE, CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISOLONE)	6
5003101031401	ARM B / R-DHAP	Yes	06/06/2005	PCOP	3
5003101091626	ARM B / R-DHAP	Yes	16/11/2006	GEMOX	5
5003101141624	ARM B / R-DHAP	Yes	04/02/2010	DHAOX	1
5003101221057	ARM B / R-DHAP	Yes	13/03/2008	NAVELBINE	-
5003101641047	ARM B / R-DHAP	Yes	29/03/2007	GEMOX	4
5003101641079	ARM B / R-DHAP	Yes	26/09/2008	CYTARABINE, ETOPOSIDE	2
5003102341003	ARM B / R-DHAP	Yes	06/09/2004	GEMCITABINE - OXALIPLATINE - RITUXIMAB	3
5003601801003	ARM B / R-DHAP	Yes	12/09/2005	CVP	3
5003603201050	ARM B / R-DHAP	Yes	18/07/2008	SEE MEDICAL REPORT PAGE 2 AND 3 (B-ALL-PROTOCOL)	3
5003605301610	ARM B / R-DHAP	Yes	02/11/2006	CVP REFRACTORY / 2ND LINE : 4 CEPP (MINUS CYCLOPHOSPHAMIDE) ON 04/01/2007	3
5003605701404	ARM B / R-DHAP	Yes	16/01/2009	CHOP	3
5003611301002	ARM B / R-DHAP	Yes	20/12/2004	CYTARABINE AND METHOTREXATE (INTRATHECAL)	22
N = 28					

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

Randomization Number	Arm of treatment	Radiotherapy	Date of radiotherapy	Site of radiotherapy	Dose of radiotherapy (Gy)
5003101021631	ARM A / R-ICE	Yes	07/10/2008	TOTAL BODY IRRADIATION	2
5003102341416	ARM A / R-ICE	Yes	28/01/2008	MEDIASTINAL	-
5003602901601	ARM A / R-ICE	Yes	-	RIGHT ADRENAL AND LEFT LEG (SKIN)	-
5003603801202	ARM A / R-ICE	Yes	13/05/2008	RIGHT KNEE + FEMUR	30
5003604801205	ARM A / R-ICE	Yes	24/09/2007		22
5003632201054	ARM A / R-ICE	Yes	05/12/2008	LEFT DISTAL SHANK	30
5003643501202	ARM A / R-ICE	Yes	04/08/2008	RIGHT NECK AND SUPRACLAVICULAR AREA	30
5003101221057	ARM B / R-DHAP	Yes	-	MEDIASTINAL + ABDOMEN	-
5003101641079	ARM B / R-DHAP	Yes	24/11/2008	ABDOMINAL (ILIAC RIGHT)	30
5003606701005	ARM B / R-DHAP	Yes	02/05/2007	RIGHT THIGH (20 GY) + DORSAL LESION (20 GY)	20
5003609301620	ARM B / R-DHAP	Yes	11/03/2009	LEFT ABDOMINAL WALL AND RIGHT NECK	40
5003632201015	ARM B / R-DHAP	Yes	06/10/2005	HYPODERMIC : INGUINAL, THIGH, LOWER LEG, SOLE OF FOOT, FOOT : LEFT SIDE	20
N = 12					

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

Randomization Number	Arm of treatment	Immunotherapy	Date of immunotherapy	Specify immunotherapy
5003101641047	ARM B / R-DHAP	Yes	20/09/2007	RITUXIMAB / OFATUMUMAB
5003609301620	ARM B / R-DHAP	Yes	-	RITUXIMAB MAINTENANCE ON GOING
5003632201015	ARM B / R-DHAP	Yes	23/02/2006	MABTHERA
N = 3				

Listing 6.6-23 Progression/relapse n°2 – Tranpslant (induction ITT)

Randomization Number	Arm of treatment	Transplantation	Date of transplantation	Conditioning Regimen
5003101021631	ARM A / R-ICE	Yes	09/10/2008	SEATTLE
5003605701404	ARM B / R-DHAP	Yes	09/03/2009	BEAM
N = 2				

Listing 6.6-24 Progression/relapse n°2 – Other treatments (induction ITT)

Randomization Number	Arm of treatment	Other treatment	Date of other treatment	Specify other treatment
5003102491619	ARM A / R-ICE	Yes	11/08/2008	DONOR LYMPHOCYTES INFUSIONS
5003101071607	ARM B / R-DHAP	Yes	21/04/2006	SURGERY INGUINAL NODE
5003605301610	ARM B / R-DHAP	Yes	-	PALLIATIVE CARE
N = 3				

Table 6.6-33 Progression/relapse n°2 – Response after additional treatments (induction ITT)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Response after new treatment				
COMPLETE RESPONSE	1	5	3	18
UNCONFIRMED COMPLETE RESPONSE	1	5	0	0
PARTIAL RESPONSE	3	16	0	0
STABLE DISEASE	1	5	1	6
PROGRESSIVE DISEASE	10	53	10	59
NOT EVALUATED	2	11	2	12
Missing	1	5	1	6
Total	19	100	17	100

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)

Rituximab : Dose received (% of planned dose)		Actual arm of induction			
		ARM A / R-ICE		ARM B / R-DHAP	
		N	%	N	%
Cycle 1	<75%	23	10	21	9
	[75-90%[	3	1	6	3
	[90-110%[	211	88	201	88
	[110-125%[	2	1	0	0
	>125%	0	0	0	0
	Total	239	100	228	100
Cycle 2	<75%	2	1	2	1
	[75-90%[	5	2	8	4
	[90-110%[	215	96	202	95
	[110-125%[	3	1	0	0
	>125%	0	0	0	0
	Total	225	100	212	100
Cycle 3	<75%	2	1	0	0
	[75-90%[	3	1	7	4
	[90-110%[	197	97	185	96
	[110-125%[	2	1	1	1
	>125%	0	0	0	0
	Total	204	100	193	100

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

Etoposide : Dose received (% of planned dose)		N	%
Cycle 1	<75%	5	2
	[75-90%[	8	3
	[90-110%[	226	95
	[110-125%[	0	0
	>125%	0	0
	Total	239	100
Cycle 2	<75%	6	3
	[75-90%[	7	3
	[90-110%[	211	94
	[110-125%[	1	0
	>125%	0	0
	Total	225	100

Etoposide : Dose received (% of planned dose)		**N**	**%**
Cycle 3	**<75%**	7	3
	[75-90%[	7	3
	[90-110%[	189	93
	[110-125%[	1	0
	>125%	0	0
	Total	204	100
Carboplatine : Dose received (% of planned dose)		**N**	**%**
Cycle 1	**<75%**	11	5
	[75-90%[	38	16
	[90-110%[	142	60
	[110-125%[	32	13
	>125%	15	6
	Total	238	100
Cycle 2	**<75%**	12	5
	[75-90%[	39	17
	[90-110%[	124	55
	[110-125%[	31	14
	>125%	18	8
	Total	224	100
Cycle 3	**<75%**	13	6
	[75-90%[	35	17
	[90-110%[	116	57
	[110-125%[	29	14
	>125%	10	5
	Total	203	100
Ifosfamide : Dose received (% of planned dose)		**N**	**%**
Cycle 1	**<75%**	5	2
	[75-90%[	7	3
	[90-110%[	226	95
	[110-125%[	0	0
	>125%	0	0
	Total	238	100
Cycle 2	**<75%**	7	3
	[75-90%[	8	4
	[90-110%[	209	93
	[110-125%[	0	0
	>125%	0	0
	Total	224	100

Etoposide : Dose received (% of planned dose)		N	%
Cycle 3	<75%	8	4
	[75-90%[	6	3
	[90-110%[	188	93
	[110-125%[	0	0
	>125%	0	0
	Total	202	100

Table 6.7-3 Induction – Frequency of percentage of planned dose received by cycle for R-DHAP (induction safety population)

Dexamethasone : Dose received (% of planned dose)		N	%
Cycle 1	<75%	0	0
	[75-90%[	2	1
	[90-110%[	215	94
	[110-125%[	0	0
	>125%	12	5
	Total	229	100
Cycle 2	<75%	2	1
	[75-90%[	0	0
	[90-110%[	200	94
	[110-125%[	0	0
	>125%	11	5
	Total	213	100
Cycle 3	<75%	1	1
	[75-90%[	2	1
	[90-110%[	184	94
	[110-125%[	0	0
	>125%	9	5
	Total	196	100
Cisplatine : Dose received (% of planned dose)		**N**	**%**
Cycle 1	<75%	3	1
	[75-90%[	12	5
	[90-110%[	213	93
	[110-125%[	0	0
	>125%	0	0
	Total	228	100
Cycle 2	<75%	11	5
	[75-90%[	15	7
	[90-110%[	186	88
	[110-125%[	0	0
	>125%	0	0
	Total	212	100

Dexamethasone : Dose received (% of planned dose)		**N**	**%**
Cycle 3	**<75%**	23	12
	[75-90%[	15	8
	[90-110%[	153	79
	[110-125%[	2	1
	>125%	1	1
	Total	194	100
Cytarabine : Dose received (% of planned dose)		**N**	**%**
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)

G-CSF - nb of days		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
Cycle 1	N	179	186
	Mean	6.8	6.8
	Std	2.76	2.73
	Median	8.0	8.0
	Min	1	1
	Max	21	15
Cycle 2	N	185	184
	Mean	7.0	7.2
	Std	2.89	2.79
	Median	8.0	8.0
	Min	1	1
	Max	16	16
Cycle 3	N	181	170
	Mean	8.9	8.5
	Std	3.06	4.27
	Median	8.0	8.0
	Min	1	1
	Max	20	43

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

G-CSF - dosage (µg/day)		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
Cycle 3	N	180	167
	Mean	560.9	535.4
	Std	857.04	884.73
	Median	480.0	368.0
	Min	8	6
	Max	6000	6000

Table 6.7-6 Consolidation - Percentage of planned dose received for BEAM (induction safety population)

BCNU : Dose received (% of planned dose)	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
<75%	2	2	5	4
[75-90%[	5	4	6	5
[90-110%[	114	93	118	90
[110-125%[	0	0	1	1
>125%	1	1	1	1
Total	122	100	131	100

Etoposide : Dose received (% of planned dose)	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
<75%	7	6	7	5
[75-90%[	6	5	6	5
[90-110%[	103	84	107	82
[110-125%[	0	0	2	2
>125%	6	5	9	7
Total	122	100	131	100

Melphalan : Dose received (% of planned dose)	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
<75%	3	2	3	2
[75-90%[	3	2	8	6
[90-110%[	116	95	119	91
[110-125%[	0	0	1	1
>125%	0	0	0	0
Total	122	100	131	100

Cytarabine : Dose received (% of planned dose)	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
<75%	25	20	17	13
[75-90%[	2	2	9	7
[90-110%[	94	77	103	79
[110-125%[	1	1	2	2
>125%	0	0	0	0
Total	122	100	131	100

Listing 6.7-1 Consolidation – Other types of growth factors (induction safety population)

Randomization Number	Actual arm of induction	Other Growth Factor
5003101051056	ARM A / R-ICE	NEULASTA
5003102541052	ARM A / R-ICE	PEGFILGASTRIM 6 MG
5003619301621	ARM A / R-ICE	PEG - GCSF
5003101051050	ARM B / R-DHAP	PEGFILGASTRIM
5003102541636	ARM B / R-DHAP	PEGFILGRASTIM 6 MG
5003607201408	ARM B / R-DHAP	LENOGRASTIM (+ MUG-CSF)
N = 6		

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

G-CSF	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
DAY 1	23	27	14	15
DAY 5	24	28	26	29
OTHER	38	44	50	55
Missing	1	1	1	1
Total	86	100	91	100

6.7.2. Overview of toxicity profile

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

			Actual arm of induction																		
			ARM A / R-ICE									ARM B / R-DHAP									
			Grade									Grade									
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	5	>=3	NE	Total
	Cycle number																					
Grade allergy	1	N	10	228	6	1	2	1	0	3	1	239	13	214	7	4	2	0	0	2	3	230
		%	4	95	3	0	1	0	0	1	0	100	6	93	3	2	1	0	0	1	1	100
	2	N	4	220	3	1	0	0	0	0	1	225	1	210	1	0	0	0	0	0	4	215
		%	2	98	1	0	0	0	0	0	0	100	0	98	0	0	0	0	0	0	2	100
	3	N	5	197	4	1	0	0	0	0	2	204	5	188	4	0	1	0	0	1	3	196
		%	2	97	2	0	0	0	0	0	1	100	3	96	2	0	1	0	0	1	2	100
Grade auditory	1	N	2	236	1	0	1	0	0	1	1	239	7	220	2	5	0	0	0	0	3	230
		%	1	99	0	0	0	0	0	0	0	100	3	96	1	2	0	0	0	0	1	100
	2	N	0	224	0	0	0	0	0	0	1	225	11	200	5	5	1	0	0	1	4	215
		%	0	100	0	0	0	0	0	0	0	100	5	93	2	2	0	0	0	0	2	100
	3	N	2	199	1	1	0	0	0	0	3	204	9	184	6	3	0	0	0	0	3	196
		%	1	98	0	0	0	0	0	0	1	100	5	94	3	2	0	0	0	0	2	100
Grade blood	1	N	193	43	21	35	34	103	0	137	3	239	205	22	20	30	26	129	0	155	3	230
		%	81	18	9	15	14	43	0	57	1	100	89	10	9	13	11	56	0	67	1	100
	2	N	188	33	19	43	51	75	0	126	4	225	190	20	14	47	57	72	0	129	5	215
		%	84	15	8	19	23	33	0	56	2	100	88	9	7	22	27	33	0	60	2	100
	3	N	174	27	10	25	58	81	0	139	3	204	172	20	7	21	41	103	0	144	4	196
		%	85	13	5	12	28	40	0	68	1	100	88	10	4	11	21	53	0	73	2	100

			Actual arm of induction																		
			ARM A / R-ICE									ARM B / R-DHAP									
			Grade									Grade									
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	5	>=3	NE	Total
Grade cardiovascular	1	N	14	224	5	4	3	2	0	5	1	239	13	214	5	5	2	0	1	3	3	230
		%	6	94	2	2	1	1	0	2	0	100	6	93	2	2	1	0	0	1	1	100
	2	N	2	222	1	1	0	0	0	0	1	225	12	199	4	5	2	1	0	3	4	215
		%	1	99	0	0	0	0	0	0	0	100	6	93	2	2	1	0	0	1	2	100
	3	N	3	199	1	1	1	0	0	1	2	204	14	179	3	6	3	2	0	5	3	196
		%	1	98	0	0	0	0	0	0	1	100	7	91	2	3	2	1	0	3	2	100
Grade coagulation	1	N	5	230	1	2	0	2	0	2	4	239	5	220	3	1	0	1	0	1	5	230
		%	2	96	0	1	0	1	0	1	2	100	2	96	1	0	0	0	0	0	2	100
	2	N	3	218	2	1	0	0	0	0	4	225	8	202	5	1	0	2	0	2	5	215
		%	1	97	1	0	0	0	0	0	2	100	4	94	2	0	0	1	0	1	2	100
	3	N	6	193	4	1	1	0	0	1	5	204	5	187	5	0	0	0	0	0	4	196
		%	3	95	2	0	0	0	0	0	2	100	3	95	3	0	0	0	0	0	2	100
Grade skin	1	N	26	211	12	13	1	0	0	1	2	239	23	204	16	6	1	0	0	1	3	230
		%	11	88	5	5	0	0	0	0	1	100	10	89	7	3	0	0	0	0	1	100
	2	N	19	204	12	6	1	0	0	1	2	225	10	201	3	6	1	0	0	1	4	215
		%	8	91	5	3	0	0	0	0	1	100	5	93	1	3	0	0	0	0	2	100
	3	N	19	182	10	8	1	0	0	1	3	204	16	177	7	8	1	0	0	1	3	196
		%	9	89	5	4	0	0	0	0	1	100	8	90	4	4	1	0	0	1	2	100
Grade gastrointestinal	1	N	105	133	51	42	7	5	0	12	1	239	87	140	50	28	8	1	0	9	3	230
		%	44	56	21	18	3	2	0	5	0	100	38	61	22	12	3	0	0	4	1	100
	2	N	81	143	44	28	7	2	0	9	1	225	79	132	41	27	10	1	0	11	4	215
		%	36	64	20	12	3	1	0	4	0	100	37	61	19	13	5	0	0	5	2	100
	3	N	59	143	31	26	2	0	0	2	2	204	55	137	30	19	5	1	0	6	4	196
		%	29	70	15	13	1	0	0	1	1	100	28	70	15	10	3	1	0	3	2	100

			Actual arm of induction																		
			ARM A / R-ICE									ARM B / R-DHAP									
			Grade									Grade									
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	5	>=3	NE	Total
Grade hepatic	**1**	**N**	32	206	19	11	1	1	0	2	1	239	32	195	16	13	3	0	0	3	3	230
		%	13	86	8	5	0	0	0	1	0	100	14	85	7	6	1	0	0	1	1	100
	2	**N**	26	198	18	3	4	1	0	5	1	225	28	183	19	5	4	0	0	4	4	215
		%	12	88	8	1	2	0	0	2	0	100	13	85	9	2	2	0	0	2	2	100
	3	**N**	21	181	15	5	1	0	0	1	2	204	27	166	18	8	1	0	0	1	3	196
		%	10	89	7	2	0	0	0	0	1	100	14	85	9	4	1	0	0	1	2	100
Grade infection with febrile neutropenia	**1**	**N**	30	208	0	3	19	6	2	27	1	239	39	188	1	8	25	4	1	30	3	230
		%	13	87	0	1	8	3	1	11	0	100	17	82	0	3	11	2	0	13	1	100
	2	**N**	20	204	2	0	13	4	1	18	1	225	11	200	0	4	7	0	0	7	4	215
		%	9	91	1	0	6	2	0	8	0	100	5	93	0	2	3	0	0	3	2	100
	3	**N**	8	194	1	1	6	0	0	6	2	204	14	179	1	1	10	1	1	12	3	196
		%	4	95	0	0	3	0	0	3	1	100	7	91	1	1	5	1	1	6	2	100
Grade infection without febrile neutropenia	**1**	**N**	18	220	4	4	10	0	0	10	1	239	23	203	4	9	10	0	0	10	4	230
		%	8	92	2	2	4	0	0	4	0	100	10	88	2	4	4	0	0	4	2	100
	2	**N**	11	213	4	3	4	0	0	4	1	225	21	190	4	7	8	0	2	10	4	215
		%	5	95	2	1	2	0	0	2	0	100	10	88	2	3	4	0	1	5	2	100
	3	**N**	17	185	3	9	5	0	0	5	2	204	15	178	2	9	4	0	0	4	3	196
		%	8	91	1	4	2	0	0	2	1	100	8	91	1	5	2	0	0	2	2	100
Grade metabolic	**1**	**N**	31	207	16	8	5	2	0	7	1	239	43	183	19	13	9	2	0	11	4	230
		%	13	87	7	3	2	1	0	3	0	100	19	80	8	6	4	1	0	5	2	100
	2	**N**	23	201	14	5	3	1	0	4	1	225	50	161	26	11	10	3	0	13	4	215
		%	10	89	6	2	1	0	0	2	0	100	23	75	12	5	5	1	0	6	2	100
	3	**N**	18	184	11	4	3	0	0	3	2	204	41	152	16	10	8	7	0	15	3	196
		%	9	90	5	2	1	0	0	1	1	100	21	78	8	5	4	4	0	8	2	100

			Actual arm of induction																		
			ARM A / R-ICE									ARM B / R-DHAP									
			Grade									Grade									
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	5	>=3	NE	Total
Grade neurology	**1**	**N**	21	217	12	4	3	2	0	5	1	239	17	209	8	4	4	1	0	5	4	230
		%	9	91	5	2	1	1	0	2	0	100	7	91	3	2	2	0	0	2	2	100
	2	**N**	15	209	10	4	0	1	0	1	1	225	23	188	12	6	4	1	0	5	4	215
		%	7	93	4	2	0	0	0	0	0	100	11	87	6	3	2	0	0	2	2	100
	3	**N**	13	189	10	1	2	0	0	2	2	204	17	176	8	8	0	1	0	1	3	196
		%	6	93	5	0	1	0	0	1	1	100	9	90	4	4	0	1	0	1	2	100
Grade pulmonary	**1**	**N**	12	226	4	2	2	4	0	6	1	239	18	208	12	4	1	1	0	2	4	230
		%	5	95	2	1	1	2	0	3	0	100	8	90	5	2	0	0	0	1	2	100
	2	**N**	10	214	4	3	3	0	0	3	1	225	16	194	10	3	3	0	0	3	5	215
		%	4	95	2	1	1	0	0	1	0	100	7	90	5	1	1	0	0	1	2	100
	3	**N**	8	194	4	2	2	0	0	2	2	204	12	181	8	2	1	0	1	2	3	196
		%	4	95	2	1	1	0	0	1	1	100	6	92	4	1	1	0	1	1	2	100
Grade renal	**1**	**N**	8	230	4	2	1	1	0	2	1	239	37	190	17	12	7	1	0	8	3	230
		%	3	96	2	1	0	0	0	1	0	100	16	83	7	5	3	0	0	3	1	100
	2	**N**	7	217	3	4	0	0	0	0	1	225	43	168	24	13	4	2	0	6	4	215
		%	3	96	1	2	0	0	0	0	0	100	20	78	11	6	2	1	0	3	2	100
	3	**N**	7	195	4	2	1	0	0	1	2	204	45	148	31	7	5	2	0	7	3	196
		%	3	96	2	1	0	0	0	0	1	100	23	76	16	4	3	1	0	4	2	100
Other toxicity	**1**	**N**	60	173	31	19	8	2	0	10	6	239	70	153	22	37	9	1	1	11	7	230
		%	25	72	13	8	3	1	0	4	3	100	30	67	10	16	4	0	0	5	3	100
	2	**N**	52	166	22	24	6	0	0	6	7	225	59	150	27	27	5	0	0	5	6	215
		%	23	74	10	11	3	0	0	3	3	100	27	70	13	13	2	0	0	2	3	100
	3	**N**	39	160	20	14	3	2	0	5	5	204	50	142	25	20	5	0	0	5	4	196
		%	19	78	10	7	1	1	0	2	2	100	26	72	13	10	3	0	0	3	2	100

Listing 6.7-2 Other toxicities during induction (induction safety population)

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003101051004	ARM A / R-ICE	YES	abdominal pain	2	2
5003101051056	ARM A / R-ICE	YES	EPISTAXIS	2	3
5003101051068	ARM A / R-ICE	YES	HEADACHE POST G-CSF	1	1
5003101051068	ARM A / R-ICE	YES	BONE PAIN POST G-CSF	1	1
5003101071029	ARM A / R-ICE	YES	ANXIETY	1	1
5003101071029	ARM A / R-ICE	YES	ANXIETY	2	2
5003101071029	ARM A / R-ICE	YES	ANXIETY	3	2
5003101071059	ARM A / R-ICE	YES	ASTHENIA	1	2
5003101071059	ARM A / R-ICE	YES	SHOULDER PAIN	1	3
5003101091602	ARM A / R-ICE	YES	HEMORRHAGE	1	3
5003101091602	ARM A / R-ICE	YES	HEMORRHAGE	2	3
5003101131030	ARM A / R-ICE	YES	ASTHENIA	1	3
5003101131030	ARM A / R-ICE	YES	ASTHENIA	2	3
5003101131058	ARM A / R-ICE	YES	ASTHENIA	2	2
5003101131062	ARM A / R-ICE	YES	ASTHENIA	1	2
5003101131062	ARM A / R-ICE	YES	HEADACHE	2	2
5003101131062	ARM A / R-ICE	YES	FEVER	2	2
5003101131062	ARM A / R-ICE	YES	BONE PAIN	3	3
5003101131072	ARM A / R-ICE	YES	SEQUELAE OF RIGHT INTERNAL JUGULAR VEIN THROMBOSIS	1	3
5003101131409	ARM A / R-ICE	YES	ASTHENIA	2	1
5003101141406	ARM A / R-ICE	YES	HEADACHE	2	2
5003101171637	ARM A / R-ICE	YES	MUCOSITIS	1	1
5003101171644	ARM A / R-ICE	YES	ASTHENIA	1	2
5003101171644	ARM A / R-ICE	YES	ASTHENIA	2	2
5003101171644	ARM A / R-ICE	YES	ASTHENIA	3	1
5003101211628	ARM A / R-ICE	YES	HEMORRHAGE / BLEEDING (HEMATOMA)	3	1
5003101251205	ARM A / R-ICE	YES	ASTHENIA	1	1
5003101251205	ARM A / R-ICE	YES	FEVER	3	2
5003101391039	ARM A / R-ICE	YES	FEVER	1	1
5003101391039	ARM A / R-ICE	YES	FEVER	3	1
5003101431046	ARM A / R-ICE	YES	ASTHENIA	2	1
5003101431046	ARM A / R-ICE	YES	PAIN DUE TO G-CSF	2	1
5003101431622	ARM A / R-ICE	YES	ASTHENIA	1	1
5003101431622	ARM A / R-ICE	YES	ALOPECIA	2	2
5003101431622	ARM A / R-ICE	YES	ASTHENIA	3	2
5003101431622	ARM A / R-ICE	YES	ALOPECIA	3	2
5003101431622	ARM A / R-ICE	YES	EPISTAXIS	3	1
5003101441036	ARM A / R-ICE	YES	HEADACHE	1	1
5003101441036	ARM A / R-ICE	YES	ZONA	3	2
5003101441036	ARM A / R-ICE	YES	ASTHENIA	3	1
5003101491042	ARM A / R-ICE	YES	FLUID RETENTION	1	1
5003101491042	ARM A / R-ICE	YES	FLUID RETENTION	2	1
5003101491042	ARM A / R-ICE	YES	FLUID RETENTION	3	1
5003101601404	ARM A / R-ICE	YES	GENERAL STATUS ALTERATION	1	2

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003101601404	ARM A / R-ICE	YES	GENERAL STATUS ALTERATION	2	3
5003101601404	ARM A / R-ICE	YES	DEPRESSION	2	2
5003101601404	ARM A / R-ICE	YES	ARTHRITIS (RIGHT KNEE)	2	2
5003101621026	ARM A / R-ICE	YES	FEVER	3	1
5003101621055	ARM A / R-ICE	YES	PALPITATION	2	1
5003101621055	ARM A / R-ICE	YES	FEVER	2	1
5003101621055	ARM A / R-ICE	YES	FATIGUE	2	2
5003101621055	ARM A / R-ICE	YES	PALPITATION	3	1
5003101621055	ARM A / R-ICE	YES	FATIGUE	3	3
5003101621055	ARM A / R-ICE	YES	CEPHALEA	3	1
5003101621615	ARM A / R-ICE	YES	ASYMPTOMATIC PULMONARY EMBOLISM	3	1
5003101641618	ARM A / R-ICE	YES	ASTHENIA	2	1
5003101641618	ARM A / R-ICE	YES	ASTHENIA	3	1
5003102321024	ARM A / R-ICE	YES	INFERIOR LIMBS EDEMA	1	1
5003102341045	ARM A / R-ICE	YES	CHIRURGICAL CYST	1	1
5003102341049	ARM A / R-ICE	YES	ASTHENIA	1	2
5003102341202	ARM A / R-ICE	YES	VASO-VAGAL SYNCOPE	1	2
5003102341202	ARM A / R-ICE	YES	VASO-VAGAL SYNCOPE	2	2
5003102441011	ARM A / R-ICE	YES	ASTHENIA	1	1
5003102441011	ARM A / R-ICE	YES	ASTHENIA	2	2
5003102441011	ARM A / R-ICE	YES	ASTHENIA	3	2
5003102491616	ARM A / R-ICE	YES	WEIGHT LOSS	1	2
5003102491616	ARM A / R-ICE	YES	OEDEMA RIGHT LEG	1	2
5003102491616	ARM A / R-ICE	YES	FATIGUE	1	2
5003102491616	ARM A / R-ICE	YES	FATIGUE	2	2
5003102491616	ARM A / R-ICE	YES	FATIGUE	3	1
5003102491619	ARM A / R-ICE	YES	ABDOMINAL CRAMPS (PAIN)	1	3
5003102491619	ARM A / R-ICE	YES	FLUID RETENTION	1	2
5003102541052	ARM A / R-ICE	YES	ASTHENIA	1	2
5003102541052	ARM A / R-ICE	YES	ASTHENIA	2	2
5003102541052	ARM A / R-ICE	YES	ASTHENIA	3	1
5003601401605	ARM A / R-ICE	YES	HEMORRHAGE / BLEEDING WITHOUT SURGERY (GASTRIC ULCER)	1	3
5003601601002	ARM A / R-ICE	YES	FATIGUE	2	3
5003601601003	ARM A / R-ICE	YES	MILD PAIN W/URINATION	1	1
5003601601003	ARM A / R-ICE	YES	MILD PAIN W/URINATION	2	1
5003601601003	ARM A / R-ICE	YES	MILD PAIN W/URINATION	3	1
5003601601005	ARM A / R-ICE	YES	PAIN	1	1
5003601601005	ARM A / R-ICE	YES	LOWER EXTREMITY EDEMA	1	1
5003601601005	ARM A / R-ICE	YES	FATIGUE	1	1
5003601601005	ARM A / R-ICE	YES	LOWER EXTREMITY EDEMA	2	1
5003601601005	ARM A / R-ICE	YES	FATIGUE	2	1
5003601601005	ARM A / R-ICE	YES	PAIN	3	2
5003601601005	ARM A / R-ICE	YES	LOWER EXTREMITY EDEMA	3	1
5003601601005	ARM A / R-ICE	YES	FATIGUE	3	2
5003601601401	ARM A / R-ICE	YES	FATIGUE	1	3

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003601601401	ARM A / R-ICE	YES	FATIGUE	2	2
5003601601401	ARM A / R-ICE	YES	FATIGUE	3	2
5003603201038	ARM A / R-ICE	YES	FEVER	1	1
5003603201038	ARM A / R-ICE	YES	EDEMA	3	1
5003603201213	ARM A / R-ICE	YES	NAUSEA	2	2
5003603201213	ARM A / R-ICE	YES	VOMITING	2	2
5003603201409	ARM A / R-ICE	YES	EDEMA ; HANDS, FACE, SHANKS	1	1
5003603801608	ARM A / R-ICE	YES	GIT- MUCOSITIS	1	2
5003604301013	ARM A / R-ICE	YES	NAUSEA	1	2
5003604301013	ARM A / R-ICE	YES	CONSTIPATION	1	1
5003604301013	ARM A / R-ICE	YES	FATIGUE	2	1
5003604301013	ARM A / R-ICE	YES	NAUSEA	3	2
5003604301013	ARM A / R-ICE	YES	FATIGUE	3	1
5003604901006	ARM A / R-ICE	YES	NOSE BLEEDING	1	1
5003604901006	ARM A / R-ICE	YES	RIGHT KNEE HEMATOMA	1	1
5003604901006	ARM A / R-ICE	YES	NOSE BLEEDING	2	1
5003604901006	ARM A / R-ICE	YES	NOSE BLEEDING	3	1
5003605701401	ARM A / R-ICE	YES	CONSTITUTIONAL FATIGUE	1	1
5003605701401	ARM A / R-ICE	YES	CONSTITUTIONAL FATIGUE	2	1
5003605701401	ARM A / R-ICE	YES	CONSTITUTIONAL FATIGUE	3	1
5003606201617	ARM A / R-ICE	YES	VISUAL FUNCTION LEFT EYE	2	2
5003606201617	ARM A / R-ICE	YES	NUMBNESS IN THROAT	2	2
5003606301207	ARM A / R-ICE	YES	LYMPHATIC OEDEMA: LIMB (LEGS)	1	2
5003606501409	ARM A / R-ICE	YES	COUGH	1	1
5003606501409	ARM A / R-ICE	YES	FEVER	2	1
5003606501409	ARM A / R-ICE	YES	FATIGUE	3	1
5003606501409	ARM A / R-ICE	YES	VOMITING	3	1
5003606701003	ARM A / R-ICE	YES	ASTHENIA	1	1
5003606701003	ARM A / R-ICE	YES	ASTHENIA	2	1
5003606701003	ARM A / R-ICE	YES	ASTHENIA	3	1
5003607201016	ARM A / R-ICE	YES	MENTAL HEALTH PROBLEM (MOOD SWINGS)	2	1
5003607201032	ARM A / R-ICE	YES	FATIGUE	1	2
5003607201032	ARM A / R-ICE	YES	NIGHT SWEATS	2	9
5003607201045	ARM A / R-ICE	YES	HBV REACTIVATION	2	2
5003607201045	ARM A / R-ICE	YES	HBV REACTIVATION	3	2
5003607501403	ARM A / R-ICE	YES	VASOVAGAL ATTACK	1	2
5003607701405	ARM A / R-ICE	YES	ASTHENIA	1	3
5003607701405	ARM A / R-ICE	YES	ASTHENIA	2	1
5003607701405	ARM A / R-ICE	YES	ASTHENIA	3	1
5003610201611	ARM A / R-ICE	YES	SLIGHT HEADACHE (FRONTAL)	1	1
5003610301211	ARM A / R-ICE	YES	DIZZINESS (POSTURAL)	1	2
5003610301211	ARM A / R-ICE	YES	DIZZINESS (POSTURAL)	2	2
5003610301211	ARM A / R-ICE	YES	DIZZINESS (POSTURAL)	3	2
5003610301617	ARM A / R-ICE	YES	ABDOMINAL PAIN (COLIC)	1	2
5003610301617	ARM A / R-ICE	YES	LEFT LEG SWELLING	1	2

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003610501031	ARM A / R-ICE	YES	LETHARGY	1	2
5003610501031	ARM A / R-ICE	YES	ANOREXIA	1	2
5003610501031	ARM A / R-ICE	YES	PYREXIA	1	1
5003610501031	ARM A / R-ICE	YES	LETHARGY	2	2
5003610501031	ARM A / R-ICE	YES	ANOREXIA	2	2
5003610501031	ARM A / R-ICE	YES	PYREXIA	2	1
5003610501031	ARM A / R-ICE	YES	LETHARGY	3	2
5003610501031	ARM A / R-ICE	YES	ANOREXIA	3	2
5003610501031	ARM A / R-ICE	YES	PYREXIA	3	1
5003612501011	ARM A / R-ICE	YES	ALP / ALT / CREATININE	1	1
5003612501011	ARM A / R-ICE	YES	PLATELETS	1	4
5003612501011	ARM A / R-ICE	YES	PLATELETS	2	9
5003612501011	ARM A / R-ICE	YES	ABDOMINAL PAIN (MILD)	3	1
5003612501011	ARM A / R-ICE	YES	PLATELETS	3	4
5003612501015	ARM A / R-ICE	YES	CONSTITUTIONAL SYMPTOMS	1	1
5003612501015	ARM A / R-ICE	YES	CONSTITUTIONAL SYMPTOMS	2	1
5003612501021	ARM A / R-ICE	YES	FATIGUE	1	1
5003612501021	ARM A / R-ICE	YES	FATIGUE	2	1
5003612501021	ARM A / R-ICE	YES	FATIGUE	3	1
5003612501021	ARM A / R-ICE	YES	ETOPOSIDE REACTION	3	1
5003613301210	ARM A / R-ICE	YES	PAIN - FACE (DURING CHEMO. OF INDUCTION CYCLE ONE)	1	1
5003613301210	ARM A / R-ICE	YES	PAIN - MUSCULOSKELETAL (BACK)	2	1
5003614501002	ARM A / R-ICE	YES	FEVER	1	1
5003614501002	ARM A / R-ICE	YES	ABDOMINAL PAIN	1	2
5003614501002	ARM A / R-ICE	YES	FATIGUE	1	2
5003614501002	ARM A / R-ICE	YES	FEVER	2	1
5003614501002	ARM A / R-ICE	YES	ABDOMINAL PAIN	2	1
5003614501002	ARM A / R-ICE	YES	FATIGUE	2	1
5003614501002	ARM A / R-ICE	YES	PLEURITIC CHEST PAIN	2	1
5003614501002	ARM A / R-ICE	YES	FEVER	3	1
5003615501028	ARM A / R-ICE	YES	PAIN (CHEST)	3	2
5003615501028	ARM A / R-ICE	YES	PAIN (BACK)	3	2
5003615501201	ARM A / R-ICE	YES	LETHARGY	1	1
5003615501201	ARM A / R-ICE	YES	LETHARGY	2	1
5003615501201	ARM A / R-ICE	YES	LETHARGY	3	1
5003615501404	ARM A / R-ICE	YES	PYREXIA	1	1
5003615501404	ARM A / R-ICE	YES	FATIGUE	1	1
5003615501404	ARM A / R-ICE	YES	PAIN (GUM)	1	1
5003615501404	ARM A / R-ICE	YES	EPISTAXIS	2	1
5003615501404	ARM A / R-ICE	YES	EPISTAXIS	3	1
5003615501404	ARM A / R-ICE	YES	FATIGUE	3	1
5003616501005	ARM A / R-ICE	YES	FATIGUE	1	2
5003616501005	ARM A / R-ICE	YES	FATIGUE	2	2
5003616501005	ARM A / R-ICE	YES	FATIGUE	3	2
5003617201010	ARM A / R-ICE	YES	EKZEMA HERPETICATUM SEE DERMATOLOGY / SKIN	1	2

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003617501024	ARM A / R-ICE	YES	PROBABLE PULMONARY EMBOLISM	3	4
5003617501606	ARM A / R-ICE	YES	BONE PAIN	1	1
5003617501606	ARM A / R-ICE	YES	FATIGUE	1	1
5003617501606	ARM A / R-ICE	YES	BONE PAIN	2	1
5003618301405	ARM A / R-ICE	YES	PAIN	1	2
5003618301405	ARM A / R-ICE	YES	FEBRILE NEUTROPENIA	1	4
5003618301405	ARM A / R-ICE	YES	PAIN	2	2
5003619301008	ARM A / R-ICE	YES	INSOMNIA	1	1
5003619301008	ARM A / R-ICE	YES	VOMITING	1	1
5003619301008	ARM A / R-ICE	YES	MILD NAUSEA	1	1
5003620301011	ARM A / R-ICE	YES	PAIN	1	1
5003620301011	ARM A / R-ICE	YES	CONSTITUTIONAL SYMPTOMS	1	1
5003620301011	ARM A / R-ICE	YES	PAIN	2	1
5003620301011	ARM A / R-ICE	YES	CONSTITUTIONAL SYMPTOMS	2	1
5003620301017	ARM A / R-ICE	YES	CONSTITUTIONAL SYMPTOMS	3	1
5003620301017	ARM A / R-ICE	YES	THROMBUS (VASCULAR ACCESS RELATED)	3	3
5003620501406	ARM A / R-ICE	YES	PATIENT HAS HAD GOUT FOR LAST 10 YRS. FLARED UP AGAIN BEFORE CYCLE 2	2	2
5003622201022	ARM A / R-ICE	YES	PAIN LEFT UPPER LEG	1	1
5003622201022	ARM A / R-ICE	YES	OEDEMA AND RED SWELLING OF BOTH FEETS	2	2
5003622201022	ARM A / R-ICE	YES	TUMOR PAIN LEFT UPPER LEG	3	2
5003622201207	ARM A / R-ICE	YES	WEAK LEGS	1	1
5003622201207	ARM A / R-ICE	YES	FATIGUE	2	1
5003630201055	ARM A / R-ICE	YES	ACUTE CHOLECYSTITIS	2	3
5003642501030	ARM A / R-ICE	YES	EDEMA HEAD + NECK	1	1
5003642501030	ARM A / R-ICE	YES	HEADACHE	2	2
5003642501030	ARM A / R-ICE	YES	SHOULDER PAIN	2	2
5003642501030	ARM A / R-ICE	YES	EDEMA HEAD + NECK	2	2
5003642501410	ARM A / R-ICE	YES	CONSTIPATION	1	1
5003642501410	ARM A / R-ICE	YES	DIARRHEA	1	2
5003642501410	ARM A / R-ICE	YES	FATIGUE	1	2
5003642501410	ARM A / R-ICE	YES	FATIGUE	2	2
5003101021601	ARM B / R-DHAP	YES	BACK PAIN	1	3
5003101021601	ARM B / R-DHAP	YES	FEVER	1	2
5003101031019	ARM B / R-DHAP	YES	URINARY RETENTION	1	4
5003101031067	ARM B / R-DHAP	YES	ASTHENIA	1	2
5003101031067	ARM B / R-DHAP	YES	THORACIC PAIN	1	2
5003101031411	ARM B / R-DHAP	YES	ASTHENIA	2	1
5003101031411	ARM B / R-DHAP	YES	ASTHENIA	3	1
5003101031412	ARM B / R-DHAP	YES	ASTHENIA	3	1
5003101051050	ARM B / R-DHAP	YES	GASTRIC PAIN	3	2
5003101051050	ARM B / R-DHAP	YES	HAEMATEMESIS	3	3
5003101051063	ARM B / R-DHAP	YES	NAUSEAS	1	2
5003101051063	ARM B / R-DHAP	YES	VOMITING	1	2
5003101051063	ARM B / R-DHAP	YES	NAUSEAS	2	2

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003101051063	ARM B / R-DHAP	YES	FEVER	3	1
5003101071408	ARM B / R-DHAP	YES	HEADACHE	1	1
5003101071408	ARM B / R-DHAP	YES	ASTHENIA	3	1
5003101071414	ARM B / R-DHAP	YES	ARTICULAR PAIN	1	1
5003101071414	ARM B / R-DHAP	YES	ASTHENIA	1	1
5003101071414	ARM B / R-DHAP	YES	ARTICULAR PAIN	2	1
5003101071414	ARM B / R-DHAP	YES	ASTHENIA	2	1
5003101071414	ARM B / R-DHAP	YES	ARTICULAR PAIN	3	1
5003101071414	ARM B / R-DHAP	YES	ASTHENIA	3	1
5003101071418	ARM B / R-DHAP	YES	ASTHENIA	1	1
5003101071418	ARM B / R-DHAP	YES	ASTHENIA	2	1
5003101071643	ARM B / R-DHAP	YES	ASTHENIA	1	1
5003101071643	ARM B / R-DHAP	YES	ASTHENIA	2	1
5003101071643	ARM B / R-DHAP	YES	CREATINEMIA	2	1
5003101071643	ARM B / R-DHAP	YES	ASTHENIA	3	1
5003101091022	ARM B / R-DHAP	YES	EDEMA LIMB	1	2
5003101091022	ARM B / R-DHAP	YES	EDEMA LIMB	2	1
5003101091022	ARM B / R-DHAP	YES	EDEMA LIMB	3	1
5003101091025	ARM B / R-DHAP	YES	ASTHENIA	1	2
5003101091025	ARM B / R-DHAP	YES	ASTHENIA	2	1
5003101091025	ARM B / R-DHAP	YES	ASTHENIA	3	2
5003101131060	ARM B / R-DHAP	YES	HAEMOPTYSIS	2	1
5003101131209	ARM B / R-DHAP	YES	ASTHENIA	1	1
5003101131209	ARM B / R-DHAP	YES	ALOPECIA	2	1
5003101131209	ARM B / R-DHAP	YES	ALOPECIA	3	1
5003101141645	ARM B / R-DHAP	YES	HEADACHE	1	1
5003101141645	ARM B / R-DHAP	YES	GASTRIC PAIN	1	1
5003101141645	ARM B / R-DHAP	YES	OTOPOLYPUS	2	1
5003101141645	ARM B / R-DHAP	YES	OTOPOLYPUS	3	1
5003101171633	ARM B / R-DHAP	YES	ASTHENIA	1	1
5003101171633	ARM B / R-DHAP	YES	HICCUP	2	2
5003101171633	ARM B / R-DHAP	YES	HICCUP	3	1
5003101351012	ARM B / R-DHAP	YES	ASTHENIA	1	2
5003101351012	ARM B / R-DHAP	YES	ASTHENIA	3	1
5003101391646	ARM B / R-DHAP	YES	METABOLIC HYPERURICEMIA ARTHRITIS	1	1
5003101431037	ARM B / R-DHAP	YES	BONE PAIN DUE TO GCSF	1	2
5003101461629	ARM B / R-DHAP	YES	ASTHENIA	1	2
5003101461629	ARM B / R-DHAP	YES	ASTHENIA	2	2
5003101461629	ARM B / R-DHAP	YES	ASTHENIA	3	2
5003101541611	ARM B / R-DHAP	YES	HEADACHE	1	1
5003101541611	ARM B / R-DHAP	YES	FATIGUE	3	2
5003101601066	ARM B / R-DHAP	YES	BLEEDING	1	2
5003101601066	ARM B / R-DHAP	YES	PAIN OF THE RIGHT ANKLE	1	2
5003101601066	ARM B / R-DHAP	YES	BLEEDING	3	2
5003101601066	ARM B / R-DHAP	YES	EPIGASTRIC PAIN	3	2

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003101601076	ARM B / R-DHAP	YES	FATIGUE	1	2
5003101601076	ARM B / R-DHAP	YES	FATIGUE	2	2
5003101601076	ARM B / R-DHAP	YES	FATIGUE	3	2
5003101601610	ARM B / R-DHAP	YES	FEBRILE NEUTROPENIA WITHOUT INFECTION, NO IDENTIFIED GERM	2	2
5003101641018	ARM B / R-DHAP	YES	ASTHENIA	1	2
5003101641018	ARM B / R-DHAP	YES	ASTHENIA	2	2
5003101641018	ARM B / R-DHAP	YES	ASTHENIA	3	2
5003101641047	ARM B / R-DHAP	YES	FATIGUE	3	2
5003101641079	ARM B / R-DHAP	YES	ABDOMINAL PAIN	1	1
5003101641079	ARM B / R-DHAP	YES	FATIGUE	1	1
5003101641079	ARM B / R-DHAP	YES	FATIGUE	2	1
5003101641623	ARM B / R-DHAP	YES	WEIGHT LOSS	1	1
5003101641623	ARM B / R-DHAP	YES	ANOREXIA	1	2
5003101641623	ARM B / R-DHAP	YES	ALTERATION OF GENERAL STATUS	1	2
5003101641623	ARM B / R-DHAP	YES	WEIGHT LOSS	2	1
5003101641623	ARM B / R-DHAP	YES	ANOREXIA	2	2
5003101641623	ARM B / R-DHAP	YES	ALTERATION OF GENERAL STATUS	2	2
5003101641623	ARM B / R-DHAP	YES	WEIGHT LOSS	3	1
5003101641623	ARM B / R-DHAP	YES	ANOREXIA	3	2
5003101641623	ARM B / R-DHAP	YES	ALTERATION OF GENERAL STATUS	3	2
5003102161604	ARM B / R-DHAP	YES	FLU-LIKE SYNDROME	2	2
5003102161604	ARM B / R-DHAP	YES	ABDOMINAL PAIN	2	2
5003102161604	ARM B / R-DHAP	YES	DEGRADATION OF PERFORMANCE STATUS	2	2
5003102341003	ARM B / R-DHAP	YES	THORACIC PAINS	1	2
5003102341064	ARM B / R-DHAP	YES	OEDEMA	3	1
5003102411069	ARM B / R-DHAP	YES	HICCOUGH	2	2
5003102411069	ARM B / R-DHAP	YES	FLU-LIKE SYNDROM	2	2
5003102411069	ARM B / R-DHAP	YES	FLU-LIKE SYNDROM	3	1
5003102541016	ARM B / R-DHAP	YES	Fatigue	1	2
5003102541016	ARM B / R-DHAP	YES	Weight loss	1	1
5003102541016	ARM B / R-DHAP	YES	Fatigue	2	2
5003102541034	ARM B / R-DHAP	YES	PAIN LEFT LUMBAGOS	1	2
5003102541034	ARM B / R-DHAP	YES	SWEALING	1	2
5003102541034	ARM B / R-DHAP	YES	PAIN LEFT LUMBAGOS	2	2
5003102541034	ARM B / R-DHAP	YES	SWEALING	2	2
5003102541034	ARM B / R-DHAP	YES	PAIN LEFT LUMBAGOS	3	2
5003102541034	ARM B / R-DHAP	YES	SWEALING	3	2
5003102541636	ARM B / R-DHAP	YES	FATIGUE	1	1
5003102541636	ARM B / R-DHAP	YES	LOSS OF WEIGHT	1	1
5003102541636	ARM B / R-DHAP	YES	FATIGUE	2	1
5003102541636	ARM B / R-DHAP	YES	LOSS OF WEIGHT	2	1
5003102541636	ARM B / R-DHAP	YES	FATIGUE	3	1
5003103161041	ARM B / R-DHAP	YES	THROMBOSIS	3	3
5003103161206	ARM B / R-DHAP	YES	NAUSEA	1	2
5003103161206	ARM B / R-DHAP	YES	NAUSEA	2	2

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003103161206	ARM B / R-DHAP	YES	NAUSEA	3	1
5003601201018	ARM B / R-DHAP	YES	PULMONARY EMBOLISM	1	2
5003601301015	ARM B / R-DHAP	YES	PAINFUL SWELLING LEFT ARM : THROMBOSIS (PICC)	1	2
5003601301015	ARM B / R-DHAP	YES	FATIGUE	1	2
5003601301015	ARM B / R-DHAP	YES	PAINFUL SWELLING LEFT ARM : THROMBOSIS (PICC)	2	2
5003601301015	ARM B / R-DHAP	YES	FATIGUE	2	1
5003601401001	ARM B / R-DHAP	YES	PAIN	1	3
5003601601402	ARM B / R-DHAP	YES	MUSCULOSKELETAL - OTHER (PATIENT FELL AND BRUISED HER EYE)	2	1
5003601801603	ARM B / R-DHAP	YES	HEMORRHAGE, GASTRO-INTESTINAL - COLON	1	3
5003601801603	ARM B / R-DHAP	YES	OCULAR - BLURRED VISION	1	1
5003601801603	ARM B / R-DHAP	YES	HEMORRHAGE, GASTRO-INTESTINAL - COLON	2	1
5003601801603	ARM B / R-DHAP	YES	OCULAR - BLURRED VISION	2	1
5003601801603	ARM B / R-DHAP	YES	HEMORRHAGE, GASTRO-INTESTINAL - COLON	3	3
5003601881601	ARM B / R-DHAP	YES	HEADACHE	3	1
5003601881602	ARM B / R-DHAP	YES	INSOMNIA	1	1
5003601881602	ARM B / R-DHAP	YES	PAIN	1	2
5003601881602	ARM B / R-DHAP	YES	FEVER	2	1
5003601881602	ARM B / R-DHAP	YES	INSOMNIA	2	1
5003601881602	ARM B / R-DHAP	YES	PAIN	3	1
5003602301009	ARM B / R-DHAP	YES	PERIPHERAL OEDEMA	1	1
5003602301009	ARM B / R-DHAP	YES	PERIPHERAL OEDEMA	2	1
5003602301009	ARM B / R-DHAP	YES	TUMOR LYSIS SYNDROME	2	3
5003602301009	ARM B / R-DHAP	YES	BONE PAIN	2	2
5003602301009	ARM B / R-DHAP	YES	PERIPHERAL OEDEMA	3	1
5003602801204	ARM B / R-DHAP	YES	DEEP VENOUS THROMBOSIS OF SUBCANIAN VEIN RIGHT SIDE	1	2
5003602801204	ARM B / R-DHAP	YES	DEEP VENOUS THROMBOSIS OF SUBCANIAN VEIN RIGHT SIDE	2	2
5003603201034	ARM B / R-DHAP	YES	EDEMA RIGHT ARM WITHOUT THROMBOSIS	2	1
5003603201050	ARM B / R-DHAP	YES	EXSICCOSIS	2	3
5003603701001	ARM B / R-DHAP	YES	DISLOCATED HUMERUS FRACTURE, HOSPITALISATION 28/1 - 22/2/05	1	3
5003603701001	ARM B / R-DHAP	YES	FATIGUE	2	3
5003603801007	ARM B / R-DHAP	YES	FATIGUE	2	2
5003603801007	ARM B / R-DHAP	YES	FATIGUE	3	2
5003603801010	ARM B / R-DHAP	YES	NAUSEA	1	2
5003603801010	ARM B / R-DHAP	YES	DORSALGIA	2	2
5003603801010	ARM B / R-DHAP	YES	DORSALGIA	3	2
5003604301202	ARM B / R-DHAP	YES	SWOLLEN RIGHT ARM	1	1
5003604701002	ARM B / R-DHAP	YES	BONE PAIN	1	2
5003604701012	ARM B / R-DHAP	YES	THROMBOEMBOLIC CEREBRAL INFARCTION	1	4
5003604701012	ARM B / R-DHAP	YES	* CARDIAC FAILURE	1	5
5003604701012	ARM B / R-DHAP	YES	1 FEBRILE NEUTROPENIA	1	4
5003604901004	ARM B / R-DHAP	YES	ORAL THRUSH	2	1
5003604901007	ARM B / R-DHAP	YES	LOW BACK PAIN	1	1
5003604901007	ARM B / R-DHAP	YES	THROAT PAIN	1	1
5003604901007	ARM B / R-DHAP	YES	NOSE BLEEDING	1	1
5003604901603	ARM B / R-DHAP	YES	INSOMNIA	1	1

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003604901603	ARM B / R-DHAP	YES	FATIGUE	1	2
5003604901603	ARM B / R-DHAP	YES	HEADACHE	1	1
5003604901603	ARM B / R-DHAP	YES	CENTRAL CATHETER EXIT SITE BLEEDING	1	1
5003604901603	ARM B / R-DHAP	YES	FATIGUE	2	1
5003604901603	ARM B / R-DHAP	YES	INSOMNIA	3	1
5003604901603	ARM B / R-DHAP	YES	FATIGUE	3	2
5003605301203	ARM B / R-DHAP	YES	DEPRESSION	1	2
5003605301203	ARM B / R-DHAP	YES	MUSCULOSKELETAL	1	1
5003605301203	ARM B / R-DHAP	YES	DEPRESSION	2	2
5003606201410	ARM B / R-DHAP	YES	BADE PAIN	1	2
5003606501601	ARM B / R-DHAP	YES	FATIGUE	1	1
5003606501601	ARM B / R-DHAP	YES	WEAKNESS	1	2
5003606501601	ARM B / R-DHAP	YES	DIFFICULTY SLEEPING	1	2
5003606501601	ARM B / R-DHAP	YES	PAIN LOWER BACK	1	1
5003606501601	ARM B / R-DHAP	YES	FATIGUE	2	2
5003606501601	ARM B / R-DHAP	YES	DIFFICULTY SLEEPING	2	3
5003606501601	ARM B / R-DHAP	YES	PAIN LOWER BACK	2	1
5003606701005	ARM B / R-DHAP	YES	ASTHENIA	1	1
5003606701005	ARM B / R-DHAP	YES	ASTHENIA	2	2
5003606701005	ARM B / R-DHAP	YES	ASTHENIA	3	2
5003607201408	ARM B / R-DHAP	YES	WORSENING OF GENERAL STATUS	3	2
5003607201623	ARM B / R-DHAP	YES	KERATITIS MARGINALIS BOTHSIDES	1	2
5003607201623	ARM B / R-DHAP	YES	BACKACHE DUE TO APPLICATION OF NEUPOGEN	2	2
5003607301603	ARM B / R-DHAP	YES	PAIN (HEADACHE)	3	3
5003607501401	ARM B / R-DHAP	YES	OCULAR - POSSIBLE CHOROIDAL INFECTION RT EYE / ENGORGEMENT LT. RETINAL VASCULATURE	3	2
5003609301609	ARM B / R-DHAP	YES	PAIN: HEADACH	1	1
5003609301609	ARM B / R-DHAP	YES	PAIN: HEADACH	2	1
5003610201212	ARM B / R-DHAP	YES	NAUSEA	1	1
5003610201212	ARM B / R-DHAP	YES	VOMITING	1	1
5003610201212	ARM B / R-DHAP	YES	NAUSEA	2	1
5003610201212	ARM B / R-DHAP	YES	VOMITING	2	1
5003610301613	ARM B / R-DHAP	YES	EPISTAXIS	1	2
5003610501402	ARM B / R-DHAP	YES	TIRED EYES	1	1
5003610501402	ARM B / R-DHAP	YES	ELEVATED LDH	1	2
5003610501402	ARM B / R-DHAP	YES	TIRED EYES	2	1
5003610501402	ARM B / R-DHAP	YES	SENSATION OF CONSTRICTION AROUND NECK AND HOARSENESS	2	1
5003610501402	ARM B / R-DHAP	YES	ELEVATED LDH	2	3
5003610501402	ARM B / R-DHAP	YES	PAIN	2	1
5003610501402	ARM B / R-DHAP	YES	ELEVATED LDH	3	2
5003610701403	ARM B / R-DHAP	YES	SWEALING HEAD + NECK	1	2
5003610701403	ARM B / R-DHAP	YES	SLIGHT NAUSEA	1	1
5003610701403	ARM B / R-DHAP	YES	PAIN NIGHT	2	1
5003610701403	ARM B / R-DHAP	YES	NIGHT SWEAT	2	1
5003611301002	ARM B / R-DHAP	YES	ALLERGY TO DRESSING USED ON HICKMONS CATHETER - SKIN RASH	1	2

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003611301002	ARM B / R-DHAP	YES	HEADACHE	1	1
5003611301002	ARM B / R-DHAP	YES	ALLERGY TO DRESSING USED ON HICKMONS CATHETER - SKIN RASH	2	1
5003611301002	ARM B / R-DHAP	YES	HEADACHE	2	1
5003611301003	ARM B / R-DHAP	YES	COUGH	1	1
5003611301003	ARM B / R-DHAP	YES	CORYZA	1	1
5003611301003	ARM B / R-DHAP	YES	COUGH	2	1
5003611301003	ARM B / R-DHAP	YES	LETHARGY	2	1
5003611301003	ARM B / R-DHAP	YES	COUGH	3	1
5003611301003	ARM B / R-DHAP	YES	FEVER	3	1
5003612501016	ARM B / R-DHAP	YES	FATIGUE	1	1
5003612501016	ARM B / R-DHAP	YES	SWELLING : NECK	1	1
5003612501016	ARM B / R-DHAP	YES	HICCOUGH	1	1
5003612501016	ARM B / R-DHAP	YES	FATIGUE	2	2
5003612501016	ARM B / R-DHAP	YES	FATIGUE	3	2
5003612501019	ARM B / R-DHAP	YES	PAIN RIGHT GROIN	1	1
5003612501019	ARM B / R-DHAP	YES	ABDOMINAL PAIN	1	9
5003612501019	ARM B / R-DHAP	YES	PAIN RIGHT GROIN	2	9
5003612501019	ARM B / R-DHAP	YES	FATIGUE	2	2
5003612501019	ARM B / R-DHAP	YES	ABDOMINAL PAIN	2	9
5003612501019	ARM B / R-DHAP	YES	PAIN RIGHT GROIN	3	9
5003612501019	ARM B / R-DHAP	YES	ABDOMINAL PAIN	3	3
5003614301407	ARM B / R-DHAP	YES	LETHARGY	1	1
5003614501022	ARM B / R-DHAP	YES	BACK PAIN	1	2
5003614501022	ARM B / R-DHAP	YES	SORE THROAT + EYES	1	2
5003614501022	ARM B / R-DHAP	YES	SORE THROAT + EYES	2	2
5003614501022	ARM B / R-DHAP	YES	INSOMNIA	2	2
5003615501007	ARM B / R-DHAP	YES	DYSPNEA	1	3
5003615501029	ARM B / R-DHAP	YES	PAIN (UPPER ABDOMEN)	1	2
5003615501029	ARM B / R-DHAP	YES	PAIN (UPPER ABDOMEN)	2	1
5003615501029	ARM B / R-DHAP	YES	EPISTAXIS	2	1
5003616301212	ARM B / R-DHAP	YES	LYMPHATICS	2	1
5003616301212	ARM B / R-DHAP	YES	LYMPHATICS	3	1
5003616501003	ARM B / R-DHAP	YES	FATIGUE	1	2
5003616501003	ARM B / R-DHAP	YES	FATIGUE	2	2
5003616501003	ARM B / R-DHAP	YES	FATIGUE	3	2
5003617201021	ARM B / R-DHAP	YES	DETECTION OF HCV-RNA WITHIN STEM CELL APHERESIS - IT IS ASSUMEND THAT IT'S A FRESH INFECTION, BECAUSE PRE-FINDINGS FROM 08.12.05 N.A.D LABORATORY CHEMICAL NO INDICATION OF HEPATOSIS	3	3
5003617201629	ARM B / R-DHAP	YES	HYPOKALAEMIA	2	2
5003617201629	ARM B / R-DHAP	YES	HYPOMAGNESEMIA	2	2
5003617301616	ARM B / R-DHAP	YES	BONE PAIN	1	3
5003617301616	ARM B / R-DHAP	YES	BONE PAIN	2	2
5003617301616	ARM B / R-DHAP	YES	BONE PAIN	3	2
5003617301619	ARM B / R-DHAP	YES	BACK PAIN	1	1
5003617301619	ARM B / R-DHAP	YES	BACK PAIN	3	1

Randomization Number	Actual arm of induction	Other	Toxicity	Cycle number	Grade
5003617501006	ARM B / R-DHAP	YES	HYPOCALCEMIA	1	1
5003617501006	ARM B / R-DHAP	YES	INFECTION BASED ON INCREASE CRP	1	2
5003617501006	ARM B / R-DHAP	YES	BILATERAL PITTING OEDEMA	1	2
5003617501026	ARM B / R-DHAP	YES	ABDOMINAL PAIN	1	3
5003618201030	ARM B / R-DHAP	YES	PETECHIAE	1	2
5003618201030	ARM B / R-DHAP	YES	FUO	1	3
5003618201030	ARM B / R-DHAP	YES	CONJUNCTIVITIS SICCA	1	2
5003618201030	ARM B / R-DHAP	YES	PAIN BACK	2	2
5003618201030	ARM B / R-DHAP	YES	PETECHIAE	3	1
5003619301006	ARM B / R-DHAP	YES	RESPIRATORY (COUGH)	2	1
5003619301006	ARM B / R-DHAP	YES	BONE PAIN	2	1
5003619301006	ARM B / R-DHAP	YES	FATIGUE	3	1
5003619301006	ARM B / R-DHAP	YES	CHEMO-REFRACTORY DISEASE	3	1
5003619301006	ARM B / R-DHAP	YES	RESPIRATORY (COUGH)	3	1
5003619301016	ARM B / R-DHAP	YES	FATIGUE	1	1
5003619301016	ARM B / R-DHAP	YES	TOOTH EXTRACTION	2	2
5003619301016	ARM B / R-DHAP	YES	FATIGUE	2	1
5003619301016	ARM B / R-DHAP	YES	FATIGUE	3	1
5003622201014	ARM B / R-DHAP	YES	FATIGUE	2	1
5003622201014	ARM B / R-DHAP	YES	FATIGUE	3	1
5003622201607	ARM B / R-DHAP	YES	BONE PAIN	1	2
5003623501408	ARM B / R-DHAP	YES	BONE PAIN (CYCLE 1)	1	3
5003628201404	ARM B / R-DHAP	YES	PAIN (POSSIBLY G-CSF RELATED)	1	2
5003628201404	ARM B / R-DHAP	YES	PAIN (POSSIBLY G-CSF RELATED)	2	2
5003628201404	ARM B / R-DHAP	YES	PAIN (POSSIBLY G-CSF RELATED)	3	2
5003638501023	ARM B / R-DHAP	YES	BONE PAIN WITH G-CSF	1	2
5003638501023	ARM B / R-DHAP	YES	BONE PAIN WITH G-CSF	2	1
N = 472					

Listing 6.7-3 Other toxicities during consolidation (induction safety population)

Randomization Number	Actual arm of induction	Specify other toxicity 1	Grade Other toxicity 1	Specify other toxicity 2	Grade Other toxicity 2
5003101021605	ARM A / R-ICE	FEVER	1		-
5003101021631	ARM A / R-ICE	DERMATOLOGY / SKIN	2		-
5003101031401	ARM B / R-DHAP	ASTHENIA	3		-
5003101031621	ARM A / R-ICE	ASTHENIA	2		-
5003101061617	ARM B / R-DHAP	HERPETIC MUCOSITIS	2		-
5003101071029	ARM A / R-ICE	ANXIETY	2		-
5003101071408	ARM B / R-DHAP	ALLERGY CUTANEUS	1		-
5003101071418	ARM B / R-DHAP	CUTANEOUS ALLERGY (ANTIBIOTIC)	2		-
5003101071643	ARM B / R-DHAP	HYPONATREMIA	4	PULMONARY EMBOLISM	4
5003101131072	ARM A / R-ICE	FEVER	2	HEMORRHOIDS	2
5003101131209	ARM B / R-DHAP	ASTHENIA	3		-
5003101131409	ARM A / R-ICE	ABDOMINAL PAIN	2		-
5003101171637	ARM A / R-ICE	FEVER	1	PULMONARY	1
5003101251021	ARM B / R-DHAP	CUTANEOUS ALLERGY DUE TO ARACYTINE	1		-
5003101281033	ARM A / R-ICE	ALLERGY	3		-
5003101351012	ARM B / R-DHAP	metabolic	4	GLUCOSE	2
5003101391207	ARM B / R-DHAP	FEVER WITH UNKNOWN ORIGIN	1		-
5003101491042	ARM A / R-ICE	PULMONARY	4		-
5003101541415	ARM B / R-DHAP	CREATININE	1		-
5003101541611	ARM B / R-DHAP	MACULAR HEMORRHAGE	2	ACUTE NOISE REDUCTION (EAR)	2
5003101621026	ARM A / R-ICE	FEBRILE NEUTROPENIA	3	RETRO-STERNAL PAIN	2
5003101641623	ARM B / R-DHAP	PULMONARY : DYSPNEA	1	BILATERAL PLEURAL EFFUSION	2
5003102161604	ARM B / R-DHAP	FEVER	2	RIGORS, CHILLS	1
5003102341061	ARM A / R-ICE	FEVER	2	CUTANEOUS ERUPTION	1
5003102341064	ARM B / R-DHAP	HALLUCINATION	1		-
5003102411069	ARM B / R-DHAP	CUTANEOUS REACTION	1		-
5003102491619	ARM A / R-ICE	FATIGUE + FLUID RETENTION + PAIN (EYE-TOE) + DERMATOLOGY (CUTANEOUS RASH AFTER ARA-C AND PRURITIS)	2	METABOLIC (INCREASED AF + HYPOMAGNESEMIA + HYPOUREMIA + HYPOALBUMINEMIA + HYPERBILIRUBINE + HYPONATREMIA + HYPOKALEMIA + INCREASED GAMMA GT) + PULMONARY (DYSPNOE)	2
5003102541034	ARM B / R-DHAP	ASTHENIA	1		-
5003102541636	ARM B / R-DHAP	ASTHENIA	2	PETECHIA	1
5003102541640	ARM B / R-DHAP	ALLERGIC REACTION TO DMSO	3		-
5003103161041	ARM B / R-DHAP	UNEXPLAINED FEVER	2	DIABETES	3
5003103161206	ARM B / R-DHAP	FEVER	1	HYPOTENSION	2
5003601201604	ARM B / R-DHAP	GVHD LIKE SKIN REACTION	1		-
5003601301015	ARM B / R-DHAP	ANXIETY	2	RASH	2
5003601601602	ARM B / R-DHAP	HYPERGLYCEMIA	3	FEVER W/ NEGATIVE CULTURES	1
5003601881401	ARM A / R-ICE	CUTANEOUS ERUPTION	1		-
5003601881601	ARM B / R-DHAP	HEADACHE	2	ALLERGY	3
5003601881602	ARM B / R-DHAP	FEVER	1	DRUG ERUPTION	1
5003602301009	ARM B / R-DHAP	RASH / DESQUAMATION	2		-
5003602801011	ARM A / R-ICE	TOXOALLERGY EXANTHEMA	2		-

Randomization Number	Actual arm of induction	Specify other toxicity 1	Grade Other toxicity 1	Specify other toxicity 2	Grade Other toxicity 2
5003602801012	ARM A / R-ICE	ABNORMAL COAGULATION WITH BLEEDING TO URINE BLADDER	2		-
5003603301401	ARM B / R-DHAP	abdominal pain	2	HAEMOPTYSIS (INTERMITTENT)	1
5003603801002	ARM A / R-ICE	COAGULATION	1		-
5003604201202	ARM B / R-DHAP	FEAR : PSYCHOTIC	2		-
5003604301013	ARM A / R-ICE	RASH DUE TO ENGRAFTMENT SYNDROME	3		-
5003604701002	ARM B / R-DHAP	MOOD DISORDER	2		-
5003604701602	ARM B / R-DHAP	FOLLICULITIS	1		-
5003604901004	ARM B / R-DHAP	METABOLIC	1		-
5003604901007	ARM B / R-DHAP	HYPERTHYROIDISM	2	RASH DESQUAMATION	2
5003604901603	ARM B / R-DHAP	PRURITUS	2	RASH / DESQUAMATION	2
5003605701401	ARM A / R-ICE	CANDIDA-VAGINITIS	1	FEVER IN NEUTROPENIA	1
5003606201617	ARM A / R-ICE	09.12.2005 ZYLOTOXIN A-POS	2		-
5003606201620	ARM B / R-DHAP	HEADACHES	2		-
5003606201626	ARM B / R-DHAP	AMPHOTERICIN-B ASSOCIATED DRY-FEVER	2	IMIPENEM ASSOCIATED RASH	2
5003606501601	ARM B / R-DHAP	NEUTROPENIA	4	ANOREXIA	2
5003607201408	ARM B / R-DHAP	ARA-C ASSOCIATED EXANTHEMA	2		-
5003607501403	ARM A / R-ICE	FAINT	1	HYPOTENSION	1
5003607701007	ARM A / R-ICE	ERYTHEMA	2		-
5003607701405	ARM A / R-ICE	FEVER	1		-
5003609301018	ARM B / R-DHAP	HYPOKALEMIA	1	HYPOMAGNESEMIA	1
5003609301206	ARM B / R-DHAP	FEBRILE NEUTROPENIA	3	HYPOKALIAEMIA	4
5003609301609	ARM B / R-DHAP	FEBRILE NEUTROPENIA	3		-
5003610301209	ARM B / R-DHAP	HEADACHES	2	HYPOKALEMIA	1
5003610301613	ARM B / R-DHAP	LOWER BACK PAIN	2		-
5003610501031	ARM A / R-ICE	PYREXIA	2	DIARRHOEA	1
5003610501402	ARM B / R-DHAP	PULMONARY (COUGH)	1	RASH	2
5003614501022	ARM B / R-DHAP	FEBRILE NEUTROPENIA	3	RASH (FACE, UPPER TRUNK)	2
5003614501032	ARM B / R-DHAP	NEUTROPENIC TYPHLITIS	3	RASH	2
5003616301403	ARM A / R-ICE	ALLERGIC REACTION	1		-
5003617201613	ARM B / R-DHAP	BURNING EYES	1		-
5003617301619	ARM B / R-DHAP	HYPOKALEMIA	3	RASH	1
5003618301405	ARM A / R-ICE	ALLERGIC REACTION	2	PETECHIAE	2
5003619301621	ARM A / R-ICE	HEADACHE	1		-
5003620501602	ARM B / R-DHAP	DYSPHAGIA	2	NAUSEA	2
5003621501412	ARM B / R-DHAP	FOLLICULLITIS (FACE + AXILLA)	2		-
5003622201207	ARM A / R-ICE	ZVK INFECTION	3		-
5003623501408	ARM B / R-DHAP	VOMITING X 4	2		-
5003632201606	ARM B / R-DHAP	THROMBOSIS VENA SUBCLAVIA, JUGULARIS EXTERNA, INTERNA RIGHT AS RESULT OF INFECTION	3		-
N = 78					

6.7.3. Adverse events

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

Randomization Number	First Randomization Date	AE number	Adverse event description	Start date of adverse event	Non hematological toxicity grade	Hematological toxicity grade	Date of outcome	AE outcome	Seriousness criteria	Date of death	Response at death	Reason for death	Specify reason of death
5003603201027	26/01/2006	1	SEVERE PNEUMONIA AND DEATH FROM SEPTIC SHOCK PRIOR TO START WITH STUDY MEDICATION (DEATH 26012006)	25/01/2006	-	-	-	FATAL / DEATH	Yes	26/01/2006	NOT EVALUATED	OTHER REASON	SEPTIC SHOCK
5003603201627	28/03/2007	1	SEPSIS WITH REFRACTORY LACTIC ACIDOSIS AFTER GASTRIC PERFORATION	31/03/2007	LIFE THREATENING	SEVERE	-	FATAL / DEATH	Yes	03/04/2007	PROGRESSIVE DISEASE	OTHER REASON	SEE ATTACHED LETTER / PROGRESSION FORM WILL FOLLOW
N = 2													

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

Randomization Number	Actual arm of induction	AE number	Adverse event description	Start date of adverse event	Date of 1st cycle	Time from starting date to date of cycle 1 (days)	Seriousness criteria
5003101141406	ARM A / R-ICE	1	EDEMA RELATED TO ALLERGIC REACTION	15/09/2005	17/09/2005	-2	No
5003618501008	ARM A / R-ICE	1	INFECTION WITHOUT FEBRILE NEUTROPENIA	21/01/2007	22/01/2007	-1	No
5003101391207	ARM B / R-DHAP	1	RESPIRATORY INFECTION (E. COLI STREPTOCOCCUS PNEUMONIAE)	01/02/2006	11/02/2006	-10	No
5003102361203	ARM B / R-DHAP	1	DYSPNEA / HYPOXY	25/11/2003	26/11/2003	-1	No
5003604201028	ARM B / R-DHAP	1	ALLERGIC ANAPHYLACTIC REACTION DUE TO RITUXIMAB	02/02/2006	03/02/2006	-1	Yes
5003604201056	ARM B / R-DHAP	1	RENAL FUNCTION : CLEARANCE DECREASE	29/04/2008	15/05/2008	-16	No
5003609301018	ARM B / R-DHAP	1	CHEST INFECTION	07/06/2008	15/06/2008	-8	Yes
5003612501019	ARM B / R-DHAP	1	HIGH CREATININE LEVEL (GRADE 3)	03/09/2007	06/09/2007	-3	Yes
N = 8							

6.7.4. Serious adverse events

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

Randomization Number	First Randomization Date	AE number	Adverse event description	Start date of adverse event	Non hematological toxicity grade	Hematological toxicity grade	Date of outcome	AE outcome	Seriousness criteria	Date of death	Response at death	Reason for death	Specify reason of death
5003603201027	26/01/2006	1	SEVERE PNEUMONIA AND DEATH FROM SEPTIC SHOCK PRIOR TO START WITH STUDY MEDICATION (DEATH 26012006)	25/01/2006	-	-	-	FATAL	Yes	26/01/2006	NOT EVALUATED	OTHER REASON	SEPTIC SHOCK
5003603201627	28/03/2007	1	SEPSIS WITH REFRACTORY LACTIC ACIDOSIS AFTER GASTRIC PERFORATION	31/03/2007	LIFE THREATENING	SEVERE	-	FATAL	Yes	03/04/2007	PROGRESSIVE DISEASE	OTHER REASON	SEE ATTACHED LETTER / PROGRESSION FORM WILL FOLLOW
N = 2													

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

Randomization Number	First Randomization Date	Arm of treatment	Date of 2nd randomization	Arm of 2nd randomization	SAE diagnosis	SAE: date of start	AE/SAE: date of end	Outcome	Sponsor Causality
5003613301007	14/11/2006	ARM A / R-ICE	31/01/2007	RITUXIMAB	HYPOTENSIVE STATE. ATRIAL FIBRILLATION	21/11/2006	-	Unknown	Related
5003613301007	14/11/2006	ARM A / R-ICE	31/01/2007	RITUXIMAB	ACUTE RENAL IMPAIREMENT	03/01/2007	08/01/2007	Recovered without sequelae	Related
5003613301404	14/11/2006	ARM B / R-DHAP	08/02/2007	OBSERVATION	BRADYCARDIA	19/11/2006	-	Unknown	Related
5003613301404	14/11/2006	ARM B / R-DHAP	08/02/2007	OBSERVATION	FEVER, NAUSEA AND VOMITING	13/05/2007	-	Not yet recovered	Unrelated
5003613301404	14/11/2006	ARM B / R-DHAP	08/02/2007	OBSERVATION	VOMITING AND DIARRHEA INCREASED CREATININE LEVEL	23/05/2007	-	Not yet recovered	Related
N = 5									

Listing 6.7-8 Serious adverse events (induction safety population)

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003101031621	ARM A / R-ICE	RITUXIMAB	FEMALE	55	SEPTIC SHOCK WITH PNEUMONIA	06/07/2006	LIFE THREATENING	LIFE THREATENING	Yes	Yes	RECOVERED	33
5003101031621	ARM A / R-ICE	RITUXIMAB	FEMALE	55	PULMONARY ASPERGILLOSIS	06/07/2006	LIFE THREATENING	LIFE THREATENING	Yes	Yes	RECOVERED	50
5003101031621	ARM A / R-ICE	RITUXIMAB	FEMALE	55	BRONCHITIS TO PNEUMOCOCCUS	18/01/2007	SEVERE	MILD	Yes	No	RECOVERED	64
5003101031621	ARM A / R-ICE	RITUXIMAB	FEMALE	55	PULMONARY INFECTION TO PSEUDOMONAS AERUGINOSA WITH HEMOPTYSIA	02/06/2007	SEVERE	MILD	Yes	No	RECOVERED	72
5003101051056	ARM A / R-ICE	OBSERVATION	MALE	64	HEARING LOSS	03/04/2007	SEVERE	-	Yes	No	ONGOING	-
5003101051068	ARM A / R-ICE	NOT APPLICABLE	MALE	63	SEPTIC SHOCK	05/09/2007	LIFE THREATENING	LIFE THREATENING	No	No	RECOVERED	-
5003101051068	ARM A / R-ICE	NOT APPLICABLE	MALE	63	ESCHERICHIA COLI INFECTION	15/08/2007	SEVERE	NORMAL	No	No	RECOVERED	5
5003101051603	ARM A / R-ICE	NOT APPLICABLE	FEMALE	56	OESOPHAGUS CARCINOMA	09/02/2005	LIFE THREATENING	-	No	No	FATAL	0
5003101051612	ARM A / R-ICE	OBSERVATION	MALE	36	Cardiac infarction	28/06/2004	SEVERE	MILD	No	No	RECOVERED	4
5003101131030	ARM A / R-ICE	NOT APPLICABLE	FEMALE	48	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
5003101251205	ARM A / R-ICE	OBSERVATION	MALE	54	HYPERTHERMIA	15/07/2004	MODERATE	LIFE THREATENING	No	No	RECOVERED	3
5003101251205	ARM A / R-ICE	OBSERVATION	MALE	54	FEBRILE NEUTROPENIA	20/08/2004	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	10
5003101281017	ARM A / R-ICE	NOT APPLICABLE	MALE	60	ATRIAL FIBRILLATION HYPOTENSION	25/11/2004	LIFE THREATENING	MODERATE	Yes	Yes	RECOVERED	3
5003101281017	ARM A / R-ICE	NOT APPLICABLE	MALE	60	ASPERGILLOSIS	03/12/2004	SEVERE	LIFE THREATENING	No	Yes	RECOVERED	7
5003101281017	ARM A / R-ICE	NOT APPLICABLE	MALE	60	SEVERE GASTRIC INTESTINAL BLEEDING	29/11/2004	LIFE THREATENING	LIFE THREATENING	No	Yes	RECOVERED	12
5003101281017	ARM A / R-ICE	NOT APPLICABLE	MALE	60	SYNCOPE	25/11/2004	SEVERE	SEVERE	No	Yes	RECOVERED	0
5003101431622	ARM A / R-ICE	RITUXIMAB	MALE	49	INTERSTITIAL PNEUMOPATHY	19/09/2005	SEVERE	MILD	No	No	RECOVERED	-
5003101431622	ARM A / R-ICE	RITUXIMAB	MALE	49	BRUTAL NEUTROPENIA APPEARANCE	10/10/2005	UNKNOWN	SEVERE	Yes	Yes	RECOVERED	15

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003101491042	ARM A / R-ICE	RITUXIMAB	MALE	46	RESPIRATORY DISTRESS WITH SEPTICEMIA	26/05/2006	LIFE THREATENING	LIFE THREATENING	Yes	No	RECOVERED WITH SEQUELAE	3
5003101601404	ARM A / R-ICE	NOT APPLICABLE	FEMALE	65	PULMONARY EFFUSION AND OEDEMA-DYSPNEA GRADE 3-4 , DETERIORATED CARDIAC FUNCTION- RENAL INSUFFICIENCY	30/07/2005	SEVERE	MILD	Yes	Yes	RECOVERED	11
5003101621026	ARM A / R-ICE	OBSERVATION	MALE	64	PNEUMOPATHY INTERSTITIAL	15/11/2005	MODERATE	MODERATE	No	No	RECOVERED	8
5003101621055	ARM A / R-ICE	OBSERVATION	FEMALE	64	FEBRILE NEUTROPENIA GR 3	26/10/2006	-	SEVERE	Yes	No	RECOVERED	7
5003101621615	ARM A / R-ICE	OBSERVATION	MALE	64	HEPATITIS	14/10/2004	SEVERE	NORMAL	No	No	RECOVERED	33
5003102161413	ARM A / R-ICE	NOT APPLICABLE	MALE	48	SEPTIC SHOCK RESULTING IN DEATH	03/11/2006	DEATH	SEVERE	Yes	Yes	FATAL	2
5003102341202	ARM A / R-ICE	RITUXIMAB	FEMALE	56	SEPTICAEMIA (STREPTOCOCCUS PNEUMONIAE)	28/01/2004	SEVERE	LIFE THREATENING	No	No	RECOVERED	20
5003102491616	ARM A / R-ICE	NOT APPLICABLE	MALE	46	HYPOVOLEMIC SHOCK AND ARTERIAL BLEEDING OF OESOPHAGUS	02/07/2004	LIFE THREATENING	LIFE THREATENING	No	No	RECOVERED	5
5003102491616	ARM A / R-ICE	NOT APPLICABLE	MALE	46	SEPTIC SHOCK DUE TO GRAM NEGATIVE INFECTION AND NEUTROPENIC SEPSIS	17/07/2004	LIFE THREATENING	LIFE THREATENING	Yes	Yes	RECOVERED	4
5003102541625	ARM A / R-ICE	NOT APPLICABLE	MALE	25	ACUTE HEPATITIS	31/07/2005	LIFE THREATENING	-	Yes	Yes	RECOVERED WITH SEQUELAE	87
5003601401002	ARM A / R-ICE	RITUXIMAB	MALE	56	INFECTION	09/07/2004	SEVERE	LIFE THREATENING	No	No	RECOVERED	12
5003601401002	ARM A / R-ICE	RITUXIMAB	MALE	56	ACUTE NON-LYMPHOCYTIC LEUKEMIA = AML	15/06/2006	UNKNOWN	UNKNOWN	Yes	-	FATAL	24
5003601401006	ARM A / R-ICE	OBSERVATION	FEMALE	62	KLEBSIELLA PNEUMONIAE	08/07/2007	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	11
5003601401602	ARM A / R-ICE	RITUXIMAB	MALE	41	septicaemia	04/11/2004	LIFE THREATENING	LIFE THREATENING	No	No	RECOVERED	3
5003601401602	ARM A / R-ICE	RITUXIMAB	MALE	41	MYOCARDITIS	06/08/2006	LIFE THREATENING	UNKNOWN	Yes	No	FATAL	0
5003601401602	ARM A / R-ICE	RITUXIMAB	MALE	41	HYPOTENSION	04/11/2004	LIFE THREATENING	-	No	No	RECOVERED	3
5003601401602	ARM A / R-ICE	RITUXIMAB	MALE	41	GASTRO INTESTINAL SYMPTOMS (DIARRHEA)	04/11/2004	SEVERE	-	No	No	RECOVERED	3
5003601401605	ARM A / R-ICE	NOT APPLICABLE	FEMALE	57	CONFUSION POSITIVE BABINSKI SIGN RIGHT SIDE	25/09/2006	SEVERE	NORMAL	Yes	No	RECOVERED	15
5003601401605	ARM A / R-ICE	NOT APPLICABLE	FEMALE	57	GASTRIC BLEEDING / ULCER	10/10/2006	SEVERE	SEVERE	Yes	No	RECOVERED	2

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003601601005	ARM A / R-ICE	OBSERVATION	FEMALE	53	GRADE 3 CELLULITIS + GRADE 3 NEUTROPENIC FEVER RESULTING IN HOSPITALIZATION FROM 15/02/2008-19/02/2008. ANEMIA DURING HOSPITALIZATION GRADE 4.	15/02/2008	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	39
5003601601401	ARM A / R-ICE	NOT APPLICABLE	MALE	59	ADMISSION FOR FEBRILE NEUTROPENIA WITH POSITIVE BLOOD CULTURE. ISCHEMIC / INFECTIONS COLITIS	03/05/2004	LIFE THREATENING	LIFE THREATENING	Yes	Yes	RECOVERED	7
5003602201601	ARM A / R-ICE	RITUXIMAB	FEMALE	55	HERPES ZOSTER INFECTION WITH INVOLVEMENT OF FACE , LEFT TRIGEMINUS	09/05/2005	MODERATE	NORMAL	Yes	No	RECOVERED	122
5003602901002	ARM A / R-ICE	NOT APPLICABLE	MALE	64	CAVITATING PNEUMONIA	24/02/2005	SEVERE	MILD	Yes	Yes	RECOVERED	10
5003602901002	ARM A / R-ICE	NOT APPLICABLE	MALE	64	FEBRILE NEUTROPENIA, PULMONARY INFECTION	05/02/2005	SEVERE	LIFE THREATENING	Yes	Yes	RECOVERED	8
5003602901201	ARM A / R-ICE	NOT APPLICABLE	FEMALE	31	PULMONARY EMBOLISM	07/03/2004	SEVERE	NORMAL	No	No	RECOVERED	3
5003602901201	ARM A / R-ICE	NOT APPLICABLE	FEMALE	31	PNEUMONIA	07/04/2004	SEVERE	SEVERE	Yes	No	RECOVERED	10
5003602901401	ARM A / R-ICE	NOT APPLICABLE	MALE	60	CVA (CEREBRAL VASCULAR ACCIDENT). AFTER THE SECOND COURSE THE PATIENT WAS DIAGNOSED WITH TIA (DURING THE SEPSIS PERIOD). LATER WE FOUND RESIDUAL NEUROLOGIC SIGNS THUS WE CAN SAY IT WAS CVA	20/12/2004	LIFE THREATENING	UNKNOWN	No	No	RECOVERED WITH SEQUELAE	65
5003602901401	ARM A / R-ICE	NOT APPLICABLE	MALE	60	E COLI BACTEREMIA, NEUTROPENIC FEVER	20/12/2004	LIFE THREATENING	LIFE THREATENING	Yes	No	RECOVERED	6
5003602901601	ARM A / R-ICE	OBSERVATION	MALE	63	SUBDURAL HEMATOMA. ON 12/01/05 THE PATIENT WAS ADMITTED FOR FURTHER THERAPY. ON THE 17/01/05 HE COMPLAINED ABOUT HEADACHES AND THUS UNDERWENT HEAD CT SCAN.	17/01/2005	SEVERE	NORMAL	No	No	RECOVERED	34
5003603301201	ARM A / R-ICE	NOT APPLICABLE	FEMALE	49	DEHYDRATION	17/04/2004	SEVERE	MILD	Yes	No	RECOVERED	3
5003603301201	ARM A / R-ICE	NOT APPLICABLE	FEMALE	49	GRAM NEGATIVE SEPSIS	12/07/2004	LIFE THREATENING	MODERATE	No	No	RECOVERED	2
5003603701004	ARM A / R-ICE	NOT APPLICABLE	MALE	64	PULMONARY INFECTION / SEPTIC SHOCK	21/08/2005	DEATH	DEATH	Yes	No	FATAL	11
5003603801203	ARM A / R-ICE	RITUXIMAB	FEMALE	53	DEHYDRATATION	09/12/2004	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	11
5003603801203	ARM A / R-ICE	RITUXIMAB	FEMALE	53	FEBRILE NEUTROPENIA	09/12/2004	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	11

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003604301013	ARM A / R-ICE	OBSERVATION	MALE	41	HEADACHE DUE TO LUMBAR PUNCTURE	11/01/2008	SEVERE	-	No	No	RECOVERED	11
5003604301618	ARM A / R-ICE	NOT APPLICABLE	MALE	55	PATIENT CAUGHT COLD DURING NADIR. LEAD TO NEUTROPENIC SEPSIS REQUIRING HOSPITALISATION	07/03/2006	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	5
5003604801014	ARM A / R-ICE	NOT APPLICABLE	MALE	62	LEUCOENCEPHALOPATHY, CARDIAC ARRHYTHMIA	21/02/2007	LIFE THREATENING	MODERATE	Yes	Yes	RECOVERED	50
5003605301010	ARM A / R-ICE	NOT APPLICABLE	MALE	55	ADMITTED TO HOSPITAL WITH RIGHT-SIDED CHEST WALL PAIN. SUBSEQUENTLY DEVELOPED A TYPICAL ZOSTER RASH IN TA DISTRIBUTION	02/09/2007	MODERATE	LIFE THREATENING	Yes	No	RECOVERED	5
5003605301010	ARM A / R-ICE	NOT APPLICABLE	MALE	55	BOWEL OBSTRUCTION	24/09/2007	SEVERE	LIFE THREATENING	No	Yes	RECOVERED	5
5003605301601	ARM A / R-ICE	NOT APPLICABLE	MALE	61	PRESUMED MYOCARDIAL EVENT	20/06/2004	LIFE THREATENING	MODERATE	No	Yes	FATAL	0
5003605701401	ARM A / R-ICE	RITUXIMAB	FEMALE	30	BACTERIAL PNEUMONIA	18/09/2007	MODERATE	NORMAL	Yes	Yes	RECOVERED	3
5003605701401	ARM A / R-ICE	RITUXIMAB	FEMALE	30	PERONAEUS PARESIS LEFT AND CRUSH KIDNEY (GRADE 3) DUE TO RHABDOMYOLYSIS AFTER HEROIN INJECTION AND UNRESPONSIVE SYNDROME (TRAUMA)	17/10/2007	SEVERE	NORMAL	No	Yes	RECOVERED WITH SEQUELAE	9
5003605701401	ARM A / R-ICE	RITUXIMAB	FEMALE	30	HOSPITALIZATION DUE TO PNEUMONIA	14/02/2007	SEVERE	MILD	No	No	RECOVERED	9
5003605701601	ARM A / R-ICE	OBSERVATION	FEMALE	62	HERPES ZOSTER TH 10 (LEFT SIDE) WITH NORMAL ANC	04/05/2005	SEVERE	NORMAL	No	Yes	RECOVERED	150
5003605901003	ARM A / R-ICE	NOT APPLICABLE	FEMALE	48	INFECTION WITH NORMAL ANC	17/06/2005	SEVERE	NORMAL	No	No	RECOVERED	7
5003605901003	ARM A / R-ICE	NOT APPLICABLE	FEMALE	48	SECOND CANCER HODGKIN LYMPHOMA , MIXED CELLULARITY	03/10/2007	-	-	No	No	RECOVERED	70
5003606201605	ARM A / R-ICE	RITUXIMAB	MALE	42	MECHANICAL ILEUS, SIGMAPERFORATION WITH RETROPERITONEAL ABSCESS	16/06/2004	LIFE THREATENING	NORMAL	No	Yes	RECOVERED	27
5003606201617	ARM A / R-ICE	RITUXIMAB	FEMALE	54	INFECTION, FEVER	12/01/2006	SEVERE	-	No	Yes	RECOVERED	13
5003606301207	ARM A / R-ICE	OBSERVATION	MALE	37	RIGHT UPPER MOLAR DENTAL ABSCESS	01/12/2004	SEVERE	LIFE THREATENING	No	No	RECOVERED	2
5003606301207	ARM A / R-ICE	OBSERVATION	MALE	37	DENTAL CARIES - REQURING FULL UPPER DENTAL CLEARANCE AND PARTIAL LOWER DENTAL CLEARANCE / DENTAL PREVIOUSLY REPORTED HISTORY OF DENTAL DECAY OVER MANY YEARS	20/02/2005	MODERATE	NORMAL	No	No	RECOVERED	68

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5003606301207	ARM A / R-ICE	OBSERVATION	MALE	37	HIGH GRADE UROTHELIAL CARCINOMA	20/03/2008	LIFE THREATENING	-	Yes	No	FATAL	568
5003606301612	ARM A / R-ICE	NOT APPLICABLE	FEMALE	58	FEBRILE NEUTROPENIA	18/04/2005	MILD	LIFE THREATENING	No	No	RECOVERED	2
5003607201045	ARM A / R-ICE	NOT APPLICABLE	MALE	48	SEPTIC MULTIPLE ORGAN FAILURE IN A CONTEXT OF PANCYTOPENIA	12/08/2007	DEATH	DEATH	Yes	No	FATAL	6
5003607701405	ARM A / R-ICE	RITUXIMAB	MALE	49	FATIGUE, ASTHENIA	06/05/2008	SEVERE	MODERATE	No	No	RECOVERED	3
5003608701013	ARM A / R-ICE	RITUXIMAB	MALE	54	GASTROINTESTINAL BLEEDING (NEUTROPENIC COLITIS)	03/09/2007	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	4
5003609301608	ARM A / R-ICE	NOT APPLICABLE	MALE	43	CELLULITIS - LEFT LEG	19/11/2004	SEVERE	MILD	No	No	RECOVERED	4
5003609301608	ARM A / R-ICE	NOT APPLICABLE	MALE	43	FEVER OF UNKNOWN ORIGIN, NOT NEUTROPENIC	26/12/2004	SEVERE	MILD	No	No	RECOVERED	24
5003610201612	ARM A / R-ICE	NOT APPLICABLE	FEMALE	56	IMPLANTATION OF TRACHEOBRONCHIAL STENT BECAUSE OF DYSPNEA, CANCER RELATED BECAUSE OF MEDIASTINAL INVOLVEMENT	12/05/2005	SEVERE	MODERATE	No	No	ONGOING	-
5003610201612	ARM A / R-ICE	NOT APPLICABLE	FEMALE	56	FEVER WITH PULMONARY INFILTRATION, BRONCHOSCOPY PERFORMED: ASPERGILLOSIS	13/07/2005	LIFE THREATENING	LIFE THREATENING	No	No	FATAL	10
5003610501031	ARM A / R-ICE	OBSERVATION	MALE	54	IFOSFAMIDE ENCEPHALOPATHY	04/05/2008	SEVERE	-	Yes	No	RECOVERED	2
5003610501031	ARM A / R-ICE	OBSERVATION	MALE	54	LINE INFECTION	02/05/2008	LIFE THREATENING	SEVERE	No	No	RECOVERED	79
5003610501031	ARM A / R-ICE	OBSERVATION	MALE	54	VENO OCCLUSIVE DISEASE	27/06/2008	MODERATE	-	Yes	No	RECOVERED WITH SEQUELAE	23
5003612501011	ARM A / R-ICE	OBSERVATION	FEMALE	41	PANCYTOPENIA	03/04/2007	-	LIFE THREATENING	Yes	No	RECOVERED	2
5003612501011	ARM A / R-ICE	OBSERVATION	FEMALE	41	PANCYTOPENIA - NEUTROPENIC SEPSIS (GRADE 4)	20/04/2007	-	LIFE THREATENING	Yes	No	RECOVERED	7
5003612501012	ARM A / R-ICE	NOT APPLICABLE	FEMALE	55	PULMONARY EMBOLISM	24/04/2007	SEVERE	MILD	No	No	RECOVERED	13
5003612501012	ARM A / R-ICE	NOT APPLICABLE	FEMALE	55	DIARRHOEA AND DEHYDRATION	30/04/2007	MODERATE	-	No	No	RECOVERED	11
5003612501012	ARM A / R-ICE	NOT APPLICABLE	FEMALE	55	FEBRILE NEUTROPENIA / DIARRHEA GRADE 2 / NAUSEA AND VOMITING GRADE 2	17/05/2007	MODERATE	LIFE THREATENING	Yes	Yes	RECOVERED	18
5003614501002	ARM A / R-ICE	NOT APPLICABLE	MALE	27	NEUTROPENIC SEPSIS	25/09/2006	MILD	LIFE THREATENING	Yes	No	RECOVERED	5

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5003615501018	ARM A / R-ICE	NOT APPLICABLE	FEMALE	49	HIGH TEMPERATURE AND DROP IN BLOOD PRESSSURE	10/09/2007	SEVERE	-	Yes	No	RECOVERED	22
5003615501201	ARM A / R-ICE	NOT APPLICABLE	MALE	56	RENAL LITHIASIS	17/11/2006	SEVERE	MILD	No	No	RECOVERED WITH SEQUELAE	1
5003616301403	ARM A / R-ICE	RITUXIMAB	MALE	36	PULMONARY EMBOLISM	07/04/2006	LIFE THREATENING	UNKNOWN	No	No	RECOVERED	0
5003616301615	ARM A / R-ICE	RITUXIMAB	MALE	63	CHRONIC COUGH, DRY NON PRODUCTIVE ASSOCIATED WITH FEBRILE ILLNESS FOR 2 WEEKS. DIAGNOSED WITH PNEUMONIA 14082006	15/08/2006	DEATH	MILD	Yes	No	FATAL	17
5003616501005	ARM A / R-ICE	NOT APPLICABLE	FEMALE	59	SEPSIS	16/02/2007	DEATH	DEATH	No	No	FATAL	5
5003620301011	ARM A / R-ICE	NOT APPLICABLE	MALE	41	FEVER	15/10/2007	MILD	MILD	No	Yes	RECOVERED	3
5003620301017	ARM A / R-ICE	NOT APPLICABLE	MALE	59	INFECTED PICC LINE	24/03/2008	SEVERE	-	Yes	No	RECOVERED	5
5003620501406	ARM A / R-ICE	OBSERVATION	MALE	44	GRADE 4 NEUTROPENIA, PROBABLY RITUXIMAB INDUCED, NO SEQUELAE, MORE INFORMATION TO FOLLOW, NEUT 0.13	13/03/2008	-	LIFE THREATENING	Yes	No	RECOVERED	13
5003620501406	ARM A / R-ICE	OBSERVATION	MALE	44	DIARRHOEA AND VOMITING	12/12/2007	SEVERE	MILD	No	No	RECOVERED	5
5003621301014	ARM A / R-ICE	NOT APPLICABLE	FEMALE	58	RENAL FAILURE ACUTE	01/11/2007	SEVERE	-	Yes	Yes	RECOVERED	5
5003621301014	ARM A / R-ICE	NOT APPLICABLE	FEMALE	58	THROMBOCYTOPENIA	01/11/2007	-	SEVERE	Yes	Yes	RECOVERED	-
5003622201210	ARM A / R-ICE	NOT APPLICABLE	MALE	54	RETROSTERNAL PRESSURE CONTINUING RIGHT ARM	08/03/2006	SEVERE	NORMAL	Yes	Yes	RECOVERED	6
5003622501604	ARM A / R-ICE	OBSERVATION	MALE	47	CHEST INFECTION	10/01/2008	SEVERE	LIFE THREATENING	No	No	RECOVERED	4
5003624501017	ARM A / R-ICE	NOT APPLICABLE	MALE	52	ABDOMINAL PAIN, HICKMAN LINE INFECTION, NEUTROPENIC	19/08/2007	SEVERE	LIFE THREATENING	Yes	Yes	RECOVERED	5
5003630201055	ARM A / R-ICE	NOT APPLICABLE	FEMALE	62	ANEMIA + THROMBOPENIA	17/04/2008	-	LIFE THREATENING	Yes	No	RECOVERED	26
5003630201055	ARM A / R-ICE	NOT APPLICABLE	FEMALE	62	GASTROINTESTINAL TOXICITY WITH VOMITING MUCOSITIS / (CANDIDA) PARENTERAL NUTITION	27/04/2008	LIFE THREATENING	-	Yes	No	RECOVERED	13
5003630201055	ARM A / R-ICE	NOT APPLICABLE	FEMALE	62	INFECTION WITH FEBRIL NEUTROPENIA BECAUSE OF RECURRENT CYSTITIES + PNEUMONIA	27/04/2008	SEVERE	-	No	No	RECOVERED	13

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5003630201055	ARM A / R-ICE	NOT APPLICABLE	FEMALE	62	ANEMIA + THROMBOPENIA	12/06/2008	-	SEVERE	Yes	No	RECOVERED	25
5003630201055	ARM A / R-ICE	NOT APPLICABLE	FEMALE	62	(HEPATIC TOXICITY) WITH ACUTE CHOLECYSTITIS	16/06/2008	SEVERE	-	No	No	RECOVERED	44
5003630201055	ARM A / R-ICE	NOT APPLICABLE	FEMALE	62	INFECTION WITH FEBRILE NEUTROPENIA + URO SEPSIS	08/06/2008	LIFE THREATENING	-	No	No	RECOVERED	8
5003101021601	ARM B / R-DHAP	RITUXIMAB	FEMALE	48	HOSPITALISATION FOR BACK PAIN PROBABLY DUE TO G-CSF	06/10/2003	SEVERE	LIFE THREATENING	No	No	RECOVERED	3
5003101021601	ARM B / R-DHAP	RITUXIMAB	FEMALE	48	BRONCHI SUPER INFECTION DOCUMENTED : PYOCYANIC	10/01/2005	SEVERE	SEVERE	Yes	Yes	RECOVERED	24
5003101031019	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	58	RENAL FAILURE WITH URINARY RETENTION	01/01/2005	LIFE THREATENING	MODERATE	No	No	RECOVERED	3
5003101031067	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	21	HYPOTENSION (VAGAL SYNCOPE) DURING NEUTROPENIA GR 4	29/05/2007	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	1
5003101071002	ARM B / R-DHAP	NOT APPLICABLE	MALE	64	PANCYTOPENIA (SEPTIC SHOCK WITHOUT ORIGIN) SEPTICAEMIA AT PYOCIANIC BACILLUS	31/10/2003	DEATH	DEATH	Yes	No	FATAL	21
5003101071417	ARM B / R-DHAP	RITUXIMAB	FEMALE	56	GASTRO INTESTINAL BLEEDING WITH HEMATOLOGIC COLLAPSUS	30/03/2007	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	8
5003101071607	ARM B / R-DHAP	NOT APPLICABLE	MALE	59	ACUTE RENAL FAILURE	16/01/2004	LIFE THREATENING	LIFE THREATENING	Yes	Yes	RECOVERED WITH SEQUELAE	31
5003101071643	ARM B / R-DHAP	OBSERVATION	FEMALE	58	CUTANEOUS REACTION : SUSCLAVICULAR LEFT	06/12/2007	MODERATE	MILD	No	No	RECOVERED	2
5003101071643	ARM B / R-DHAP	OBSERVATION	FEMALE	58	RENAL FAILURE	02/03/2008	SEVERE	LIFE THREATENING	No	No	RECOVERED	18
5003101071643	ARM B / R-DHAP	OBSERVATION	FEMALE	58	HYPONATREMIA	22/02/2008	LIFE THREATENING	-	Yes	No	RECOVERED	3
5003101071643	ARM B / R-DHAP	OBSERVATION	FEMALE	58	PULMONARY EMBOLISM	08/03/2008	SEVERE	LIFE THREATENING	No	No	RECOVERED	12
5003101071643	ARM B / R-DHAP	OBSERVATION	FEMALE	58	MUCOSITIS	29/02/2008	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	31
5003101071643	ARM B / R-DHAP	OBSERVATION	FEMALE	58	SEPTICEMIA STAPHYLOCOCCUS EPIDERMIDIS PNEUMOPATHY	07/05/2008	LIFE THREATENING	SEVERE	Yes	No	FATAL	8
5003101091025	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	61	SEMR SEPTICEMIA (ENTEROBACTER CLOACAE)	04/07/2005	SEVERE	MILD	Yes	No	RECOVERED	12

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5003101141402	ARM B / R-DHAP	NOT APPLICABLE	MALE	63	PULMONARY HYPERTENSION, NON OBSTRUCTIVE CARDIOMYOPATHY WITH GLOBAL HEART FAILURE, LIGHT PERICARDIC EFFUSION ==> CARDIAC INSUFFICIENCY WITH ARRYTHMIA	21/06/2005	SEVERE	UNKNOWN	Yes	Yes	RECOVERED	76
5003101141624	ARM B / R-DHAP	OBSERVATION	FEMALE	64	CLOSTRIDIUM DIFFICILE INFECTION WITH THROMBOPENIA	13/12/2005	SEVERE	LIFE THREATENING	No	No	RECOVERED	50
5003101141624	ARM B / R-DHAP	OBSERVATION	FEMALE	64	DISCONFORT WITH TREMOR THAN FAINTING AND FINALLY REGAIN CONSCIOUSNESS WITHOUT DEFICIENCY. REACTION TO METRONIDAZOL (CONFUSION) + CLOSTRIDIUM DIFFICILE INFECTION	29/01/2006	SEVERE	SEVERE	No	No	RECOVERED	19
5003101161028	ARM B / R-DHAP	NOT APPLICABLE	MALE	59	CARDIAC FAILURE	22/08/2005	LIFE THREATENING	MODERATE	Yes	Yes	RECOVERED WITH SEQUELAE	-
5003101391048	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	PULMONARY EMBOLISM	08/07/2006	MODERATE	SEVERE	No	No	RECOVERED	19
5003101391048	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	STROKE CEREBRAL VASCULAR ISCHEMIA	12/08/2006	SEVERE	SEVERE	No	No	RECOVERED	9
5003101431204	ARM B / R-DHAP	NOT APPLICABLE	MALE	56	SUDDEN APPEARANCE OF APHASIA WITH LIGHT RIGHT FACIAL PARESIS AND LIGHT MOTOR DEFICIENCY OF THE RIGHT UPPER LIMB SUSPICION OF STROKE	29/12/2003	LIFE THREATENING	MILD	Yes	No	RECOVERED WITH SEQUELAE	77
5003101431204	ARM B / R-DHAP	NOT APPLICABLE	MALE	56	RE-APPEARENCE OF APHASIA	13/02/2004	SEVERE	MODERATE	Yes	Yes	RECOVERED WITH SEQUELAE	342
5003101431608	ARM B / R-DHAP	RITUXIMAB	MALE	64	PULMONARY INFECTION WITH HAEMOPHILUS INFLUENZAE	16/03/2005	SEVERE	UNKNOWN	No	No	RECOVERED	13
5003101431608	ARM B / R-DHAP	RITUXIMAB	MALE	64	SECONDARY MALIGNANCY : HEPATIC ADENOCARCINOMA	24/04/2007	LIFE THREATENING	NORMAL	No	No	FATAL	361
5003101431627	ARM B / R-DHAP	OBSERVATION	MALE	65	ACUTE RENAL INSUFFICIENCY GRADE 1 AND GENERAL STATUS DECREASED GRADE 2	10/10/2005	MODERATE	SEVERE	Yes	No	RECOVERED	2
5003101541415	ARM B / R-DHAP	OBSERVATION	MALE	53	STREPTOCOCCUS PNEUMONIAE	14/07/2007	SEVERE	-	No	No	RECOVERED	13
5003101601610	ARM B / R-DHAP	NOT APPLICABLE	MALE	49	SEVERE SEIZURE EPILEPTIC CRISIS AFTER 1ST PBSCT UNIT AND BEFORE THE SECOND PROGRAMMED ONE - REACTION DMSO ?	24/05/2004	LIFE THREATENING	LIFE THREATENING	No	No	RECOVERED	4
5003101641047	ARM B / R-DHAP	NOT APPLICABLE	MALE	45	TINNITUS	04/05/2006	MODERATE	SEVERE	Yes	Yes	RECOVERED	5
5003101641623	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	PERSISTANT COUGH -> PULMONARY INFILTRATE ON CT SCAN	28/02/2006	MODERATE	NORMAL	No	Yes	ONGOING	1600

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5003101641623	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	VOMITING	24/05/2005	SEVERE	MODERATE	Yes	No	RECOVERED	21
5003102161604	ARM B / R-DHAP	RITUXIMAB	FEMALE	55	NOSE MELANOMA	15/03/2009	SEVERE	-	No	No	RECOVERED	184
5003102181031	ARM B / R-DHAP	NOT APPLICABLE	MALE	63	VOMITING	27/06/2005	LIFE THREATENING	NORMAL	Yes	Yes	RECOVERED	30
5003102181031	ARM B / R-DHAP	NOT APPLICABLE	MALE	63	INFECTION WITHOUT NEUTROPENIA (POSITIVE HEMOCULTURETO PYOCIANIC BACILLUS)	04/08/2005	SEVERE	MODERATE	Yes	Yes	RECOVERED	9
5003102411054	ARM B / R-DHAP	OBSERVATION	MALE	64	ATRIAL FIBRILLATION	26/10/2006	SEVERE	LIFE THREATENING	No	Yes	RECOVERED	0
5003102411054	ARM B / R-DHAP	OBSERVATION	MALE	64	HYPERGLYCEMIA DUE TO DEXAMETHASONE	06/11/2006	SEVERE	NORMAL	Yes	No	RECOVERED	4
5003102411054	ARM B / R-DHAP	OBSERVATION	MALE	64	SEPSIS - VAC INFECTION : STAPHYLOCOCCUS	14/01/2007	LIFE THREATENING	LIFE THREATENING	No	No	RECOVERED	19
5003102411069	ARM B / R-DHAP	OBSERVATION	MALE	63	MALIGNANT CHICKEN POX INFECTION	23/11/2007	SEVERE	SEVERE	No	No	RECOVERED	14
5003102541034	ARM B / R-DHAP	OBSERVATION	MALE	26	LEFT PNEUMONIA	04/10/2005	MODERATE	UNKNOWN	No	No	RECOVERED	10
5003103161041	ARM B / R-DHAP	RITUXIMAB	FEMALE	49	TROMBOSIS WITH INFERIOR EDEMA	27/03/2006	SEVERE	LIFE THREATENING	No	No	RECOVERED	3
5003103161206	ARM B / R-DHAP	RITUXIMAB	FEMALE	34	COLLAPSE WITH POSSIBLE SEPTIC ORIGIN	06/03/2006	LIFE THREATENING	LIFE THREATENING	Yes	No	RECOVERED	1
5003601201201	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	32	REDUCED CONDITION, INFECTION WITH FOCUS, REQUIRING IV ANTIBIOTICS, PNEUMONIA	01/05/2004	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	3
5003601201201	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	32	REDUCED CONDITION, INFECTION WITH FOCUS, URINARY TRACT INFECTION, REQUIRING IV ANTIBIOTICS	17/05/2004	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	5
5003601301015	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	57	ADMISSION FOR FEBRILE NEUTROPENIA AND MUCOSITIS	18/02/2008	SEVERE	SEVERE	No	No	RECOVERED	11
5003601301015	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	57	SEVERE ONGOING NAUSEA, HYPOKALAEMIA AND HYPOMAGNESAEMIA, ANXIETY, DEPRESSION	12/03/2008	SEVERE	SEVERE	No	No	RECOVERED WITH SEQUELAE	1
5003601401001	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	48	ABDOMINAL PAIN AT TUMOUR SITE	19/11/2003	SEVERE	SEVERE	No	No	RECOVERED	11
5003601401004	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	FEVER AND MENTAL DISTURBANCES. VARICELLA LESIONS IN THE SKIN. VARICELLA ZOSTER VIRUS SEEN IN BLISTERS.	26/06/2007	DEATH	NORMAL	Yes	Yes	FATAL	61
5003601401601	ARM B / R-DHAP	OBSERVATION	MALE	58	FEVER	13/01/2004	MILD	MODERATE	No	No	RECOVERED	2
5003601401604	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	PNEUMOCYSTIS JIROVECII	17/07/2006	SEVERE	SEVERE	Yes	No	RECOVERED	19

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5003601601402	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	65	DEHYDRATION AND ELECTROLYTE IMBALANCE	08/11/2004	SEVERE	NORMAL	No	No	RECOVERED	8
5003601601402	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	65	NAUSEA AND DIARRHEA DURING CHEMOTHERAPY TREATMENT	26/11/2004	SEVERE	SEVERE	Yes	No	RECOVERED	4
5003601601402	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	65	RESPIRATORY FAILURE AND DEATH	04/01/2005	DEATH	DEATH	No	No	FATAL	9
5003601601601	ARM B / R-DHAP	RITUXIMAB	FEMALE	53	CATHETER RELATED INFECTION	02/11/2004	SEVERE	MODERATE	No	No	RECOVERED	4
5003601601602	ARM B / R-DHAP	OBSERVATION	MALE	45	ACUTE PERFORATED BOWEL	11/12/2007	LIFE THREATENING	-	Yes	Yes	RECOVERED	7
5003601601602	ARM B / R-DHAP	OBSERVATION	MALE	45	HYPERGLYCEMIA	20/01/2008	LIFE THREATENING	-	Yes	No	RECOVERED WITH SEQUELAE	2
5003601801603	ARM B / R-DHAP	NOT APPLICABLE	MALE	41	GASTROINTESTINAL BLEEDING	26/12/2004	SEVERE	SEVERE	No	No	RECOVERED	3
5003601801603	ARM B / R-DHAP	NOT APPLICABLE	MALE	41	HEMORRHAGE - GASTRO-INTESTINAL, COLON	15/02/2005	SEVERE	SEVERE	Yes	Yes	RECOVERED	2
5003601801607	ARM B / R-DHAP	OBSERVATION	FEMALE	40	HEMORRHAGIC COLITIS AND ILEUS PARALYTICUS	14/03/2008	LIFE THREATENING	LIFE THREATENING	Yes	No	RECOVERED	45
5003601801607	ARM B / R-DHAP	OBSERVATION	FEMALE	40	PERIPHERAL PARESIS OF NERVUS VII LEFT (PROBABLE ASSOCIATED WITH PREVIOUS HERPES ZOSTER)	14/05/2008	SEVERE	MILD	Yes	No	RECOVERED	30
5003602801204	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	HOSPITALIZATION DUE TO SEVERE HEMATOLOGIC TOXICITY	12/01/2005	UNKNOWN	LIFE THREATENING	Yes	No	RECOVERED	5
5003602801204	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	HOSPITALIZATION DUE TO SEVERE DEHYDRATATION, COLLAPSE AND HYPOPOTASEMIA	03/02/2005	LIFE THREATENING	SEVERE	No	Yes	RECOVERED	5
5003603201001	ARM B / R-DHAP	NOT APPLICABLE	MALE	50	NEUTROPENIA AFTER CHEMOTHERAPY, DIARRHEA, PNEUMONIA, INTENSIVE CARE	19/04/2004	LIFE THREATENING	LIFE THREATENING	Yes	No	RECOVERED WITH SEQUELAE	8
5003603201001	ARM B / R-DHAP	NOT APPLICABLE	MALE	50	NEUTROPENIA AFTER CHEMOTHERAPY, COLITIS, PERITONITIS, SEPSIS	11/05/2004	DEATH	DEATH	Yes	No	FATAL	2
5003603201034	ARM B / R-DHAP	NOT APPLICABLE	MALE	33	DIARRHEA (CLOSTRIDIUM DIFFICILE ANTIGEN)	01/09/2006	MODERATE	-	No	No	RECOVERED	14
5003603201034	ARM B / R-DHAP	NOT APPLICABLE	MALE	33	INFECTIOUS DIARRHEA (CLOSTRIDIUM DIFFICILE)	-	SEVERE	-	No	No	RECOVERED	-
5003603201034	ARM B / R-DHAP	NOT APPLICABLE	MALE	33	INFECTIOUS DIARRHEA WITH FEVER	-	SEVERE	MILD	No	No	RECOVERED	-
5003603201050	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	ACUTE RENAL FAILURE	26/10/2007	LIFE THREATENING	-	Yes	No	RECOVERED WITH SEQUELAE	31

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003603201050	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	EXSICCOSIS	03/09/2007	SEVERE	NORMAL	No	No	RECOVERED	11
5003603201050	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	NAUSEA AND VOMITING	24/09/2007	SEVERE	MILD	Yes	No	RECOVERED WITH SEQUELAE	17
5003603201053	ARM B / R-DHAP	OBSERVATION	MALE	52	DIARRHEA	24/03/2008	MODERATE	-	No	No	RECOVERED	3
5003603201205	ARM B / R-DHAP	RITUXIMAB	MALE	59	SEPSIS (PSEUDOMONAS AERUGINOSA) WITH FEVER AND CHILLS	14/01/2005	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	32
5003603301401	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	SEPTICAEMIA - GRAM POSITIVE COCCUS (2 STRAINS OF STAPHYLOCOCCUS EPIDERMITIS AND STRAIN OF ACINOBACTER	04/10/2004	SEVERE	MODERATE	Yes	No	RECOVERED	8
5003603301401	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	SEPTICAEMIA	13/12/2004	SEVERE	LIFE THREATENING	No	No	RECOVERED WITH SEQUELAE	46
5003603301401	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	MUCOSITIS	11/12/2004	LIFE THREATENING	LIFE THREATENING	Yes	No	RECOVERED	9
5003603301401	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	FEBRILE NEUTROPENIA	14/12/2004	LIFE THREATENING	LIFE THREATENING	Yes	No	RECOVERED	8
5003603301401	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	SUBACUTE SMALL BOWEL OBSTRUCTION	21/12/2004	SEVERE	LIFE THREATENING	No	Yes	RECOVERED WITH SEQUELAE	3
5003603301401	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	2ND SUBACUTE SMALL BOWEL OBSTRUCTION*	-	SEVERE	MODERATE	No	No	RECOVERED	-
5003603701001	ARM B / R-DHAP	OBSERVATION	MALE	64	FEBRILE NEUTROPENIA GRADE 3 (28.1.05) NEUTROPENIA GRADE 4 THROMBOPENIA GRADE 4	28/01/2005	SEVERE	LIFE THREATENING	No	Yes	RECOVERED	25
5003603701001	ARM B / R-DHAP	OBSERVATION	MALE	64	NAUSEA AND VOMITTING, LOSS OF APPETIT AND WEAKNESS	08/03/2005	SEVERE	MODERATE	Yes	No	RECOVERED	24
5003603701001	ARM B / R-DHAP	OBSERVATION	MALE	64	FEBRILE NEUTROPENIA GRADE 3	22/03/2005	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	23
5003603701001	ARM B / R-DHAP	OBSERVATION	MALE	64	ANEMIA CAUSED BY INSUFFICIENT ERYTHROPOIESIS AFTER STEM CELL TRANSPLANTATION	13/06/2005	UNKNOWN	SEVERE	No	No	RECOVERED	3
5003603701001	ARM B / R-DHAP	OBSERVATION	MALE	64	INFECTION (BACTEREMIA WITH PSEUDOMONAS AERUGINOSA, ENTEROCOCCUS GALLINARUM AND STAPH. EPIDERMIDIS)	20/04/2005	SEVERE	-	Yes	No	RECOVERED	5
5003603801013	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	60	NEUROTOXICITY	23/01/2007	SEVERE	MODERATE	Yes	Yes	RECOVERED WITH SEQUELAE	17
5003603901001	ARM B / R-DHAP	NOT APPLICABLE	MALE	54	PROLONGED HOSPITALIZATION (9 DAYS AFTER END TREATMENT, CYCLE 1) DUE TO SUPPORTIVE CARE NEED	03/11/2004	SEVERE	LIFE THREATENING	Yes	No	FATAL	16

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003604201028	ARM B / R-DHAP	NOT APPLICABLE	MALE	65	ALLERGIC ANAPHYLACTIC REACTION DUE TO RITUXIMAB	02/02/2006	SEVERE	-	Yes	Yes	RECOVERED	0
5003604301607	ARM B / R-DHAP	NOT APPLICABLE	MALE	61	LOWER RESPIRATORY TRACT INFECTION	14/09/2004	SEVERE	NORMAL	Yes	No	RECOVERED	3
5003604701012	ARM B / R-DHAP	NOT APPLICABLE	MALE	62	FEBRILE NEUTROPENIA	30/04/2007	DEATH	LIFE THREATENING	Yes	Yes	FATAL	4
5003604701012	ARM B / R-DHAP	NOT APPLICABLE	MALE	62	RESPIRATORY INSUFFICIENCY	30/04/2007	LIFE THREATENING	LIFE THREATENING	Yes	Yes	FATAL	4
5003604701012	ARM B / R-DHAP	NOT APPLICABLE	MALE	62	THROMBOEMBOLIC CEREBRAL INFARCTION	03/05/2007	LIFE THREATENING	LIFE THREATENING	No	Yes	FATAL	1
5003604701012	ARM B / R-DHAP	NOT APPLICABLE	MALE	62	CARDIAC INSUFFICIENCY	30/04/2007	DEATH	DEATH	No	Yes	FATAL	4
5003604701015	ARM B / R-DHAP	RITUXIMAB	MALE	56	MENTAL - HEALTH - DISORDER : DEPRESSION	15/10/2007	SEVERE	-	No	No	RECOVERED	7
5003604701015	ARM B / R-DHAP	RITUXIMAB	MALE	56	PANCYTOPENIA, COPROSTASIS	23/03/2008	MILD	MILD	No	No	RECOVERED	3
5003604801006	ARM B / R-DHAP	RITUXIMAB	MALE	53	FEBRILE NEUTROPENIA	16/02/2006	SEVERE	LIFE THREATENING	No	No	RECOVERED	7
5003604901004	ARM B / R-DHAP	RITUXIMAB	FEMALE	52	LINE SEPSIS - PSEUDOMONAS AERUGINOSA	21/06/2006	SEVERE	SEVERE	No	Yes	RECOVERED	13
5003604901004	ARM B / R-DHAP	RITUXIMAB	FEMALE	52	PROLONG FEVER, SUSP. LUL PNEUMONIA	08/01/2006	MODERATE	MODERATE	No	No	RECOVERED	2
5003604901004	ARM B / R-DHAP	RITUXIMAB	FEMALE	52	FEVER, SUSP. PNEUMONIA	04/02/2007	MODERATE	SEVERE	No	Yes	RECOVERED	7
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	ACUTE RENAL FAILURE	27/04/2008	SEVERE	MODERATE	Yes	No	FATAL	139
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	CMV INFECTION	19/07/2008	SEVERE	MODERATE	Yes	No	RECOVERED	5
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	SUPERFICIAL BLEEDING AFTER REMUVAL OF PORTACATH	12/08/2008	MILD	MODERATE	No	No	RECOVERED	1
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	THROMBOCYTOPENIA	17/08/2008	-	LIFE THREATENING	Yes	No	RECOVERED	3
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	BRONCHOPNEUMONIA, EXTENSIVE DIFFUSE ALVEOLAR DAMAGE	04/09/2008	DEATH	-	Yes	No	FATAL	9
5003605301610	ARM B / R-DHAP	RITUXIMAB	MALE	60	CULTURE NEGATIVE NEUTROPENIC FEVER	28/02/2005	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	11
5003605301610	ARM B / R-DHAP	RITUXIMAB	MALE	60	CULTURE NEGATIVE NEUTROPENIC FEVER / ABSOLUTE NEUTROPHIL COUNT 0.95 109/L	14/03/2005	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	8
5003606301012	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	63	HYPOXIC CARDIAC ARREST FOLLOWING VOMITING ASPIRATION	21/01/2008	LIFE THREATENING	LIFE THREATENING	Yes	No	FATAL	22

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003606301012	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	63	CANDIDA GUILLERMOND SEPTICAEMIA	21/01/2008	DEATH	-	Yes	No	FATAL	22
5003606301012	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	63	CMV ENTEROCOLITIS AND CMV ADRENALITIS	21/01/2008	LIFE THREATENING	-	Yes	-	FATAL	22
5003606301012	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	63	FEBRILE NEUTROPENIA	16/01/2008	-	SEVERE	Yes	-	RECOVERED	12
5003606301604	ARM B / R-DHAP	OBSERVATION	MALE	61	UPPER RESPIRATORY TRACT INFECTION	26/07/2004	SEVERE	MODERATE	No	Yes	RECOVERED	3
5003606301604	ARM B / R-DHAP	OBSERVATION	MALE	61	NEPHROTOXICITY (ASSOCIATED WITH CYTARABINE)	11/10/2004	MILD	NORMAL	Yes	Yes	RECOVERED WITH SEQUELAE	206
5003606301604	ARM B / R-DHAP	OBSERVATION	MALE	61	SOCIAL HOSPITAL ADMISSION	24/09/2004	MODERATE	LIFE THREATENING	No	No	RECOVERED	10
5003606301604	ARM B / R-DHAP	OBSERVATION	MALE	61	ACUTE RENAL FAILURE SECONDARY TO PRE RENAL DEHYDRATATION WITH DIARRHOEA	11/10/2004	MODERATE	LIFE THREATENING	No	No	RECOVERED	3
5003606301604	ARM B / R-DHAP	OBSERVATION	MALE	61	MYELODYSPLASTIC SYNDROME	05/02/2008	-	MODERATE	Yes	-	FATAL	503
5003606301606	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	40	STAPHYLOCOCCAL SEPSIS WITH BACTERAEMIA AND CENTRAL VENOUS CATHETER TUNNEL INFECTION	04/09/2004	SEVERE	LIFE THREATENING	No	No	RECOVERED	8
5003607301603	ARM B / R-DHAP	OBSERVATION	MALE	64	GASTRO-INTESTINAL BLEED	12/09/2004	LIFE THREATENING	SEVERE	No	No	RECOVERED	10
5003607301622	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	65	GRAM NEGATIVE SEPTICAEMIA	25/01/2007	DEATH	DEATH	Yes	Yes	FATAL	1
5003607501401	ARM B / R-DHAP	RITUXIMAB	MALE	54	FOLLOWING FIRST RITUXIMAB MAINTENANCE NEUTROPHILS 0.21 ABSOLUTE VALUE	03/01/2007	-	LIFE THREATENING	Yes	No	RECOVERED	9
5003609301018	ARM B / R-DHAP	RITUXIMAB	MALE	38	CHEST INFECTION	08/06/2008	SEVERE	-	No	Yes	RECOVERED	37
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	ACQUIRED TYPE 4 RENAL TUBULAR ACIDOSIS CAUSING REFRACTORY HYPERKALEMIA GRADE 2 FROM 05/01/2007-06/01/2007 GRADE 3 FROM 06/01/2007-09/01/2007, DECREASE GRADE 2 09/012007-11/01/2007 THEN FULLY RESOLVED	05/01/2007	SEVERE	-	Yes	No	RECOVERED WITH SEQUELAE	6
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	NEUTROPENIC SEPSIS	21/06/2007	SEVERE	SEVERE	Yes	No	RECOVERED	6
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	CHEST INFECTION	21/08/2007	MODERATE	-	Yes	No	RECOVERED	11
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	LOWER RESPIRATORY TRACT INFECTION	01/02/2008	SEVERE	-	Yes	No	RECOVERED WITH SEQUELAE	7
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	RESPIRATORY TRACT INFECTION WITH NEUTROPENIA	14/04/2008	LIFE THREATENING	SEVERE	Yes	No	RECOVERED	14

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003612501019	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	51	HIGH CREATININE LEVEL (GRADE 3)	06/09/2007	SEVERE	-	No	Yes	RECOVERED	18
5003612501019	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	51	ADMITTED WITH HYPOKALEMIA (GRADE 3) WITH POTASSIUM = 2.5 MMOL/L SECONDARY TO DIARRHEA (GRADE 2)	10/10/2007	SEVERE	-	Yes	No	RECOVERED	4
5003614501022	ARM B / R-DHAP	RITUXIMAB	MALE	37	FEBRILE NEUTROPENIA	17/12/2007	LIFE THREATENING	LIFE THREATENING	No	No	RECOVERED	6
5003614501032	ARM B / R-DHAP	RITUXIMAB	MALE	53	NEUTROPENIC SEPSIS + RENAL IMPAIRMENT	16/04/2008	MILD	LIFE THREATENING	Yes	No	RECOVERED	8
5003615501004	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	64	THROMBOCYTOPENIA	23/10/2006	-	LIFE THREATENING	Yes	No	RECOVERED	56
5003615501004	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	64	NEUTROPENIA	20/11/2006	-	LIFE THREATENING	Yes	No	RECOVERED	7
5003615501007	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	52	STROKE (ISCHAEMIC)	19/01/2007	LIFE THREATENING	-	No	Yes	RECOVERED WITH SEQUELAE	34
5003616501411	ARM B / R-DHAP	NOT APPLICABLE	MALE	63	VASOVAGAL EVENT - PATIENT COMPLAINED OF FEELING FAINT, THEN FELL TO THE FLOOR, VOMITTED THREE TIMES	07/07/2008	MODERATE	-	No	No	RECOVERED	1
5003617201021	ARM B / R-DHAP	OBSERVATION	FEMALE	50	ACTIVE INFECTION WITH HEPATITIS C (GENOME 1B) AFTER STEM CELL APHERESIS	23/12/2005	MILD	SEVERE	No	No	ONGOING	-
5003617301616	ARM B / R-DHAP	RITUXIMAB	MALE	44	NAUSEA ; VOMITING ; DEHYDRATION	06/03/2006	MODERATE	MILD	Yes	No	RECOVERED	2
5003617301619	ARM B / R-DHAP	OBSERVATION	FEMALE	19	LOWER RESPIRATORY TRACT INFECTION	16/02/2006	SEVERE	NORMAL	Yes	No	RECOVERED	5
5003617501026	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	59	NEUTROPENIC SEPSIS	19/12/2007	SEVERE	LIFE THREATENING	Yes	No	RECOVERED	8
5003618201030	ARM B / R-DHAP	RITUXIMAB	FEMALE	45	HERPES ZOSTER (OPHTALMIC NERVE RIGHT	19/05/2007	SEVERE	MILD	No	Yes	RECOVERED	60
5003618201030	ARM B / R-DHAP	RITUXIMAB	FEMALE	45	INTERMITTEND HYPESTHESIA OF LEFT LEG, HAND AND LIPS, TONGUE. ON 02/09/2007 REDUCTION OF VISUAL FIELD LEFT WITH SPONTANEOUS REMISSION	03/09/2007	MILD	-	-	No	RECOVERED	3
5003618501025	ARM B / R-DHAP	OBSERVATION	MALE	59	INFECTION WITH FEBRILE NEUTROPENIA	-	SEVERE	SEVERE	No	No	RECOVERED	-
5003619301006	ARM B / R-DHAP	NOT APPLICABLE	MALE	53	WOKE AT 4AM-5AM ON 12/06/2006 WITH DEEP ACHE IN THIGHS + PELVIS. ADMITTED ON 12/06/2006 WITH GCSF INDUCED BONE PAIN. NEUTROPENIC INITIALLY, BUT COUNT RECOVERED QUICKLY.	12/06/2006	SEVERE	SEVERE	Yes	No	RECOVERED	1

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003619301006	ARM B / R-DHAP	NOT APPLICABLE	MALE	53	RESECTION OF SEGMENT 4B/5 LIVER, AND OPEN CHOLECYSTECTOMY AND OPERATIVE CHOLANGIOGRAM	05/09/2006	MODERATE	MODERATE	No	Yes	RECOVERED	6
5003619501010	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	45	CHEST INFECTION (RESPIRATORY RATE : 26, APYREXIAL, CRP 320, HYPOXIC, CHEST X-RAY : NEW CONSOLIDATION COLLAPSE LEFT LOWER LOBE)	22/02/2007	SEVERE	MODERATE	No	No	RECOVERED	5
5003619501010	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	45	SEPSIS	04/04/2007	DEATH	-	No	No	FATAL	2
5003620501602	ARM B / R-DHAP	RITUXIMAB	FEMALE	60	NEUTROPENIA	22/03/2007	-	LIFE THREATENING	Yes	No	RECOVERED	11
5003620501602	ARM B / R-DHAP	RITUXIMAB	FEMALE	60	PATIENT FELL AT HOME, FRACTURED FACE & RIGHT KNEE, 3 DAYS LATER BECAME INFECTED : ADMITTED TO HOSP. NEUTS 0.25	28/05/2007	MILD	LIFE THREATENING	Yes	No	RECOVERED	2
5003620501602	ARM B / R-DHAP	RITUXIMAB	FEMALE	60	INFECTION WITH NEUTROPENIA POST ENGRAFTMENT	28/06/2007	LIFE THREATENING	-	No	No	RECOVERED	21
5003622201607	ARM B / R-DHAP	OBSERVATION	MALE	55	ACUTE RENAL FAILURE WITH EXSICCOSIS AFTER DIARRHEA AND VOMITING	29/12/2004	SEVERE	-	Yes	Yes	RECOVERED	1475
5003622201625	ARM B / R-DHAP	RITUXIMAB	MALE	59	ACUTE RENAL FAILURE	02/01/2007	MODERATE	-	Yes	Yes	RECOVERED	7
5003623501405	ARM B / R-DHAP	NOT APPLICABLE	MALE	58	PATIENT DIED OF PNEUMONIA RELATED TO THE LYMPHOMA WHICH HAS BEEN CONFIRMED IN THE CORONER'S AUTOPSY REPORT	26/07/2007	UNKNOWN	LIFE THREATENING	No	Yes	FATAL	0
5003623501408	ARM B / R-DHAP	OBSERVATION	MALE	53	NEUTROPENIC SEPSIS	29/11/2007	SEVERE	-	No	No	RECOVERED	4
5003623501408	ARM B / R-DHAP	OBSERVATION	MALE	53	KLEBSIELLA SEPSIS	25/01/2008	SEVERE	SEVERE	No	No	RECOVERED	11
5003631201011	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	61	SEPSIS (GRAM POS) IN NEUTROPENIA	23/12/2004	LIFE THREATENING	LIFE THREATENING	Yes	Yes	FATAL	6
5003631201012	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	58	ACUTE RENAL FAILURE	26/12/2004	MODERATE	-	Yes	Yes	RECOVERED WITH SEQUELAE	11
5003631201012	ARM B / R-DHAP	NOT APPLICABLE	FEMALE	58	FEVER BEFORE NEUTROPENIA, SUSPECTED SINUSITIS MAXILLARY, LATE PROVEN ASPERGILLOMA OF SINUS MAXILLARY	24/05/2005	SEVERE	-	Yes	Yes	RECOVERED	31
N = 257												

6.7.5. Deaths

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

Randomization Number	First Randomization Date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003603201627	28/03/2007	MALE	49	03/04/2007	OTHER REASON	SEE ATTACHED LETTER / PROGRESSION FORM WILL FOLLOW	PROGRESSIVE DISEASE
5003609201013	14/03/2005	MALE	44	20/09/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003614301614	16/06/2005	MALE	59	25/03/2007	OTHER CANCER		NOT EVALUATED
5003603201027	26/01/2006	MALE	54	26/01/2006	OTHER REASON	SEPTIC SHOCK	NOT EVALUATED
N = 4							

6.7.6. Laboratory tests

Table 6.7-9 Hemoglobin (induction safety population)

R-ICE arm

	Hemoglobin (g/dl)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	238	12.95	1.796	13.10	7.8	17.4	238	0.00	0.000	0.00	0.0	0.0
C1 between D7 and D10	212	11.75	1.746	11.90	7.6	16.0	211	-1.16	1.400	-1.30	-4.9	5.0
C1 around D14	210	11.08	1.611	11.05	6.9	15.8	209	-1.85	1.282	-1.90	-5.4	2.1
C2 pre-cycle	224	11.05	1.461	10.90	7.2	15.6	223	-1.96	1.475	-2.00	-6.0	2.0
C2 between D7 and D10	191	10.50	1.425	10.60	6.5	14.1	190	-2.53	1.693	-2.50	-6.8	2.5
C2 around D14	190	10.10	1.550	10.00	6.7	15.6	189	-2.96	1.889	-3.10	-7.7	3.9
C3 pre-cycle	202	10.29	1.393	10.30	7.1	14.7	201	-2.72	1.867	-2.90	-8.1	3.4
C3 between D7 and D10	173	9.84	1.413	9.90	6.5	14.3	173	-3.21	2.008	-3.20	-9.0	2.1
C3 around D14	187	9.56	1.532	9.40	5.4	15.0	186	-3.54	2.140	-3.60	-8.9	3.3
FU n°1	165	11.12	1.512	11.30	7.1	16.5	164	-2.04	1.954	-2.30	-7.0	5.1
FU n°2	155	12.32	1.554	12.40	8.5	16.9	155	-0.88	2.087	-1.00	-7.5	4.6
FU n°3	127	12.75	1.667	13.10	7.6	16.0	127	-0.49	2.077	-0.30	-7.8	5.6
FU n°4	114	12.81	1.639	12.95	6.0	15.6	114	-0.49	1.865	-0.40	-7.2	5.2
FU n°5	102	12.87	1.708	12.95	7.6	17.1	102	-0.38	1.889	-0.35	-6.4	4.7
FU n°6	86	13.15	1.660	13.30	8.6	15.9	86	-0.13	1.918	-0.20	-6.4	5.7
FU n°7	94	13.00	1.932	13.45	1.3	16.2	94	-0.37	2.450	0.00	-11.6	5.7
FU n°8	108	13.28	1.579	13.35	7.9	16.4	108	0.03	1.983	0.00	-6.4	6.6
FU n°9	88	13.33	1.613	13.50	7.3	16.1	88	-0.04	2.017	0.25	-7.9	5.4
FU n°10	73	13.52	1.599	13.80	7.1	16.8	73	0.07	1.824	0.20	-5.7	5.7
FU n°11	62	13.36	1.570	13.40	9.2	16.1	62	0.18	1.828	0.30	-5.2	5.9
FU n°12	43	13.75	1.549	14.10	7.3	16.9	43	0.61	1.686	0.70	-4.6	4.5
FU n°13	23	14.02	1.261	14.20	12.2	16.0	23	0.70	1.440	0.80	-1.9	3.7
FU n°14	18	13.54	1.549	13.20	10.6	16.4	18	0.49	1.757	0.70	-2.4	3.1
FU n°15	6	12.78	2.349	13.30	8.7	14.7	6	-0.35	2.993	0.80	-6.0	2.0

R-DHAP arm

	Hemoglobin (g/dl)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	230	12.76	1.890	12.95	7.9	17.4	230	0.00	0.000	0.00	0.0	0.0
C1 between D7 and D10	211	12.43	1.893	12.50	7.7	17.9	211	-0.28	1.367	-0.20	-5.8	3.7
C1 around D14	201	11.10	1.785	11.20	6.5	15.4	201	-1.64	1.491	-1.70	-6.5	2.6
C2 pre-cycle	204	10.80	1.539	10.90	7.0	14.5	204	-1.99	1.527	-1.90	-7.1	2.2
C2 between D7 and D10	193	11.10	1.586	11.10	6.8	16.2	193	-1.74	1.946	-1.80	-6.4	5.7
C2 around D14	187	9.96	1.443	9.90	6.4	14.4	187	-2.77	1.979	-2.90	-7.7	3.3
C3 pre-cycle	192	10.09	1.439	10.10	6.5	14.8	192	-2.80	1.843	-2.90	-7.8	3.0
C3 between D7 and D10	174	10.13	1.441	10.05	6.4	15.9	174	-2.79	2.256	-2.90	-8.3	4.4
C3 around D14	173	9.56	1.256	9.60	6.1	13.3	173	-3.32	2.123	-3.50	-8.4	2.6
FU n°1	148	10.61	1.352	10.75	5.4	13.7	148	-2.31	2.016	-2.40	-7.4	3.7
FU n°2	151	11.14	1.742	11.20	6.2	16.2	151	-1.81	2.283	-1.90	-6.9	3.7
FU n°3	116	11.53	1.806	11.70	3.5	15.2	116	-1.61	2.290	-1.70	-8.4	3.7
FU n°4	108	11.96	1.843	12.20	6.3	16.5	108	-1.19	2.398	-1.05	-8.7	8.5
FU n°5	92	12.17	1.862	12.40	7.6	17.3	92	-0.82	2.333	-1.00	-6.9	4.5
FU n°6	76	12.56	1.783	12.85	7.5	15.7	76	-0.57	2.106	-0.35	-6.0	4.3
FU n°7	93	12.52	1.675	12.80	7.6	15.7	93	-0.58	2.062	-0.70	-7.2	4.5
FU n°8	98	12.79	1.626	13.05	8.9	16.0	98	-0.31	1.886	-0.45	-4.8	3.9
FU n°9	94	13.02	1.662	13.15	8.4	16.2	94	-0.02	2.037	-0.10	-5.7	4.6
FU n°10	76	13.28	1.359	13.30	10.4	16.4	76	0.26	1.625	0.20	-3.8	4.4
FU n°11	65	13.39	1.518	13.50	9.8	16.0	65	0.29	1.836	0.30	-4.8	4.4
FU n°12	54	13.34	2.024	13.50	4.3	16.9	54	0.33	2.536	0.50	-11.5	5.1
FU n°13	33	13.19	1.900	13.30	8.1	15.8	33	0.41	2.213	0.90	-6.0	4.9
FU n°14	24	13.23	1.775	13.30	9.7	17.1	24	0.73	1.745	0.75	-3.7	3.8
FU n°15	13	13.52	1.531	13.40	10.8	16.5	13	1.22	2.162	0.30	-2.0	5.2

Table 6.7-10 Leukocytes (induction safety population)

R-ICE arm

	Leukocytes (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	238	7.218	3.5755	6.330	1.60	32.40	238	0.000	0.0000	0.000	0.00	0.00
C1 between D7 and D10	211	5.937	7.4357	4.000	0.10	71.60	210	-1.323	7.9063	-2.005	-26.70	64.03
C1 around D14	210	6.114	7.4096	3.250	0.10	60.90	209	-1.079	7.1615	-2.400	-15.10	53.33
C2 pre-cycle	223	6.152	4.5052	4.900	1.00	31.60	222	-1.163	5.0209	-1.500	-27.70	23.96
C2 between D7 and D10	190	5.177	5.6565	3.450	0.10	46.20	189	-2.099	6.2282	-2.910	-15.30	38.10
C2 around D14	191	11.284	13.5026	6.400	0.10	88.50	190	3.749	13.1206	-0.200	-22.40	83.10
C3 pre-cycle	201	6.528	4.8019	5.100	1.40	44.60	200	-0.806	5.2676	-1.030	-30.00	34.10
C3 between D7 and D10	172	5.905	6.2766	3.600	0.10	29.80	172	-1.498	7.0660	-2.700	-31.20	24.70
C3 around D14	186	14.398	14.0356	8.250	0.20	70.90	185	6.859	13.8754	2.200	-14.40	63.39
FU n°1	163	5.337	3.0629	4.580	0.10	17.40	162	-1.562	4.0766	-1.350	-25.50	10.30
FU n°2	154	4.919	2.4989	4.500	0.58	14.75	154	-2.144	3.9347	-1.800	-31.40	7.30
FU n°3	126	4.856	2.5853	4.300	1.02	16.80	126	-1.803	3.0996	-1.905	-13.80	9.20
FU n°4	112	5.251	2.5716	4.800	0.45	15.80	112	-1.414	2.6311	-1.050	-13.70	8.70
FU n°5	101	5.827	6.2241	4.600	0.39	62.80	101	-0.797	6.3740	-1.000	-13.60	55.70
FU n°6	85	5.453	2.3229	5.000	2.10	15.20	85	-1.348	2.4518	-1.150	-12.60	4.90
FU n°7	93	5.941	2.4975	5.400	0.30	14.99	93	-0.884	2.5607	-0.700	-12.50	5.00
FU n°8	107	5.871	2.5841	5.200	1.69	19.30	107	-0.813	3.3952	-0.600	-13.20	10.41
FU n°9	87	5.915	2.3556	5.500	0.10	14.52	87	-1.005	2.7346	-0.710	-10.20	7.30
FU n°10	73	6.058	2.3434	5.900	1.90	13.13	73	-0.810	3.2454	-0.900	-13.20	5.70
FU n°11	62	6.638	2.5162	6.300	2.70	16.30	62	-0.578	3.0966	-0.290	-12.40	10.29
FU n°12	44	6.055	2.1689	5.970	1.46	11.10	44	-0.646	2.6569	-0.400	-9.64	3.50
FU n°13	23	6.203	2.0399	6.300	3.00	10.63	23	-0.417	2.0189	-0.770	-5.30	2.80
FU n°14	18	6.753	2.6445	6.600	2.37	11.82	18	-0.519	1.3208	-0.500	-2.40	2.30
FU n°15	6	6.553	2.9367	5.950	2.90	11.90	6	-0.248	2.0854	-0.795	-2.20	3.60

R-DHAP arm

	Leukocytes (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	230	7.057	3.4292	6.450	1.32	29.20	230	0.000	0.0000	0.000	0.00	0.00
C1 between D7 and D10	211	8.807	9.1937	5.600	0.20	52.10	211	1.685	9.7667	-0.600	-24.90	47.10
C1 around D14	202	6.933	9.5532	3.700	0.20	59.40	202	-0.096	9.9471	-2.600	-22.10	50.90
C2 pre-cycle	204	9.040	7.8282	7.150	1.20	87.30	204	2.052	8.0548	0.840	-13.40	81.50
C2 between D7 and D10	194	14.724	13.3780	10.185	0.20	66.90	194	7.855	13.4717	3.800	-12.20	61.90
C2 around D14	186	14.639	15.7351	9.650	0.40	121.90	186	7.729	15.9728	2.835	-17.50	114.20
C3 pre-cycle	192	7.875	7.1079	6.200	0.90	63.90	192	0.875	7.1568	-0.200	-12.50	57.77
C3 between D7 and D10	174	10.227	12.4628	5.050	0.13	85.90	174	3.214	12.6132	-0.390	-22.50	73.50
C3 around D14	173	11.025	12.9328	5.600	0.20	68.20	173	4.165	13.1646	-0.600	-13.00	57.70
FU n°1	147	5.550	2.9458	5.000	0.10	17.40	147	-1.274	3.9703	-0.910	-19.70	10.80
FU n°2	150	4.840	2.2975	4.490	1.20	12.40	150	-1.838	3.2455	-2.000	-12.90	7.80
FU n°3	115	4.908	2.6959	4.200	0.80	18.60	115	-1.895	3.2850	-1.820	-10.20	14.10
FU n°4	106	5.101	2.4626	4.520	1.20	18.80	106	-1.826	3.2429	-1.600	-13.10	7.50
FU n°5	91	5.538	3.8856	5.000	0.10	26.91	91	-1.737	3.9108	-1.340	-14.20	13.60
FU n°6	74	5.226	2.1935	5.100	0.90	12.20	74	-1.686	3.3853	-1.205	-17.00	6.81
FU n°7	91	5.613	2.2329	5.400	0.70	13.40	91	-1.434	3.4185	-0.800	-19.70	4.80
FU n°8	97	6.035	3.1833	5.600	0.81	29.50	97	-0.769	3.8313	-0.510	-11.50	19.00
FU n°9	93	6.220	2.2426	6.040	1.60	14.53	93	-0.609	3.4019	-0.300	-14.10	8.79
FU n°10	76	6.266	2.3836	5.790	1.80	14.40	76	-0.274	3.1807	-0.495	-7.53	8.95
FU n°11	65	6.298	1.9840	6.100	3.18	12.70	65	-0.499	3.0342	0.000	-8.64	5.60
FU n°12	54	6.274	2.1702	6.100	1.60	14.60	54	-0.896	3.7023	-0.200	-11.50	6.54
FU n°13	33	6.681	3.7435	5.760	3.30	23.00	33	-0.416	4.2138	0.300	-9.00	14.80
FU n°14	24	6.052	2.8322	5.650	3.20	15.22	24	-0.807	4.2556	-0.200	-16.30	4.72
FU n°15	14	5.470	1.6779	4.905	2.68	8.90	14	0.411	2.1336	0.700	-4.10	4.30

Table 6.7-11 Neutrophils (induction safety population)

R-ICE arm

	Neutrophils (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	229	5.234	2.9695	4.453	0.92	18.79	229	0.000	0.0000	0.000	0.00	0.00
C1 between D7 and D10	165	5.074	5.9406	3.080	0.00	46.46	161	-0.277	6.6018	-1.064	-14.52	40.76
C1 around D14	169	4.180	5.2336	2.135	0.00	32.25	166	-1.113	5.1691	-1.968	-13.74	25.49
C2 pre-cycle	194	4.146	3.5476	3.131	0.12	24.29	186	-1.080	4.3239	-1.180	-15.50	20.86
C2 between D7 and D10	151	4.262	5.4019	2.405	0.00	45.28	147	-1.143	5.6975	-1.705	-13.91	38.96
C2 around D14	160	8.254	10.6243	4.064	0.00	69.03	154	2.913	11.0414	-0.503	-14.01	65.30
C3 pre-cycle	179	4.311	3.5059	3.245	0.14	32.56	174	-0.979	4.1589	-1.028	-17.33	24.58
C3 between D7 and D10	149	5.292	6.2933	2.520	0.00	27.12	145	-0.129	7.0239	-1.536	-18.07	23.75
C3 around D14	150	10.562	11.0850	5.787	0.02	50.54	146	5.304	11.5271	1.524	-14.73	43.69
FU n°1	147	3.071	2.5234	2.356	0.00	16.53	142	-1.760	3.3576	-1.591	-14.36	11.06
FU n°2	140	2.841	2.1165	2.389	0.02	12.98	135	-2.079	2.7442	-1.938	-12.59	6.80
FU n°3	118	3.028	2.2038	2.448	0.01	12.94	115	-1.784	2.6909	-1.509	-13.45	7.97
FU n°4	107	3.185	1.7908	2.925	0.05	10.98	104	-1.513	2.2669	-1.174	-13.08	3.86
FU n°5	92	3.090	1.7294	2.738	0.40	9.50	90	-1.533	2.4386	-1.078	-12.70	2.99
FU n°6	78	3.422	1.8075	3.023	0.71	13.07	76	-1.388	2.2102	-1.200	-12.32	3.00
FU n°7	86	3.618	1.9093	3.393	0.02	11.24	83	-1.166	2.6916	-0.864	-17.66	3.19
FU n°8	102	3.515	2.0305	3.181	0.69	16.02	97	-1.142	3.0540	-0.932	-12.79	9.26
FU n°9	79	3.514	1.7707	3.271	0.20	11.47	75	-1.348	2.4334	-1.101	-8.21	4.85
FU n°10	66	3.445	1.6069	3.234	0.51	9.32	62	-1.241	2.9133	-0.816	-13.09	4.87
FU n°11	57	3.883	2.0182	3.648	0.22	13.37	54	-1.081	3.0790	-0.825	-12.60	8.74
FU n°12	42	3.456	1.5600	3.259	0.18	7.60	39	-1.234	2.5945	-0.696	-9.06	3.07
FU n°13	22	3.223	1.5694	2.987	0.69	7.06	19	-1.436	2.2063	-1.562	-6.51	2.02
FU n°14	16	3.733	2.0364	3.512	1.10	8.51	16	-1.186	1.4485	-1.261	-3.77	1.61
FU n°15	6	3.509	2.3369	3.036	1.10	7.97	5	-1.649	0.6798	-1.652	-2.54	-0.70

R-DHAP arm

	Neutrophils (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	224	5.012	2.8044	4.325	0.13	18.20	224	0.000	0.0000	0.000	0.00	0.00
C1 between D7 and D10	177	8.440	9.4980	4.416	0.00	51.58	176	3.459	9.8883	0.435	-17.87	47.73
C1 around D14	171	4.800	7.9305	2.240	0.00	54.05	169	-0.209	8.3389	-1.820	-15.10	49.22
C2 pre-cycle	173	6.079	6.3816	4.736	0.00	66.35	171	1.222	6.7682	0.173	-12.71	61.65
C2 between D7 and D10	152	13.922	13.2662	9.975	0.00	66.23	149	8.782	13.1345	4.960	-10.74	62.38
C2 around D14	150	9.452	12.8211	5.600	0.00	114.59	148	4.667	12.9444	1.027	-11.13	109.43
C3 pre-cycle	165	5.139	6.0745	3.752	0.00	58.79	163	0.336	6.4336	-0.282	-12.04	54.07
C3 between D7 and D10	143	9.581	12.1159	4.590	0.00	67.86	140	4.689	12.1001	0.875	-16.00	63.67
C3 around D14	147	8.103	10.2768	3.526	0.00	54.13	144	3.142	10.5164	-0.829	-12.93	48.81
FU n°1	134	3.003	2.2864	2.652	0.00	15.49	131	-1.763	3.1481	-1.667	-13.19	10.01
FU n°2	138	2.863	1.8720	2.498	0.30	9.92	135	-1.848	2.8117	-1.810	-10.00	6.66
FU n°3	104	2.914	2.4755	2.343	0.19	17.67	101	-1.819	3.0972	-1.970	-8.34	15.62
FU n°4	99	3.040	1.7799	2.720	0.18	10.11	98	-1.650	2.8081	-1.344	-10.94	6.50
FU n°5	80	3.472	2.7903	3.038	0.22	20.00	79	-1.492	3.6639	-1.362	-11.99	15.17
FU n°6	70	3.066	1.4012	3.168	0.55	8.78	68	-1.677	2.3925	-1.115	-9.73	4.04
FU n°7	88	3.293	1.7938	3.026	0.22	11.25	86	-1.575	2.6438	-1.420	-10.39	7.94
FU n°8	92	3.603	2.5594	3.276	0.04	24.49	91	-1.225	3.5514	-1.055	-10.50	19.66
FU n°9	83	3.829	1.8967	3.636	0.42	11.33	81	-1.010	3.1192	-0.482	-12.96	7.80
FU n°10	69	3.857	2.0205	3.350	0.68	11.38	67	-0.916	2.7784	-0.508	-8.14	6.34
FU n°11	59	3.678	1.7168	3.295	1.36	11.18	57	-1.243	2.9815	-0.739	-9.54	6.14
FU n°12	50	3.503	1.6873	3.143	0.40	10.95	49	-1.676	3.1346	-0.981	-9.06	5.07
FU n°13	31	4.178	3.2917	3.456	1.58	19.78	31	-1.070	4.0165	-1.033	-7.83	14.20
FU n°14	23	3.653	2.1527	3.141	1.57	11.73	23	-1.312	3.3271	-0.267	-12.01	2.73
FU n°15	10	3.325	1.2344	2.840	2.02	5.89	10	-0.310	1.9500	0.030	-4.40	1.96

Table 6.7-12 Platelets (induction safety population)

R-ICE arm

	Platelets (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	238	269.3	111.58	252.0	23	677	238	0.0	0.00	0.0	0	0
C1 between D7 and D10	212	173.1	102.02	166.0	7	600	211	-96.6	96.65	-88.0	-485	144
C1 around D14	209	81.1	71.04	63.0	2	401	209	-184.6	112.72	-172.0	-540	102
C2 pre-cycle	224	292.7	162.01	265.5	19	926	223	23.2	150.87	14.0	-456	533
C2 between D7 and D10	191	264.6	164.35	234.0	8	1038	190	-3.0	154.84	-11.5	-466	658
C2 around D14	190	71.2	60.37	54.0	3	373	189	-196.7	106.01	-182.0	-605	11
C3 pre-cycle	202	256.7	141.22	227.5	28	740	201	-15.9	152.94	-13.0	-473	717
C3 between D7 and D10	172	211.1	156.73	186.0	9	1088	172	-67.1	164.02	-73.0	-635	725
C3 around D14	187	61.9	59.25	43.0	5	455	186	-212.8	123.27	-201.5	-647	193
FU n°1	165	152.6	87.51	147.0	11	577	164	-114.4	111.64	-108.0	-457	214
FU n°2	155	175.2	95.36	161.0	22	747	155	-90.5	111.16	-86.0	-367	429
FU n°3	127	169.4	75.16	170.0	15	449	127	-87.2	105.63	-74.0	-457	181
FU n°4	113	175.1	80.56	175.0	7	387	113	-83.6	102.78	-62.0	-665	185
FU n°5	101	175.3	77.57	175.0	15	484	101	-84.4	103.83	-58.0	-572	106
FU n°6	86	183.8	72.09	183.0	34	358	86	-78.8	98.09	-56.0	-643	117
FU n°7	93	191.5	77.40	192.0	9	427	93	-67.3	86.41	-65.0	-332	126
FU n°8	108	195.8	80.25	191.0	2	433	108	-60.4	101.85	-43.5	-440	171
FU n°9	87	189.9	79.40	185.0	9	398	87	-76.0	87.68	-62.0	-399	100
FU n°10	74	200.8	82.71	191.0	43	564	74	-61.7	90.20	-39.5	-324	155
FU n°11	61	193.6	73.18	183.0	45	422	61	-82.5	97.27	-61.0	-385	72
FU n°12	43	206.0	79.23	198.0	5	418	43	-57.1	93.71	-34.0	-308	116
FU n°13	23	203.8	105.09	193.0	89	557	23	-55.0	77.86	-57.0	-187	97
FU n°14	18	236.3	120.97	207.0	56	476	18	-72.3	98.13	-45.0	-277	139
FU n°15	6	179.5	77.19	171.0	106	314	6	-103.7	59.49	-93.0	-197	-45

R-DHAP arm

	Platelets (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	230	275.8	156.50	250.0	25	1878	230	0.0	0.00	0.0	0	0
C1 between D7 and D10	210	127.0	99.61	107.5	4	560	210	-150.8	170.03	-127.5	-1800	258
C1 around D14	202	92.2	93.73	54.5	4	471	202	-184.8	171.26	-173.5	-1840	207
C2 pre-cycle	204	351.3	184.66	313.5	72	1288	204	76.0	191.95	62.0	-1047	977
C2 between D7 and D10	193	169.7	134.52	135.0	3	642	193	-102.3	192.69	-102.0	-1777	272
C2 around D14	187	68.0	59.65	50.0	8	311	187	-204.7	155.71	-179.0	-1655	150
C3 pre-cycle	192	271.2	137.60	242.5	71	1043	192	-1.2	145.53	11.0	-835	522
C3 between D7 and D10	174	118.9	108.58	84.5	1	558	174	-147.3	180.17	-140.0	-1847	134
C3 around D14	172	53.7	63.04	35.5	1	454	172	-206.2	117.45	-199.5	-630	152
FU n°1	147	127.5	87.19	111.0	2	417	147	-132.7	121.46	-112.0	-553	75
FU n°2	151	149.1	87.56	138.0	14	581	151	-121.7	155.34	-93.0	-1297	165
FU n°3	116	145.4	76.04	145.0	14	493	116	-114.8	161.21	-80.0	-1385	73
FU n°4	107	155.3	85.26	147.0	13	450	107	-90.4	102.54	-75.0	-489	120
FU n°5	92	166.9	100.83	157.0	4	616	92	-100.6	176.14	-71.5	-1404	443
FU n°6	76	180.5	83.15	171.0	14	475	76	-62.1	92.81	-46.5	-499	126
FU n°7	92	174.3	87.48	167.0	10	602	92	-93.5	177.04	-57.0	-1423	224
FU n°8	98	176.4	82.17	180.0	17	460	98	-90.9	179.17	-57.0	-1493	218
FU n°9	94	180.8	74.21	174.0	14	428	94	-87.2	180.61	-46.0	-1450	200
FU n°10	76	189.1	63.85	187.0	37	343	76	-64.1	109.09	-37.5	-526	185
FU n°11	65	188.3	68.48	180.0	76	387	65	-68.8	114.05	-36.0	-500	183
FU n°12	54	185.2	70.61	188.5	14	365	54	-77.8	121.89	-34.5	-525	115
FU n°13	33	183.6	61.34	199.0	65	294	33	-59.2	102.11	-40.0	-336	116
FU n°14	24	182.4	67.37	166.0	82	384	24	-56.3	114.65	-26.0	-367	138
FU n°15	14	177.0	48.10	180.0	85	247	14	-23.4	109.14	5.5	-276	144

Table 6.7-13 LDH (induction safety population)

R-ICE arm

	LDH (UI/l)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	234	509.3	392.73	399.0	103	2467	234	0.0	0.00	0.0	0	0
FU n°1	162	3.0	3.12	2.0	1	9	160	-470.3	344.25	-392.5	-2369	-115
FU n°2	151	2.3	2.52	1.0	1	9	150	-458.2	346.64	-360.5	-2368	-107
FU n°3	125	2.6	2.84	1.0	1	9	124	-449.4	349.81	-351.0	-2368	-101
FU n°4	115	2.7	2.87	2.0	1	9	114	-425.7	303.90	-332.3	-1866	-108
FU n°5	98	2.4	2.73	1.0	1	9	97	-411.7	289.00	-332.0	-1866	-115
FU n°6	81	2.4	2.78	1.0	1	9	80	-418.2	333.03	-321.0	-1866	-116
FU n°7	91	2.1	2.47	1.0	1	9	89	-408.2	304.02	-332.6	-1866	-101
FU n°8	109	2.0	2.29	1.0	1	9	107	-427.9	304.59	-335.0	-1866	-115
FU n°9	85	2.3	2.64	1.0	1	9	84	-405.8	318.94	-313.5	-1866	-115
FU n°10	73	1.9	2.35	1.0	1	9	73	-414.9	320.46	-332.0	-1866	-115
FU n°11	63	1.9	2.15	1.0	1	9	63	-438.2	340.46	-335.0	-1866	-115
FU n°12	47	2.1	2.68	1.0	1	9	47	-410.4	320.92	-332.0	-1672	-115
FU n°13	22	1.9	2.33	1.0	1	9	22	-351.0	285.91	-298.0	-1497	-115
FU n°14	17	1.6	1.93	1.0	1	9	17	-406.9	312.96	-398.0	-1497	-115
FU n°15	4	3.0	4.00	1.0	1	9	4	-432.5	81.55	-431.5	-532	-335

R-DHAP arm

	LDH (UI/l)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	228	455.4	346.59	354.0	57	2221	228	0.0	0.00	0.0	0	0
FU n°1	144	3.2	3.19	2.0	1	9	142	-414.6	279.64	-321.0	-1565	-118
FU n°2	147	2.6	2.73	2.0	1	9	146	-397.1	261.12	-311.5	-1565	-118
FU n°3	114	2.9	3.04	2.0	1	9	113	-375.5	249.68	-307.0	-1564	-118
FU n°4	104	2.6	2.89	1.0	1	9	103	-372.0	259.10	-305.0	-1564	-118
FU n°5	90	2.4	2.65	1.0	1	9	89	-392.6	278.65	-309.0	-1565	-126
FU n°6	71	2.8	3.13	1.0	1	9	70	-344.3	242.69	-275.0	-1557	-126
FU n°7	84	2.1	2.30	1.0	1	9	83	-357.1	234.88	-297.0	-1564	-126
FU n°8	96	2.2	2.61	1.0	1	9	95	-371.4	236.27	-311.0	-1548	-126
FU n°9	93	1.9	2.23	1.0	1	9	92	-367.9	235.27	-312.0	-1548	-126
FU n°10	75	1.6	1.81	1.0	1	9	75	-345.5	192.95	-297.0	-1000	-126
FU n°11	63	1.5	1.72	1.0	1	9	63	-333.2	185.31	-285.0	-1000	-126
FU n°12	52	1.9	2.37	1.0	1	9	52	-354.7	228.12	-284.5	-1246	-126
FU n°13	34	2.8	3.21	1.0	1	9	34	-382.7	245.21	-313.5	-1246	-161
FU n°14	25	1.9	2.19	1.0	1	9	25	-366.4	268.66	-276.0	-1246	-153
FU n°15	14	2.4	2.84	1.0	1	9	14	-305.7	220.66	-235.5	-1000	-161

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

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Monoclonal component				
Yes	4	2	11	6
No	186	98	182	94
Total	190	100	193	100

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

	Actual arm of induction			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
HIV Serology				
NEGATIVE	215	91	208	90
NOT DONE	22	9	22	10
HCV Serology				
NEGATIVE	204	86	202	88
POSITIVE	7	3	3	1
NOT DONE	26	11	25	11
HBs Ag Serology				
NEGATIVE	207	87	208	90
POSITIVE	6	3	3	1
NOT DONE	24	10	19	8
Total	237	100	230	100
HBs vaccination				
No	64	30	68	32
Yes	16	7	19	9
Not Done	136	63	125	59
Total	216	100	212	100

6.7.7. Vital signs

Table 6.7-16 LVEF value at relapse diagnosis (induction safety population)

		Actual arm of induction	
		ARM A / R-ICE	ARM B / R-DHAP
LVEF value (%)	N	164	148
	Mean	62.0	62.6
	Std	8.23	8.77
	Median	62.0	63.0
	Min	32	31
	Max	89	87

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

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
ECG				
Normal	154	65	157	69
Abnormal	17	7	21	9
Not done	65	28	48	21
Total	236	100	226	100
Echocardiography/isotopic method				
Normal	167	71	154	68
Abnormal	27	11	29	13
Not done	41	17	44	19
Total	235	100	227	100

Table 6.7-18 Other exams at relapse diagnosis (induction safety population)

	Arm of treatment			
	ARM A / R-ICE		ARM B / R-DHAP	
	N	%	N	%
Other exams baseline				
No	204	88	190	85
Yes	29	12	33	15
Total	233	100	223	100

Emetteur : M. Fournier
Date : 24/11/2010
Version : 2

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

SPONSOR:

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LIST OF ABBREVIATIONS

AE	Adverse Event
CRF	Case Report Form
MITT	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 $\alpha=8.10^{-5}$ (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

Arm of treatment=ARM A / R-ICE

Randomization Number	Country Code	Initials of family name	Initials of first name	Date of Birth	First Randomization Date	Date of 2nd randomization
5003613301007	Australie - Nouvelle-Zélande	JEN	RO	10/01/1944	14/11/2006	31/01/2007
5003620201405	Allemagne-Autriche	STA	BR	22/06/1950	03/04/2006	18/09/2006
5003631201412	Allemagne-Autriche	WIL	MA	27/02/1952	07/12/2007	-
N = 3						

Arm of treatment=ARM B / R-DHAP

Randomization Number	Country Code	Initials of family name	Initials of first name	Date of Birth	First Randomization Date	Date of 2nd randomization
5003613301404	Australie - Nouvelle-Zélande	KEL	ER	30/01/1946	14/11/2006	08/02/2007
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

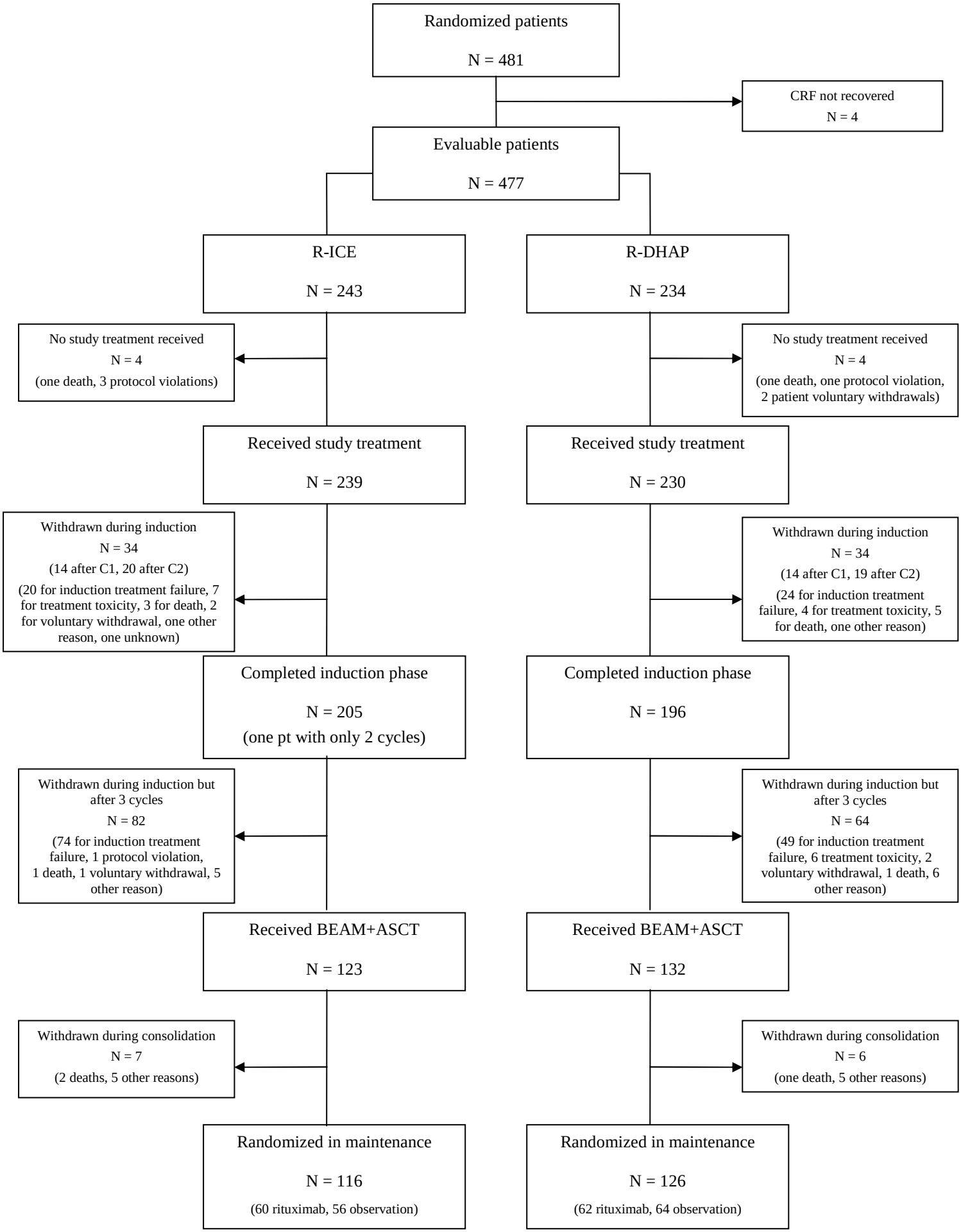
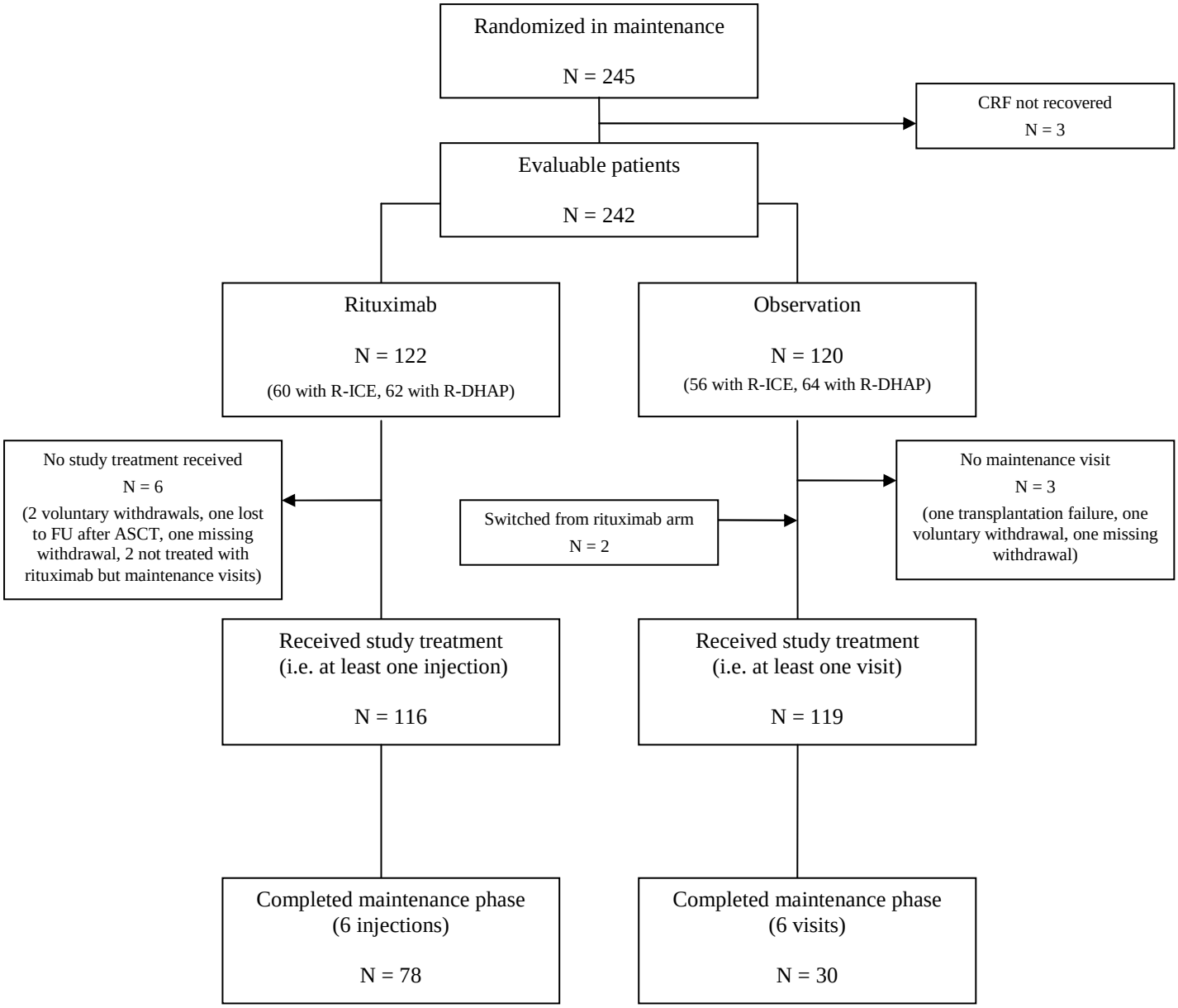


Figure 3.1-2 Disposition of patients according to arm of 2nd randomization



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)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
AT LEAST ONE CRITERIA EXCEPTION						
No	117	96	117	98	234	97
Yes	5	4	3	3	8	3
TOTAL	122	100	120	100	242	100

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)

	FULFILLED				Total
	No		Yes		
	N	%	N	%	N
CRITERIA					
Inclusion Criteria 1	1	0	241	100	242
Inclusion Criteria 2	0	0	242	100	242
Inclusion Criteria 3	0	0	242	100	242
Inclusion Criteria 4	0	0	242	100	242
Inclusion Criteria 5	0	0	242	100	242
Inclusion Criteria 6	0	0	242	100	242
Inclusion Criteria 7	0	0	242	100	242

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 (MITT)

	FULFILLED						Total
	Missing		No		Yes		
	N	%	N	%	N	%	N
CRITERIA							
Exclusion Criteria 1	0	0	242	100	0	0	242
Exclusion Criteria 2	0	0	242	100	0	0	242
Exclusion Criteria 3	1	0	241	100	0	0	242
Exclusion Criteria 4	0	0	242	100	0	0	242
Exclusion Criteria 5	0	0	242	100	0	0	242
Exclusion Criteria 6	0	0	242	100	0	0	242
Exclusion Criteria 7	0	0	242	100	0	0	242
Exclusion Criteria 8	0	0	242	100	0	0	242
Exclusion Criteria 9	0	0	239	99	3	1	242
Exlusion Criteria 10	0	0	239	99	3	1	242
Exclusion Criteria 11	0	0	241	100	1	0	242
Exclusion Criteria 12	0	0	242	100	0	0	242
Exclusion Criteria 13	0	0	242	100	0	0	242
Exclusion Criteria 14	0	0	242	100	0	0	242

Listing 3.2-1 Criteria not fulfilled (MITT)

Randomization Number	Arm of 2nd randomization	Sex	Age (years)	CRITERIA	FULFILLED
5003101031001	RITUXIMAB	MALE	65	Exclusion Criteria 11	No
5003101061617	RITUXIMAB	FEMALE	54	Exclusion Criteria 9	No
5003101171637	RITUXIMAB	FEMALE	63	Exclusion Criteria 3	Missing
5003604701002	RITUXIMAB	FEMALE	30	Exlusion Criteria 10	No
5003608301205	RITUXIMAB	FEMALE	59	Exclusion Criteria 9	No
5003638501023	RITUXIMAB	MALE	60	Exlusion Criteria 10	No
5003101071005	OBSERVATION	MALE	56	Inclusion Criteria 1	No
5003610201615	OBSERVATION	MALE	62	Exclusion Criteria 9	No
5003622501604	OBSERVATION	MALE	47	Exlusion Criteria 10	No
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 3.3-1 Withdrawals from study (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
PREMATURE WITHDRAWAL						
No	79	65	80	67	159	66
Yes	43	35	40	33	83	34
Total	122	100	120	100	242	100

Table 3.3-2 Reason of withdrawal from study (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Reason for premature withdrawal						
TRANSPLANTATION FAILURE	9	21	10	25	19	23
TREATMENT TOXICITY	3	7	0	0	3	4
PATIENT VOLONTARY WITHDRAWAL	3	7	1	3	4	5
DEATH	2	5	2	5	4	5
OTHER	26	60	27	68	53	64
Total	43	100	40	100	83	100

The main reasons for premature withdrawal were other reason (64%), which includes progression during maintenance period, and tranplantation 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 4.1-1 Eligible patients for analysis per efficacy populations

	Arm of treatment																All							
	ARM A / R-ICE								ARM B / R-DHAP															
	Arm of 2nd randomization						All		Arm of 2nd randomization						All		Arm of 2nd randomization						All	
	RITUXIMAB		OBSERVATION		NOT APPLICABLE				RITUXIMAB		OBSERVATION		NOT APPLICABLE				RITUXIMAB		OBSERVATION		NOT APPLICABLE			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Induction full analysis population																								
Yes	60	13	56	12	127	27	243	51	62	13	64	13	108	23	234	49	122	26	120	25	235	49	477	100
Induction ITT population																								
Yes	60	13	56	12	123	26	239	51	62	13	64	14	104	22	230	49	122	26	120	26	227	48	469	100
No	0	0	0	0	4	50	4	50	0	0	0	0	4	50	4	50	0	0	0	0	8	100	8	100
Maintenance ITT population																								
Yes	60	25	56	23	0	0	116	48	62	26	64	26	0	0	126	52	122	50	120	50	0	0	242	100
No	0	0	0	0	127	54	127	54	0	0	0	0	108	46	108	46	0	0	0	0	235	100	235	100
TOTAL	60	13	56	12	127	27	243	51	62	13	64	13	108	23	234	49	122	26	120	25	235	49	477	100

Table 4.1-2 Eligible patients for analysis per safety populations

	Actual arm of induction																							
	ARM A / R-ICE								ARM B / R-DHAP								All							
	Actual arm of maintenance						All		Actual arm of maintenance						All		Actual arm of maintenance						All	
	RITUXIMAB		OBSERVATION		NOT APPLICABLE				RITUXIMAB		OBSERVATION		NOT APPLICABLE				RITUXIMAB		OBSERVATION		NOT APPLICABLE			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Induction Safety population																								
Yes	59	13	56	12	124	26	239	51	57	12	63	13	110	23	230	49	116	25	119	25	234	50	469	100
Maintenance safety population																								
Yes	59	25	56	24	0	0	115	49	57	24	63	27	0	0	120	51	116	49	119	51	0	0	235	100
No	0	0	0	0	124	53	124	53	0	0	0	0	110	47	110	47	0	0	0	0	234	100	234	100
TOTAL	59	13	56	12	124	26	239	51	57	12	63	13	110	23	230	49	116	25	119	25	234	50	469	100

Listing 4.1-1 Patients excluded from MITT/safety populations

Randomization Number	Arm of treatment	First Randomization Date	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal
5003101041606	ARM A / R-ICE	03/12/2003	05/12/2003	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION	
5003603201627	ARM A / R-ICE	28/03/2007	03/04/2007	BEFORE TREATMENT	DEATH	
5003609201013	ARM A / R-ICE	14/03/2005	14/03/2005	BEFORE TREATMENT	OTHER	MEET NOT INCLUSION CRITERIAS
5003614301614	ARM A / R-ICE	16/06/2005	17/06/2005	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION	
5003101071620	ARM B / R-DHAP	29/10/2004	29/10/2004	BEFORE TREATMENT	PATIENT VOLONTARY WITHDRAWAL	
5003601601004	ARM B / R-DHAP	02/11/2007	04/11/2007	BEFORE TREATMENT	PATIENT VOLONTARY WITHDRAWAL	
5003603201005	ARM B / R-DHAP	08/10/2004	12/10/2004	BEFORE TREATMENT	MAJOR PROTOCOL VIOLATION	
5003603201027	ARM B / R-DHAP	26/01/2006	26/01/2006	BEFORE TREATMENT	DEATH	
N = 8						

Listing 4.1-2 Patients excluded from maintenance safety population

Randomization Number	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal
5003601301015	RITUXIMAB	08/02/2008	18/03/2008	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL	
5003604901602	RITUXIMAB	02/05/2005	28/06/2005	FOLLOW UP PERIOD	OTHER	LOST TO FOLLOW-UP AFTER BMT
5003608301605	RITUXIMAB	25/08/2004	13/09/2004	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL	
5003617201613	RITUXIMAB	22/09/2005	-	-	-	
5003101601610	OBSERVATION	17/05/2004	11/08/2004	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE	
5003102361203	OBSERVATION	19/02/2004	13/03/2004	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL	
5003631201619	OBSERVATION	14/06/2006	-	-	-	
N = 7						

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

Randomization Number	Arm of 2nd randomization	Actual arm of maintenance	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Comments
5003612201401	RITUXIMAB	OBSERVATION	29/09/2005	12/10/2005	FOLLOW UP PERIOD	OTHER	THE PATIENT WAS RANDOMIZED AT RITUXIMAB BUT IT WAS NOT GIVEN BECAUSE OF INCORRECTED COMMUNICATION BETWEEN US AND THE PRIVATE PRAXIS
5003617201021	RITUXIMAB	OBSERVATION	14/02/2006	17/03/2006	FOLLOW UP PERIOD	OTHER	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 (< 250 U/L)
N = 2							

4.2. Baseline data

4.2.1. Demography

Table 4.2-1 Demography (MITT)

		Arm of 2nd randomization		All
		RITUXIMAB	OBSERVATION	
Age at 1st randomization (years)	**N**	122	120	242
	Mean	51.3	50.7	51.0
	Std	10.02	11.66	10.85
	Median	54.0	53.0	54.0
	Min	19	19	19
	Max	65	65	65
Weight (kg)	**N**	122	120	242
	Mean	76.7	80.8	78.7
	Std	16.36	16.68	16.61
	Median	74.5	80.5	76.0
	Min	45	46	45
	Max	115	137	137
Height (cm)	**N**	122	120	242
	Mean	172.1	172.6	172.4
	Std	9.07	8.99	9.02
	Median	172.0	173.0	173.0
	Min	152	155	152
	Max	196	198	198
Body Area (m^2)	**N**	121	120	241
	Mean	1.879	1.925	1.902
	Std	0.2188	0.2049	0.2128
	Median	1.870	1.955	1.900
	Min	1.40	1.42	1.40
	Max	2.38	2.45	2.45

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 (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Sex						
MALE	76	62	83	69	159	66
FEMALE	46	38	37	31	83	34
Age (years)						
<40 years	17	14	22	18	39	16
>=40 years	105	86	98	82	203	84
Total	122	100	120	100	242	100

4.2.2. Initial diagnosis

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

		Arm of 2nd randomization		All
		RITUXIMAB	OBSERVATION	
Time from initial diagnosis to 1st randomization (months)	**N**	122	119	241
	Mean	38.2	36.8	37.6
	Std	41.02	41.17	41.01
	Median	24.0	20.0	21.0
	Min	2	1	1
	Max	238	174	238
Time from initial diagnostic biospsy to 1st randomization (months)	**N**	121	118	239
	Mean	36.6	35.7	36.2
	Std	36.90	39.36	38.06
	Median	23.7	19.6	20.7
	Min	2	1	1
	Max	197	171	197

Table 4.2-4 Time between intial diagnosis and 1st randomization by category (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Time from initial diagnostic biospsy to 1st randomization						
<12 months	29	24	40	34	69	29
>=12 months	92	76	78	66	170	71
TOTAL	121	100	118	100	239	100
Time from Initial Treatment to 1st randomization						
<12 months	33	27	41	35	74	31
>=12 months	89	73	76	65	165	69
TOTAL	122	100	117	100	239	100

Table 4.2-5 Characteristics at initial diagnosis (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Performance Status at initial diagnosis						
0	66	60	57	53	123	56
1	41	37	32	30	73	33
2	3	3	15	14	18	8
3	0	0	3	3	3	1
4	0	0	1	1	1	0
TOTAL	110	100	108	100	218	100

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Ann Arbor Stage at initial diagnosis						
STAGE 1	25	20	26	22	51	21
STAGE 2	35	29	33	28	68	28
STAGE 3	19	16	18	15	37	15
STAGE 4	43	35	41	35	84	35
TOTAL	122	100	118	100	240	100
B Symptom at initial diagnosis						
Yes	46	39	39	35	85	37
No	73	61	74	65	147	63
TOTAL	119	100	113	100	232	100

Table 4.2-6 International Prognostic Index and individual factors at initial diagnosis (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Performance Status at initial diagnosis						
<2	107	97	89	82	196	90
>=2	3	3	19	18	22	10
TOTAL	110	100	108	100	218	100
Ann Arbor Stage at initial diagnosis						
I-II	60	49	59	50	119	50
III-IV	62	51	59	50	121	50
TOTAL	122	100	118	100	240	100
LDH at initial diagnosis						
<= Normal	64	59	56	55	120	57
> Normal	44	41	46	45	90	43
TOTAL	108	100	102	100	210	100
Age adjusted IPI at initial diagnosis						
0	34	33	29	31	63	32
1	43	42	29	31	72	37
2	23	23	26	28	49	25
3	2	2	9	10	11	6
Subtotal 0-1	77	75	58	62	135	69
Subtotal 2-3	25	25	35	38	60	31
TOTAL	102	100	93	100	195	100
Nb of extra-nodal sites at initial diagnosis						
<=1	93	78	94	80	187	79
>1	26	22	24	20	50	21
TOTAL	119	100	118	100	237	100

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
IPI at initial diagnosis						
0	29	28	25	27	54	28
1	37	36	24	26	61	31
2	24	24	24	26	48	25
3	8	8	16	17	24	12
4	3	3	4	4	7	4
5	1	1	0	0	1	1
Subtotal 0-2	90	88	73	78	163	84
Subtotal 3-5	12	12	20	22	32	16
TOTAL	102	100	93	100	195	100

Table 4.2-7 p-values of Chi-2 test for characteristics at initial diagnosis (MITT)

Parameter	P-value (Chi-2)
Performance Status at diagnosis (<2 Vs >=2)	**0.0003**
Ann Arbor Stage at diagnosis (I-II Vs III-IV)	0.8990
LDH at diagnosis (<= 1 N Vs > 1 N)	0.5237
Age adjusted IPI at diagnosis (0-1 Vs 2-3)	**0.0473**
Extra nodal involvement at diagnosis (<=1 Vs >1)	0.7758
IPI at diagnosis (0-2 Vs 3-5)	0.0666
B Symptoms at diagnosis (No Vs Yes)	0.5128

Table 4.2-8 Anatomopathological report at initial diagnosis - review (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Histology (review) at initial diagnosis						
Lymphome diffus à grandes cellules B	33	46	29	45	62	45
Lymphome diffus à grandes cellules B (centroblastique)	7	10	9	14	16	12
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire	8	11	5	8	13	9
Lymphome diffus à grandes cellules B (immunoblastique)	4	6	3	5	7	5
Lymphome diffus à grandes cellules B (B riche en T / histiocytes)	4	6	3	5	7	5
Lymphome à grandes cellules B thymique	2	3	3	5	5	4
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale	2	3	1	2	3	2
Lymphome folliculaire grade 2	2	3	1	2	3	2
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à "petites cellules" sans précision	3	4	0	0	3	2
Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)	0	0	2	3	2	1

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
lymphome B agressif non classable	2	3	0	0	2	1
Lymphome à grandes cellules B plasmoblastique	0	0	2	3	2	1
Lymphome B non classable pour raisons techniques	1	1	1	2	2	1
Lymphome T angio-immunoblastique	0	0	1	2	1	1
Lymphome T angio-immunoblastique avec progression cytologique B	1	1	0	0	1	1
Lymphome folliculaire grade 1	1	1	0	0	1	1
Zone grise entre Hodgkin / lymphoprolifération EBV	0	0	1	2	1	1
Lymphome à grandes cellules non classable	0	0	1	2	1	1
Lymphome folliculaire grade 3 B	0	0	1	2	1	1
Lymphome à grandes cellules B non classable pour raisons techniques	1	1	0	0	1	1
Lymphome folliculaire grade 3 A	0	0	1	2	1	1
Insuffisance de matériel	1	1	1	2	2	1
TOTAL	72	100	65	100	137	100

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)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Histology (review if available, otherwise local) at initial diagnosis						
Lymphome diffus à grandes cellules B	47	52	42	51	89	51
Lymphome diffus à grandes cellules B (centroblastique)	8	9	9	11	17	10
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire	8	9	5	6	13	8
Lymphome diffus à grandes cellules B (B riche en T / histiocytes)	6	7	6	7	12	7
Lymphome diffus à grandes cellules B (immunoblastique)	4	4	3	4	7	4
Lymphome à grandes cellules B thymique	3	3	3	4	6	3
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale	2	2	1	1	3	2
Lymphome folliculaire grade 2	2	2	1	1	3	2
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B à "petites cellules" sans précision	3	3	0	0	3	2
Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)	0	0	2	2	2	1
lymphome B agressif non classable	2	2	0	0	2	1
Lymphome à grandes cellules B plasmoblastique	0	0	2	2	2	1
Lymphome diffus à grandes cellules B (anaplasique)	0	0	2	2	2	1
Lymphome B non classable pour raisons techniques	1	1	1	1	2	1

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Lymphome T angio-immunoblastique	0	0	1	1	1	1
Lymphome T angio-immunoblastique avec progression cytologique B	1	1	0	0	1	1
Lymphome folliculaire grade 1	1	1	0	0	1	1
Zone grise entre Hodgkin / lymphoprolifération EBV	0	0	1	1	1	1
Lymphome à grandes cellules non classable	0	0	1	1	1	1
Lymphome folliculaire grade 3 B	0	0	1	1	1	1
Lymphome à grandes cellules B non classable pour raisons techniques	1	1	0	0	1	1
Lymphome folliculaire grade 3 A	0	0	1	1	1	1
Insuffisance de matériel	1	1	1	1	2	1
TOTAL	90	100	83	100	173	100

4.2.3. Initial treatment

Table 4.2-10 Time between initial treatment and 1st randomization (MITT)

		Arm of 2nd randomization		All
		RITUXIMAB	OBSERVATION	
Time from initial treatment to 1st randomization (months)	**N**	122	117	239
	Mean	37.3	35.8	36.5
	Std	40.92	41.31	41.03
	Median	22.2	17.9	19.3
	Min	2	1	1
	Max	238	173	238

Table 4.2-11 Characteristics of initial treatment (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Chemotherapy regimen						
CHOP - LIKE	102	84	100	83	202	83
ACVB - LIKE	19	16	17	14	36	15
OTHER	1	1	3	3	4	2
Immunotherapy						
RITUXIMAB	63	52	62	52	125	52
UNKNOWN	0	0	1	1	1	0
.	59	48	57	48	116	48
Radiotherapy						
LOCAL	34	28	34	28	68	28
OTHER	1	1	0	0	1	0
UNKNOWN	4	3	1	1	5	2
.	83	68	85	71	168	69
TOTAL	122	100	120	100	242	100

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)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Response after first line						
COMPLETE RESPONSE	85	70	75	63	160	66
UNCONFIRMED COMPLETE RESPONSE	8	7	11	9	19	8
PARTIAL RESPONSE	19	16	21	18	40	17
STABLE DISEASE	6	5	5	4	11	5
PROGRESSIVE DISEASE	3	2	8	7	11	5
NOT EVALUATED	1	1	0	0	1	0
TOTAL	122	100	120	100	242	100

Table 4.2-13 p-value of Chi-2 test for response after 1st line (MITT)

Variable/Treatment	P-value (Chi-2)
Response after first line (CR/CRu vs others)	0.4187

4.2.4. Progression/relapse diagnosis

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

		Arm of 2nd randomization		All
		RITUXIMAB	OBSERVATION	
Time from 1st treatment to relapse diagnostic biopsy (months)	**N**	96	94	190
	Mean	43.5	41.3	42.4
	Std	43.24	43.56	43.30
	Median	28.6	22.9	25.0
	Min	3	1	1
	Max	237	172	237
Time from relapse diagnostic biopsy to 1st randomization (months)	**N**	96	97	193
	Mean	0.8	0.6	0.7
	Std	0.72	0.43	0.60
	Median	0.6	0.5	0.6
	Min	0	-0	-0
	Max	4	2	4

The following tables present the number and percentage of patients for baseline clinical assessments:

Table 4.2-15 Characteristics at relapse (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Performance Status at relapse						
0	72	59	60	50	132	55
1	46	38	51	43	97	40
2	4	3	8	7	12	5
Ann Arbor stage at relapse						
STAGE 1	20	16	21	18	41	17
STAGE 2	33	27	27	23	60	25
STAGE 3	22	18	18	15	40	17
STAGE 4	47	39	53	45	100	41
TOTAL	122	100	119	100	241	100
B symptoms at relapse						
No	97	80	93	79	190	80
Yes	24	20	24	21	48	20
TOTAL	121	100	117	100	238	100

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

		Arm of 2nd randomization		
		RITUXIMAB	OBSERVATION	All
Total of extra-nodal sites at relapse	**N**	122	119	241
	Mean	1.1	1.1	1.1
	Std	1.37	1.12	1.25
	Median	1.0	1.0	1.0
	Min	0	0	0
	Max	6	5	6

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)

	Arm of 2nd randomization					
	RITUXIMAB		OBSERVATION		All	
	N	%	N	%	N	%
Performance Status at relapse						
<2	118	97	111	93	229	95
>=2	4	3	8	7	12	5
TOTAL	122	100	119	100	241	100
Ann Arbor stage at relapse						
I-II	53	43	48	40	101	42
III-IV	69	57	71	60	140	58
TOTAL	122	100	119	100	241	100
LDH at relapse						
<=Normal	66	55	67	57	133	56
>Normal	54	45	51	43	105	44
TOTAL	120	100	118	100	238	100
Age-adjusted IPI at relapse						
0	33	28	28	24	61	26
1	51	43	53	45	104	44
2	34	28	33	28	67	28
3	2	2	3	3	5	2
Subtotal 0-1	84	70	81	69	165	70
Subtotal 2-3	36	30	36	31	72	30
TOTAL	120	100	117	100	237	100
Nb of extra-nodal sites at relapse						
<=1	92	75	89	75	181	75
>1	30	25	30	25	60	25
TOTAL	122	100	119	100	241	100
IPI at relapse						
0	32	27	18	15	50	21
1	30	25	40	34	70	30
2	31	26	37	32	68	29
3	24	20	17	15	41	17
4	3	3	5	4	8	3
Subtotal 0-2	93	78	95	81	188	79
Subtotal 3-5	27	23	22	19	49	21
TOTAL	120	100	117	100	237	100

Table 4.2-18 p-values of Chi-2 test for individual factors of IPI at progression/relapse diagnosis (MITT)

Parameter	P-value (Chi-2)
Performance Status at relapse (<2 Vs >=2)	0.2191
Ann Arbor stage at relapse (I-II Vs III-IV)	0.6251
LDH at relapse (=< 1 N Vs > 1 N)	0.7822
Age adjusted IPI at relapse (0-1 Vs 2-3)	0.8976
Total of extra nodal site at relapse (<=1 Vs >1)	0.9114
B Symptoms at relapse (No Vs Yes)	0.8963
IPI at relapse (0-2 Vs 3-5)	0.4823

Table 4.2-19 Other characteristics at relapse (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Beta 2 microglobulin (mg/l)						
<3	76	88	78	83	154	86
>=3	10	12	16	17	26	14
Total	86	100	94	100	180	100
Albumin (G/L)						
<=35	15	13	14	13	29	13
>35	97	87	96	87	193	87
Total	112	100	110	100	222	100

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

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Bone marrow Biopsy						
Not involved	99	82	98	82	197	82
Involved	13	11	8	7	21	9
Unspecified	1	1	2	2	3	1
Not Done	8	7	12	10	20	8
TOTAL	121	100	120	100	241	100
If BM involved, type of cells						
LARGE CELLS	7	54	6	75	13	62
SMALL CELLS	6	46	2	25	8	38
TOTAL	13	100	8	100	21	100

Overall, 21 patients (9%) presented an involved bone marrow biopsy at relpase, mainly with large cells (62%).

Table 4.2-21 PET scan at relapse (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
PET Scan at relapse						
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)

		Arm of 2nd randomization		
		RITUXIMAB	OBSERVATION	All
Number of sites used for evaluation of response per patient	**N**	122	120	242
	Mean	2.5	2.3	2.4
	Std	1.45	1.39	1.43
	Median	2.0	2.0	2.0
	Min	1	1	1
	Max	6	6	6
	Sum	307	271	578

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)

	Arm of 2nd randomization					
	RITUXIMAB		OBSERVATION		All	
	N	%	N	%	N	%
Histology (review) at relapse						
Lymphome diffus à grandes cellules B	31	42	32	48	63	45
Lymphome diffus à grandes cellules B (centroblastique)	14	19	12	18	26	19
Lymphome diffus à grandes cellules B (immunoblastique)	5	7	2	3	7	5
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire	4	5	2	3	6	4
Lymphome à grandes cellules B thymique	2	3	4	6	6	4
Lymphome folliculaire grade 2	2	3	2	3	4	3
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale	2	3	1	2	3	2
Lymphome B non classable pour raisons techniques	3	4	0	0	3	2
Lymphome folliculaire grade 3 B	2	3	0	0	2	1
Lymphome diffus à grandes cellules B (B riche en T / histiocytes)	0	0	2	3	2	1
Lymphome T angio-immunoblastique	1	1	1	2	2	1
Lymphome folliculaire grade 3 A	2	3	0	0	2	1
Lymphome diffus à grandes cellules B (anaplasique)	0	0	2	3	2	1
Lymphome à grandes cellules B plasmoblastique	0	0	2	3	2	1
Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)	0	0	1	2	1	1
Lymphome B à "petites cellules" non classable pour raisons techniques	1	1	0	0	1	1
lymphome B agressif non classable	1	1	0	0	1	1
Lymphome folliculaire grade 1	1	1	0	0	1	1
Lymphome folliculaire et diffus	0	0	1	2	1	1
Lymphome folliculaire non gradable	1	1	0	0	1	1
Zone grise entre Hodgkin / lymphoprolifération EBV	0	0	1	2	1	1
Insuffisance de matériel	1	1	1	2	2	1
TOTAL	73	100	66	100	139	100

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 4.2-24 Anatomopathological report at relapse – review or if missing, local (MITT)

	Arm of 2nd randomization					
	RITUXIMAB		OBSERVATION		All	
	N	%	N	%	N	%
Histology (review if available, otherwise local) at relapse						
Lymphome diffus à grandes cellules B	40	48	47	56	87	52
Lymphome diffus à grandes cellules B (centroblastique)	14	17	12	14	26	16
Lymphome à grandes cellules B thymique	2	2	5	6	7	4
Lymphome diffus à grandes cellules B (immunoblastique)	5	6	2	2	7	4
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B folliculaire	4	5	2	2	6	4
Lymphome diffus à grandes cellules B (B riche en T / histiocytes)	1	1	3	4	4	2
Lymphome folliculaire grade 2	2	2	2	2	4	2
Lymphome à grandes cellules B développé (ou associé) à un Lymphome B de la zone marginale	2	2	1	1	3	2
Lymphome B non classable pour raisons techniques	3	4	0	0	3	2
Lymphome folliculaire grade 3 B	2	2	0	0	2	1
Lymphome T angio-immunoblastique	1	1	1	1	2	1
Lymphome folliculaire grade 3 A	2	2	0	0	2	1
Lymphome diffus à grandes cellules B (anaplasique)	0	0	2	2	2	1
Lymphome à grandes cellules B plasmoblastique	0	0	2	2	2	1
Insuffisance de matériel	1	1	1	1	2	1
Hodgkin à prédominance lymphocytaire nodulaire (paragranulome nodulaire)	0	0	1	1	1	1
Lymphome B à "petites cellules" non classable pour raisons techniques	1	1	0	0	1	1
lymphome B agressif non classable	1	1	0	0	1	1
Lymphome à grandes cellules non classable	0	0	1	1	1	1
Lymphome folliculaire grade 1	1	1	0	0	1	1
Lymphome folliculaire et diffus	0	0	1	1	1	1
Lymphome folliculaire non gradable	1	1	0	0	1	1
Zone grise entre Hodgkin / lymphoprolifération EBV	0	0	1	1	1	1
TOTAL	83	100	84	100	167	100

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)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Medical relevant history						
Yes	83	68	85	71	168	69
No	39	32	35	29	74	31
At least one persisting disease						
Yes	59	48	66	55	125	52
No	63	52	54	45	117	48
Total	122	100	120	100	242	100

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)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Concomitant treatment at randomization						
Yes	67	55	75	63	142	59
No	55	45	45	38	100	41
At least one due to symptoms related to lymphoma						
Yes	13	11	28	23	41	17
No	109	89	92	77	201	83
Total	122	100	120	100	242	100

4.3. Evaluation after induction treatment

Table 4.3-1 Bonemarrow biopsy after induction (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Bone marrow biopsy after induction						
NHL negative	15	12	18	15	33	14
NHL positive	1	1	1	1	2	1
Indeterminate	0	0	1	1	1	0
Not Done	106	87	97	83	203	85
TOTAL	122	100	117	100	239	100

Table 4.3-2 PET scan after induction (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
PET scan after induction						
NEGATIVE	36	30	24	21	60	25
POSITIVE	15	13	14	12	29	12
NOT DONE	69	58	78	67	147	62
TOTAL	120	100	116	100	236	100

Table 4.3-3 Number of sites used for response evaluation after induction (MITT)

		Arm of 2nd randomization		All
		RITUXIMAB	OBSERVATION	
Number of sites used for evaluation of response per patient	**N**	122	118	240
	Mean	2.5	2.3	2.4
	Std	1.45	1.44	1.45
	Median	2.0	2.0	2.0
	Min	1	1	1
	Max	6	6	6
	Sum	307	270	577

The lesions'codification is presented in section §6.4.

Table 4.3-4 Response after induction (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Response after induction treatment				
COMPLETE RESPONSE	52	43	48	40
UNCONFIRMED COMPLETE RESPONSE	21	17	21	18
PARTIAL RESPONSE	47	39	45	38
STABLE DISEASE	2	2	5	4
Missing	0	0	1	1
Total	122	100	120	100

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)

Arm of 2nd randomization	Nb patients	Nb responders (CR/CRu)	CR rate (%)	95% CI lower	95% CI upper
RITUXIMAB	122	73	59.8	50.6	68.6
OBSERVATION	120	69	57.5	48.1	66.5

Table 4.3-6 Difference between CR rates after induction (MITT)

	Difference between CR rates (%)	95% CI lower	95% CI upper	p-value
Rituximab vs Observation	2.3	-10.1	14.7	0.7121

Following tables describe details about mobilization:

Table 4.3-7 Collection failure (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Collection failure				
Missing	0	0	1	1
No	119	98	116	97
Yes	3	2	3	3
Total	122	100	120	100

Table 4.3-8 Reason of collection failure (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Collection failure - reason				
NOT ENOUGH CELLS	0	0	1	33
OTHER CAUSE	3	100	2	67
Total	3	100	3	100

Table 4.3-9 Mobilization – Collected cells (MITT)

			Arm of 2nd randomization	
			RITUXIMAB	OBSERVATION
Collection failure				
No	Collected Cells	N	119	114
		Mean	6.217	17.421
		Std	4.0184	75.5999
		Median	5.240	5.220
		Min	1.36	2.00
		Max	28.54	629.00
Yes	Collected Cells	N	2	3
		Mean	6.250	7.313
		Std	4.4831	6.9400
		Median	6.250	5.100
		Min	3.08	1.75
		Max	9.42	15.09
All	Collected Cells	N	121	117
		Mean	6.217	17.162
		Std	4.0057	74.6387
		Median	5.240	5.220
		Min	1.36	1.75
		Max	28.54	629.00

Table 4.3-10 Mobilization – Number of collections (MITT)

			Arm of 2nd randomization	
			RITUXIMAB	OBSERVATION
Collection failure				
No	Number of collections	N	119	115
		Mean	1.8	1.7
		Std	0.93	0.82
		Median	2.0	2.0
		Min	1	1
		Max	5	4
Yes	Number of collections	N	2	3
		Mean	1.0	1.7
		Std	0.00	0.58
		Median	1.0	2.0
		Min	1	1
		Max	1	2

			Arm of 2nd randomization	
			RITUXIMAB	OBSERVATION
Total	Number of collections	N	121	118
		Mean	1.8	1.7
		Std	0.93	0.82
		Median	2.0	2.0
		Min	1	1
		Max	5	4

Table 4.3-11 Mobilization – Source of stem cells (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Source of Stem Cells				
Peripheral source	118	98	117	99
Bone marrow	2	2	1	1
Peripheral source + Bone marrow	1	1	0	0
Total	121	100	118	100

Table 4.3-12 Consolidation – Period of collection (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Period of collections				
Before C1	1	1	2	2
C1-C2	2	2	3	3
C2-C3	35	29	25	21
After C3	83	69	87	74
Total	121	100	117	100

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)

		Arm of 2nd randomization			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
Response after induction treatment	**Collection failure**				
CR/CRu/PR	**Missing**	0	0	1	1
	No	117	96	110	92
	Yes	3	2	3	3
Other	**Missing**	0	0	0	0
	No	2	2	6	5
	Yes	0	0	0	0
Total		122	100	120	100

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)

Arm of 2nd randomization	Nb patients	Nb responders with successful mobilization	MARR (%)	95% CI lower	95% CI upper
RITUXIMAB	122	117	95.9	1.3	9.3
OBSERVATION	120	110	91.7	4.1	14.8

Table 4.3-15 Mobilization Adjusted Response Rate (MITT)

	Difference between MARR (%)	95% CI lower	95% CI upper	p-value
Rituximab vs Observation	4.2	-1.8	10.3	0.1719

Table 4.3-16 Consolidation – Time intervals with collection and transplantation (MITT)

		Arm of 2nd randomization	
		RITUXIMAB	OBSERVATION
Time fom C3 to 1st collection date (days)	**N**	121	117
	Mean	-0.9	1.0
	Std	89.40	61.19
	Median	13.0	13.0
	Min	-966	-580
	Max	56	55
Time from 1st collection date to 1st administration of BEAM (days)	**N**	121	118
	Mean	40.3	41.2
	Std	91.11	62.14
	Median	28.0	28.0
	Min	6	8
	Max	1017	625
Time from 1st collection date to transplantation (days)	**N**	121	118
	Mean	46.6	47.4
	Std	91.08	62.08
	Median	35.0	35.0
	Min	12	14
	Max	1023	631
Time from 1st administration of BEAM to transplantation (days)	**N**	122	119
	Mean	6.3	6.3
	Std	0.60	0.86
	Median	6.0	6.0
	Min	5	0
	Max	10	9
Time from transplantation to 2nd randomization date (days)	**N**	122	120
	Mean	7.2	8.3
	Std	17.38	16.10
	Median	5.5	8.0
	Min	-77	-84
	Max	68	70

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)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Date of last contact earlier than 01/06/2010 (stopping date)				
No	68	56	53	44
Yes	54	44	67	56
Date of last contact earlier than 01/09/2009				
No	114	93	110	92
Yes	8	7	10	8
Total	122	100	120	100

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)

	Arm of 2nd randomization	N	Median	Min	Max
Follow-up (months)	ALL	242	44	1	76
Follow-up (months)	RITUXIMAB	122	43	1	76
Follow-up (months)	OBSERVATION	120	44	1	74

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)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Events				
No event	67	55	64	53
New treatment out of progression	1	1	4	3
Progression/relapse	46	38	46	38
Death without progression	8	7	6	5
TOTAL	122	100	120	100

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)

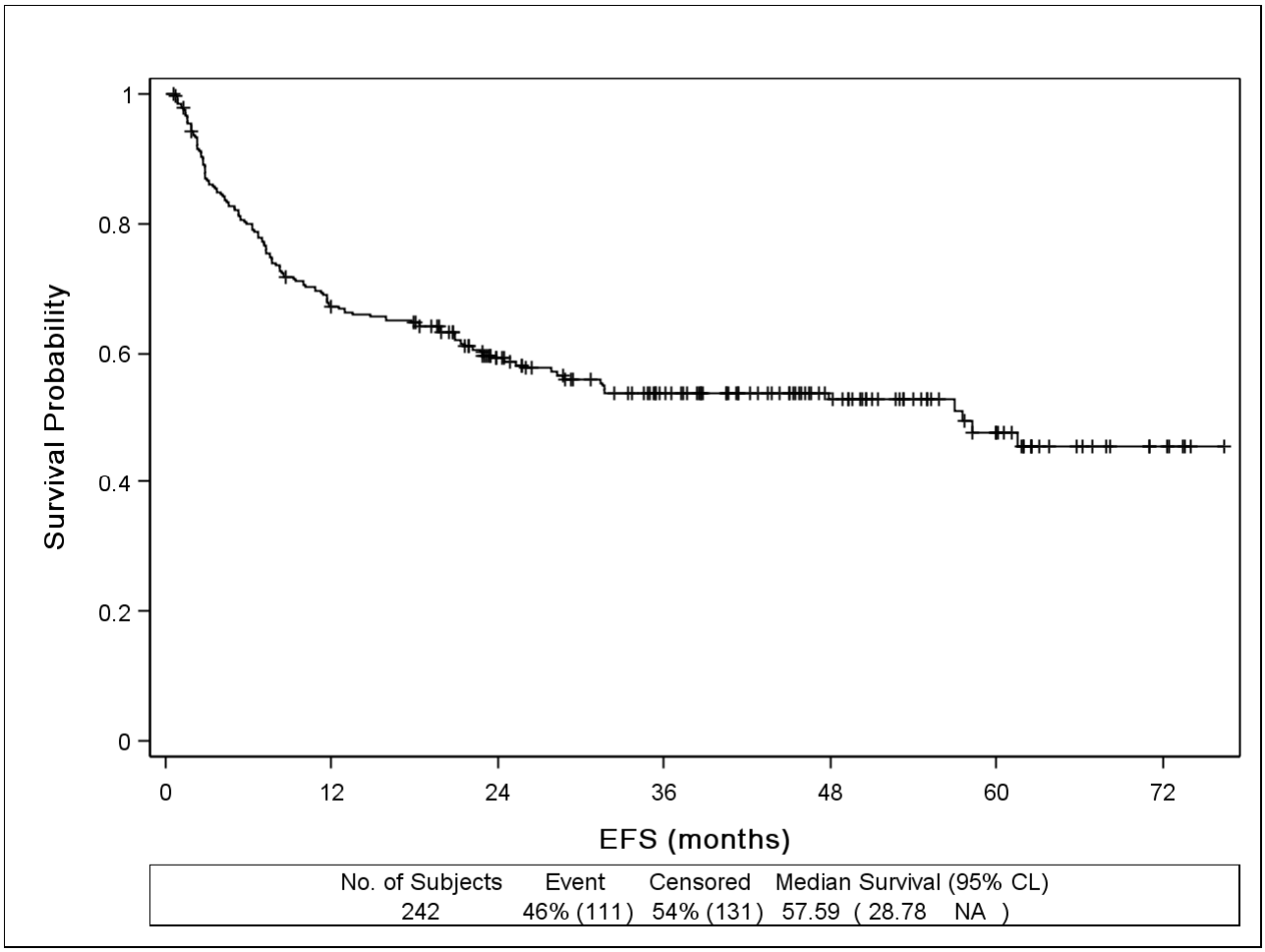


Table 4.5-2 Primary criterion – Duration of Event-Free Survival (MITT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	242	58	29	-	1	76

Table 4.5-3 Primary criterion – Kaplan-Meier estimates for Event-Free Survival (MITT)

Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
12	67.2	60.9	72.8	158
24	59.2	52.6	65.2	118
36	53.8	47.0	60.1	86
48	52.8	45.8	59.3	53
60	47.8	39.5	55.6	26
72	45.6	36.6	54.1	6

Figure 4.5-2 Primary criterion – Event-Free Survival according to treatment arm (MITT)

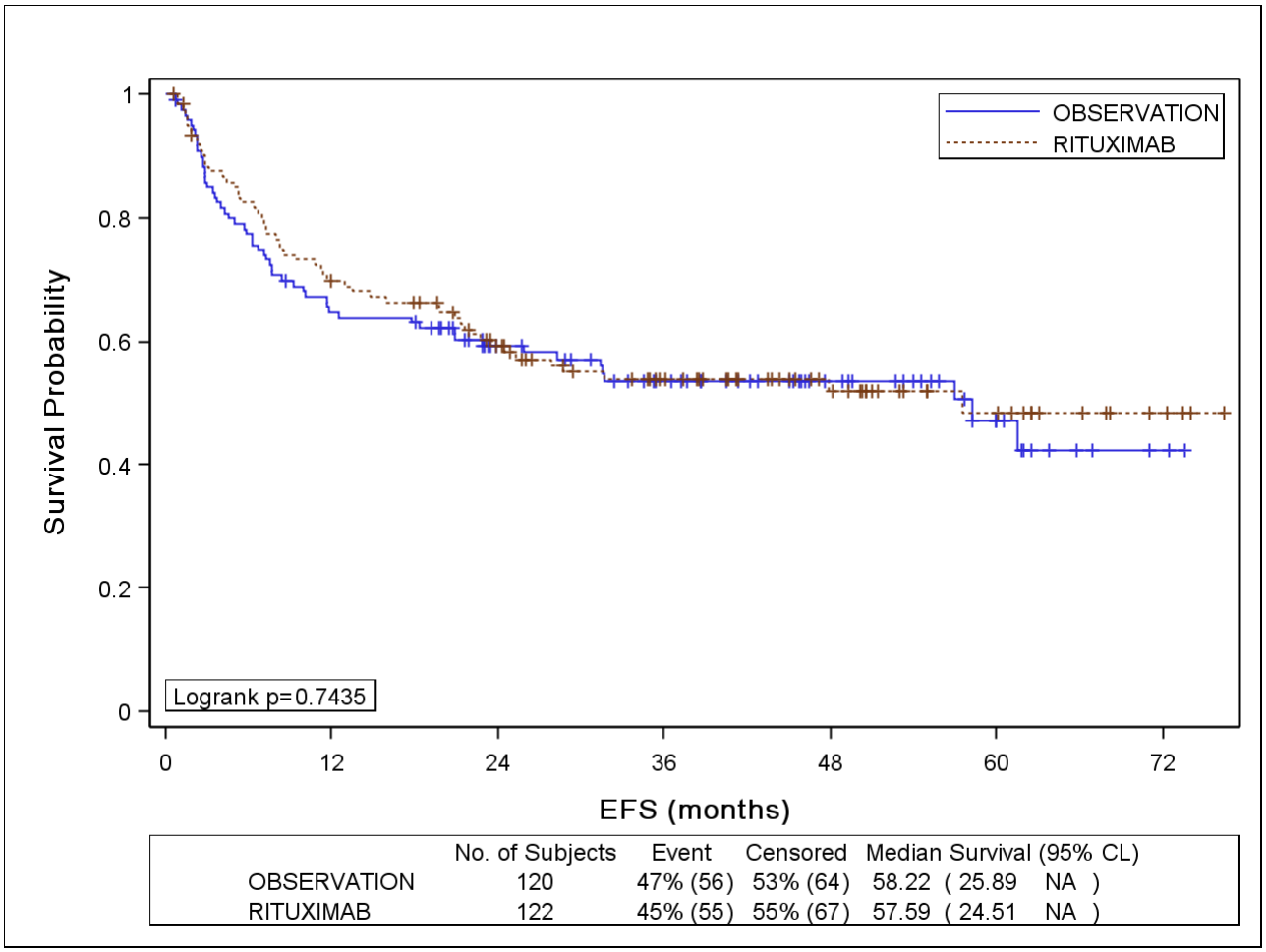


Table 4.5-4 Primary criterion – Duration of Event-Free Survival according to treatment arm (MITT)

	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	RITUXIMAB	122	58	25	-	1	76
EFS (months)	OBSERVATION	120	58	26	-	1	74

Table 4.5-5 Primary criterion – Kaplan-Meier estimates for Event-Free Survival according to treatment arm (MITT)

Arm of 2nd randomization	Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
RITUXIMAB	12	69.8	60.7	77.2	82
RITUXIMAB	24	59.2	49.7	67.5	62
RITUXIMAB	36	53.9	44.3	62.6	44
RITUXIMAB	48	52.0	42.0	61.1	27
RITUXIMAB	60	48.5	37.1	59.1	14
RITUXIMAB	72	48.5	37.1	59.1	4
OBSERVATION	12	64.6	55.3	72.5	76
OBSERVATION	24	59.3	49.8	67.5	56
OBSERVATION	36	53.7	43.9	62.5	42
OBSERVATION	48	53.7	43.9	62.5	26
OBSERVATION	60	47.2	35.0	58.3	12
OBSERVATION	72	42.4	28.6	55.6	2

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)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
rituximab	0.7436	0.940	0.648	1.363

Table 4.5-7 Primary criterion – Stratified Analayis according to induction treatment and response to induction (CR/CRu vs others) - Hazard ratio of rituximab arm for Event-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
rituximab	0.7373	0.938	0.643	1.367

4.5.2. Secondary criteria

4.5.2.1. Progression-Free Survival

Progression-Free survival is measured from date of 2nd randomization to date of progression/relapse or death from any cause.

Figure 4.5-3 Secondary criteria – Progression-Free Survival (MITT)

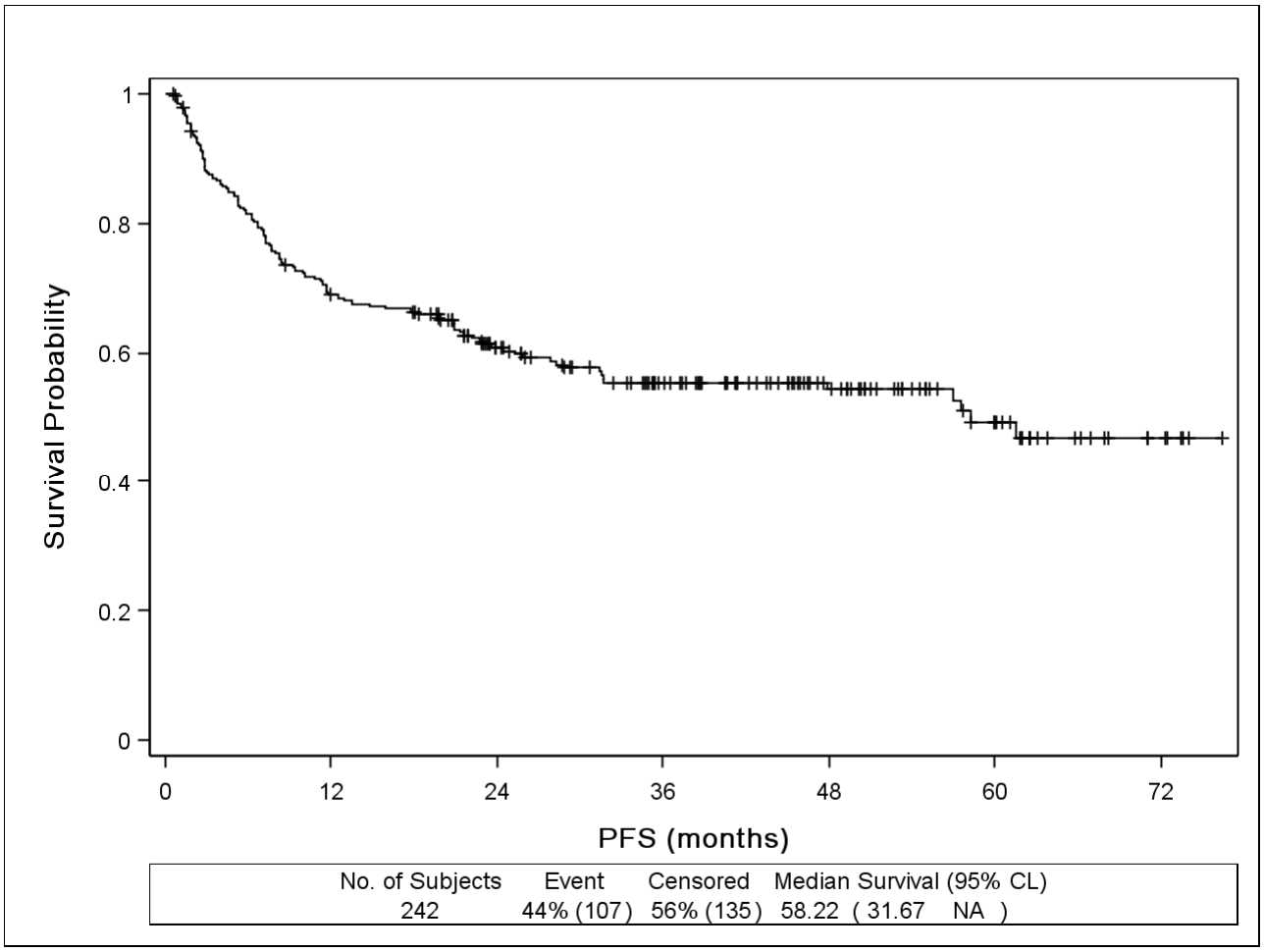


Table 4.5-8 Secondary criteria – Duration of Progression -Free Survival (MITT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	242	58	32	-	1	76

Table 4.5-9 Secondary criteria – Kaplan-Meier estimates for Progression -Free Survival (MITT)

Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
12	68.9	62.6	74.4	162
24	60.8	54.2	66.8	120
36	55.4	48.6	61.7	86
48	54.4	47.4	60.8	53
60	49.2	40.7	57.1	26
72	47.0	37.8	55.6	6

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

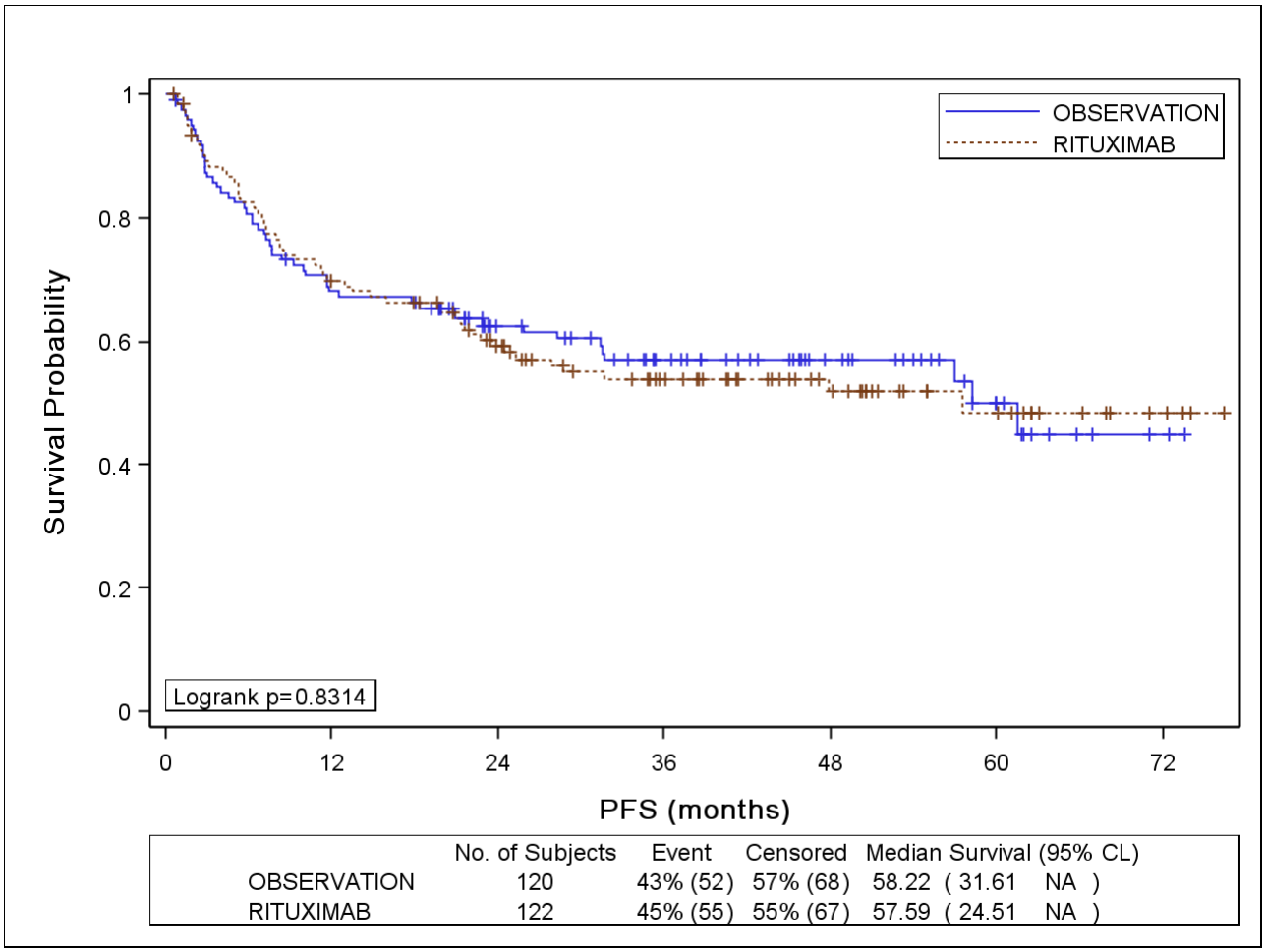


Table 4.5-10 Secondary criteria – Duration of Progression -Free Survival according to treatment arm (MITT)

	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	RITUXIMAB	122	58	25	-	1	76
PFS (months)	OBSERVATION	120	58	32	-	1	74

Table 4.5-11 Secondary criteria – Kaplan-Meier estimates for Progression -Free Survival according to treatment arm (MITT)

Arm of 2nd randomization	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
RITUXIMAB	12	69.8	60.7	77.2	82
RITUXIMAB	24	59.2	49.7	67.5	62
RITUXIMAB	36	53.9	44.3	62.6	44
RITUXIMAB	48	52.0	42.0	61.1	27
RITUXIMAB	60	48.5	37.1	59.1	14
RITUXIMAB	72	48.5	37.1	59.1	4
OBSERVATION	12	68.0	58.8	75.6	80
OBSERVATION	24	62.6	53.1	70.7	58
OBSERVATION	36	56.9	47.1	65.6	42
OBSERVATION	48	56.9	47.1	65.6	26

Arm of 2nd randomization	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
OBSERVATION	60	50.0	37.4	61.4	12
OBSERVATION	72	45.0	30.4	58.5	2

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)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
rituximab	0.8316	1.042	0.713	1.522

Table 4.5-13 Secondary criteria – Stratified Analayis according to induction treatment and response to induction (CR/CRu vs others) - Hazard ratio of rituximab arm for Progression-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
rituximab	0.8219	1.045	0.712	1.535

4.5.2.2. Overall Survival

Overall survival is measured from date of 2nd randomization to date of death from any cause.

Figure 4.5-5 Secondary criteria – Overall Survival (MITT)

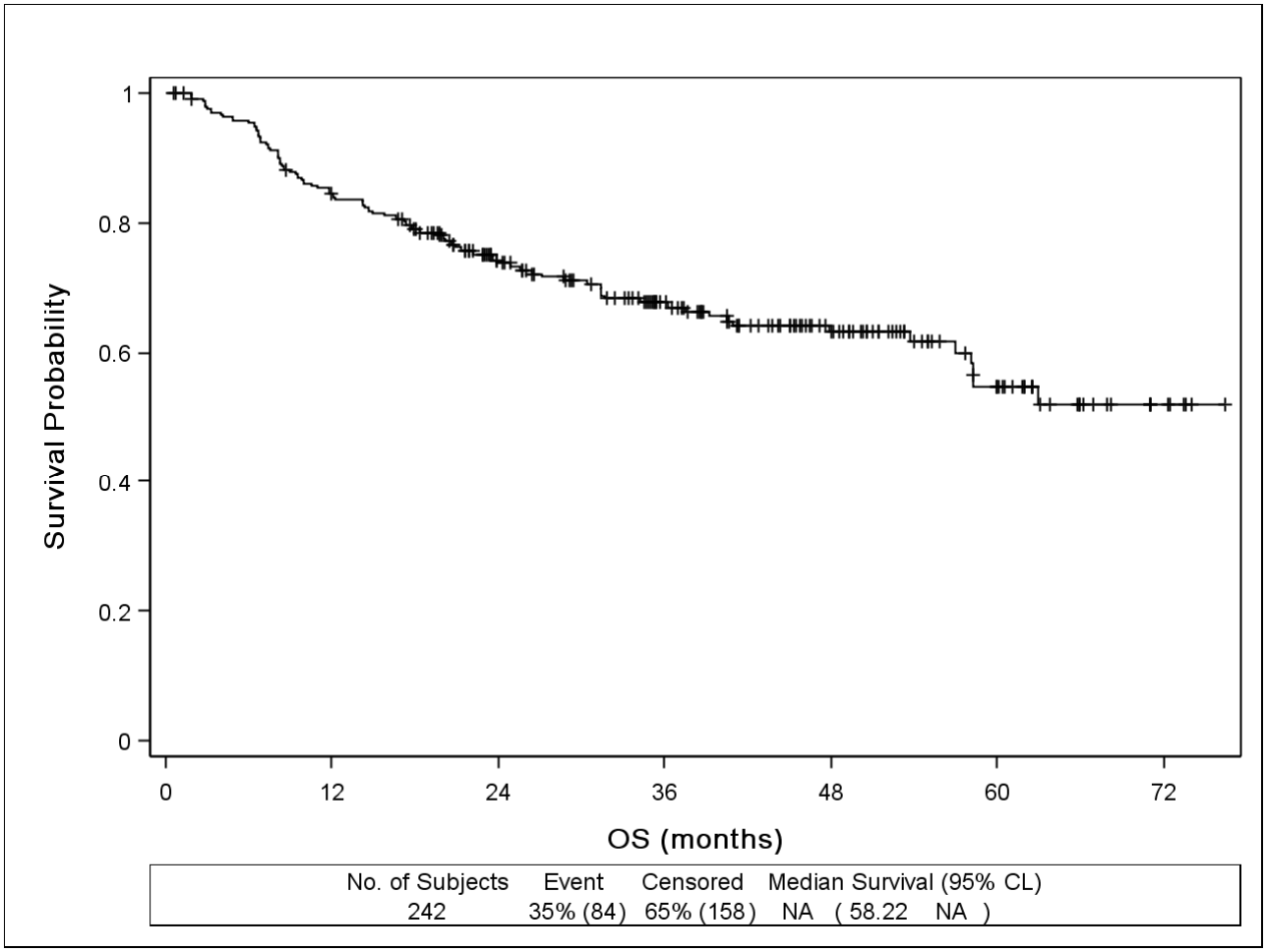


Table 4.5-14 Secondary criteria – Duration of Overall Survival (MITT)

	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	242	-	58	-	1	76

Table 4.5-15 Secondary criteria – Kaplan-Meier estimates for Overall Survival (MITT)

Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
12	84.4	79.2	88.5	199
24	73.7	67.5	78.9	145
36	67.7	61.0	73.5	104
48	63.1	55.9	69.5	63
60	54.8	45.4	63.3	30
72	51.9	41.3	61.5	6

Figure 4.5-6 Secondary criteria – Overall Survival according to treatment arm (MITT)

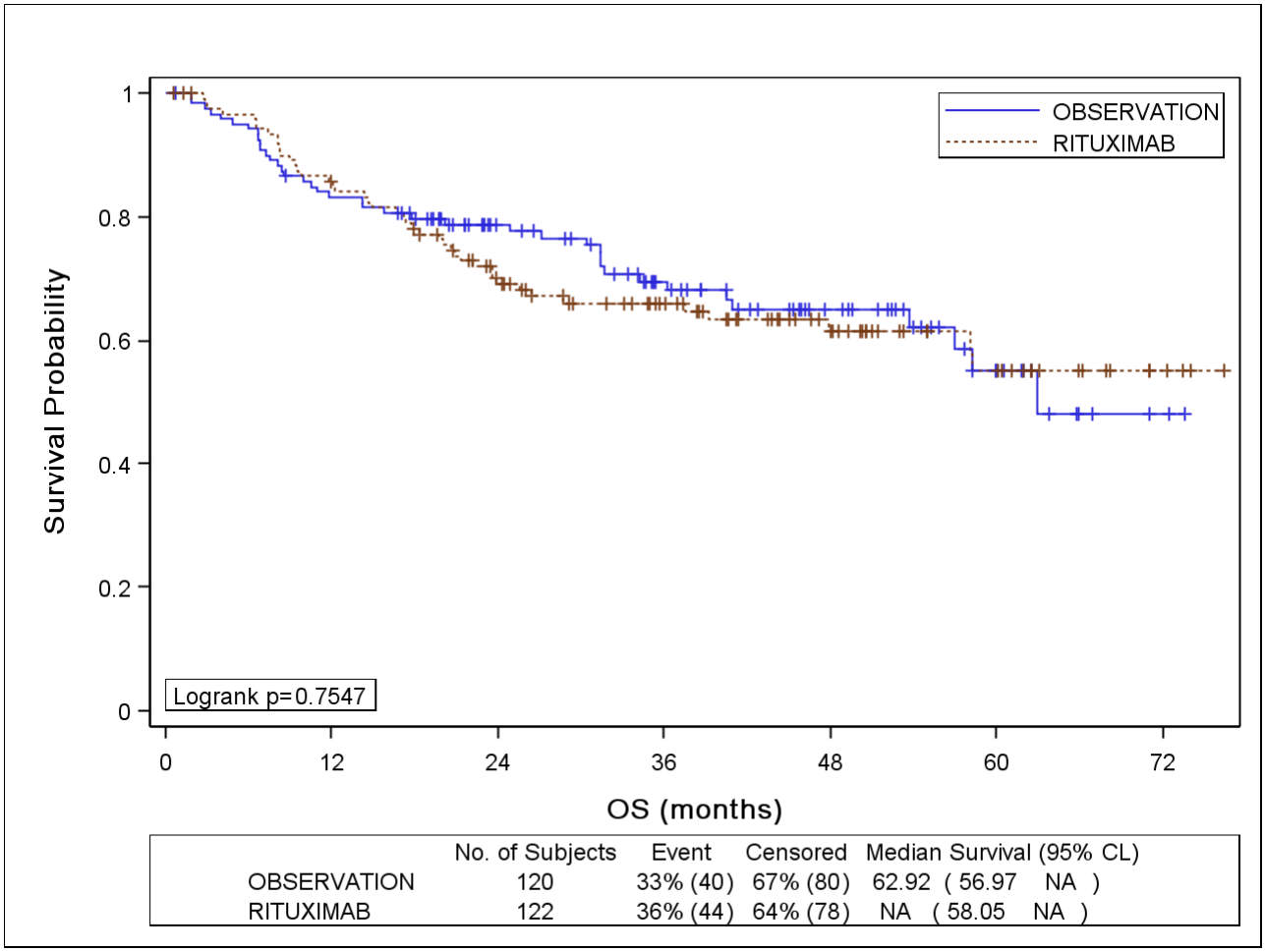


Table 4.5-16 Secondary criteria – Duration of Overall Survival according to treatment arm (MITT)

	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	RITUXIMAB	122	-	58	-	1	76
OS (months)	OBSERVATION	120	63	57	-	1	74

Table 4.5-17 Secondary criteria – Kaplan-Meier estimates for Overall Survival according to treatment arm (MITT)

Arm of 2nd randomization	Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
RITUXIMAB	12	85.7	78.0	90.9	101
RITUXIMAB	24	69.1	59.8	76.6	73
RITUXIMAB	36	66.0	56.5	74.0	54
RITUXIMAB	48	61.5	51.2	70.3	32
RITUXIMAB	60	55.0	42.2	66.1	17
RITUXIMAB	72	55.0	42.2	66.1	4
OBSERVATION	12	83.2	75.1	88.8	98
OBSERVATION	24	78.8	70.2	85.1	72
OBSERVATION	36	69.5	59.6	77.4	50
OBSERVATION	48	64.9	54.3	73.7	31
OBSERVATION	60	55.0	40.8	67.1	13
OBSERVATION	72	48.1	30.4	63.8	2

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)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
rituximab	0.7550	1.071	0.698	1.643

Table 4.5-19 Secondary criteria – Stratified Analayis according to induction treatment and response to induction (CR/CRu vs others) - Hazard ratio of rituximab arm for Progression-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
rituximab	0.9110	1.025	0.664	1.583

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)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Response at the end of maintenance (including deaths for not evaluated patients)				
COMPLETE RESPONSE	65	53	53	44
UNCONFIRMED COMPLETE RESPONSE	8	7	8	7
PARTIAL RESPONSE	7	6	9	8
STABLE DISEASE	0	0	1	1
PROGRESSIVE DISEASE	31	25	36	30
DEATH	0	0	2	2
NOT EVALUATED	8	7	7	6
Missing	3	2	4	3
Total	122	100	120	100

Table 4.5-21 Overall response rate at the end of maintenance (MITT)

Arm of 2nd randomization	Nb patients	Nb responders (CR/CRu/PR)	OR rate (%)	95% CI lower	95% CI upper
RITUXIMAB	122	80	65.6	56.4	73.9
OBSERVATION	120	70	58.3	49.0	67.3

Table 4.5-22 Difference between CR rates at the end of maintenance (MITT)

	Difference between OR rates (%)	95% CI lower	95% CI upper	p-value
Rituximab vs Observation	7.2	-5.0	19.4	0.2460

Table 4.5-23 Complete response rate at the end of maintenance (MITT)

Arm of 2nd randomization	Nb patients	Nb responders (CR/CRu)	CR rate (%)	95% CI lower	95% CI upper
RITUXIMAB	122	73	59.8	50.6	68.6
OBSERVATION	120	61	50.8	41.6	60.1

Table 4.5-24 Difference between CR rates at the end of maintenance (MITT)

	Difference between CR rates (%)	95% CI lower	95% CI upper	p-value
Rituximab vs Observation	9.0	-3.5	21.5	0.1590

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)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Response at the end of maintenance (including deaths for all patients)				
COMPLETE RESPONSE	62	51	53	44
UNCONFIRMED COMPLETE RESPONSE	8	7	8	7
PARTIAL RESPONSE	6	5	9	8
STABLE DISEASE	0	0	1	1
PROGRESSIVE DISEASE	18	15	19	16
DEATH	17	14	19	16
NOT EVALUATED	8	7	7	6
Missing	3	2	4	3
Total	122	100	120	100

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)

Arm of 2nd randomization	Nb patients	Nb responders (CR/CRu/PR)	OR rate (%)	95% CI lower	95% CI upper
RITUXIMAB	122	76	62.3	53.1	70.9
OBSERVATION	120	70	58.3	49.0	67.3

Table 4.5-27 Difference between CR rates at the end of maintenance, including all deaths during maintenance period (MITT)

	Difference between OR rates (%)	95% CI lower	95% CI upper	p-value
Rituximab vs Observation	4.0	-8.4	16.3	0.5288

Table 4.5-28 Complete response rate at the end of maintenance, including all deaths during maintenance period (MITT)

Arm of 2nd randomization	Nb patients	Nb responders (CR/CRu)	CR rate (%)	95% CI lower	95% CI upper
RITUXIMAB	122	70	57.4	48.1	66.3
OBSERVATION	120	61	50.8	41.6	60.1

Table 4.5-29 Difference between CR rates at the end of maintenance, including all deaths during maintenance period (MITT)

	Difference between CR rates (%)	95% CI lower	95% CI upper	p-value
Rituximab vs Observation	6.5	-6.0	19.1	0.3071

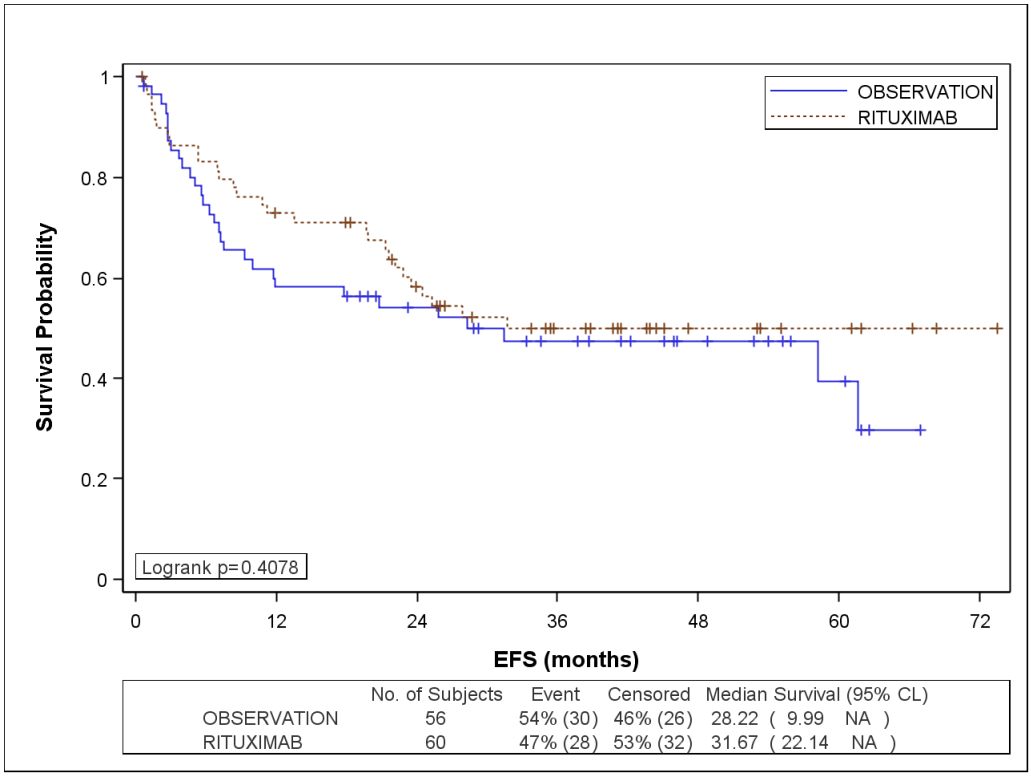
4.5.3. Exploratory analyses

4.5.3.1. Subgroup analyis

4.5.3.1.1. By induction treatment

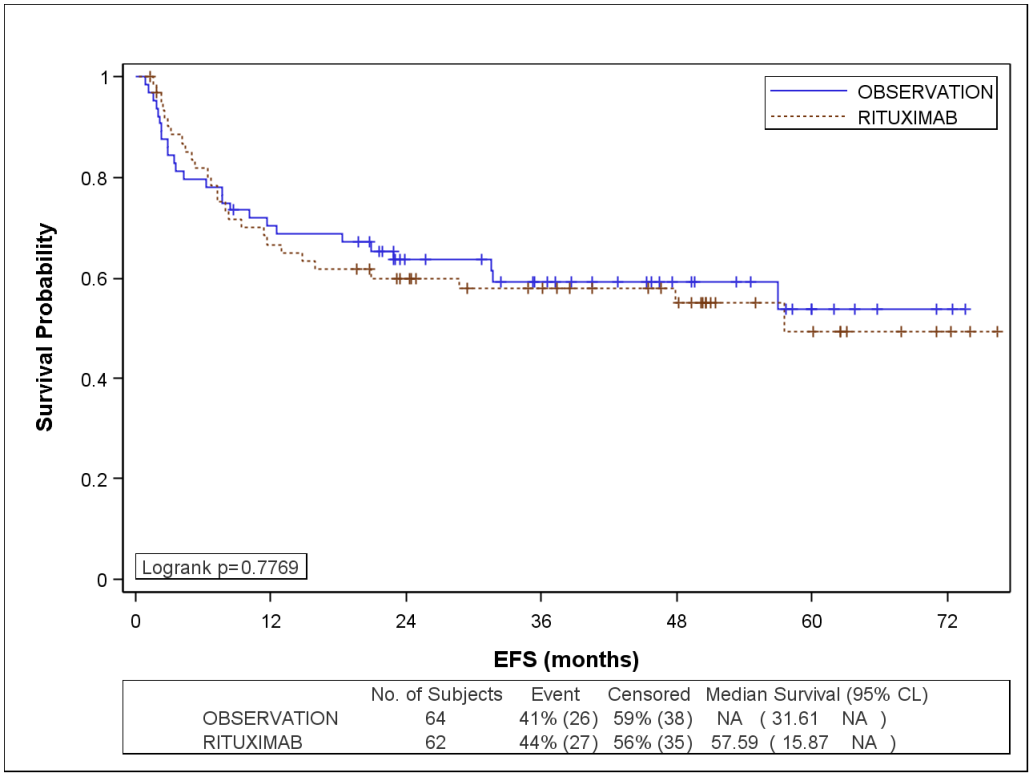
Figure 4.5-7 Exploratory analyses – Event-Free Survival according to treatment arm by induction treatment (MITT)

Induction treatment=ARM A / R-ICE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	56	54% (30)	46% (26)	28.22 (9.99 NA)
RITUXIMAB	60	47% (28)	53% (32)	31.67 (22.14 NA)

Induction treatment=ARM B / R-DHAP



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	64	41% (26)	59% (38)	NA (31.61 NA)
RITUXIMAB	62	44% (27)	56% (35)	57.59 (15.87 NA)

Table 4.5-30 Exploratory analyses – Duration of Event-Free Survival according to treatment arm by induction treatment (MITT)

Induction treatment	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
ARM A / R-ICE	RITUXIMAB	60	32	22	-	1	73
ARM A / R-ICE	OBSERVATION	56	28	10	-	1	67
ARM B / R-DHAP	RITUXIMAB	62	58	16	-	1	76
ARM B / R-DHAP	OBSERVATION	64	-	32	-	1	74

Table 4.5-31 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to treatment arm by induction treatment (MITT)

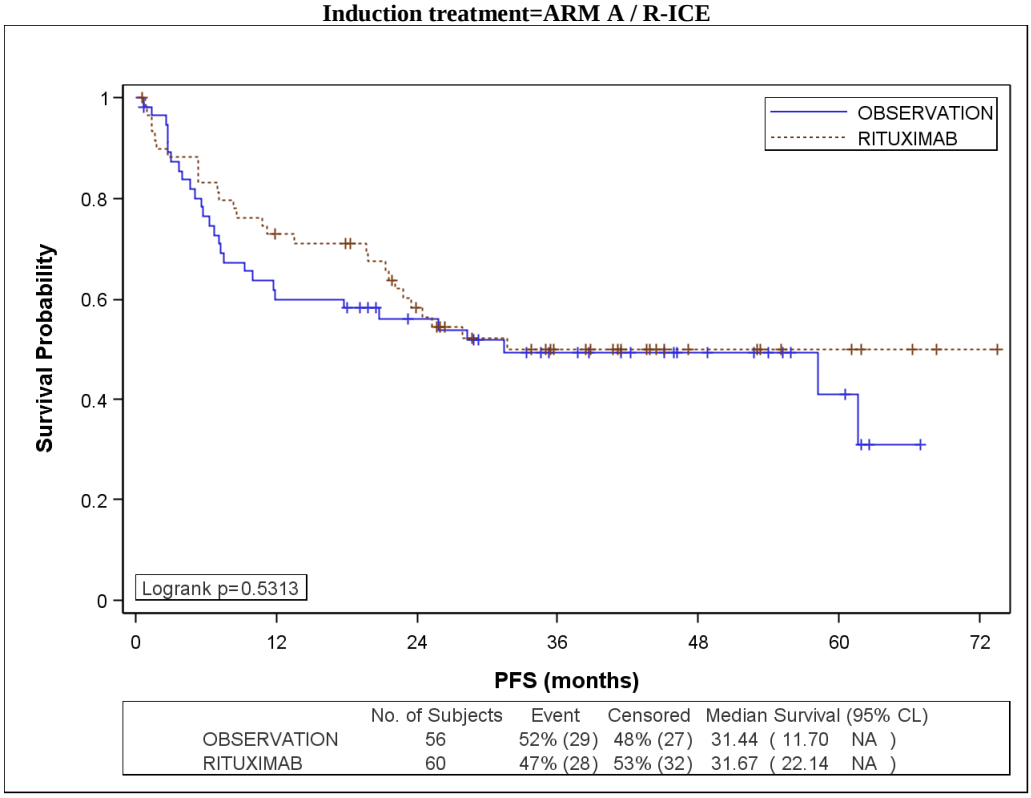
Induction treatment	Arm of 2nd randomization	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
ARM A / R-ICE	RITUXIMAB	12	72.9	59.6	82.4	42
ARM A / R-ICE	RITUXIMAB	24	58.2	44.3	69.8	30
ARM A / R-ICE	RITUXIMAB	36	49.9	36.0	62.3	18
ARM A / R-ICE	RITUXIMAB	48	49.9	36.0	62.3	8
ARM A / R-ICE	RITUXIMAB	60	49.9	36.0	62.3	5
ARM A / R-ICE	RITUXIMAB	72	49.9	36.0	62.3	1
ARM A / R-ICE	OBSERVATION	12	58.2	44.1	69.9	32
ARM A / R-ICE	OBSERVATION	24	54.3	40.2	66.4	25
ARM A / R-ICE	OBSERVATION	36	47.6	33.5	60.3	18
ARM A / R-ICE	OBSERVATION	48	47.6	33.5	60.3	11
ARM A / R-ICE	OBSERVATION	60	39.6	21.9	56.9	5
ARM A / R-ICE	OBSERVATION	72	29.7	11.0	51.4	0
ARM B / R-DHAP	RITUXIMAB	12	66.7	53.3	77.1	40
ARM B / R-DHAP	RITUXIMAB	24	59.9	46.4	71.1	32
ARM B / R-DHAP	RITUXIMAB	36	57.9	44.2	69.3	26
ARM B / R-DHAP	RITUXIMAB	48	55.0	40.9	67.0	19
ARM B / R-DHAP	RITUXIMAB	60	49.5	33.2	63.9	9
ARM B / R-DHAP	RITUXIMAB	72	49.5	33.2	63.9	3
ARM B / R-DHAP	OBSERVATION	12	70.2	57.4	79.9	44
ARM B / R-DHAP	OBSERVATION	24	63.6	50.4	74.1	31
ARM B / R-DHAP	OBSERVATION	36	59.2	45.6	70.5	24
ARM B / R-DHAP	OBSERVATION	48	59.2	45.6	70.5	15
ARM B / R-DHAP	OBSERVATION	60	53.8	37.6	67.5	7
ARM B / R-DHAP	OBSERVATION	72	53.8	37.6	67.5	2

Table 4.5-32 Exploratory analyses – Hazard ratio of rituximab arm by induction treatment for Event-Free Survival (MITT)

Induction treatment	Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
ARM A / R-ICE	**rituximab**	0.4087	0.805	0.480	1.348
ARM B / R-DHAP	**rituximab**	0.7771	1.081	0.631	1.853

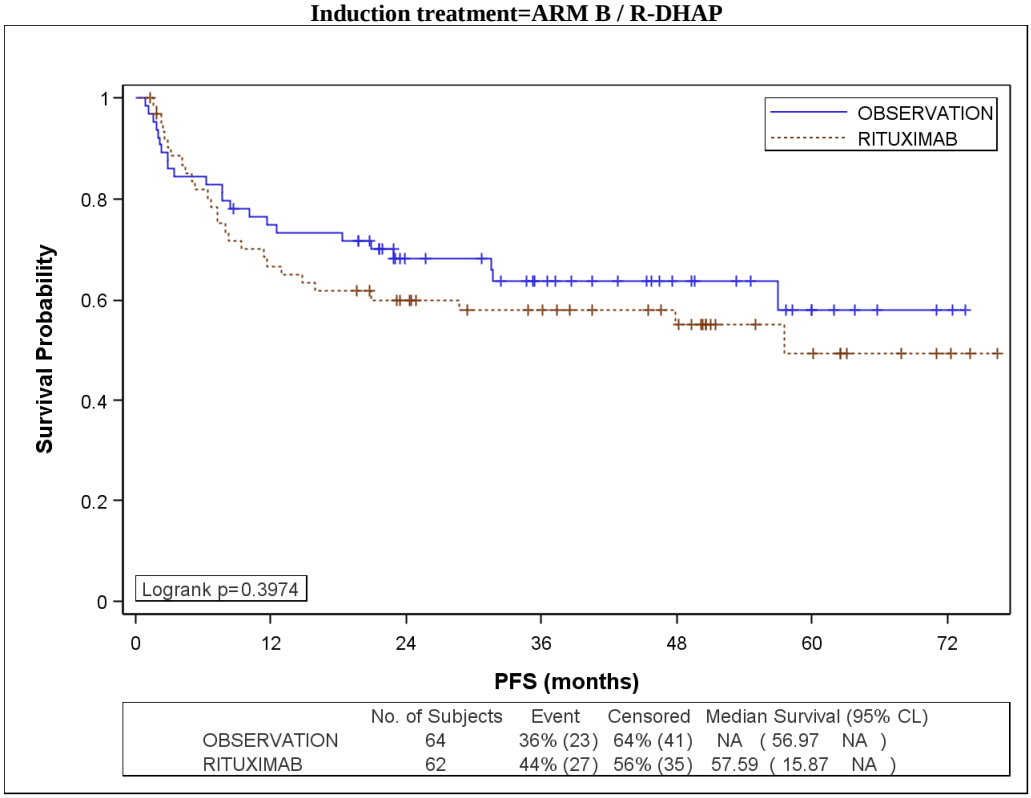
Figure 4.5-8 Exploratory analyses – Progression-Free Survival according to treatment arm by induction treatment (MITT)

Induction treatment=ARM A / R-ICE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	56	52% (29)	48% (27)	31.44 (11.70 NA)
RITUXIMAB	60	47% (28)	53% (32)	31.67 (22.14 NA)

Induction treatment=ARM B / R-DHAP



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	64	36% (23)	64% (41)	NA (56.97 NA)
RITUXIMAB	62	44% (27)	56% (35)	57.59 (15.87 NA)

Table 4.5-33 Exploratory analyses – Duration of Progression-Free Survival according to treatment arm by induction treatment (MITT)

Induction treatment	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
ARM A / R-ICE	RITUXIMAB	60	32	22	-	1	73
ARM A / R-ICE	OBSERVATION	56	31	12	-	1	67
ARM B / R-DHAP	RITUXIMAB	62	58	16	-	1	76
ARM B / R-DHAP	OBSERVATION	64	-	57	-	1	74

Table 4.5-34 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to treatment arm by induction treatment (MITT)

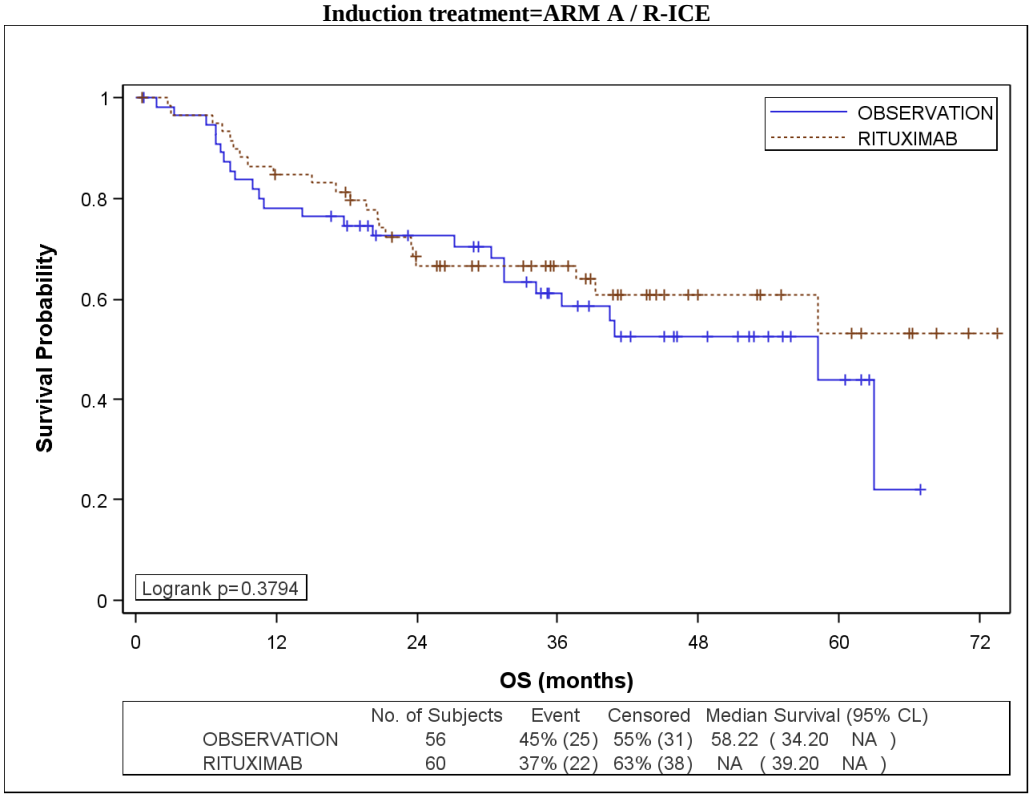
Induction treatment	Arm of 2nd randomization	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
ARM A / R-ICE	RITUXIMAB	12	72.9	59.6	82.4	42
ARM A / R-ICE	RITUXIMAB	24	58.2	44.3	69.8	30
ARM A / R-ICE	RITUXIMAB	36	49.9	36.0	62.3	18
ARM A / R-ICE	RITUXIMAB	48	49.9	36.0	62.3	8
ARM A / R-ICE	RITUXIMAB	60	49.9	36.0	62.3	5
ARM A / R-ICE	RITUXIMAB	72	49.9	36.0	62.3	1
ARM A / R-ICE	OBSERVATION	12	60.0	45.9	71.6	33
ARM A / R-ICE	OBSERVATION	24	56.1	42.0	68.1	26
ARM A / R-ICE	OBSERVATION	36	49.5	35.3	62.1	18
ARM A / R-ICE	OBSERVATION	48	49.5	35.3	62.1	11
ARM A / R-ICE	OBSERVATION	60	41.2	22.9	58.7	5
ARM A / R-ICE	OBSERVATION	72	30.9	11.4	53.1	0
ARM B / R-DHAP	RITUXIMAB	12	66.7	53.3	77.1	40
ARM B / R-DHAP	RITUXIMAB	24	59.9	46.4	71.1	32
ARM B / R-DHAP	RITUXIMAB	36	57.9	44.2	69.3	26
ARM B / R-DHAP	RITUXIMAB	48	55.0	40.9	67.0	19
ARM B / R-DHAP	RITUXIMAB	60	49.5	33.2	63.9	9
ARM B / R-DHAP	RITUXIMAB	72	49.5	33.2	63.9	3
ARM B / R-DHAP	OBSERVATION	12	74.9	62.4	83.8	47
ARM B / R-DHAP	OBSERVATION	24	68.1	55.0	78.2	32
ARM B / R-DHAP	OBSERVATION	36	63.6	49.8	74.5	24
ARM B / R-DHAP	OBSERVATION	48	63.6	49.8	74.5	15
ARM B / R-DHAP	OBSERVATION	60	57.8	40.8	71.6	7
ARM B / R-DHAP	OBSERVATION	72	57.8	40.8	71.6	2

Table 4.5-35 Exploratory analyses – Hazard ratio of rituximab arm by induction treatment for Progression-Free Survival (MITT)

Induction treatment	Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
ARM A / R-ICE	**rituximab**	0.5319	0.847	0.504	1.425
ARM B / R-DHAP	**rituximab**	0.3989	1.271	0.728	2.217

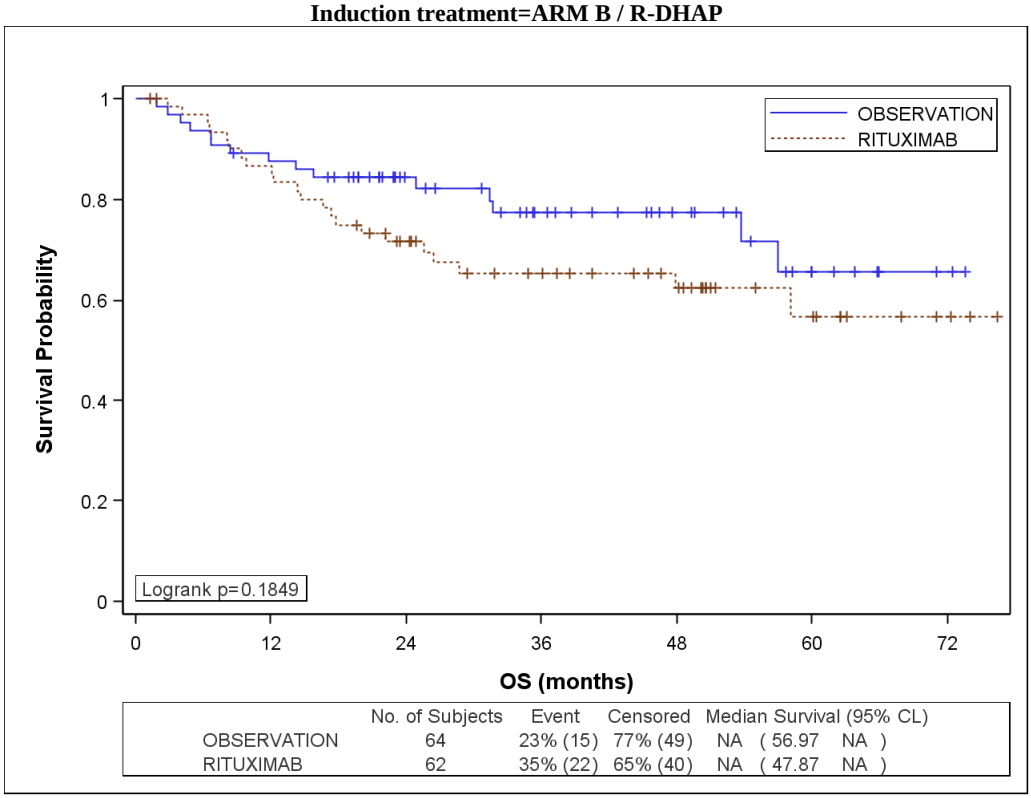
Figure 4.5-9 Exploratory analyses – Overall Survival according to treatment arm by induction treatment (MITT)

Induction treatment=ARM A / R-ICE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	56	45% (25)	55% (31)	58.22 (34.20 NA)
RITUXIMAB	60	37% (22)	63% (38)	NA (39.20 NA)

Induction treatment=ARM B / R-DHAP



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	64	23% (15)	77% (49)	NA (56.97 NA)
RITUXIMAB	62	35% (22)	65% (40)	NA (47.87 NA)

Table 4.5-36 Exploratory analyses – Duration of Overall Survival according to treatment arm by induction treatment (MITT)

Induction treatment	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
ARM A / R-ICE	RITUXIMAB	60	-	39	-	1	73
ARM A / R-ICE	OBSERVATION	56	58	34	-	1	67
ARM B / R-DHAP	RITUXIMAB	62	-	48	-	1	76
ARM B / R-DHAP	OBSERVATION	64	-	57	-	2	74

Table 4.5-37 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to treatment arm by induction treatment (MITT)

Induction treatment	Arm of 2nd randomization	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
ARM A / R-ICE	RITUXIMAB	12	84.7	72.7	91.8	49
ARM A / R-ICE	RITUXIMAB	24	66.7	52.8	77.3	35
ARM A / R-ICE	RITUXIMAB	36	66.7	52.8	77.3	25
ARM A / R-ICE	RITUXIMAB	48	60.9	45.9	72.9	11
ARM A / R-ICE	RITUXIMAB	60	53.3	33.7	69.4	7
ARM A / R-ICE	RITUXIMAB	72	53.3	33.7	69.4	1
ARM A / R-ICE	OBSERVATION	12	78.2	64.8	87.0	43
ARM A / R-ICE	OBSERVATION	24	72.5	58.5	82.4	34
ARM A / R-ICE	OBSERVATION	36	61.2	46.3	73.1	23
ARM A / R-ICE	OBSERVATION	48	52.7	37.1	66.1	13
ARM A / R-ICE	OBSERVATION	60	43.9	24.0	62.2	5
ARM A / R-ICE	OBSERVATION	72	21.9	1.9	56.0	0
ARM B / R-DHAP	RITUXIMAB	12	86.7	75.1	93.1	52
ARM B / R-DHAP	RITUXIMAB	24	71.5	58.2	81.2	38
ARM B / R-DHAP	RITUXIMAB	36	65.4	51.5	76.2	29
ARM B / R-DHAP	RITUXIMAB	48	62.4	47.9	74.0	21
ARM B / R-DHAP	RITUXIMAB	60	56.7	39.4	70.8	10
ARM B / R-DHAP	RITUXIMAB	72	56.7	39.4	70.8	3
ARM B / R-DHAP	OBSERVATION	12	87.5	76.5	93.5	55
ARM B / R-DHAP	OBSERVATION	24	84.3	72.8	91.2	38
ARM B / R-DHAP	OBSERVATION	36	77.2	63.6	86.3	27
ARM B / R-DHAP	OBSERVATION	48	77.2	63.6	86.3	18
ARM B / R-DHAP	OBSERVATION	60	65.8	45.3	80.1	8
ARM B / R-DHAP	OBSERVATION	72	65.8	45.3	80.1	2

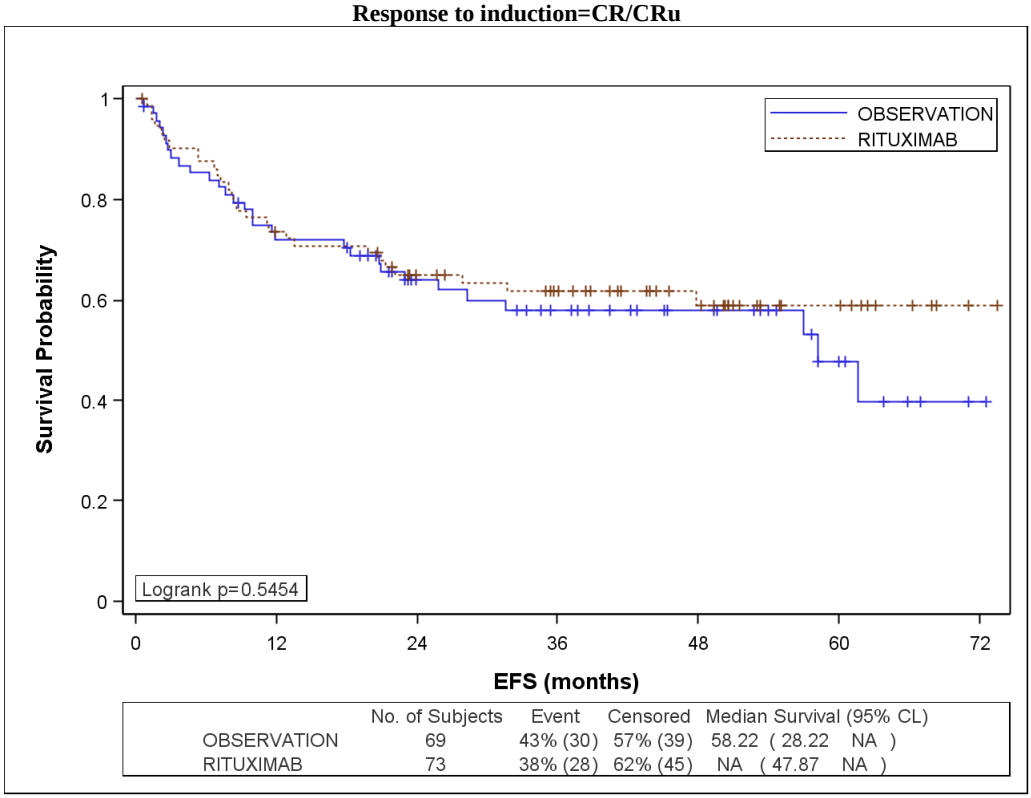
Table 4.5-38 Exploratory analyses – Hazard ratio of rituximab arm by induction treatment for Overall Survival (MITT)

Induction treatment	Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
ARM A / R-ICE	**rituximab**	0.3809	0.774	0.436	1.374
ARM B / R-DHAP	**rituximab**	0.1884	1.554	0.806	2.995

4.5.3.1.2. By response to induction

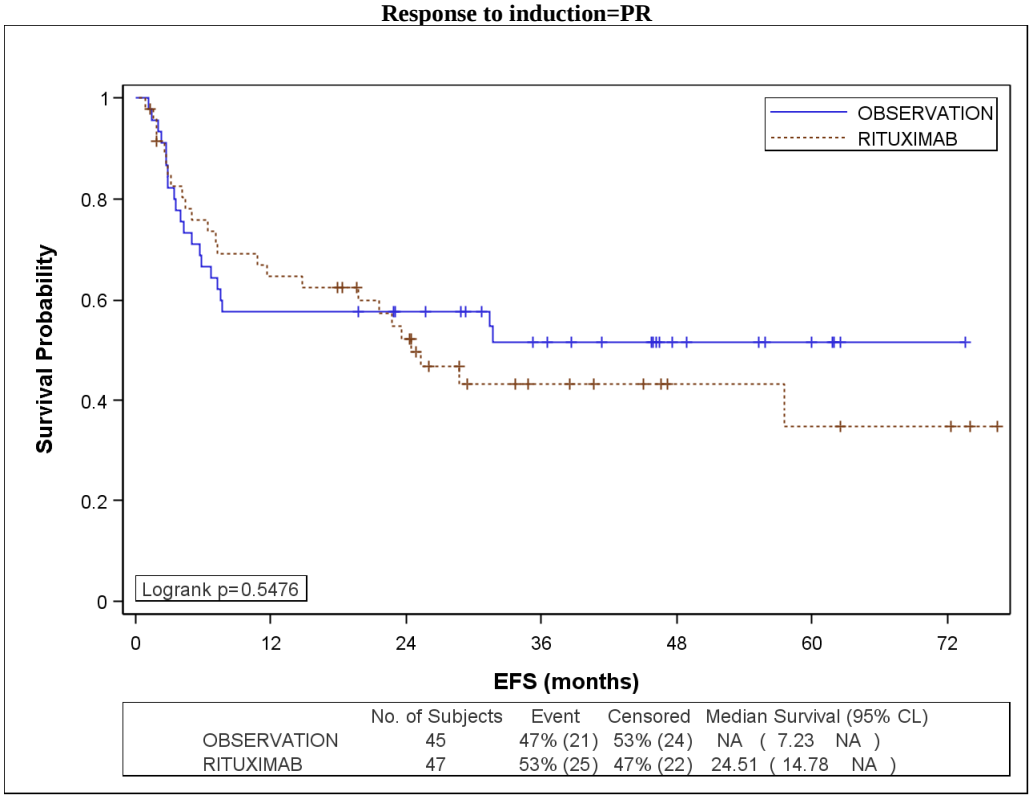
Figure 4.5-10 Exploratory analyses – Event-Free Survival according to treatment arm by response to induction (MITT)

Response to induction=CR/CRu



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	69	43% (30)	57% (39)	58.22 (28.22 NA)
RITUXIMAB	73	38% (28)	62% (45)	NA (47.87 NA)

Response to induction=PR



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	45	47% (21)	53% (24)	NA (7.23 NA)
RITUXIMAB	47	53% (25)	47% (22)	24.51 (14.78 NA)

Table 4.5-39 Exploratory analyses – Duration of Event-Free Survival according to treatment arm by response to induction (MITT)

Response to induction	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
CR/CRu	RITUXIMAB	73	-	48	-	1	73
CR/CRu	OBSERVATION	69	58	28	-	1	73
PR	RITUXIMAB	47	25	15	-	1	76
PR	OBSERVATION	45	-	7	-	1	74

Table 4.5-40 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to treatment arm by response to induction (MITT)

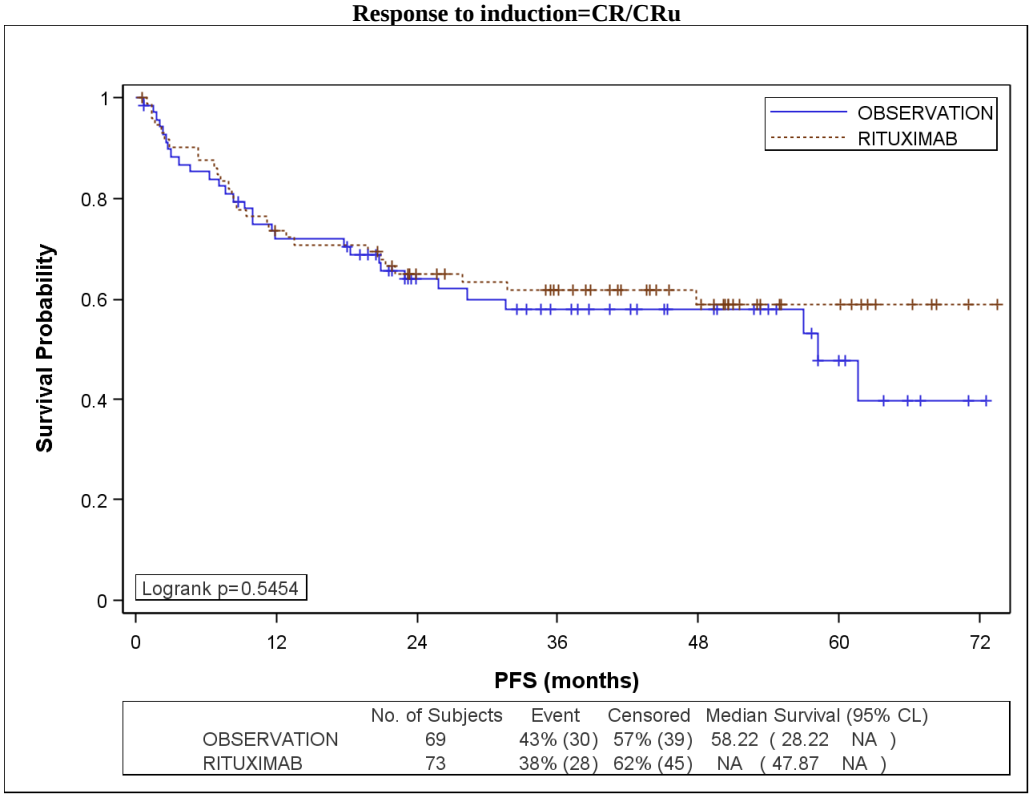
Response to induction	Arm of 2nd randomization	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	RITUXIMAB	12	73.6	61.8	82.3	52
CR/CRu	RITUXIMAB	24	65.0	52.7	74.8	41
CR/CRu	RITUXIMAB	36	61.7	49.2	71.9	34
CR/CRu	RITUXIMAB	48	59.0	45.9	69.9	22
CR/CRu	RITUXIMAB	60	59.0	45.9	69.9	10
CR/CRu	RITUXIMAB	72	59.0	45.9	69.9	1
CR/CRu	OBSERVATION	12	71.9	59.6	81.1	48
CR/CRu	OBSERVATION	24	63.9	51.1	74.2	33
CR/CRu	OBSERVATION	36	58.1	44.9	69.2	26
CR/CRu	OBSERVATION	48	58.1	44.9	69.2	18
CR/CRu	OBSERVATION	60	47.9	31.0	63.0	8
CR/CRu	OBSERVATION	72	39.9	20.7	58.5	1
PR	RITUXIMAB	12	64.6	48.9	76.6	29
PR	RITUXIMAB	24	52.4	36.7	65.9	21
PR	RITUXIMAB	36	43.4	27.8	58.0	10
PR	RITUXIMAB	48	43.4	27.8	58.0	5
PR	RITUXIMAB	60	34.7	16.5	53.8	4
PR	RITUXIMAB	72	34.7	16.5	53.8	3
PR	OBSERVATION	12	57.8	42.1	70.6	26
PR	OBSERVATION	24	57.8	42.1	70.6	23
PR	OBSERVATION	36	51.7	35.7	65.5	16
PR	OBSERVATION	48	51.7	35.7	65.5	8
PR	OBSERVATION	60	51.7	35.7	65.5	4
PR	OBSERVATION	72	51.7	35.7	65.5	1

Table 4.5-41 Exploratory analyses – Hazard ratio of rituximab arm by response to induction for Event-Free Survival (MITT)

Response to induction	Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
CR/CRu	**rituximab**	0.5453	0.853	0.509	1.428
PR	**rituximab**	0.5486	1.195	0.668	2.137

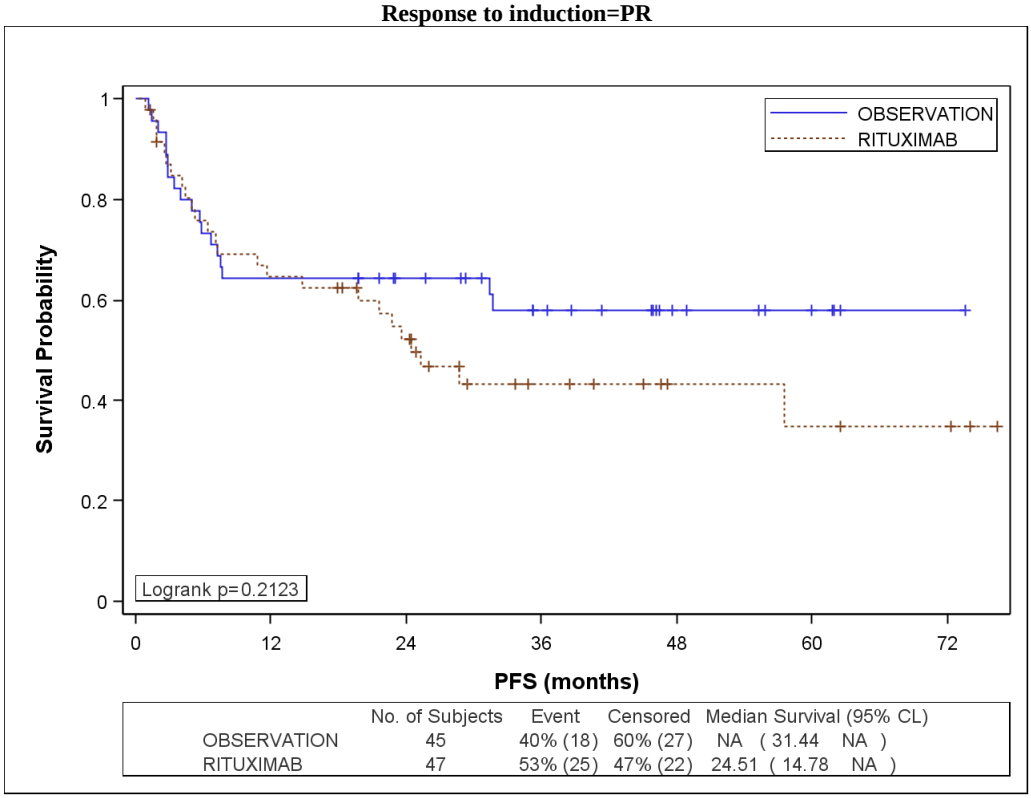
Figure 4.5-11 Exploratory analyses – Progression-Free Survival according to treatment arm by response to induction (MITT)

Response to induction=CR/CRu



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	69	43% (30)	57% (39)	58.22 (28.22 NA)
RITUXIMAB	73	38% (28)	62% (45)	NA (47.87 NA)

Response to induction=PR



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	45	40% (18)	60% (27)	NA (31.44 NA)
RITUXIMAB	47	53% (25)	47% (22)	24.51 (14.78 NA)

Table 4.5-42 Exploratory analyses – Duration of Progression-Free Survival according to treatment arm by response to induction (MITT)

Response to induction	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
CR/CRu	RITUXIMAB	73	-	48	-	1	73
CR/CRu	OBSERVATION	69	58	28	-	1	73
PR	RITUXIMAB	47	25	15	-	1	76
PR	OBSERVATION	45	-	31	-	1	74

Table 4.5-43 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to treatment arm by response to induction (MITT)

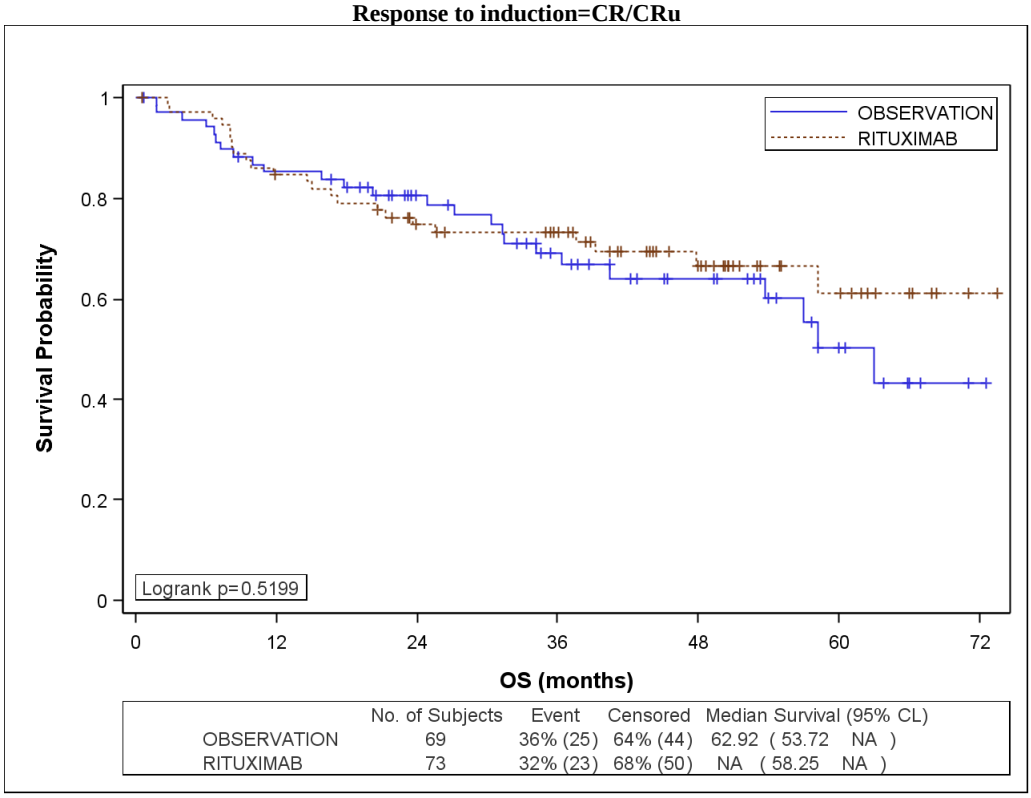
Response to induction	Arm of 2nd randomization	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	RITUXIMAB	12	73.6	61.8	82.3	52
CR/CRu	RITUXIMAB	24	65.0	52.7	74.8	41
CR/CRu	RITUXIMAB	36	61.7	49.2	71.9	34
CR/CRu	RITUXIMAB	48	59.0	45.9	69.9	22
CR/CRu	RITUXIMAB	60	59.0	45.9	69.9	10
CR/CRu	RITUXIMAB	72	59.0	45.9	69.9	1
CR/CRu	OBSERVATION	12	71.9	59.6	81.1	48
CR/CRu	OBSERVATION	24	63.9	51.1	74.2	33
CR/CRu	OBSERVATION	36	58.1	44.9	69.2	26
CR/CRu	OBSERVATION	48	58.1	44.9	69.2	18
CR/CRu	OBSERVATION	60	47.9	31.0	63.0	8
CR/CRu	OBSERVATION	72	39.9	20.7	58.5	1
PR	RITUXIMAB	12	64.6	48.9	76.6	29
PR	RITUXIMAB	24	52.4	36.7	65.9	21
PR	RITUXIMAB	36	43.4	27.8	58.0	10
PR	RITUXIMAB	48	43.4	27.8	58.0	5
PR	RITUXIMAB	60	34.7	16.5	53.8	4
PR	RITUXIMAB	72	34.7	16.5	53.8	3
PR	OBSERVATION	12	64.4	48.7	76.5	29
PR	OBSERVATION	24	64.4	48.7	76.5	24
PR	OBSERVATION	36	58.0	41.5	71.4	16
PR	OBSERVATION	48	58.0	41.5	71.4	8
PR	OBSERVATION	60	58.0	41.5	71.4	4
PR	OBSERVATION	72	58.0	41.5	71.4	1

Table 4.5-44 Exploratory analyses – Hazard ratio of rituximab arm by response to induction for Progression-Free Survival (MITT)

Response to induction	Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
CR/CRu	**rituximab**	0.5453	0.853	0.509	1.428
PR	**rituximab**	0.2155	1.468	0.800	2.694

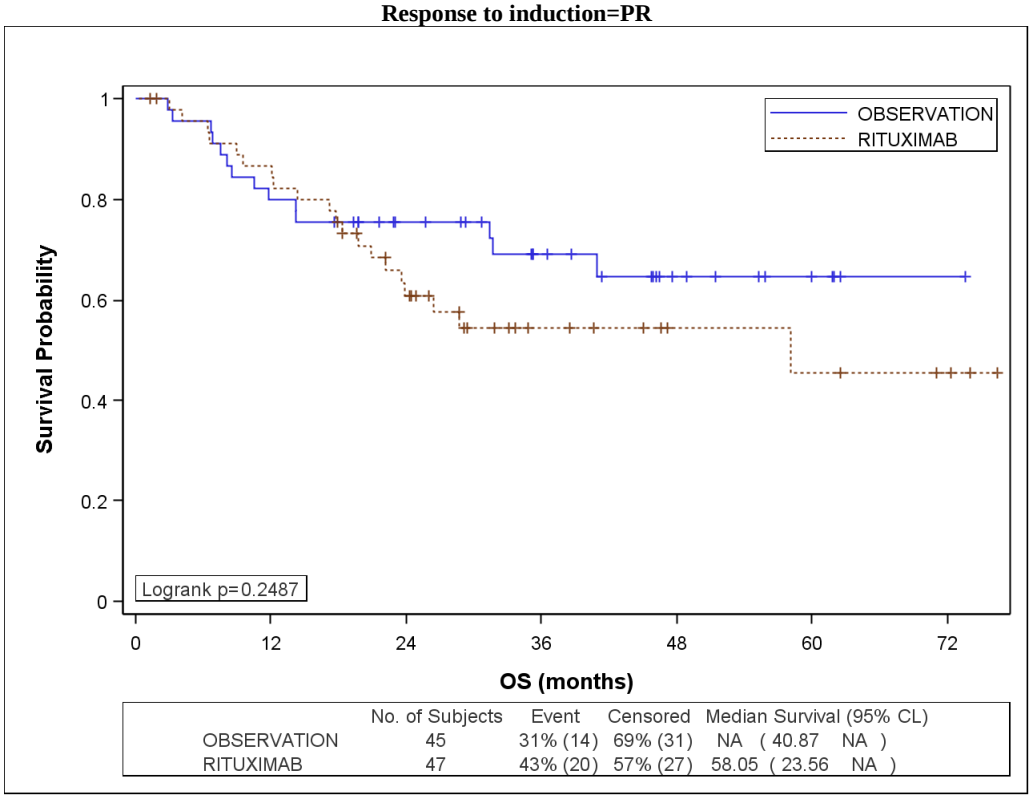
Figure 4.5-12 Exploratory analyses – Overall Survival according to treatment arm by response to induction (MITT)

Response to induction=CR/CRu



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	69	36% (25)	64% (44)	62.92 (53.72 NA)
RITUXIMAB	73	32% (23)	68% (50)	NA (58.25 NA)

Response to induction=PR



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	45	31% (14)	69% (31)	NA (40.87 NA)
RITUXIMAB	47	43% (20)	57% (27)	58.05 (23.56 NA)

Table 4.5-45 Exploratory analyses – Duration of Overall Survival according to treatment arm by response to induction (MITT)

Response to induction	Arm of 2nd randomization	N	Median	95% CI lower	95% CI Upper	Min	Max
CR/CRu	RITUXIMAB	73	-	58	-	1	73
CR/CRu	OBSERVATION	69	63	54	-	1	73
PR	RITUXIMAB	47	58	24	-	1	76
PR	OBSERVATION	45	-	41	-	3	74

Table 4.5-46 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to treatment arm by response to induction (MITT)

Response to induction	Arm of 2nd randomization	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	RITUXIMAB	12	84.7	74.1	91.2	60
CR/CRu	RITUXIMAB	24	74.7	62.9	83.2	48
CR/CRu	RITUXIMAB	36	73.1	61.1	82.0	42
CR/CRu	RITUXIMAB	48	66.7	53.5	77.0	25
CR/CRu	RITUXIMAB	60	61.2	44.5	74.2	11
CR/CRu	RITUXIMAB	72	61.2	44.5	74.2	1
CR/CRu	OBSERVATION	12	85.2	74.3	91.8	57
CR/CRu	OBSERVATION	24	80.6	68.9	88.3	43
CR/CRu	OBSERVATION	36	69.0	55.4	79.1	31
CR/CRu	OBSERVATION	48	64.2	49.9	75.3	21
CR/CRu	OBSERVATION	60	50.5	32.5	66.0	9
CR/CRu	OBSERVATION	72	43.3	23.7	61.5	1
PR	RITUXIMAB	12	86.7	72.7	93.8	39
PR	RITUXIMAB	24	60.8	44.6	73.6	24
PR	RITUXIMAB	36	54.5	37.9	68.4	11
PR	RITUXIMAB	48	54.5	37.9	68.4	6
PR	RITUXIMAB	60	45.4	24.5	64.3	5
PR	RITUXIMAB	72	45.4	24.5	64.3	3
PR	OBSERVATION	12	80.0	65.1	89.1	36
PR	OBSERVATION	24	75.6	60.2	85.6	27
PR	OBSERVATION	36	69.0	52.1	80.9	18
PR	OBSERVATION	48	64.7	46.6	78.0	9
PR	OBSERVATION	60	64.7	46.6	78.0	4
PR	OBSERVATION	72	64.7	46.6	78.0	1

Table 4.5-47 Exploratory analyses – Hazard ratio of rituximab arm by response to induction for Overall Survival (MITT)

Response to induction	Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
CR/CRu	**rituximab**	0.5197	0.830	0.471	1.463
PR	**rituximab**	0.2518	1.493	0.752	2.962

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)

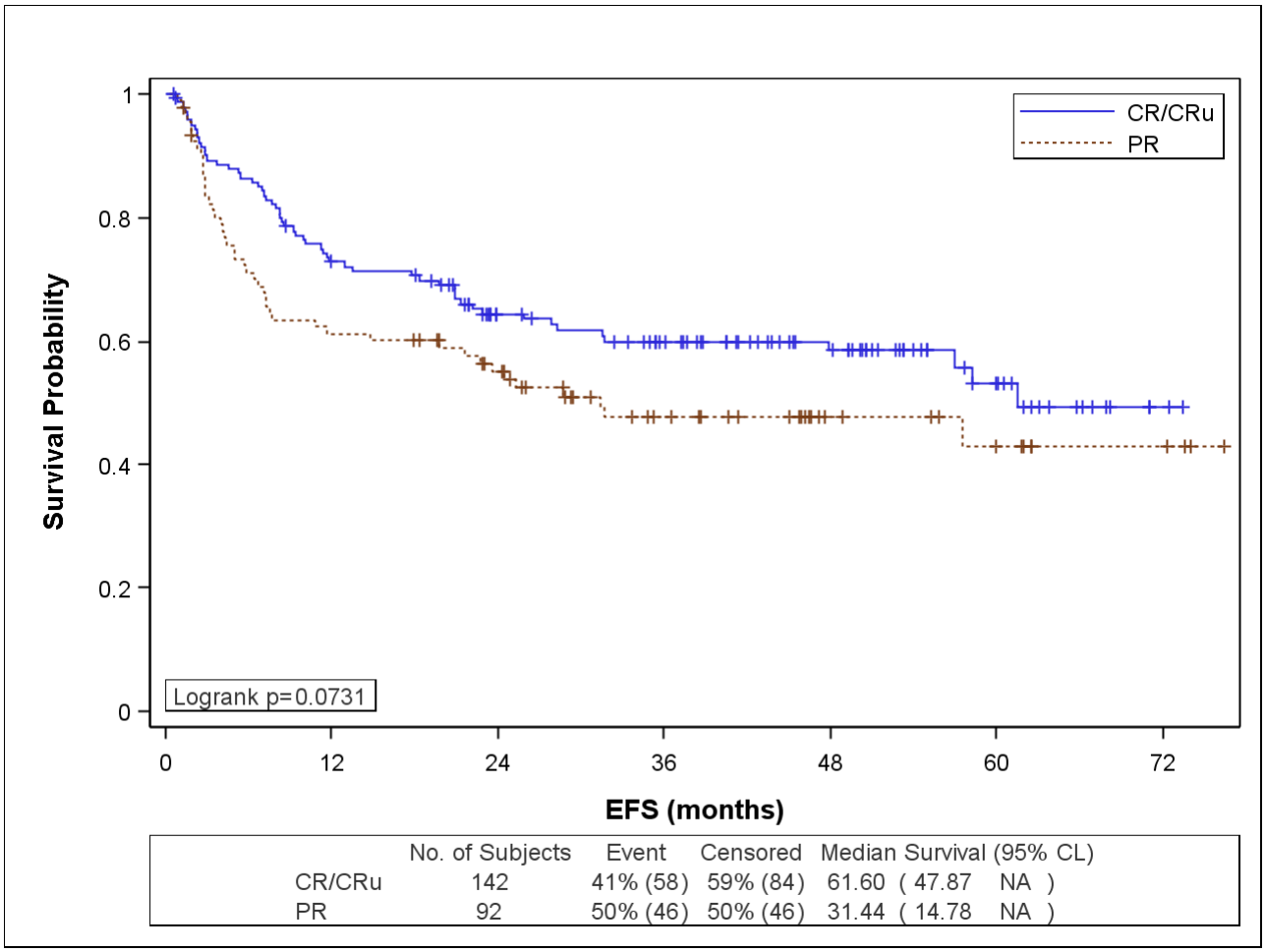


Table 4.5-48 Exploratory analyses – Duration of Event-Free Survival according to response after induction (MITT)

Response after induction	N	Median	95% CI lower	95% CI Upper	Min	Max
CR/CRu	142	62	48	-	1	73
PR	92	31	15	-	1	76

Table 4.5-49 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to response after induction (MITT)

Response after induction	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	72.8	64.6	79.4	100
CR/CRu	24	64.5	55.9	71.9	74
CR/CRu	36	60.0	51.1	67.8	60
CR/CRu	48	58.5	49.4	66.6	40
CR/CRu	60	53.1	41.9	63.0	18

Response after induction	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	72	49.3	36.7	60.8	2
PR	12	61.2	50.3	70.4	55
PR	24	55.2	44.3	64.8	44
PR	36	47.8	36.6	58.1	26
PR	48	47.8	36.6	58.1	13
PR	60	43.0	29.7	55.6	8
PR	72	43.0	29.7	55.6	4

Table 4.5-50 Exploratory analyses – Hazard ratio of CR/CRu after induction for Event-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
CR/CRu	0.0748	0.703	0.477	1.036

Figure 4.5-14 Exploratory analyses – Progression-Free Survival according to response after induction (MITT)

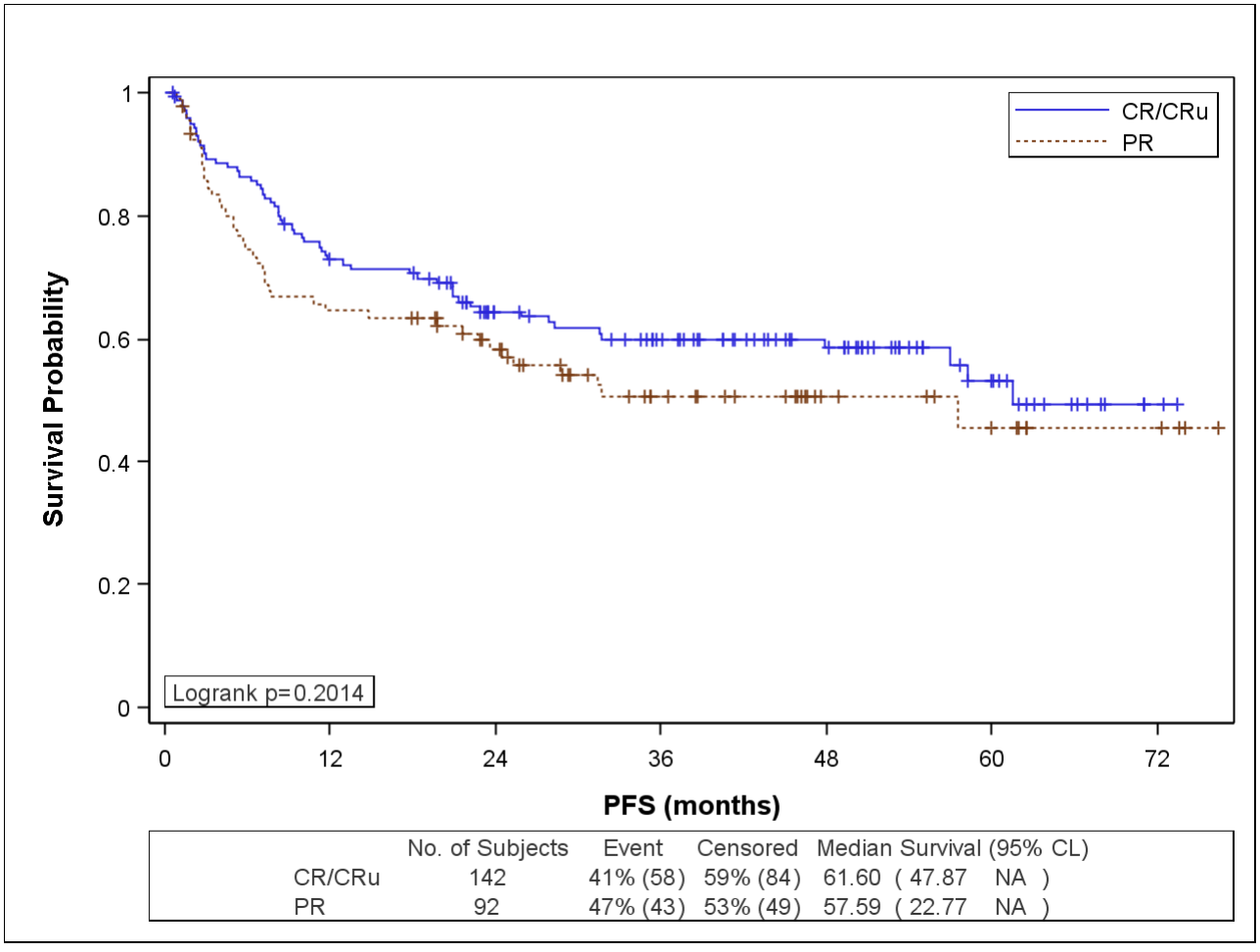


Table 4.5-51 Exploratory analyses – Duration of Progression-Free Survival according to response after induction (MITT)

Response after induction	N	Median	95% CI lower	95% CI Upper	Min	Max
CR/CRu	142	62	48	-	1	73
PR	92	58	23	-	1	76

Table 4.5-52 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to response after induction (MITT)

Response after induction	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	72.8	64.6	79.4	100
CR/CRu	24	64.5	55.9	71.9	74
CR/CRu	36	60.0	51.1	67.8	60
CR/CRu	48	58.5	49.4	66.6	40
CR/CRu	60	53.1	41.9	63.0	18
CR/CRu	72	49.3	36.7	60.8	2
PR	12	64.5	53.7	73.4	58
PR	24	58.4	47.4	67.9	45
PR	36	50.8	39.4	61.1	26
PR	48	50.8	39.4	61.1	13
PR	60	45.7	31.8	58.6	8
PR	72	45.7	31.8	58.6	4

Table 4.5-53 Exploratory analyses – Hazard ratio of CR/CRu after induction for Progression-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
CR/CRu	0.2028	0.774	0.521	1.148

Figure 4.5-15 Exploratory analyses – Overall Survival according to response after induction (MITT)

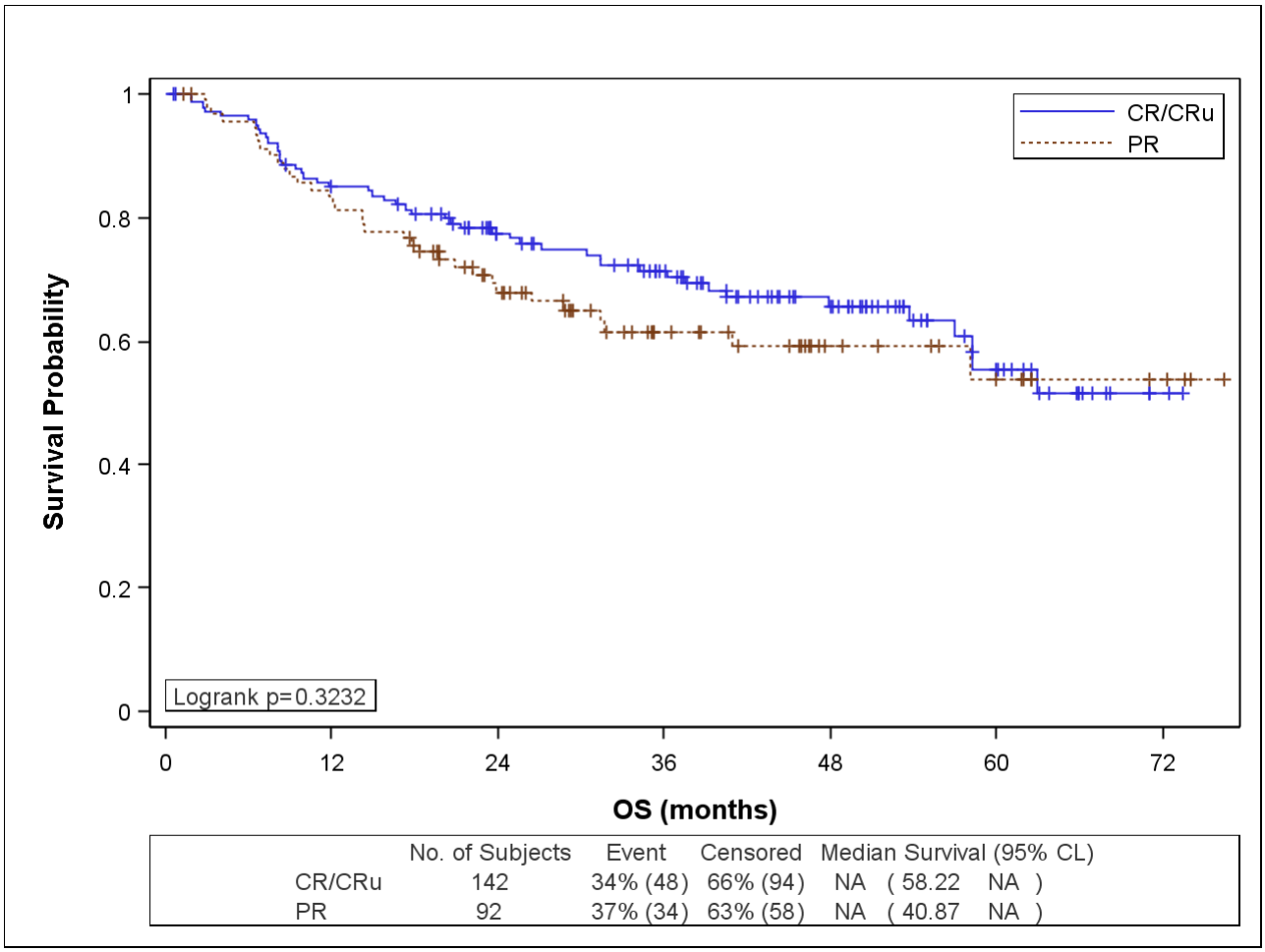


Table 4.5-54 Exploratory analyses – Duration of Overall Survival according to response after induction (MITT)

Response after induction	N	Median	95% CI lower	95% CI Upper	Min	Max
CR/CRu	142	-	58	-	1	73
PR	92	-	41	-	1	76

Table 4.5-55 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to response after induction (MITT)

Response after induction	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	85.0	77.9	89.9	117
CR/CRu	24	77.5	69.5	83.6	91
CR/CRu	36	71.3	62.7	78.3	73
CR/CRu	48	65.7	56.3	73.5	46
CR/CRu	60	55.5	43.1	66.3	20
CR/CRu	72	51.6	37.7	63.8	2
PR	12	83.3	73.9	89.6	75
PR	24	68.0	57.0	76.7	51
PR	36	61.6	49.9	71.3	29
PR	48	59.1	46.9	69.4	15

Response after induction	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
PR	60	53.7	38.4	66.8	9
PR	72	53.7	38.4	66.8	4

Table 4.5-56 Exploratory analyses – Hazard ratio of CR/CRu after induction for Overall Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
CR/CRu	0.3242	0.801	0.516	1.245

4.5.3.2.2. According to prior rituximab

Figure 4.5-16 Exploratory analyses – Event-Free Survival according to prior rituximab (MITT)

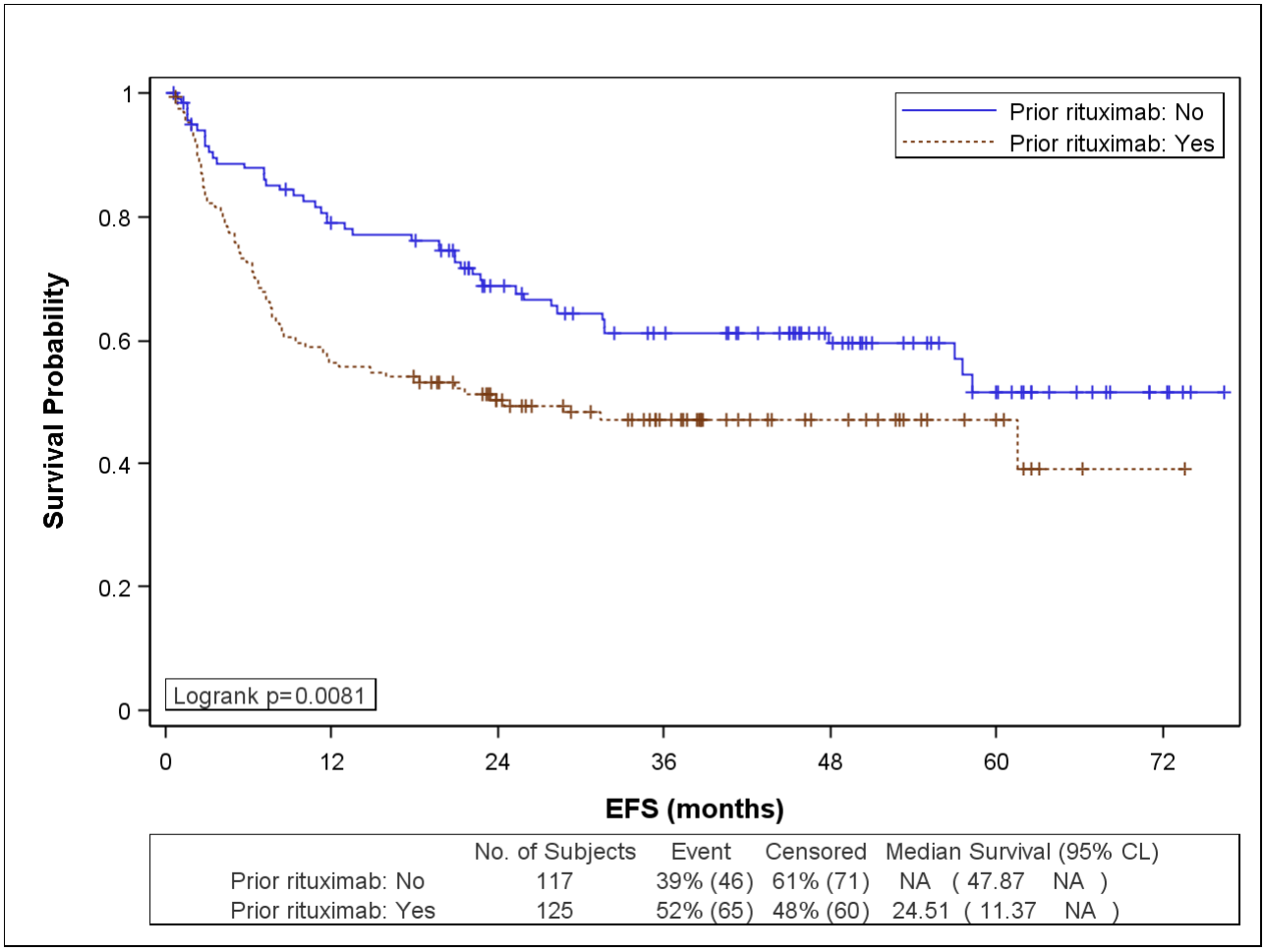


Table 4.5-57 Exploratory analyses – Duration of Event-Free Survival according to prior rituximab (MITT)

Prior treatment with Rituximab	N	Median	95% CI lower	95% CI Upper	Min	Max
No	117	-	48	-	1	76
Yes	125	25	11	-	1	74

Table 4.5-58 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to prior rituximab (MITT)

Prior treatment with Rituximab	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
No	12	78.9	70.2	85.4	88
No	24	68.7	59.1	76.4	67
No	36	61.2	51.2	69.7	53
No	48	59.5	49.3	68.4	36
No	60	51.8	39.5	62.7	18
No	72	51.8	39.5	62.7	5
Yes	12	56.5	47.3	64.6	70
Yes	24	50.5	41.3	58.9	51
Yes	36	47.2	37.9	55.9	33
Yes	48	47.2	37.9	55.9	17
Yes	60	47.2	37.9	55.9	8
Yes	72	39.3	23.6	54.6	1

Table 4.5-59 Exploratory analyses – Hazard ratio of no prior rituximab for Event-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior rituximab: No	0.0089	0.602	0.412	0.880

Figure 4.5-17 Exploratory analyses – Progression-Free Survival according to prior rituximab (MITT)

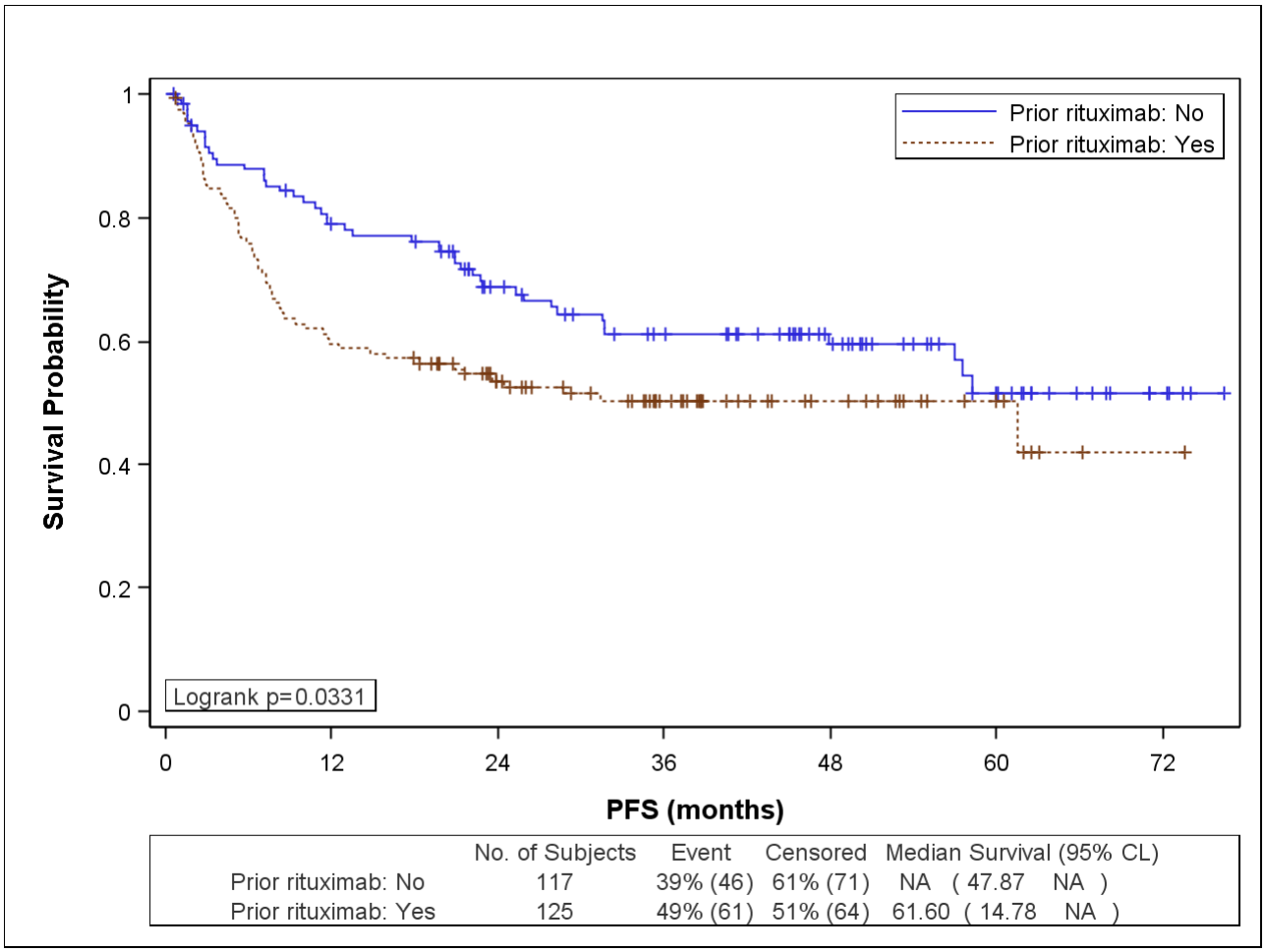


Table 4.5-60 Exploratory analyses – Duration of Progression-Free Survival according to prior rituximab (MITT)

Prior treatment with Rituximab	N	Median	95% CI lower	95% CI Upper	Min	Max
No	117	-	48	-	1	76
Yes	125	62	15	-	1	74

Table 4.5-61 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to prior rituximab (MITT)

Prior treatment with Rituximab	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
No	12	78.9	70.2	85.4	88
No	24	68.7	59.1	76.4	67
No	36	61.2	51.2	69.7	53
No	48	59.5	49.3	68.4	36
No	60	51.8	39.5	62.7	18
No	72	51.8	39.5	62.7	5
Yes	12	59.7	50.5	67.7	74
Yes	24	53.7	44.4	62.0	53
Yes	36	50.3	40.9	59.0	33
Yes	48	50.3	40.9	59.0	17

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)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior rituximab: No	0.0344	0.660	0.449	0.970

Figure 4.5-18 Exploratory analyses – Overall Survival according to prior rituximab (MITT)

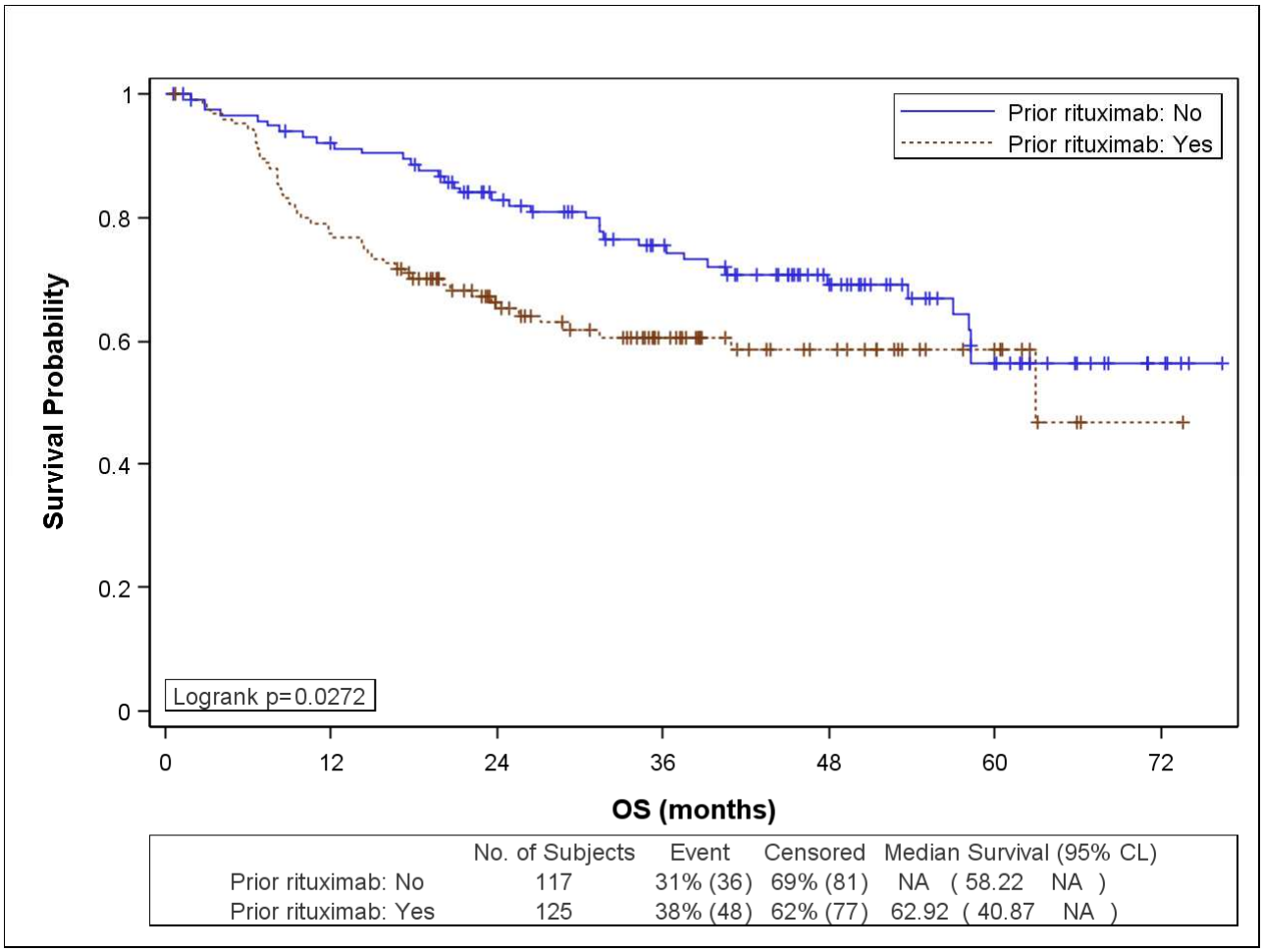


Table 4.5-63 Exploratory analyses – Duration of Overall Survival according to prior rituximab (MITT)

Prior treatment with Rituximab	N	Median	95% CI lower	95% CI Upper	Min	Max
No	117	-	58	-	1	76
Yes	125	63	41	-	1	74

Table 4.5-64 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to prior rituximab (MITT)

Prior treatment with Rituximab	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
No	12	92.1	85.4	95.8	103
No	24	82.9	74.5	88.8	83
No	36	75.5	66.0	82.6	65
No	48	69.1	58.8	77.4	42
No	60	56.5	43.0	68.0	20
No	72	56.5	43.0	68.0	5
Yes	12	77.4	69.0	83.8	96
Yes	24	65.2	55.9	73.0	62
Yes	36	60.6	50.9	69.0	39
Yes	48	58.5	48.1	67.4	21
Yes	60	58.5	48.1	67.4	10
Yes	72	46.8	24.5	66.3	1

Table 4.5-65 Exploratory analyses – Hazard ratio of no prior rituximab for Overall Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior rituximab: No	0.0287	0.614	0.397	0.951

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)

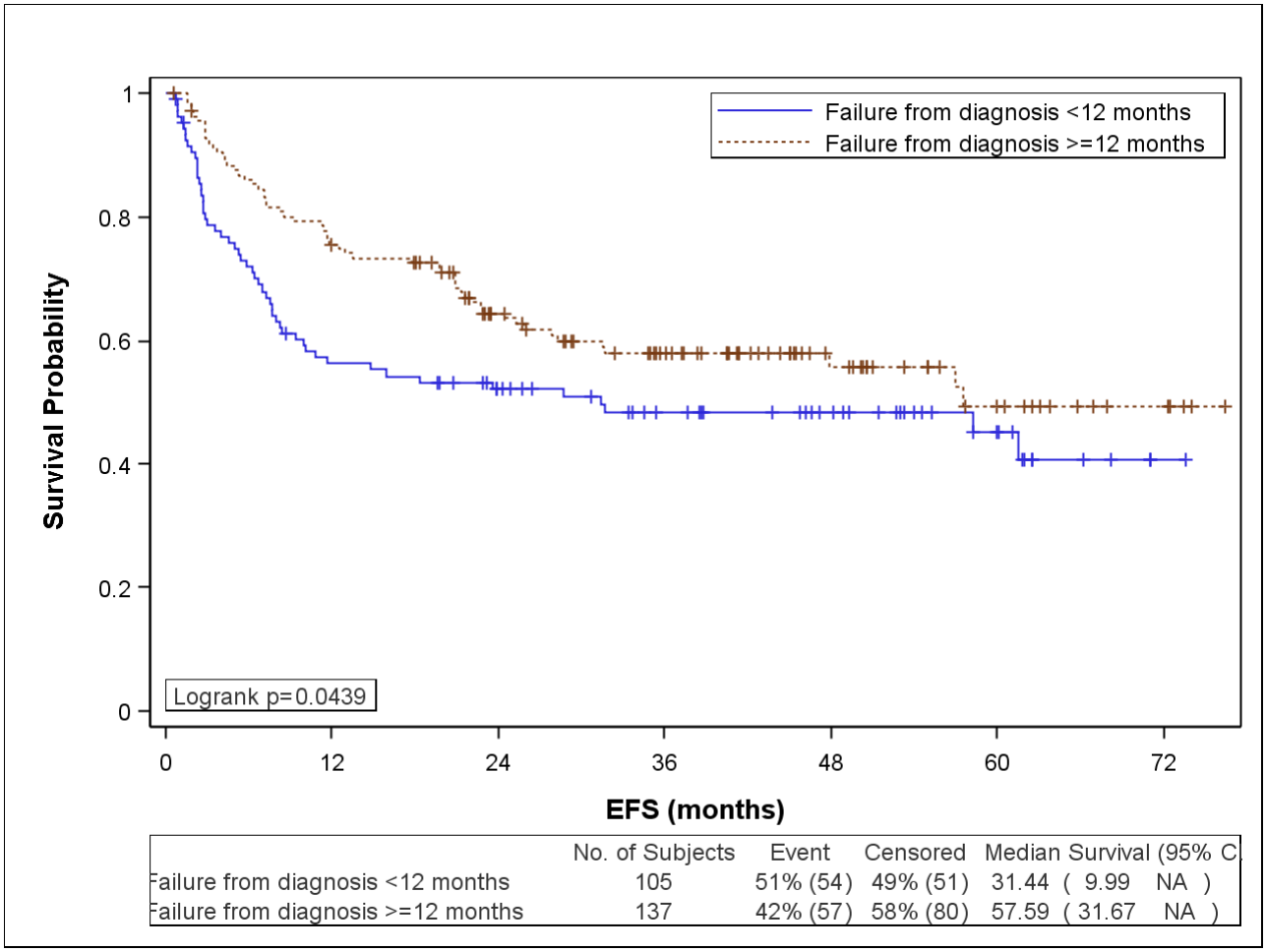


Table 4.5-66 Exploratory analyses – Duration of Event-Free Survival according to failure from diagnosis (MITT)

Failure from diagnosis	N	Median	95% CI lower	95% CI Upper	Min	Max
< 12 months	105	31	10	-	1	74
>= 12 months	137	58	32	-	1	76

Table 4.5-67 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to failure from diagnosis (MITT)

Failure from diagnosis	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
< 12 months	12	56.3	46.1	65.2	57
< 12 months	24	52.2	42.1	61.4	46
< 12 months	36	48.4	38.2	57.9	34
< 12 months	48	48.4	38.2	57.9	25
< 12 months	60	45.2	33.9	55.8	13
< 12 months	72	40.7	27.7	53.3	1
>= 12 months	12	75.6	67.4	82.0	101
>= 12 months	24	64.5	55.6	72.0	72

Failure from diagnosis	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
>= 12 months	36	57.9	48.7	66.0	52
>= 12 months	48	55.9	46.1	64.5	28
>= 12 months	60	49.3	37.1	60.4	13
>= 12 months	72	49.3	37.1	60.4	5

Table 4.5-68 Exploratory analyses – Hazard ratio of failure from diagnosis <12 months for Event-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Failure from diagnosis < 12 months	0.0453	1.463	1.008	2.124

Figure 4.5-20 Exploratory analyses – Progression-Free Survival according to failure from diagnosis (MITT)

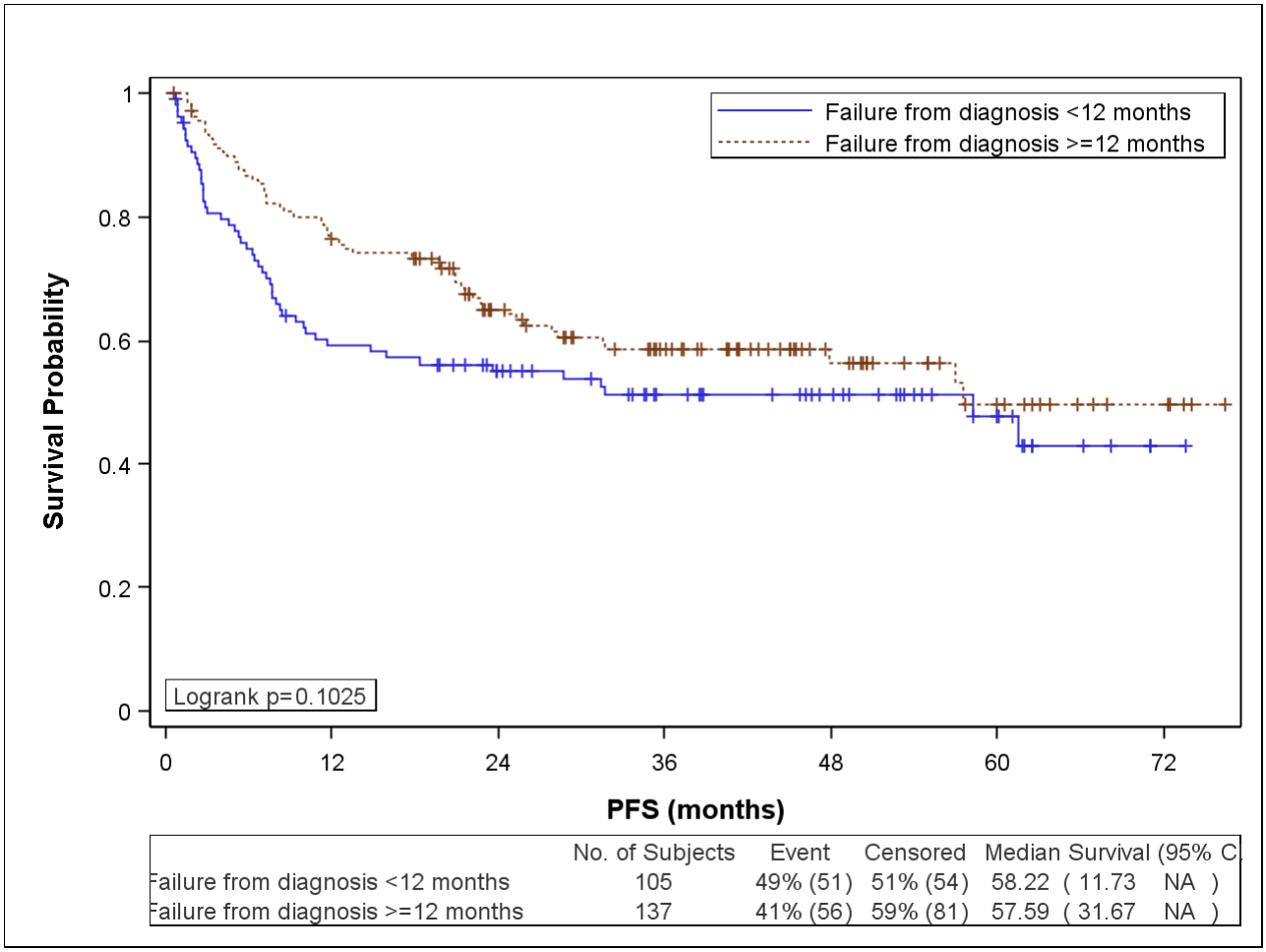


Table 4.5-69 Exploratory analyses – Duration of Progression-Free Survival according to failure from diagnosis (MITT)

Failure from diagnosis	N	Median	95% CI lower	95% CI Upper	Min	Max
< 12 months	105	58	12	-	1	74
>= 12 months	137	58	32	-	1	76

Table 4.5-70 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to failure from diagnosis (MITT)

Failure from diagnosis	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
< 12 months	12	59.2	49.0	68.0	60
< 12 months	24	55.1	45.0	64.2	48
< 12 months	36	51.3	41.0	60.7	34
< 12 months	48	51.3	41.0	60.7	25
< 12 months	60	47.9	36.3	58.6	13
< 12 months	72	43.1	29.5	56.0	1
>= 12 months	12	76.3	68.2	82.6	102
>= 12 months	24	65.1	56.3	72.6	72
>= 12 months	36	58.5	49.2	66.6	52
>= 12 months	48	56.4	46.7	65.1	28
>= 12 months	60	49.8	37.5	61.0	13
>= 12 months	72	49.8	37.5	61.0	5

Table 4.5-71 Exploratory analyses – Hazard ratio of no failure from diagnosis <12 months for Progression-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Failure from diagnosis < 12 months	0.1041	1.370	0.937	2.003

Figure 4.5-21 Exploratory analyses – Overall Survival according to failure from diagnosis (MITT)

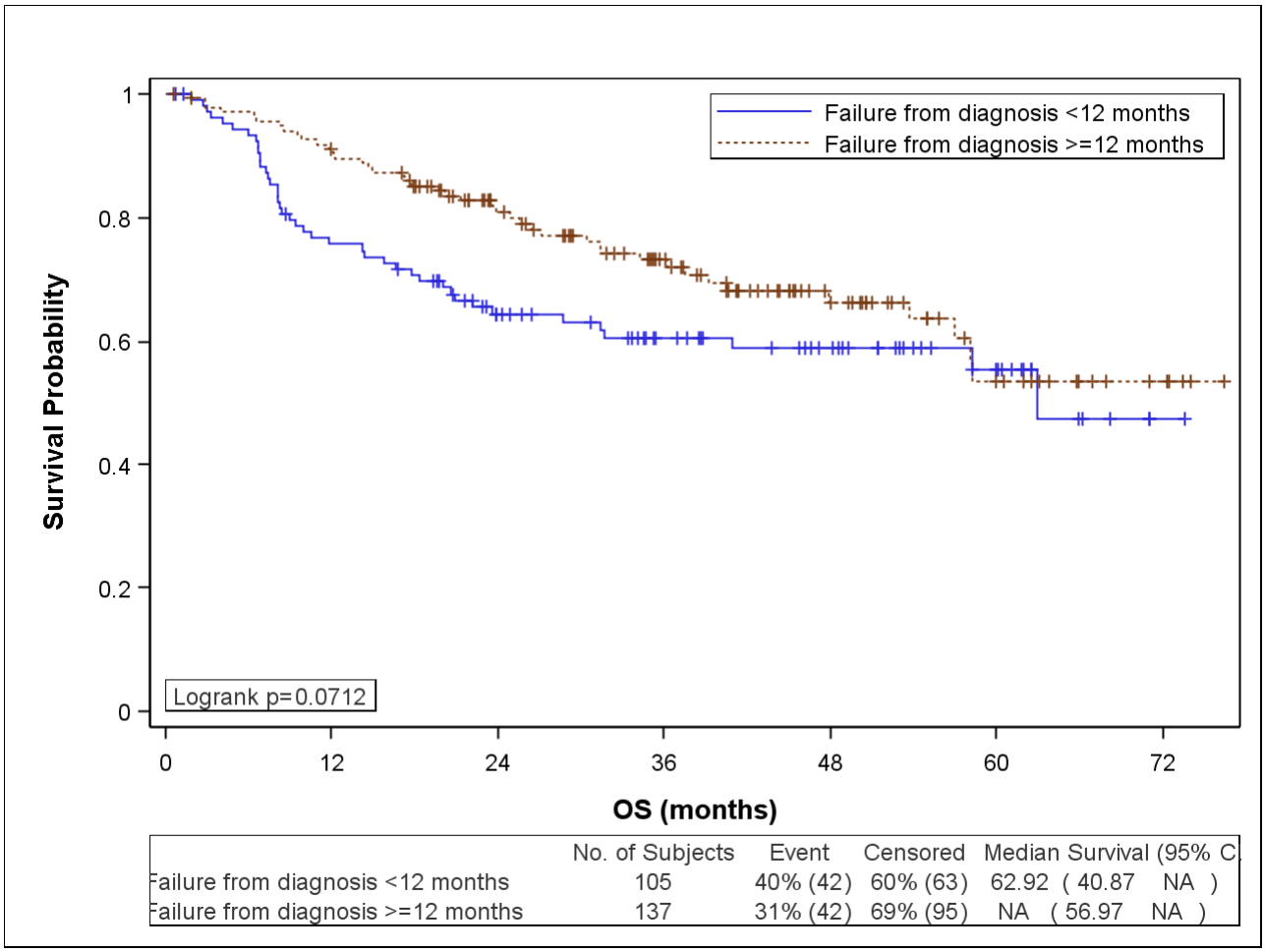


Table 4.5-72 Exploratory analyses – Duration of Overall Survival according to failure from diagnosis (MITT)

Failure from diagnosis	N	Median	95% CI lower	95% CI Upper	Min	Max
< 12 months	105	63	41	-	1	74
>= 12 months	137	-	57	-	1	76

Table 4.5-73 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to failure from diagnosis (MITT)

Failure from diagnosis	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
< 12 months	12	75.7	66.2	82.9	77
< 12 months	24	64.4	54.2	72.9	55
< 12 months	36	60.5	50.0	69.5	40
< 12 months	48	58.8	48.1	68.1	29
< 12 months	60	55.4	43.1	66.0	15
< 12 months	72	47.4	29.5	63.4	1
>= 12 months	12	91.1	84.9	94.9	122
>= 12 months	24	80.9	73.0	86.7	90
>= 12 months	36	73.1	64.2	80.2	64
>= 12 months	48	66.3	56.1	74.7	34

Failure from diagnosis	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
>= 12 months	60	53.7	39.3	66.0	15
>= 12 months	72	53.7	39.3	66.0	5

Table 4.5-74 Exploratory analyses – Hazard ratio of no failure from diagnosis<12 months for Overall Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Failure from diagnosis < 12 months	0.0730	1.480	0.964	2.270

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)

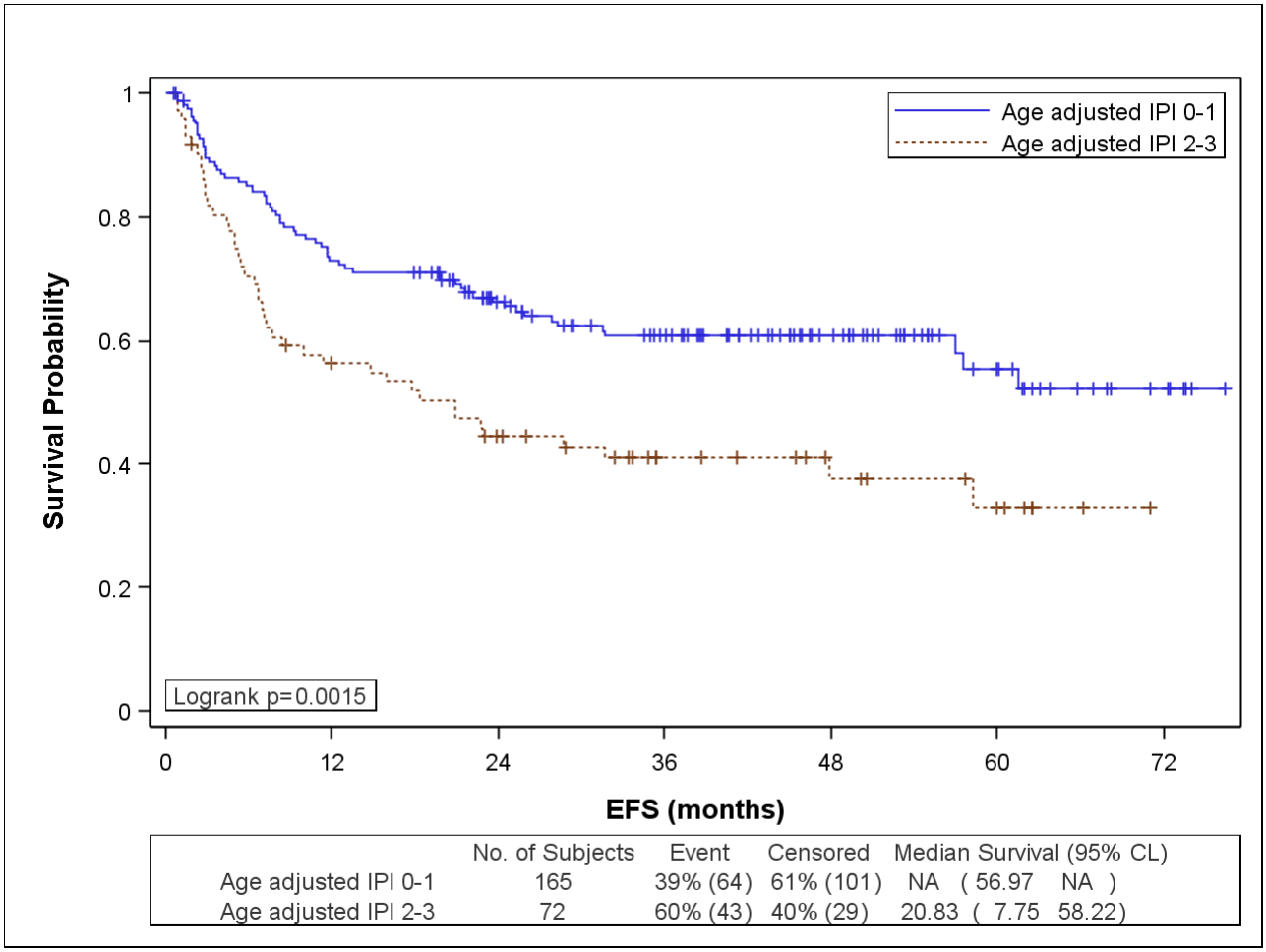


Table 4.5-75 Exploratory analyses – Duration of Event-Free Survival according to age-adjusted IPI (MITT)

Age-adjusted IPI	N	Median	95% CI lower	95% CI Upper	Min	Max
0-1	165	-	57	-	1	76
2-3	72	21	8	58	1	71

Table 4.5-76 Exploratory analyses – Kaplan-Meier estimates for Event-Free Survival according to age-adjusted IPI (MITT)

Age-adjusted IPI	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
0-1	12	72.8	65.3	79.0	118
0-1	24	66.3	58.3	73.0	89
0-1	36	60.7	52.5	68.0	69
0-1	48	60.7	52.5	68.0	42
0-1	60	55.4	44.9	64.8	19
0-1	72	52.2	40.4	62.7	6
2-3	12	56.3	44.0	66.9	38
2-3	24	44.5	32.6	55.7	28
2-3	36	41.0	29.3	52.4	17
2-3	48	37.6	25.3	49.8	11
2-3	60	32.9	19.6	46.8	7
2-3	72	32.9	19.6	46.8	0

Table 4.5-77 Exploratory analyses – Hazard ratio of no age-adjusted IPI for Event-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age adjusted IPI 0-1	0.0018	0.539	0.366	0.794

Figure 4.5-23 Exploratory analyses – Progression-Free Survival according to age-adjusted IPI (MITT)

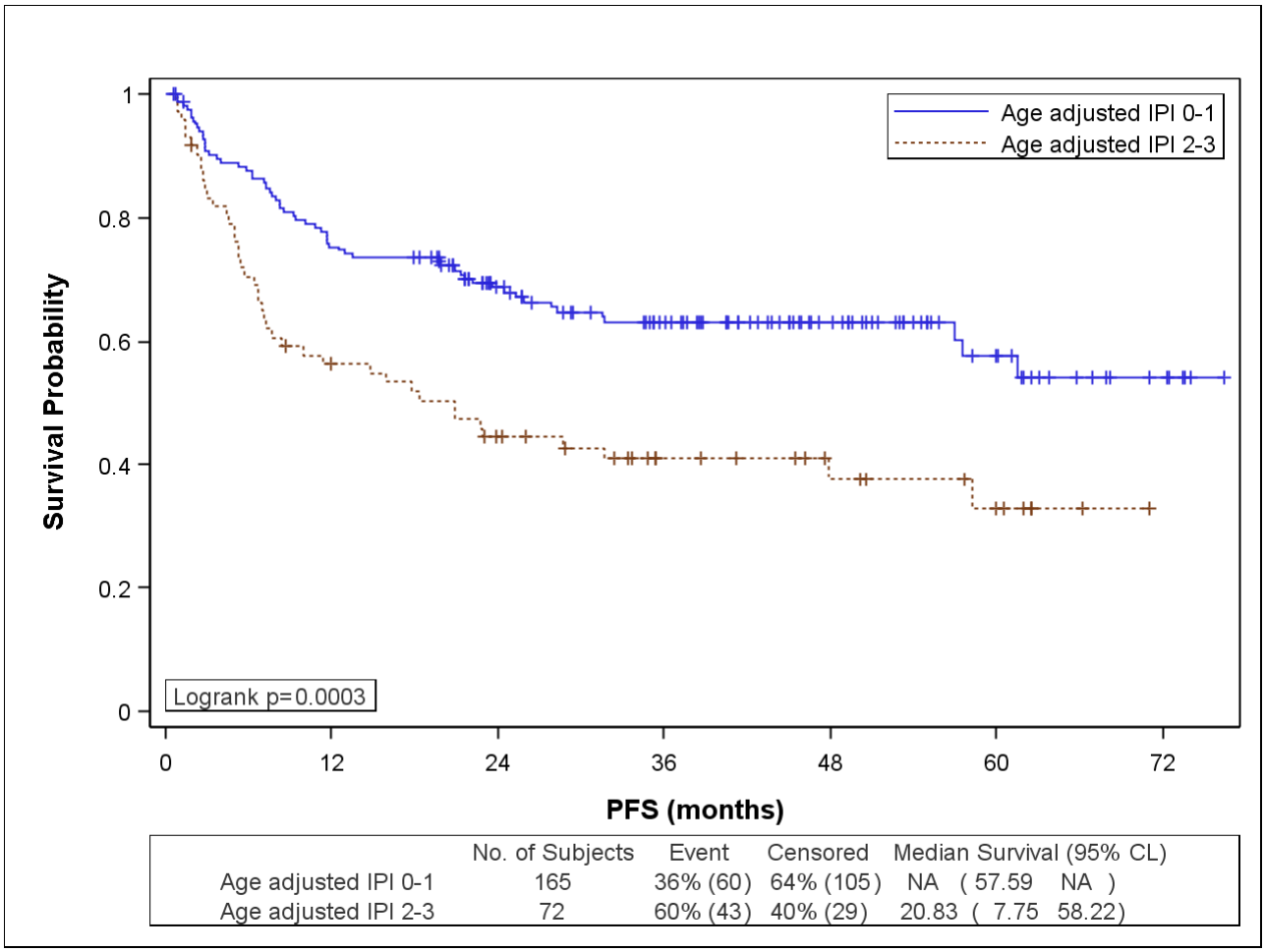


Table 4.5-78 Exploratory analyses – Duration of Progression-Free Survival according to age-adjusted IPI (MITT)

Age-adjusted IPI	N	Median	95% CI lower	95% CI Upper	Min	Max
0-1	165	-	58	-	1	76
2-3	72	21	8	58	1	71

Table 4.5-79 Exploratory analyses – Kaplan-Meier estimates for Progression-Free Survival according to age-adjusted IPI (MITT)

Age-adjusted IPI	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
0-1	12	75.3	67.9	81.2	122
0-1	24	68.7	60.9	75.3	91
0-1	36	63.1	54.8	70.3	69
0-1	48	63.1	54.8	70.3	42
0-1	60	57.6	46.8	67.0	19
0-1	72	54.2	42.1	64.9	6
2-3	12	56.3	44.0	66.9	38
2-3	24	44.5	32.6	55.7	28
2-3	36	41.0	29.3	52.4	17
2-3	48	37.6	25.3	49.8	11

Age-adjusted IPI	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
2-3	60	32.9	19.6	46.8	7
2-3	72	32.9	19.6	46.8	0

Table 4.5-80 Exploratory analyses – Hazard ratio of no age-adjusted IPI for Progression-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age adjusted IPI 0-1	0.0004	0.493	0.333	0.730

Figure 4.5-24 Exploratory analyses – Overall Survival according to age-adjusted IPI (MITT)

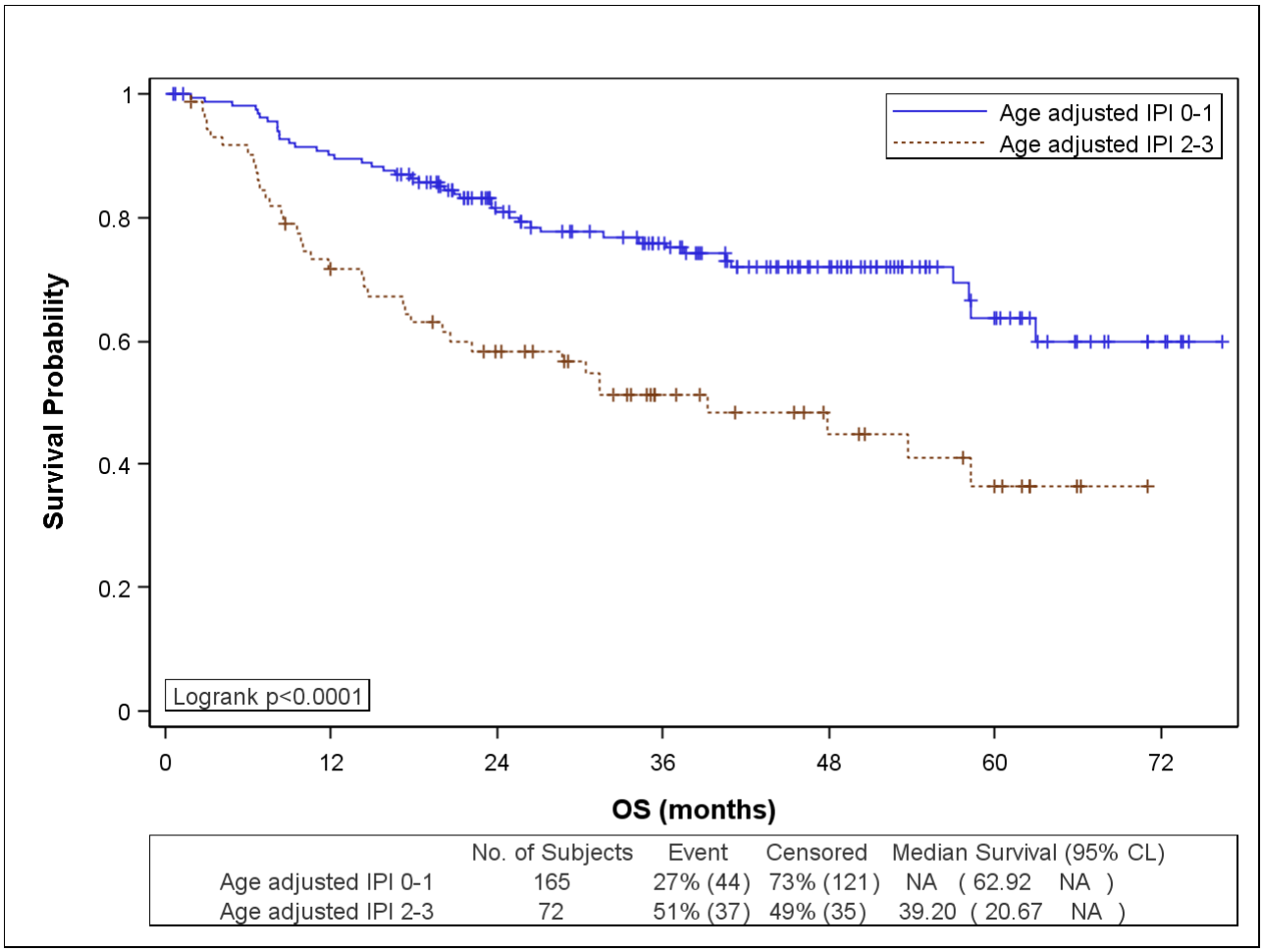


Table 4.5-81 Exploratory analyses – Duration of Overall Survival according to age-adjusted IPI (MITT)

Age-adjusted IPI	N	Median	95% CI lower	95% CI Upper	Min	Max
0-1	165	-	63	-	1	76
2-3	72	39	21	-	2	71

Table 4.5-82 Exploratory analyses – Kaplan-Meier estimates for Overall Survival according to age-adjusted IPI (MITT)

Age-adjusted IPI	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
0-1	12	90.1	84.4	93.8	146
0-1	24	80.8	73.6	86.2	106
0-1	36	76.0	68.2	82.1	83
0-1	48	72.0	63.5	78.8	50
0-1	60	63.8	51.8	73.6	22
0-1	72	59.9	45.9	71.3	6
2-3	12	71.7	59.7	80.7	49
2-3	24	58.4	46.0	69.0	37
2-3	36	51.2	38.6	62.5	21
2-3	48	45.1	31.4	57.8	13
2-3	60	36.4	21.6	51.4	8
2-3	72	36.4	21.6	51.4	0

Table 4.5-83 Exploratory analyses – Hazard ratio of no age-adjusted IPI for Overall Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age adjusted IPI 0-1	<.0001	0.413	0.266	0.640

4.5.3.3. Multivariate Cox models

Table 4.5-84 Exploratory analyses – Multivariate Cox model for Event-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior treatment with Rituximab: No	0.1979	0.748	0.481	1.164
Failure from diagnosis < 12 months	0.4658	1.179	0.757	1.836
Age-adjusted IPI 2-3	**0.0030**	1.846	1.231	2.769
Response after complete induction: PR	0.2050	1.295	0.868	1.933
Arm of treatment: ARM A / R-ICE	0.0853	1.417	0.953	2.106
Arm of 2nd randomization: RITUXIMAB	0.9208	1.020	0.685	1.520

Table 4.5-85 Exploratory analyses – Multivariate Cox model for Progression-Free Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior treatment with Rituximab: No	0.3509	0.808	0.516	1.265
Failure from diagnosis < 12 months	0.4536	1.188	0.757	1.863
Age-adjusted IPI 2-3	**0.0007**	2.028	1.348	3.052
Response after complete induction: PR	0.4286	1.180	0.784	1.776
Arm of treatment: ARM A / R-ICE	0.0676	1.457	0.973	2.181
Arm of 2nd randomization: RITUXIMAB	0.6104	1.111	0.741	1.666

Table 4.5-86 Exploratory analyses – Multivariate Cox model for Overall Survival (MITT)

Parameter	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Prior treatment with Rituximab: No	0.2874	0.760	0.459	1.260
Failure from diagnosis < 12 months	0.5665	1.159	0.700	1.917
Age-adjusted IPI 2-3	**0.0004**	2.252	1.433	3.539
Response after complete induction: PR	0.4638	1.186	0.752	1.871
Arm of treatment: ARM A / R-ICE	0.0716	1.511	0.964	2.368
Arm of 2nd randomization: RITUXIMAB	0.4822	1.175	0.749	1.842

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)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
New treatment out of progression				
Yes	1	1	4	3
No	121	99	116	97
Total	122	100	120	100

Table 4.5-88 Type of non study or new treatment out of progression (MITT)

	Arm of 2nd randomization					
	RITUXIMAB		OBSERVATION		NOT APPLICABLE	
	N	%	N	%	N	%
Chemotherapy						
No	0	0	4	100	0	0
Yes	1	100	0	0	0	0
Radiotherapy						
Yes	0	0	4	100	0	0
No	1	100	0	0	0	0
Immunotherapy						
No	1	100	4	100	0	0
Transplantation						
No	1	100	4	100	0	0
Other treatment						
No	1	100	4	100	0	0
Total	1	100	4	100	0	0

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)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Progression/relapse n°1				
Yes	47	39	46	38
No	75	61	74	62
Progression/relapse n°2				
Yes	11	9	9	8
No	111	91	111	93
Progression/relapse n°3				
Yes	4	3	3	3
No	118	97	117	98
Progression/relapse n°4				
Yes	1	1	1	1
No	121	99	119	99
Progression/relapse n°5				
Yes	0	0	1	1
No	122	100	119	99
Total	122	100	120	100

Table 4.5-90 Progression/relapse n°1 – Period (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Period of Progression / Relapse				
TREATMENT PERIOD	8	17	2	4
FOLLOW UP PERIOD	39	83	44	96
Total	47	100	46	100

Table 4.5-91 Progression/relapse n°1 –Involvement (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Initial involvement				
Yes	31	66	25	54
No	16	34	21	46
New involvement				
Yes	28	60	22	48
No	19	40	24	52
Nodal involvement				
Yes	34	72	29	63
No	13	28	17	37
Extra-nodal involvement				
Yes	27	57	27	59
No	20	43	19	41
Total	47	100	46	100

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)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
LDH > Upper Limit				
Not Done	3	6	3	7
Yes	24	51	21	46
No	20	43	22	48
Stage III - IV				
Not Done	2	4	2	4
Yes	29	62	29	63
No	16	34	15	33
PS >= 2				
Missing	0	0	1	2
Not Done	4	9	2	4
Yes	9	19	12	26
No	34	72	31	67
Extra-nodal sites >= 2				
Not Done	1	2	1	2
Yes	14	30	12	26
No	32	68	33	72
Total	47	100	46	100

Table 4.5-93 Progression/relapse n°1 – Progression/relapse treatment (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Progression / Relapse treatment				
Missing	2	4	1	2
Yes	44	94	44	96
No	1	2	1	2
Total	47	100	46	100

Table 4.5-94 Progression/relapse n°1 – Type of progression/relapse treatment (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Chemotherapy				
Not Done	0	0	1	2
Yes	35	80	32	73
No	9	20	11	25
Radiotherapy				
Not Done	0	0	1	2
Yes	12	27	15	34
No	32	73	28	64
Immunotherapy				
Not Done	0	0	1	2
Yes	10	23	12	27
No	34	77	31	70
Transplantation				
Not Done	0	0	1	2
Yes	11	25	4	9
No	33	75	39	89
Other treatment				
Not Done	0	0	1	2
Yes	8	18	5	11
No	36	82	38	86
Total	44	100	44	100

Details of treatment are listed in section §6.6.3.

Table 4.5-95 Progression/relapse n°1 – Response after additional treatments (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Response after new treatment				
COMPLETE RESPONSE	9	20	9	20
UNCONFIRMED COMPLETE RESPONSE	1	2	2	5
PARTIAL RESPONSE	7	16	6	14
STABLE DISEASE	2	5	5	11
PROGRESSIVE DISEASE	21	48	13	30
NOT EVALUATED	4	9	8	18
Missing	0	0	1	2
Total	44	100	44	100

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.

Table 5.1-1 Number of maintenance visits (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Nb of maintenance visits				
1	16	14	5	4
2	9	8	19	16
3	2	2	22	18
4	9	8	21	18
5	2	2	22	18
6	78	67	30	25
Total	116	100	119	100

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):

Table 5.1-2 Last maintenance visit (MSAP)

Last maintenance visit	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Cycle 1				
Yes	116	100	119	100
Cycle 2				
Yes	100	86	116	97
No	16	14	3	3
Cycle 3				
Yes	91	78	102	86
No	25	22	17	14
Cycle 4				
Yes	89	77	88	74
No	27	23	31	26
Cycle 5				
Yes	80	69	67	56
No	36	31	52	44
Cycle 6				
Yes	78	67	48	40
No	38	33	71	60

Table 5.1-3 Time between maintenance visits (MSAP)

		Actual arm of maintenance	
		RITUXIMAB	OBSERVATION
Time between cycles 1 and 2 (days)	**N**	100	114
	Mean	58.7	66.9
	Std	8.27	28.21
	Median	56.0	63.0
	Min	14	23
	Max	90	201
Time between cycles 2 and 3 (days)	**N**	91	95
	Mean	58.6	78.1
	Std	10.29	31.37
	Median	56.0	70.0
	Min	40	33
	Max	142	203
Time between cycles 3 and 4 (days)	**N**	89	73
	Mean	59.6	68.9
	Std	8.87	23.98
	Median	56.0	63.0
	Min	52	20
	Max	112	174
Time between cycles 4 and 5 (days)	**N**	80	52
	Mean	60.3	76.6
	Std	11.39	32.66
	Median	56.0	70.0
	Min	35	28
	Max	132	182
Time between cycles 5 and 6 (days)	**N**	77	30
	Mean	58.7	71.2
	Std	5.47	31.24
	Median	56.0	63.0
	Min	49	22
	Max	78	203

Table 5.1-4 Maintenance - Percentage of planned dose received by cycle for rituximab (MSAP)

Dose received (% of planned dose)			Actual arm of maintenance RITUXIMAB
Rituximab	**Cycle 1**	**N**	116
		Mean	98.6
		Std	4.04
		Median	99.5
		Min	85
		Max	107
	Cycle 2	**N**	100
		Mean	98.6
		Std	4.33
		Median	99.8
		Min	85
		Max	107
	Cycle 3	**N**	91
		Mean	98.8
		Std	4.27
		Median	99.8
		Min	85
		Max	107
	Cycle 4	**N**	89
		Mean	98.7
		Std	4.36
		Median	99.9
		Min	85
		Max	107
	Cycle 5	**N**	80
		Mean	98.6
		Std	4.44
		Median	99.6
		Min	85
		Max	107
	Cycle 6	**N**	78
		Mean	98.7
		Std	4.50
		Median	99.7
		Min	85
		Max	107

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 5.2-1 Incidence of toxicities during consolidation phase (MSAP)

		Actual arm of maintenance																	
		RITUXIMAB									OBSERVATION								
		Grade									Grade								
		All Tox.	0	1	2	3	4	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade Infection	N	91	25	3	21	62	5	67	0	116	90	28	9	12	66	3	69	1	119
	%	78	22	3	18	53	4	58	0	100	76	24	8	10	55	3	58	1	100
Grade Neurologic	N	3	113	2	1	0	0	0	0	116	9	109	4	4	1	0	1	1	119
	%	3	97	2	1	0	0	0	0	100	8	92	3	3	1	0	1	1	100
Grade Mucositis	N	80	36	20	38	19	3	22	0	116	91	27	19	40	21	11	32	1	119
	%	69	31	17	33	16	3	19	0	100	76	23	16	34	18	9	27	1	100
Grade Hepatic	N	18	98	10	7	1	0	1	0	116	24	94	12	6	6	0	6	1	119
	%	16	84	9	6	1	0	1	0	100	20	79	10	5	5	0	5	1	100
Grade Gastrointestinal	N	69	47	20	33	16	0	16	0	116	72	46	15	35	18	4	22	1	119
	%	59	41	17	28	14	0	14	0	100	61	39	13	29	15	3	18	1	100
Grade Renal	N	16	100	9	5	2	0	2	0	116	18	100	9	8	1	0	1	1	119
	%	14	86	8	4	2	0	2	0	100	15	84	8	7	1	0	1	1	100
Grade Cardiovascular	N	18	98	7	7	4	0	4	0	116	13	105	4	6	3	0	3	1	119
	%	16	84	6	6	3	0	3	0	100	11	88	3	5	3	0	3	1	100
Other toxicity	N	34	1	9	17	7	1	8	81	116	37	0	11	14	8	4	12	82	119
	%	29	1	8	15	6	1	7	70	100	31	0	9	12	7	3	10	69	100

Table 5.2-2 Patients with RBC and platelets transfusions during consolidation (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
At least one RBC transfusion				
No	20	17	17	14
Yes	96	83	100	84
.	0	0	2	2
At least one platelets transfusion				
No	3	3	4	3
Yes	113	97	113	95
.	0	0	2	2
Total	116	100	119	100

Table 5.2-3 Time intervals for hematological recovery after transplant (MSAP)

		Actual arm of maintenance	
		RITUXIMAB	OBSERVATION
Neutrophils > 1 Giga/l (days after transplant)	**N**	113	110
	Mean	15.0	24.0
	Std	15.41	77.04
	Median	11.0	12.0
	Min	0	0
	Max	144	733
Neutrophils > 0.5 Giga/l (days after transplant)	**N**	112	111
	Mean	11.6	21.8
	Std	5.43	76.71
	Median	11.0	11.0
	Min	-30	-22
	Max	28	733
Platelets > 20 Giga/l (days after transplant)	**N**	114	114
	Mean	12.6	22.9
	Std	6.87	75.69
	Median	11.0	12.0
	Min	1	0
	Max	48	733

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)

		Actual arm of maintenance																		
		RITUXIMAB										OBSERVATION								
		Grade										Grade								
		All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade allergy	**N**	1	109	0	0	1	0	0	1	6	116	1	95	0	0	1	0	1	23	119
	%	1	94	0	0	1	0	0	1	5	100	1	80	0	0	1	0	1	19	100
Grade auditory	**N**	8	102	2	4	2	0	0	2	6	116	0	96	0	0	0	0	0	23	119
	%	7	88	2	3	2	0	0	2	5	100	0	81	0	0	0	0	0	19	100
Grade blood	**N**	79	31	18	13	25	23	0	48	6	116	56	41	14	16	9	17	26	22	119
	%	68	27	16	11	22	20	0	41	5	100	47	34	12	13	8	14	22	18	100
Grade cardiovascular	**N**	5	105	3	2	0	0	0	0	6	116	5	92	1	3	0	1	1	22	119
	%	4	91	3	2	0	0	0	0	5	100	4	77	1	3	0	1	1	18	100
Grade coagulation	**N**	6	103	3	0	3	0	0	3	7	116	1	94	1	0	0	0	0	24	119
	%	5	89	3	0	3	0	0	3	6	100	1	79	1	0	0	0	0	20	100
Grade skin	**N**	21	89	15	6	0	0	0	0	6	116	20	77	12	6	2	0	2	22	119
	%	18	77	13	5	0	0	0	0	5	100	17	65	10	5	2	0	2	18	100
Grade gastrointestinal	**N**	33	77	22	11	0	0	0	0	6	116	31	66	15	12	2	2	4	22	119
	%	28	66	19	9	0	0	0	0	5	100	26	55	13	10	2	2	3	18	100
Grade hepatic	**N**	14	96	11	2	1	0	0	1	6	116	13	84	9	2	1	1	2	22	119
	%	12	83	9	2	1	0	0	1	5	100	11	71	8	2	1	1	2	18	100
Grade infection	**N**	43	67	7	27	6	1	2	9	6	116	30	67	10	11	7	2	9	22	119
	%	37	58	6	23	5	1	2	8	5	100	25	56	8	9	6	2	8	18	100
Grade viral infection	**N**	9	101	2	4	2	1	0	3	6	116	8	89	1	6	1	0	1	22	119
	%	8	87	2	3	2	1	0	3	5	100	7	75	1	5	1	0	1	18	100
Grade metabolic	**N**	20	90	13	3	3	1	0	4	6	116	13	84	10	2	1	0	1	22	119
	%	17	78	11	3	3	1	0	3	5	100	11	71	8	2	1	0	1	18	100

		Actual arm of maintenance																	
		RITUXIMAB									OBSERVATION								
		Grade									Grade								
		All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade neurology	**N**	20	90	11	6	2	0	1	3	6	116	15	82	7	7	1	0	1	22	119
	%	17	78	9	5	2	0	1	3	5	100	13	69	6	6	1	0	1	18	100
Grade pulmonary	**N**	18	92	10	5	1	2	0	3	6	116	15	82	10	4	0	1	1	22	119
	%	16	79	9	4	1	2	0	3	5	100	13	69	8	3	0	1	1	18	100
Grade renal	**N**	10	100	6	1	3	0	0	3	6	116	10	87	8	2	0	0	0	22	119
	%	9	86	5	1	3	0	0	3	5	100	8	73	7	2	0	0	0	18	100
Other Toxicity	**N**	41	69	15	20	5	0	1	6	6	116	37	60	20	16	1	0	1	22	119
	%	35	59	13	17	4	0	1	5	5	100	31	50	17	13	1	0	1	18	100

NE = Not Evaluated

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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
At least one neutrophils value <1 G/L during M3-M12 post transplant				
Yes	36	31	30	25
No	80	69	89	75
Total	116	100	119	100

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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
At least one neutrophils value <1 G/L during M3-M12 post transplant (excluding values after additional treatment)				
Yes	11	9	7	6
No	105	91	112	94
Total	116	100	119	100

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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
At least one RBC transfusion				
No	2	2	3	3
Yes	11	9	17	14
.	103	89	99	83
At least one platelets transfusion				
No	7	6	8	7
Yes	6	5	12	10
.	103	89	99	83
Total	116	100	119	100

5.2.2. Description of adverse events

Among maintenance safety population, ***regarding only AEs post 2nd 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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Patient with at least one AE				
Yes	67	58	58	49
No	49	42	61	51
Patient with at least one AE within 100 days after ASCT				
Yes	54	47	50	42
No	62	53	69	58
Patient with at least one AE more than 100 days after ASCT				
Yes	35	30	20	17
No	81	70	99	83
Total	116	100	119	100

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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Total number of AEs	162	100	99	100

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
System Organ Class					
INFECTIONS AND INFESTATIONS	**Total number of AEs**	76	47	37	37
	Preferred Term				
	INFECTION	10	6	3	3
	HERPES ZOSTER	5	3	6	6
	BRONCHITIS	5	3	1	1
	SEPSIS	2	1	3	3
	PNEUMONIA	4	2	1	1
	LOWER RESPIRATORY TRACT INFECTION	4	2	1	1
	CATHETER RELATED INFECTION	2	1	2	2
	NEUTROPENIC INFECTION	2	1	2	2
	FOLLICULITIS	2	1	1	1
	BRONCHOPNEUMONIA	2	1	1	1
	ESCHERICHIA URINARY TRACT INFECTION	1	1	2	2
	CENTRAL LINE INFECTION	2	1	1	1
	NEUTROPENIC SEPSIS	3	2	0	0
	CATHETER SEPSIS	2	1	1	1
	CANDIDIASIS	3	2	0	0
	ORAL HERPES	2	1	0	0
	URINARY TRACT INFECTION	1	1	1	1
	SEPTIC SHOCK	1	1	1	1
	SINUSITIS	2	1	0	0
	HAEMOPHILUS INFECTION	2	1	0	0
	CYTOMEGALOVIRUS INFECTION	1	1	1	1
	RESPIRATORY TRACT INFECTION	2	1	0	0
	PSEUDOMONAS INFECTION	1	1	0	0
	BRONCHOPULMONARY ASPERGILLOSIS	1	1	0	0
	BRONCHITIS PNEUMOCOCCAL	1	1	0	0
	PERTUSSIS	1	1	0	0
	ESCHERICHIA SEPSIS	1	1	0	0
	GASTROENTERITIS	1	1	0	0
	STAPHYLOCOCCAL SEPSIS	0	0	1	1
	CLOSTRIDIAL INFECTION	0	0	1	1
	INFLUENZA	0	0	1	1
	STAPHYLOCOCCAL INFECTION	1	1	0	0

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
	DIARRHOEA INFECTIOUS	1	1	0	0
	PNEUMONIA PNEUMOCOCCAL	0	0	1	1
	STREPTOCOCCAL SEPSIS	1	1	0	0
	VARICELLA	0	0	1	1
	ENTEROCOLITIS INFECTIOUS	0	0	1	1
	PNEUMOCYSTIS JIROVECI PNEUMONIA	1	1	0	0
	GASTROENTERITIS VIRAL	0	0	1	1
	PNEUMONIA FUNGAL	1	1	0	0
	BACTERAEMIA	0	0	1	1
	PNEUMONIA BACTERIAL	1	1	0	0
	VIRAL INFECTION	1	1	0	0
	UPPER RESPIRATORY TRACT INFECTION	1	1	0	0
	PNEUMONIA INFLUENZAL	0	0	1	1
	BRONCHIECTASIS	1	1	0	0
	LOCALISED INFECTION	1	1	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total number of AEs	36	22	19	19
	Preferred Term				
	FEBRILE NEUTROPENIA	8	5	12	12
	NEUTROPENIA	14	9	1	1
	LEUKOPENIA	4	2	2	2
	THROMBOCYTOPENIA	3	2	1	1
	LYMPHOPENIA	3	2	0	0
	HAEMATOTOXICITY	1	1	1	1
	ANAEMIA	0	0	2	2
	FEBRILE BONE MARROW APLASIA	2	1	0	0
	THROMBOTIC THROMBOCYTOPENIC PURPURA	1	1	0	0

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
GASTROINTESTINAL DISORDERS	Total number of AEs	14	9	9	9
	Preferred Term				
	DIARRHOEA	3	2	4	4
	STOMATITIS	3	2	1	1
	NAUSEA	2	1	0	0
	VOMITING	1	1	1	1
	GASTROINTESTINAL DISORDER	1	1	0	0
	ABDOMINAL PAIN	1	1	0	0
	ILEUS	0	0	1	1
	FAECALOMA	1	1	0	0
	DENTAL CARIES	0	0	1	1
	GASTROINTESTINAL HAEMORRHAGE	1	1	0	0
	GASTROINTESTINAL INFLAMMATION	0	0	1	1
	GINGIVAL PAIN	1	1	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Total number of AEs	9	6	11	11
	Preferred Term				
	MUCOSAL INFLAMMATION	4	2	7	7
	PYREXIA	3	2	2	2
	ASTHENIA	1	1	0	0
	HYPERTHERMIA	0	0	1	1
	INFLAMMATION	0	0	1	1
	CATHETER SITE HAEMORRHAGE	1	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Total number of AEs	5	3	2	2
	Preferred Term				
	BRONCHOPNEUMOPATHY	1	1	1	1
	LUNG DISORDER	1	1	1	1
	INTERSTITIAL LUNG DISEASE	1	1	0	0
	LUNG INFILTRATION	1	1	0	0
	COUGH	1	1	0	0
NERVOUS SYSTEM DISORDERS	Total number of AEs	3	2	3	3
	Preferred Term				
	LOSS OF CONSCIOUSNESS	0	0	1	1
	CEREBRAL ISCHAEMIA	0	0	1	1
	TRANSIENT ISCHAEMIC ATTACK	1	1	0	0
	LEUKOENCEPHALOPATHY	1	1	0	0
	PARESIS	0	0	1	1
	HYPOAESTHESIA	1	1	0	0

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
METABOLISM AND NUTRITION DISORDERS	Total number of AEs	3	2	2	2
	Preferred Term				
	HYPOKALAEMIA	1	1	1	1
	ANOREXIA	1	1	0	0
	FOOD INTOLERANCE	0	0	1	1
	HYPERMAGNESAEMIA	1	1	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Total number of AEs	3	2	2	2
	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	1
	MYELODYSPLASTIC SYNDROME	0	0	1	1
IMMUNE SYSTEM DISORDERS	Total number of AEs	3	2	1	1
	Preferred Term				
	HYPOGAMMAGLOBULINAEMIA	3	2	1	1
INVESTIGATIONS	Total number of AEs	2	1	2	2
	Preferred Term				
	CYTOMEGALOVIRUS TEST POSITIVE	0	0	1	1
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	1	1	0	0
	C-REACTIVE PROTEIN INCREASED	1	1	0	0
	LIVER FUNCTION TEST ABNORMAL	0	0	1	1
CARDIAC DISORDERS	Total number of AEs	1	1	2	2
	Preferred Term				
	MYOCARDIAL INFARCTION	0	0	1	1
	MYOCARDITIS	1	1	0	0
	ATRIAL FIBRILLATION	0	0	1	1
VASCULAR DISORDERS	Total number of AEs	2	1	1	1
	Preferred Term				
	JUGULAR VEIN THROMBOSIS	1	1	0	0
	HYPOTENSION	1	1	0	0
	THROMBOSIS	0	0	1	1

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Total number of AEs	1	1	2	2
	Preferred Term				
	DRUG TOXICITY	1	1	0	0
	THROMBOSIS IN DEVICE	0	0	1	1
	SUBDURAL HAEMATOMA	0	0	1	1
RENAL AND URINARY DISORDERS	Total number of AEs	2	1	1	1
	Preferred Term				
	RENAL FAILURE	1	1	0	0
	RENAL FAILURE ACUTE	0	0	1	1
	RENAL TUBULAR ACIDOSIS	1	1	0	0
EAR AND LABYRINTH DISORDERS	Total number of AEs	1	1	1	1
	Preferred Term				
	DEAFNESS	0	0	1	1
	TINNITUS	1	1	0	0
HEPATOBILIARY DISORDERS	Total number of AEs	0	0	2	2
	Preferred Term				
	HEPATITIS	0	0	1	1
	LIVER DISORDER	0	0	1	1
PSYCHIATRIC DISORDERS	Total number of AEs	0	0	1	1
	Preferred Term				
	CONFUSIONAL STATE	0	0	1	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Total number of AEs	1	1	0	0
	Preferred Term				
	RHABDOMYOLYSIS	1	1	0	0
SOCIAL CIRCUMSTANCES	Total number of AEs	0	0	1	1
	Preferred Term				
	SOCIAL STAY HOSPITALISATION	0	0	1	1

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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Total number of AEs within 100 days after ASCT	87	100	75	100

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
System Organ Class					
INFECTIONS AND INFESTATIONS	Total number of AEs	31	36	24	32
	Preferred Term				
	INFECTION	6	7	2	3
	SEPSIS	2	2	3	4
	CATHETER RELATED INFECTION	2	2	2	3
	HERPES ZOSTER	1	1	2	3
	NEUTROPENIC INFECTION	2	2	1	1
	URINARY TRACT INFECTION	1	1	1	1
	FOLLICULITIS	1	1	1	1
	BRONCHOPNEUMONIA	1	1	1	1
	ESCHERICHIA URINARY TRACT INFECTION	0	0	2	3
	CYTOMEGALOVIRUS INFECTION	1	1	1	1
	NEUTROPENIC SEPSIS	2	2	0	0
	CANDIDIASIS	2	2	0	0
	CATHETER SEPSIS	1	1	1	1
	CENTRAL LINE INFECTION	1	1	1	1
	ESCHERICHIA SEPSIS	1	1	0	0
	STAPHYLOCOCCAL SEPSIS	0	0	1	1
	CLOSTRIDIAL INFECTION	0	0	1	1
	STAPHYLOCOCCAL INFECTION	1	1	0	0
	DIARRHOEA INFECTIOUS	1	1	0	0
	STREPTOCOCCAL SEPSIS	1	1	0	0
	VARICELLA	0	0	1	1
	PNEUMONIA FUNGAL	1	1	0	0
	BACTERAEMIA	0	0	1	1
	ORAL HERPES	1	1	0	0
	PNEUMONIA	1	1	0	0
	RESPIRATORY TRACT INFECTION	1	1	0	0
	PNEUMONIA INFLUENZAL	0	0	1	1
	LOWER RESPIRATORY TRACT INFECTION	0	0	1	1

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total number of AEs	22	25	15	20
	Preferred Term				
	FEBRILE NEUTROPENIA	7	8	11	15
	NEUTROPENIA	7	8	0	0
	THROMBOCYTOPENIA	2	2	1	1
	LYMPHOPENIA	2	2	0	0
	HAEMATOTOXICITY	1	1	1	1
	ANAEMIA	0	0	2	3
	FEBRILE BONE MARROW APLASIA	2	2	0	0
	LEUKOPENIA	1	1	0	0
GASTROINTESTINAL DISORDERS	Total number of AEs	13	15	8	11
	Preferred Term				
	DIARRHOEA	3	3	4	5
	STOMATITIS	3	3	1	1
	NAUSEA	2	2	0	0
	VOMITING	1	1	0	0
	GASTROINTESTINAL DISORDER	1	1	0	0
	ABDOMINAL PAIN	1	1	0	0
	ILEUS	0	0	1	1
	FAECALOMA	1	1	0	0
	DENTAL CARIES	0	0	1	1
	GASTROINTESTINAL HAEMORRHAGE	1	1	0	0
	GASTROINTESTINAL INFLAMMATION	0	0	1	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Total number of AEs	7	8	10	13
	Preferred Term				
	MUCOSAL INFLAMMATION	4	5	6	8
	PYREXIA	1	1	2	3
	ASTHENIA	1	1	0	0
	HYPERTHERMIA	0	0	1	1
	INFLAMMATION	0	0	1	1
	CATHETER SITE HAEMORRHAGE	1	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Total number of AEs	5	6	2	3
	Preferred Term				
	BRONCHOPNEUMOPATHY	1	1	1	1
	LUNG DISORDER	1	1	1	1
	INTERSTITIAL LUNG DISEASE	1	1	0	0
	LUNG INFILTRATION	1	1	0	0
	COUGH	1	1	0	0

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
METABOLISM AND NUTRITION DISORDERS	Total number of AEs	3	3	2	3
	Preferred Term				
	HYPOKALAEMIA	1	1	1	1
	ANOREXIA	1	1	0	0
	FOOD INTOLERANCE	0	0	1	1
	HYPERMAGNESAEMIA	1	1	0	0
INVESTIGATIONS	Total number of AEs	2	2	2	3
	Preferred Term				
	CYTOMEGALOVIRUS TEST POSITIVE	0	0	1	1
	GAMMA-GLUTAMYLTRANSFERASE INCREASED	1	1	0	0
	C-REACTIVE PROTEIN INCREASED	1	1	0	0
	LIVER FUNCTION TEST ABNORMAL	0	0	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Total number of AEs	1	1	2	3
	Preferred Term				
	DRUG TOXICITY	1	1	0	0
	THROMBOSIS IN DEVICE	0	0	1	1
	SUBDURAL HAEMATOMA	0	0	1	1
EAR AND LABYRINTH DISORDERS	Total number of AEs	1	1	1	1
	Preferred Term				
	DEAFNESS	0	0	1	1
	TINNITUS	1	1	0	0
CARDIAC DISORDERS	Total number of AEs	0	0	2	3
	Preferred Term				
	MYOCARDIAL INFARCTION	0	0	1	1
	ATRIAL FIBRILLATION	0	0	1	1
HEPATOBILIARY DISORDERS	Total number of AEs	0	0	2	3
	Preferred Term				
	HEPATITIS	0	0	1	1
	LIVER DISORDER	0	0	1	1
VASCULAR DISORDERS	Total number of AEs	1	1	1	1
	Preferred Term				
	HYPOTENSION	1	1	0	0
	THROMBOSIS	0	0	1	1
RENAL AND URINARY DISORDERS	Total number of AEs	1	1	1	1
	Preferred Term				
	RENAL FAILURE ACUTE	0	0	1	1
	RENAL TUBULAR ACIDOSIS	1	1	0	0
NERVOUS SYSTEM DISORDERS	Total number of AEs	0	0	1	1
	Preferred Term				
	PARESIS	0	0	1	1

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
PSYCHIATRIC DISORDERS	Total number of AEs	0	0	1	1
	Preferred Term				
	CONFUSIONAL STATE	0	0	1	1
SOCIAL CIRCUMSTANCES	Total number of AEs	0	0	1	1
	Preferred Term				
	SOCIAL STAY HOSPITALISATION	0	0	1	1

Table 5.2-11 Summary of adverse events more than 100 days after ASCT by frequency of SOC and PT (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Total number of AEs more than 100 days after ASCT	75	100	24	100

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
System Organ Class					
INFECTIONS AND INFESTATIONS	Total number of AEs	45	60	13	54
	Preferred Term				
	HERPES ZOSTER	4	5	4	17
	BRONCHITIS	5	7	1	4
	INFECTION	4	5	1	4
	PNEUMONIA	3	4	1	4
	LOWER RESPIRATORY TRACT INFECTION	4	5	0	0
	SEPTIC SHOCK	1	1	1	4
	SINUSITIS	2	3	0	0
	HAEMOPHILUS INFECTION	2	3	0	0
	PSEUDOMONAS INFECTION	1	1	0	0
	ORAL HERPES	1	1	0	0
	BRONCHOPULMONARY ASPERGILLOSIS	1	1	0	0
	BRONCHITIS PNEUMOCOCCAL	1	1	0	0
	BRONCHOPNEUMONIA	1	1	0	0
	PERTUSSIS	1	1	0	0
	GASTROENTERITIS	1	1	0	0
	INFLUENZA	0	0	1	4
	PNEUMONIA PNEUMOCOCCAL	0	0	1	4
	ENTEROCOLITIS INFECTIOUS	0	0	1	4
	PNEUMOCYSTIS JIROVECI PNEUMONIA	1	1	0	0
	GASTROENTERITIS VIRAL	0	0	1	4
	CENTRAL LINE INFECTION	1	1	0	0
	FOLLICULITIS	1	1	0	0
	ESCHERICHIA URINARY TRACT INFECTION	1	1	0	0
	CATHETER SEPSIS	1	1	0	0
	NEUTROPENIC INFECTION	0	0	1	4
	PNEUMONIA BACTERIAL	1	1	0	0
	VIRAL INFECTION	1	1	0	0
	UPPER RESPIRATORY TRACT INFECTION	1	1	0	0
	CANDIDIASIS	1	1	0	0
	NEUTROPENIC SEPSIS	1	1	0	0
	RESPIRATORY TRACT INFECTION	1	1	0	0
	BRONCHIECTASIS	1	1	0	0
	LOCALISED INFECTION	1	1	0	0

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	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
NERVOUS SYSTEM DISORDERS	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
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	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
IMMUNE SYSTEM DISORDERS	Total number of AEs	3	4	1	4
	Preferred Term				
	HYPOGAMMAGLOBULINAEMIA	3	4	1	4
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Total number of AEs	2	3	1	4
	Preferred Term				
	PYREXIA	2	3	0	0
	MUCOSAL INFLAMMATION	0	0	1	4
GASTROINTESTINAL DISORDERS	Total number of AEs	1	1	1	4
	Preferred Term				
	VOMITING	0	0	1	4
	GINGIVAL PAIN	1	1	0	0
VASCULAR DISORDERS	Total number of AEs	1	1	0	0
	Preferred Term				
	JUGULAR VEIN THROMBOSIS	1	1	0	0
RENAL AND URINARY DISORDERS	Total number of AEs	1	1	0	0
	Preferred Term				
	RENAL FAILURE	1	1	0	0

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
CARDIAC DISORDERS	Total number of AEs	1	1	0	0
	Preferred Term				
	MYOCARDITIS	1	1	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Total number of AEs	1	1	0	0
	Preferred Term				
	RHABDOMYOLYSIS	1	1	0	0

Table 5.2-12 Characteristics of adverse events (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Non hematological toxicity grade				
NORMAL	1	1	0	0
MILD	4	2	3	3
MODERATE	54	33	20	20
SEVERE	66	41	61	62
LIFE THREATENING	9	6	7	7
DEATH	3	2	0	0
UNKNOWN	7	4	2	2
Missing	18	11	6	6
Hematological toxicity grade				
NORMAL	13	8	6	6
MILD	16	10	6	6
MODERATE	7	4	7	7
SEVERE	32	20	14	14
LIFE THREATENING	49	30	46	46
UNKNOWN	7	4	4	4
Missing	38	23	16	16
Relation with study drugs				
No	81	50	66	67
Yes	79	49	32	32
Missing	2	1	1	1
Action taken with study drug				
No	140	86	97	98
Yes	21	13	0	0
Missing	1	1	2	2
Antibiotherapy				
No	60	37	43	43
Yes	94	58	53	54
Not Done	1	1	0	0
Missing	7	4	3	3
AE outcome				
RECOVERED	138	85	91	92
RECOVERED WITH SEQUELAE	8	5	4	4
ONGOING	8	5	1	1
FATAL	7	4	3	3
Missing	1	1	0	0
Total	162	100	99	100

Table 5.2-13 Action taken with study drugs due to AEs (MSAP)

	Actual arm of maintenance	
	RITUXIMAB	
	N	%
Specify action taken with study drug		
PERMANENT TREATMENT DISCONTINUATION	3	14
TEMPORARY TREATMENT DISCONTINUATION	17	81
DOSE REGIMEN ADAPTATION	1	5
Total	21	100

Table 5.2-14 Characteristics of adverse events within 100 days after ASCT (MSAP)

AE within 100 days after ASCT	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Non hematological toxicity grade				
NORMAL	1	1	0	0
MILD	2	2	3	4
MODERATE	20	23	12	16
SEVERE	46	53	51	68
LIFE THREATENING	4	5	5	7
DEATH	1	1	0	0
UNKNOWN	4	5	2	3
Missing	9	10	2	3
Hematological toxicity grade				
NORMAL	3	3	5	7
MILD	5	6	5	7
MODERATE	4	5	3	4
SEVERE	13	15	7	9
LIFE THREATENING	39	45	42	56
UNKNOWN	2	2	2	3
Missing	21	24	11	15
Relation with study drugs				
No	47	54	50	67
Yes	39	45	25	33
Missing	1	1	0	0
Action taken with study drug				
No	82	94	75	100
Yes	5	6	0	0
Antibiotherapy				
No	27	31	28	37
Yes	55	63	45	60

AE within 100 days after ASCT	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Missing	5	6	2	3
AE outcome				
RECOVERED	78	90	71	95
RECOVERED WITH SEQUELAE	3	3	2	3
ONGOING	4	5	1	1
FATAL	2	2	1	1
Total	87	100	75	100

Table 5.2-15 Action taken with study drugs due to AEs within 100 days after ASCT (MSAP)

AE within 100 days after ASCT	Actual arm of maintenance	
	RITUXIMAB	
	N	%
Specify action taken with study drug		
PERMANENT TREATMENT DISCONTINUATION	1	20
TEMPORARY TREATMENT DISCONTINUATION	4	80
Total	5	100

Table 5.2-16 Characteristics of adverse events more than 100 days after ASCT (MSAP)

AE more than 100 days after ASCT	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Non hematological toxicity grade				
MILD	2	3	0	0
MODERATE	34	45	8	33
SEVERE	20	27	10	42
LIFE THREATENING	5	7	2	8
DEATH	2	3	0	0
UNKNOWN	3	4	0	0
Missing	9	12	4	17
Hematological toxicity grade				
NORMAL	10	13	1	4
MILD	11	15	1	4
MODERATE	3	4	4	17
SEVERE	19	25	7	29
LIFE THREATENING	10	13	4	17
UNKNOWN	5	7	2	8
Missing.	17	23	5	21

AE more than 100 days after ASCT	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Relation with study drugs				
No	34	45	16	67
Yes	40	53	7	29
Missing	1	1	1	4
Action taken with study drug				
No	58	77	22	92
Yes	16	21	0	0
Missing	1	1	2	8
Antibiotherapy				
No	33	44	15	63
Yes	39	52	8	33
Not Done	1	1	0	0
Missing	2	3	1	4
AE outcome				
RECOVERED	60	80	20	83
RECOVERED WITH SEQUELAE	5	7	2	8
ONGOING	4	5	0	0
FATAL	5	7	2	8
Missing	1	1	0	0
Total	75	100	24	100

Table 5.2-17 Action taken with study drugs due to AEs more than 100 days after ASCT (MSAP)

AE more than 100 days after ASCT	Actual arm of maintenance	
	RITUXIMAB	
	N	%
Specify action taken with study drug		
PERMANENT TREATMENT DISCONTINUATION	2	13
TEMPORARY TREATMENT DISCONTINUATION	13	81
DOSE REGIMEN ADAPTATION	1	6
Total	16	100

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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Patient with a corrective treatment				
No	10	15	8	14
Yes	57	85	50	86
Total	67	100	58	100

137 AEs in rituximab arm (85%) were associated with a corrective treatment versus 83 AEs (884%) in observation arm.

Table 5.2-19 Corrective treatments for AE (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
AE with a corrective treatment				
Yes	137	85	83	84
No	25	15	16	16
Total	162	100	99	100

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 2nd 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.

Table 5.3-1 Patients with SAE (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Patient with at least one SAE				
Yes	24	21	16	13
No	92	79	103	87
Total	116	100	119	100
Patient with at least one SAE within 100 days after ASCT				
Yes	14	12	15	13
No	102	88	104	87
Patient with at least one SAE more than 100 days after ASCT				
Yes	14	12	5	4
No	102	88	114	96
Total	116	100	119	100

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%).

The following list presents all SAEs post 2nd randomization with fatal outcome:

Listing 5.3-1 Serious adverse events with fatal outcome (MSAP)

Randomization Number	Actual arm of induction	Actual arm of maintenance	Transplantation date	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003101431608	ARM B / R-DHAP	RITUXIMAB	13/04/2004	MALE	64	SECONDARY MALIGNANCY : HEPATIC ADENOCARCINOMA	24/04/2007	LIFE THREATENING	NORMAL	No	No	FATAL	361
5003601401002	ARM A / R-ICE	RITUXIMAB	06/07/2004	MALE	56	ACUTE NON-LYMPHOCYTIC LEUKEMIA = AML	15/06/2006	UNKNOWN	UNKNOWN	Yes	-	FATAL	24
5003601401004	ARM B / R-DHAP	RITUXIMAB	15/12/2006	FEMALE	62	FEVER AND MENTAL DISTURBANCES. VARICELLA LESIONS IN THE SKIN. VARICELLA ZOSTER VIRUS SEEN IN BLISTERS.	26/06/2007	DEATH	NORMAL	Yes	Yes	FATAL	61
5003601401602	ARM A / R-ICE	RITUXIMAB	01/11/2004	MALE	41	MYOCARDITIS	06/08/2006	LIFE THREATENING	UNKNOWN	Yes	No	FATAL	0
5003604901603	ARM B / R-DHAP	RITUXIMAB	18/06/2008	FEMALE	62	BRONCHOPNEUMONIA, EXTENSIVE DIFFUSE ALVEOLAR DAMAGE	04/09/2008	DEATH	-	Yes	No	FATAL	9
5003616301615	ARM A / R-ICE	RITUXIMAB	21/12/2005	MALE	63	CHRONIC COUGH, DRY NON PRODUCTIVE ASSOCIATED WITH FEBRILE ILLNESS FOR 2 WEEKS. DIAGNOSED WITH PNEUMONIA 14082006	15/08/2006	DEATH	MILD	Yes	No	FATAL	17
5003101071643	ARM B / R-DHAP	OBSERVATION	27/02/2008	FEMALE	58	SEPTICEMIA STAPHYLOCOCCUS EPIDERMIDIS PNEUMOPATHY	07/05/2008	LIFE THREATENING	SEVERE	Yes	No	FATAL	8
5003606301207	ARM A / R-ICE	OBSERVATION	23/11/2004	MALE	37	HIGH GRADE UROTHELIAL CARCINOMA	20/03/2008	LIFE THREATENING	-	Yes	No	FATAL	568
5003606301604	ARM B / R-DHAP	OBSERVATION	21/09/2004	MALE	61	MYELODYSPLASTIC SYNDROME	05/02/2008	-	MODERATE	Yes	-	FATAL	503
N = 9													

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)

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
Total number of SAEs		43	100	22	100
System Organ Class					
INFECTIONS AND INFESTATIONS	**Total number of SAEs**	25	58	6	27
	Preferred Term				
	PNEUMONIA	3	7	0	0
	LOWER RESPIRATORY TRACT INFECTION	2	5	1	5
	BRONCHOPNEUMONIA	2	5	0	0
	SEPSIS	2	5	0	0
	HERPES ZOSTER	2	5	0	0
	PSEUDOMONAS INFECTION	1	2	0	0
	SEPTIC SHOCK	1	2	0	0
	BRONCHOPULMONARY ASPERGILLOSIS	1	2	0	0
	BRONCHITIS PNEUMOCOCCAL	1	2	0	0
	STAPHYLOCOCCAL SEPSIS	0	0	1	5
	CLOSTRIDIAL INFECTION	0	0	1	5
	HAEMOPHILUS INFECTION	1	2	0	0
	PNEUMONIA PNEUMOCOCCAL	0	0	1	5
	STREPTOCOCCAL SEPSIS	1	2	0	0
	VARICELLA	0	0	1	5
	PNEUMOCYSTIS JIROVECI PNEUMONIA	1	2	0	0
	CATHETER RELATED INFECTION	1	2	0	0
	BACTERAEMIA	0	0	1	5
	CATHETER SEPSIS	1	2	0	0
	CYTOMEGALOVIRUS INFECTION	1	2	0	0
	PNEUMONIA BACTERIAL	1	2	0	0
	INFECTION	1	2	0	0
	NEUTROPENIC SEPSIS	1	2	0	0
	RESPIRATORY TRACT INFECTION	1	2	0	0
GASTROINTESTINAL DISORDERS	**Total number of SAEs**	3	7	3	14
	Preferred Term				
	DIARRHOEA	1	2	2	9
	FAECALOMA	1	2	0	0
	DENTAL CARIES	0	0	1	5
	GASTROINTESTINAL HAEMORRHAGE	1	2	0	0

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Total number of SAEs	3	7	2	9
	Preferred Term				
	HEPATIC NEOPLASM MALIGNANT	1	2	0	0
	MALIGNANT MELANOMA	1	2	0	0
	ACUTE LEUKAEMIA	1	2	0	0
	TRANSITIONAL CELL CARCINOMA	0	0	1	5
	MYELODYSPLASTIC SYNDROME	0	0	1	5
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total number of SAEs	3	7	2	9
	Preferred Term				
	NEUTROPENIA	2	5	1	5
	ANAEMIA	0	0	1	5
	THROMBOCYTOPENIA	1	2	0	0
NERVOUS SYSTEM DISORDERS	Total number of SAEs	2	5	2	9
	Preferred Term				
	LOSS OF CONSCIOUSNESS	0	0	1	5
	LEUKOENCEPHALOPATHY	1	2	0	0
	PARESIS	0	0	1	5
	HYPOAESTHESIA	1	2	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Total number of SAEs	2	5	1	5
	Preferred Term				
	INTERSTITIAL LUNG DISEASE	1	2	0	0
	LUNG DISORDER	0	0	1	5
	LUNG INFILTRATION	1	2	0	0
CARDIAC DISORDERS	Total number of SAEs	1	2	1	5
	Preferred Term				
	MYOCARDIAL INFARCTION	0	0	1	5
	MYOCARDITIS	1	2	0	0
RENAL AND URINARY DISORDERS	Total number of SAEs	1	2	1	5
	Preferred Term				
	RENAL FAILURE ACUTE	0	0	1	5
	RENAL TUBULAR ACIDOSIS	1	2	0	0
EAR AND LABYRINTH DISORDERS	Total number of SAEs	0	0	1	5
	Preferred Term				
	DEAFNESS	0	0	1	5
HEPATOBILIARY DISORDERS	Total number of SAEs	0	0	1	5
	Preferred Term				
	HEPATITIS	0	0	1	5
VASCULAR DISORDERS	Total number of SAEs	1	2	0	0
	Preferred Term				
	HYPOTENSION	1	2	0	0

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Total number of SAEs	0	0	1	5
	Preferred Term				
	SUBDURAL HAEMATOMA	0	0	1	5
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Total number of SAEs	1	2	0	0
	Preferred Term				
	CATHETER SITE HAEMORRHAGE	1	2	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Total number of SAEs	1	2	0	0
	Preferred Term				
	RHABDOMYOLYSIS	1	2	0	0
SOCIAL CIRCUMSTANCES	Total number of SAEs	0	0	1	5
	Preferred Term				
	SOCIAL STAY HOSPITALISATION	0	0	1	5

3 other malignancies in rituximab arm and 2 in observation arm were reported as serious (corresponding to the SOC neoplasms benign, malignant and unspecified (incl cysts and polyps)).

Table 5.3-3 Summary of serious adverse events within 100 days after ASCT by frequency of SOC and PT (MSAP)

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
Total number of SAEs within 100 days after ASCT		20	100	17	100
System Organ Class					
INFECTIONS AND INFESTATIONS	Total number of SAEs	9	45	5	29
	Preferred Term				
	SEPSIS	2	10	0	0
	STAPHYLOCOCCAL SEPSIS	0	0	1	6
	CLOSTRIDIAL INFECTION	0	0	1	6
	STREPTOCOCCAL SEPSIS	1	5	0	0
	VARICELLA	0	0	1	6
	CATHETER RELATED INFECTION	1	5	0	0
	BACTERAEMIA	0	0	1	6
	CATHETER SEPSIS	1	5	0	0
	CYTOMEGALOVIRUS INFECTION	1	5	0	0
	BRONCHOPNEUMONIA	1	5	0	0
	PNEUMONIA	1	5	0	0
	INFECTION	1	5	0	0
	LOWER RESPIRATORY TRACT INFECTION	0	0	1	6

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
GASTROINTESTINAL DISORDERS	Total number of SAEs	3	15	3	18
	Preferred Term				
	DIARRHOEA	1	5	2	12
	FAECALOMA	1	5	0	0
	DENTAL CARIES	0	0	1	6
	GASTROINTESTINAL HAEMORRHAGE	1	5	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total number of SAEs	3	15	1	6
	Preferred Term				
	NEUTROPENIA	2	10	0	0
	ANAEMIA	0	0	1	6
	THROMBOCYTOPENIA	1	5	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Total number of SAEs	2	10	1	6
	Preferred Term				
	INTERSTITIAL LUNG DISEASE	1	5	0	0
	LUNG DISORDER	0	0	1	6
	LUNG INFILTRATION	1	5	0	0
RENAL AND URINARY DISORDERS	Total number of SAEs	1	5	1	6
	Preferred Term				
	RENAL FAILURE ACUTE	0	0	1	6
	RENAL TUBULAR ACIDOSIS	1	5	0	0
EAR AND LABYRINTH DISORDERS	Total number of SAEs	0	0	1	6
	Preferred Term				
	DEAFNESS	0	0	1	6
CARDIAC DISORDERS	Total number of SAEs	0	0	1	6
	Preferred Term				
	MYOCARDIAL INFARCTION	0	0	1	6
HEPATOBILIARY DISORDERS	Total number of SAEs	0	0	1	6
	Preferred Term				
	HEPATITIS	0	0	1	6
VASCULAR DISORDERS	Total number of SAEs	1	5	0	0
	Preferred Term				
	HYPOTENSION	1	5	0	0
NERVOUS SYSTEM DISORDERS	Total number of SAEs	0	0	1	6
	Preferred Term				
	PARESIS	0	0	1	6
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Total number of SAEs	0	0	1	6
	Preferred Term				
	SUBDURAL HAEMATOMA	0	0	1	6

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Total number of SAEs	1	5	0	0
	Preferred Term				
	CATHETER SITE HAEMORRHAGE	1	5	0	0
SOCIAL CIRCUMSTANCES	Total number of SAEs	0	0	1	6
	Preferred Term				
	SOCIAL STAY HOSPITALISATION	0	0	1	6

Table 5.3-4 Summary of serious adverse events more than 100 days after ASCT by frequency of SOC and PT (MSAP)

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
Total number of SAEs more than 100 days after ASCT		23	100	5	100
System Organ Class					
INFECTIONS AND INFESTATIONS	Total number of SAEs	16	70	1	20
	Preferred Term				
	HERPES ZOSTER	2	9	0	0
	PNEUMONIA	2	9	0	0
	LOWER RESPIRATORY TRACT INFECTION	2	9	0	0
	PSEUDOMONAS INFECTION	1	4	0	0
	SEPTIC SHOCK	1	4	0	0
	BRONCHOPULMONARY ASPERGILLOSIS	1	4	0	0
	BRONCHITIS PNEUMOCOCCAL	1	4	0	0
	BRONCHOPNEUMONIA	1	4	0	0
	HAEMOPHILUS INFECTION	1	4	0	0
	PNEUMONIA PNEUMOCOCCAL	0	0	1	20
	PNEUMOCYSTIS JIROVECI PNEUMONIA	1	4	0	0
	PNEUMONIA BACTERIAL	1	4	0	0
	NEUTROPENIC SEPSIS	1	4	0	0
	RESPIRATORY TRACT INFECTION	1	4	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Total number of SAEs	3	13	2	40
	Preferred Term				
	HEPATIC NEOPLASM MALIGNANT	1	4	0	0
	MALIGNANT MELANOMA	1	4	0	0
	ACUTE LEUKAEMIA	1	4	0	0
	TRANSITIONAL CELL CARCINOMA	0	0	1	20
	MYELODYSPLASTIC SYNDROME	0	0	1	20

		Actual arm of maintenance			
		RITUXIMAB		OBSERVATION	
		N	%	N	%
NERVOUS SYSTEM DISORDERS	Total number of SAEs	2	9	1	20
	Preferred Term				
	LOSS OF CONSCIOUSNESS	0	0	1	20
	LEUKOENCEPHALOPATHY	1	4	0	0
	HYPOAESTHESIA	1	4	0	0
CARDIAC DISORDERS	Total number of SAEs	1	4	0	0
	Preferred Term				
	MYOCARDITIS	1	4	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Total number of SAEs	1	4	0	0
	Preferred Term				
	RHABDOMYOLYSIS	1	4	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Total number of SAEs	0	0	1	20
	Preferred Term				
	NEUTROPENIA	0	0	1	20

Table 5.3-5 Characteristics of SAEs (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Non hematological toxicity grade				
MILD	3	7	0	0
MODERATE	5	12	5	23
SEVERE	20	47	12	55
LIFE THREATENING	8	19	2	9
DEATH	3	7	0	0
UNKNOWN	2	5	1	5
Missing	2	5	2	9
Hematological toxicity grade				
NORMAL	6	14	3	14
MILD	7	16	3	14
MODERATE	3	7	2	9
SEVERE	7	16	4	18
LIFE THREATENING	8	19	5	23
UNKNOWN	3	7	0	0
Missing	9	21	5	23
Relation with study drugs				
No	18	42	15	68
Yes	24	56	7	32
Missing	1	2	0	0
Action taken with study drug				
No	30	70	21	95
Yes	12	28	0	0
Missing	1	2	1	5
Antibiotherapy				
No	13	30	11	50
Yes	27	63	9	41
Missing	3	7	2	9
AE outcome				
RECOVERED	32	74	18	82
RECOVERED WITH SEQUELAE	4	9	0	0
ONGOING	1	2	1	5
FATAL	6	14	3	14
Total	43	100	22	100

Table 5.3-6 Action taken with study drugs due to SAE (MSAP)

	Actual arm of maintenance	
	RITUXIMAB	
	N	%
Specify action taken with study drug		
PERMANENT TREATMENT DISCONTINUATION	2	17
TEMPORARY TREATMENT DISCONTINUATION	10	83
Total	12	100

Table 5.3-7 Characteristics of SAEs within 100 days after ASCT (MSAP)

SAE within 100 days after ASCT	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Non hematological toxicity grade				
MILD	2	10	0	0
MODERATE	1	5	5	29
SEVERE	10	50	10	59
LIFE THREATENING	3	15	1	6
DEATH	1	5	0	0
UNKNOWN	1	5	1	6
Missing	2	10	0	0
Hematological toxicity grade				
NORMAL	1	5	3	18
MILD	3	15	3	18
MODERATE	3	15	1	6
SEVERE	2	10	3	18
LIFE THREATENING	6	30	4	24
Missing	5	25	3	18
Relation with study drugs				
No	12	60	13	76
Yes	8	40	4	24
Action taken with study drug				
No	16	80	17	100
Yes	4	20	0	0
Antibiotherapy				
No	7	35	8	47
Yes	12	60	8	47
Missing	1	5	1	6
AE outcome				
RECOVERED	16	80	15	88
RECOVERED WITH SEQUELAE	2	10	0	0
ONGOING	1	5	1	6
FATAL	1	5	1	6
Total	20	100	17	100

Table 5.3-8 Action taken with study drugs due to SAE within 100 days after ASCT (MSAP)

SAE within 100 days after ASCT	Actual arm of maintenance RITUXIMAB	
	N	%
Specify action taken with study drug		
PERMANENT TREATMENT DISCONTINUATION	1	25
TEMPORARY TREATMENT DISCONTINUATION	3	75
Total	4	100

Table 5.3-9 Characteristics of SAEs more than 100 days after ASCT (MSAP)

SAE more than 100 days after ASCT	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Non hematological toxicity grade				
MILD	1	4	0	0
MODERATE	4	17	0	0
SEVERE	10	43	2	40
LIFE THREATENING	5	22	1	20
DEATH	2	9	0	0
UNKNOWN	1	4	0	0
Missing	0	0	2	40
Hematological toxicity grade				
NORMAL	5	22	0	0
MILD	4	17	0	0
MODERATE	0	0	1	20
SEVERE	5	22	1	20
LIFE THREATENING	2	9	1	20
UNKNOWN	3	13	0	0
Missing	4	17	2	40
Relation with study drugs				
No	6	26	2	40
Yes	16	70	3	60
Missing	1	4	0	0
Action taken with study drug				
No	14	61	4	80
Yes	8	35	0	0
Missing	1	4	1	20
Antibiotherapy				
No	6	26	3	60
Yes	15	65	1	20
Missing	2	9	1	20
AE outcome				
RECOVERED	16	70	3	60

SAE more than 100 days after ASCT	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
RECOVERED WITH SEQUELAE	2	9	0	0
FATAL	5	22	2	40
Total	23	100	5	100

Table 5.3-10 Action taken with study drugs due to SAE more than 100 days after ASCT (MSAP)

SAE more than 100 days after ASCT	Actual arm of maintenance	
	RITUXIMAB	
	N	%
Specify action taken with study drug		
PERMANENT TREATMENT DISCONTINUATION	1	13
TEMPORARY TREATMENT DISCONTINUATION	7	88
Total	8	100

5.3.1.2. Corrective treatments

Table 5.3-11 Patients with corrective treatment (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Patient with a corrective treatment				
No	2	8	4	25
Yes	22	92	12	75
Total	24	100	16	100

Table 5.3-12 Corrective treatments for AE (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
AE with a corrective treatment				
No	2	15	3	21
Yes	11	85	11	79
Total	13	100	14	100

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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Deaths				
Yes	43	37	38	32
No	73	63	81	68
Total	116	100	119	100

Table 5.3-14 Cause of death (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Reason for death				
LYMPHOMA	30	70	30	79
TOXICITY OF STUDY TREATMENT	3	7	1	3
CONCURRENT ILLNESS	2	5	0	0
OTHER CANCER	2	5	2	5
TOXICITY OF ADDITIONNAL TREATMENT	3	7	3	8
OTHER REASON	2	5	2	5
UNKNOWN	1	2	0	0
Total	43	100	38	100

See details of deaths in the following lists:

Listing 5.3-2 Deaths (MSAP)

Randomization Number	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003101031001	RITUXIMAB	21/10/2003	22/10/2003	MALE	65	06/05/2004	LYMPHOMA		PROGRESSIVE DISEASE
5003101031401	RITUXIMAB	25/11/2004	26/11/2004	MALE	60	30/11/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003101051050	RITUXIMAB	16/10/2006	11/10/2006	MALE	62	19/02/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101071408	RITUXIMAB	25/04/2006	03/04/2006	FEMALE	57	03/10/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101071417	RITUXIMAB	17/07/2007	06/07/2007	FEMALE	56	03/10/2008	LYMPHOMA		NOT EVALUATED
5003101131409	RITUXIMAB	16/06/2006	14/06/2006	MALE	55	09/06/2007	UNKNOWN		NOT EVALUATED
5003101251035	RITUXIMAB	16/11/2005	14/11/2005	MALE	55	10/05/2007	LYMPHOMA		NOT EVALUATED
5003101281033	RITUXIMAB	15/11/2005	04/10/2005	MALE	61	16/02/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003101431608	RITUXIMAB	23/04/2004	13/04/2004	MALE	64	19/04/2008	OTHER CANCER		UNCONFIRMED COMPLETE RESPONSE
5003101431622	RITUXIMAB	13/07/2005	18/07/2005	MALE	49	18/10/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101481614	RITUXIMAB	17/09/2004	07/09/2004	MALE	58	20/07/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003101491042	RITUXIMAB	09/05/2006	18/05/2006	MALE	46	05/02/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003102491619	RITUXIMAB	27/12/2004	03/01/2005	MALE	60	04/11/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003601401002	RITUXIMAB	22/07/2004	06/07/2004	MALE	56	09/07/2006	CONCURRENT ILLNESS	ACUTE NON LYMPHOCYTIC LEUKEMIA	UNCONFIRMED COMPLETE RESPONSE
5003601401004	RITUXIMAB	19/12/2006	15/12/2006	FEMALE	62	26/08/2007	TOXICITY OF STUDY TREATMENT		COMPLETE RESPONSE
5003601401402	RITUXIMAB	04/05/2005	10/05/2005	MALE	63	14/11/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003601401602	RITUXIMAB	27/10/2004	01/11/2004	MALE	41	06/08/2006	OTHER REASON	PERIMYOCARDITE	COMPLETE RESPONSE
5003601881401	RITUXIMAB	07/11/2006	10/11/2006	MALE	63	06/02/2008	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003602801403	RITUXIMAB	31/05/2007	20/06/2007	MALE	64	29/05/2009	TOXICITY OF ADDITIONNAL TREATMENT	BILATERAL PNEUMONIA, SEPTIC SHOCK	PARTIAL RESPONSE
5003602801605	RITUXIMAB	08/11/2006	12/10/2006	FEMALE	58	26/12/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003603201628	RITUXIMAB	17/08/2007	22/08/2007	MALE	48	20/01/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003603801203	RITUXIMAB	14/03/2005	01/03/2005	FEMALE	53	25/10/2005	LYMPHOMA		PROGRESSIVE DISEASE
5003603801406	RITUXIMAB	15/05/2008	13/05/2008	MALE	31	01/03/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003604801006	RITUXIMAB	09/03/2006	13/02/2006	MALE	53	10/11/2006	LYMPHOMA		NOT EVALUATED
5003604801205	RITUXIMAB	11/07/2006	21/06/2006	MALE	34	19/01/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003604901004	RITUXIMAB	09/03/2006	25/05/2006	FEMALE	52	30/07/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003604901005	RITUXIMAB	09/05/2006	24/04/2006	FEMALE	62	11/01/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003604901603	RITUXIMAB	19/06/2008	18/06/2008	FEMALE	62	13/09/2008	TOXICITY OF STUDY TREATMENT	POST-MORTEM PATHOLOGICAL ANALYSIS WAS PERFORMED TODAY (14/09/2008)	COMPLETE RESPONSE
5003605301610	RITUXIMAB	02/05/2005	23/02/2005	MALE	60	14/07/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003606201407	RITUXIMAB	21/09/2006	13/09/2006	MALE	54	10/04/2007	TOXICITY OF ADDITIONNAL TREATMENT	CMV-PNEUMONIA, RENAL FAILURE, MULTIPLE ORGAN FAILURE AFTER AUTOLOGOUS TRANSPLANT ON 19/03/2007	PARTIAL RESPONSE
5003606201605	RITUXIMAB	29/10/2004	08/10/2004	MALE	42	17/10/2006	TOXICITY OF ADDITIONNAL TREATMENT	SEPTIC MULTIPLE ORGAN FAILURE AFTER AUTOL. TX 07/06 AND UNREL. ALLO TX 08/06 / EXTENSIVE GVHD SKIN + GUT - INTERSTITIAL PNEUMONIA HEMORRHAGIC CYSTITIS	NOT EVALUATED
5003607501401	RITUXIMAB	30/10/2006	18/10/2006	MALE	54	25/08/2007	LYMPHOMA	BRONCHOPNEUMONIA	PROGRESSIVE DISEASE
5003607701007	RITUXIMAB	09/03/2006	14/03/2006	MALE	56	01/06/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003610201206	RITUXIMAB	16/06/2005	24/06/2005	MALE	40	12/03/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003610201611	RITUXIMAB	22/06/2005	28/06/2005	FEMALE	61	13/02/2007	OTHER REASON	ORGANIC BRAIN SYNDROME	COMPLETE RESPONSE

Randomization Number	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003610501402	RITUXIMAB	28/12/2006	20/12/2006	MALE	58	13/02/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003610701014	RITUXIMAB	07/01/2008	14/01/2008	MALE	57	01/06/2010	OTHER CANCER	HODGKIN LYMPHOMA	PROGRESSIVE DISEASE
5003612301623	RITUXIMAB	16/04/2007	30/03/2007	MALE	56	23/04/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003615501014	RITUXIMAB	14/08/2007	09/08/2007	MALE	53	04/05/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003616301615	RITUXIMAB	22/12/2005	21/12/2005	MALE	63	01/09/2006	TOXICITY OF STUDY TREATMENT	PNEUMONIA	COMPLETE RESPONSE
5003616501003	RITUXIMAB	20/12/2006	05/12/2006	MALE	30	21/08/2008	CONCURRENT ILLNESS	PNEUMONIA, DEVIC'S DISEASE	NOT EVALUATED
5003617201043	RITUXIMAB	16/04/2007	19/04/2007	MALE	42	28/06/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003630201040	RITUXIMAB	09/03/2007	13/02/2007	MALE	65	21/12/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101021038	OBSERVATION	02/02/2006	09/01/2006	MALE	52	30/05/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101021605	OBSERVATION	04/02/2004	03/02/2004	MALE	58	20/06/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101071643	OBSERVATION	20/03/2008	27/02/2008	FEMALE	58	15/05/2008	TOXICITY OF STUDY TREATMENT	SEPTICEMIA STAPHYLOCOCCUS EPIDERMIDIS PNEUMOPATHY	COMPLETE RESPONSE
5003101141624	OBSERVATION	26/10/2005	10/10/2005	FEMALE	64	18/04/2010	LYMPHOMA		PROGRESSIVE DISEASE
5003101161407	OBSERVATION	17/03/2006	28/02/2006	MALE	60	20/06/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003101621026	OBSERVATION	14/09/2005	06/09/2005	MALE	64	09/02/2009	OTHER REASON	MESENTERIC INFARCTUS	COMPLETE RESPONSE
5003101621609	OBSERVATION	19/05/2004	10/05/2004	FEMALE	64	26/03/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003101621615	OBSERVATION	16/09/2004	21/09/2004	MALE	64	09/03/2006	LYMPHOMA	RELAPSE N° 3 : 3/02/2006	PROGRESSIVE DISEASE
5003101641618	OBSERVATION	19/11/2004	16/11/2004	FEMALE	49	29/11/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003102411069	OBSERVATION	24/10/2007	04/10/2007	MALE	63	16/10/2008	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003102541052	OBSERVATION	12/10/2006	05/11/2006	MALE	29	07/05/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003601401006	OBSERVATION	11/07/2007	03/07/2007	FEMALE	62	14/09/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003601401603	OBSERVATION	12/01/2006	05/01/2006	MALE	59	26/08/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003601601003	OBSERVATION	08/06/2007	29/05/2007	MALE	27	23/04/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003601601005	OBSERVATION	16/04/2008	08/04/2008	FEMALE	53	15/10/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003602801011	OBSERVATION	22/12/2006	06/12/2006	MALE	48	09/08/2007	TOXICITY OF ADDITIONNAL TREATMENT	SEPTIC SHOCK AFTER SALVAGE CHEMOTHERAPY	PROGRESSIVE DISEASE
5003602901601	OBSERVATION	27/12/2004	21/03/2005	MALE	63	04/09/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003603201038	OBSERVATION	17/01/2007	29/12/2006	FEMALE	50	20/09/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003603201213	OBSERVATION	29/05/2007	23/05/2007	MALE	54	28/03/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003603701006	OBSERVATION	30/01/2006	09/01/2006	MALE	54	12/05/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003603801002	OBSERVATION	22/12/2004	09/12/2004	FEMALE	49	21/03/2010	LYMPHOMA	DIED AFTER 1 CYCLE OF SALVAGE CHEMO FOR GENERALISED RELAPSE. IMMEDIATE REASON FOR DEATH SEPIC SHOCK	NOT EVALUATED
5003603801009	OBSERVATION	07/09/2006	05/09/2006	MALE	49	31/03/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003603801602	OBSERVATION	01/02/2005	18/01/2005	MALE	54	14/08/2007	TOXICITY OF ADDITIONNAL TREATMENT	GVHD + INFECTION POST ALLOGENEIC PBCT FROM SIBLING DONOR	COMPLETE RESPONSE
5003603801608	OBSERVATION	03/07/2008	01/07/2008	MALE	26	03/06/2009	LYMPHOMA		PROGRESSIVE DISEASE
5003606301207	OBSERVATION	02/12/2004	23/11/2004	MALE	37	09/10/2009	OTHER CANCER	METASTATIC CARCINOMA OF THE BLADDER	COMPLETE RESPONSE
5003606301604	OBSERVATION	22/09/2004	21/09/2004	MALE	61	22/06/2009	OTHER CANCER	MYELODYSPLASTIC SYNDROME	COMPLETE RESPONSE
5003607201016	OBSERVATION	11/08/2005	01/08/2005	FEMALE	54	07/03/2006	LYMPHOMA		PROGRESSIVE DISEASE

Randomization Number	Actual arm of maintenance	Date of 2nd randomization	Transplantation date	Sex	Age (years)	Date of death	Reason for death	Specify reason of death	Response at death
5003607301603	OBSERVATION	15/09/2004	10/09/2004	MALE	64	27/04/2007	LYMPHOMA		PROGRESSIVE DISEASE
5003607501403	OBSERVATION	07/02/2007	02/02/2007	MALE	56	23/10/2007	LYMPHOMA		NOT EVALUATED
5003608701008	OBSERVATION	19/05/2006	01/05/2006	MALE	57	14/10/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003610301613	OBSERVATION	23/05/2005	31/05/2005	MALE	53	29/07/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003610501031	OBSERVATION	08/07/2008	11/06/2008	MALE	54	01/09/2008	LYMPHOMA		PROGRESSIVE DISEASE
5003617201021	OBSERVATION	14/02/2006	01/02/2006	FEMALE	50	22/12/2007	OTHER REASON	RESPIRATORY INSUFFICIENCY	COMPLETE RESPONSE
5003617301619	OBSERVATION	27/04/2006	05/05/2006	FEMALE	19	24/05/2008	TOXICITY OF ADDITIONNAL TREATMENT	MULTI-ORGAN FAILURE SECONDARY TO GRAFT VERSUS HOST DISEASE FOLLOWING ALLOGENEIC BONE MARROW TRANSPLANT	COMPLETE RESPONSE
5003618301005	OBSERVATION	19/05/2006	03/05/2006	MALE	27	07/12/2006	LYMPHOMA		PROGRESSIVE DISEASE
5003618501008	OBSERVATION	18/05/2007	01/05/2007	MALE	65	30/12/2009	LYMPHOMA	ACUTE GASTROINTESTINAL TRACT HAEMORRHAGE	PARTIAL RESPONSE
5003618501025	OBSERVATION	29/04/2008	10/04/2008	MALE	59	08/01/2009	LYMPHOMA	CAUSE OF DEATH DUE TO LYMPHOMA FOUND ON POST-MORTEM	PROGRESSIVE DISEASE
5003621201020	OBSERVATION	07/12/2005	17/11/2005	FEMALE	59	14/07/2006	LYMPHOMA		PROGRESSIVE DISEASE
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)

		Actual arm of maintenance	
		RITUXIMAB	OBSERVATION
Lymphocytes (G/L)	**N**	113	115
	Mean	1.197	1.159
	Std	0.6675	0.6063
	Median	1.035	1.092
	Min	0.04	0.13
	Max	3.21	2.88
Lymphoma cells (G/L)	**N**	95	90
	Mean	0.0	0.0
	Std	0.01	0.23
	Median	0.0	0.0
	Min	0	0
	Max	0	2
ASAT (UI/L)	**N**	109	113
	Mean	28.5	25.5
	Std	14.94	11.06
	Median	25.0	22.0
	Min	8	10
	Max	89	84
ALAT (UI/L)	**N**	112	114
	Mean	30.0	31.0
	Std	24.01	23.47
	Median	23.0	23.5
	Min	7	8
	Max	141	166
beta 2 microglobulin (mg/l)	**N**	83	92
	Mean	2.867	2.178
	Std	7.1761	0.8951
	Median	1.900	2.000
	Min	0.50	0.90
	Max	67.00	6.22
Aaline phosphatase (UI/L)	**N**	113	116
	Mean	98.9	112.3
	Std	57.53	99.25
	Median	86.0	84.5
	Min	39	35
	Max	394	788

		Actual arm of maintenance	
		RITUXIMAB	OBSERVATION
Total bilirubin (µmol/l)	**N**	114	116
	Mean	10.252	9.271
	Std	6.4216	5.8981
	Median	8.250	8.000
	Min	2.00	1.71
	Max	44.00	49.00
Creatinin (µmol/l)	**N**	116	119
	Mean	78.6	79.7
	Std	16.99	18.40
	Median	77.0	79.5
	Min	46	9
	Max	155	140
Calcium (mmol/l)	**N**	109	111
	Mean	2.384	2.425
	Std	0.3475	0.6910
	Median	2.350	2.360
	Min	1.94	2.02
	Max	4.80	9.50
Sodium (mmol/l)	**N**	114	118
	Mean	140.5	139.7
	Std	2.87	3.04
	Median	141.0	140.0
	Min	133	129
	Max	150	147
Potassium (mmol/l)	**N**	114	118
	Mean	4.179	4.194
	Std	0.4091	0.4261
	Median	4.100	4.100
	Min	3.30	3.20
	Max	5.60	5.80

Table 5.4-2 Serum electrophoresis values at relapse diagnosis (induction safety population)

		Actual arm of maintenance	
		RITUXIMAB	OBSERVATION
Total protein (G/L)	**N**	102	110
	Mean	69.39	70.50
	Std	7.310	7.516
	Median	69.00	70.00
	Min	52.0	49.0
	Max	88	90
Albumin (G/L)	**N**	107	109
	Mean	41.71	41.42
	Std	5.774	6.454
	Median	42.00	41.70
	Min	27.3	25.0
	Max	62	65
Monoclonal component value (G/L)	**N**	3	3
	Mean	4.80	6.19
	Std	1.709	3.861
	Median	5.00	6.30
	Min	3.0	2.3
	Max	6	10

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)

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of induction cycles received	Nb of maintenance visits
5003101021631	ARM A / R-ICE	07/02/2006	RITUXIMAB	01/06/2006	09/05/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	22/05/2006	3	5
5003101031001	ARM A / R-ICE	24/07/2003	RITUXIMAB	21/10/2003	18/11/2003	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	22/10/2003	3	1
5003101031401	ARM B / R-DHAP	31/08/2004	RITUXIMAB	25/11/2004	30/03/2005	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	26/11/2004	3	2
5003101051050	ARM B / R-DHAP	13/07/2006	RITUXIMAB	16/10/2006	13/01/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	11/10/2006	3	2
5003101071408	ARM B / R-DHAP	14/12/2005	RITUXIMAB	25/04/2006	14/11/2006	FOLLOW UP PERIOD	OTHER	FAILURE TREATMENT	PROGRESSIVE DISEASE	03/04/2006	3	4
5003101131409	ARM A / R-ICE	07/03/2006	RITUXIMAB	16/06/2006	23/11/2006	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	14/06/2006	3	1
5003101251035	ARM B / R-DHAP	26/07/2005	RITUXIMAB	16/11/2005	31/05/2006	FOLLOW UP PERIOD	OTHER	RELAPSE NHL	PROGRESSIVE DISEASE	14/11/2005	3	4
5003101281033	ARM A / R-ICE	15/07/2005	RITUXIMAB	15/11/2005	10/01/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	04/10/2005	3	1
5003101431622	ARM A / R-ICE	26/04/2005	RITUXIMAB	13/07/2005	12/10/2005	FOLLOW UP PERIOD	TREATMENT TOXICITY		COMPLETE RESPONSE	18/07/2005	3	1
5003101491042	ARM A / R-ICE	14/02/2006	RITUXIMAB	09/05/2006	31/07/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	18/05/2006	3	1
5003102341061	ARM A / R-ICE	31/01/2007	RITUXIMAB	04/05/2007	03/12/2007	FOLLOW UP PERIOD	OTHER	POST TRANSPLANTATION RELAPSE	PROGRESSIVE DISEASE	02/05/2007	3	4
5003102541640	ARM B / R-DHAP	02/04/2007	RITUXIMAB	27/07/2007	11/09/2007	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	26/07/2007	3	1
5003601301015	ARM B / R-DHAP	21/11/2007	RITUXIMAB	08/02/2008	18/03/2008	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL		PARTIAL RESPONSE	14/02/2008	3	-
5003601401004	ARM B / R-DHAP	27/09/2006	RITUXIMAB	19/12/2006	26/06/2007	FOLLOW UP PERIOD	TREATMENT TOXICITY		COMPLETE RESPONSE	15/12/2006	3	3
5003601401402	ARM B / R-DHAP	17/02/2005	RITUXIMAB	04/05/2005	16/09/2005	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	10/05/2005	3	2
5003601881401	ARM A / R-ICE	19/07/2006	RITUXIMAB	07/11/2006	26/07/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	10/11/2006	3	4
5003603201628	ARM A / R-ICE	18/05/2007	RITUXIMAB	17/08/2007	20/03/2008	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	22/08/2007	3	4
5003603801203	ARM A / R-ICE	01/12/2004	RITUXIMAB	14/03/2005	02/05/2005	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	01/03/2005	3	1

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of induction cycles received	Nb of maintenance visits
5003603801406	ARM A / R-ICE	15/02/2008	RITUXIMAB	15/05/2008	05/08/2008	FOLLOW UP PERIOD	OTHER	PR ; START OF NEW TREATMENT	PARTIAL RESPONSE	13/05/2008	3	1
5003604701002	ARM B / R-DHAP	25/02/2005	RITUXIMAB	19/05/2005	26/10/2005	FOLLOW UP PERIOD	OTHER	PROGRESSION UNDER MAINTENANCE THERAPIE	PROGRESSIVE DISEASE	17/05/2005	3	3
5003604701015	ARM B / R-DHAP	26/09/2007	RITUXIMAB	12/12/2007	18/04/2008	FOLLOW UP PERIOD	OTHER	PATIENT REFUSED THE TREATMENT. HE COULD NOT FOLLOW THE PROTOCOL	NOT EVALUATED	19/12/2007	3	1
5003604801006	ARM B / R-DHAP	18/10/2005	RITUXIMAB	09/03/2006	16/05/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	13/02/2006	3	1
5003604801205	ARM A / R-ICE	29/03/2006	RITUXIMAB	11/07/2006	07/08/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	21/06/2006	3	1
5003604901004	ARM B / R-DHAP	22/11/2005	RITUXIMAB	09/03/2006	21/12/2006	FOLLOW UP PERIOD	OTHER	RELAPSE	PROGRESSIVE DISEASE	25/05/2006	3	2
5003604901005	ARM A / R-ICE	05/01/2006	RITUXIMAB	09/05/2006	27/07/2006	FOLLOW UP PERIOD	OTHER	BONE MARROW INVOLVEMENT	PROGRESSIVE DISEASE	24/04/2006	3	1
5003604901602	ARM B / R-DHAP	02/02/2005	RITUXIMAB	02/05/2005	28/06/2005	FOLLOW UP PERIOD	OTHER	LOST TO FOLLOW-UP AFTER BMT	NOT EVALUATED	16/06/2005	3	-
5003604901603	ARM B / R-DHAP	03/03/2008	RITUXIMAB	19/06/2008	13/09/2008	FOLLOW UP PERIOD	DEATH		COMPLETE RESPONSE	18/06/2008	3	1
5003605301610	ARM B / R-DHAP	18/11/2004	RITUXIMAB	02/05/2005	08/12/2005	FOLLOW UP PERIOD	OTHER	PROGRESSION- NEW LESION VERVICAL LYMPH NODE	PROGRESSIVE DISEASE	23/02/2005	3	4
5003605701401	ARM A / R-ICE	11/10/2006	RITUXIMAB	30/01/2007	28/11/2007	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL		COMPLETE RESPONSE	12/01/2007	3	5
5003606201407	ARM B / R-DHAP	06/06/2006	RITUXIMAB	21/09/2006	16/11/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	13/09/2006	3	1
5003607501401	ARM B / R-DHAP	19/07/2006	RITUXIMAB	30/10/2006	06/06/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	18/10/2006	3	4
5003607701007	ARM A / R-ICE	06/12/2005	RITUXIMAB	09/03/2006	21/04/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	14/03/2006	3	1
5003608301205	ARM B / R-DHAP	25/06/2004	RITUXIMAB	01/10/2004	15/06/2005	FOLLOW UP PERIOD	OTHER	INADVERTENTLY STOPPED RITUXIMAB	UNCONFIRMED COMPLETE RESPONSE	29/09/2004	3	4
5003608301605	ARM A / R-ICE	03/06/2004	RITUXIMAB	25/08/2004	13/09/2004	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL		COMPLETE RESPONSE	25/08/2004	3	-
5003610701014	ARM B / R-DHAP	24/09/2007	RITUXIMAB	07/01/2008	14/04/2008	FOLLOW UP PERIOD	OTHER	PD	COMPLETE RESPONSE	14/01/2008	3	2
5003612201401	ARM B / R-DHAP	09/05/2005	RITUXIMAB	29/09/2005	12/10/2005	FOLLOW UP PERIOD	OTHER	THE PATIENT WAS RANDOMIZED AT RITUXIMAB BUT IT WAS NOT GIVEN BECAUSE OF INCORRECTED COMMUNICATION BETWEEN US AND THE PRIVATE PRAXIS	COMPLETE RESPONSE	25/08/2005	3	6

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of induction cycles received	Nb of maintenance visits
5003612301623	ARM B / R-DHAP	13/12/2006	RITUXIMAB	16/04/2007	31/07/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	30/03/2007	3	2
5003615501014	ARM A / R-ICE	02/05/2007	RITUXIMAB	14/08/2007	04/02/2008	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	09/08/2007	3	2
5003616301615	ARM A / R-ICE	29/09/2005	RITUXIMAB	22/12/2005	01/09/2006	FOLLOW UP PERIOD	DEATH		COMPLETE RESPONSE	21/12/2005	3	4
5003617201021	ARM B / R-DHAP	17/10/2005	RITUXIMAB	14/02/2006	17/03/2006	FOLLOW UP PERIOD	OTHER	ACTIVE HEPATITIS C INFECTION AFTER APHERESIS, BAD CONDITION AFTER TRANSPLANTATION / DECISION NOT TO TREAT PATIENT WITH RITUXIMAB FURTHER AS RANDOMIZED IN STUDY	UNCONFIRMED COMPLETE RESPONSE	01/02/2006	3	6
5003617201043	ARM B / R-DHAP	25/01/2007	RITUXIMAB	16/04/2007	13/09/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	19/04/2007	3	2
5003626501605	ARM B / R-DHAP	14/09/2007	RITUXIMAB	19/12/2007	28/04/2008	FOLLOW UP PERIOD	TREATMENT TOXICITY		PARTIAL RESPONSE	09/01/2008	3	1
5003630201040	ARM B / R-DHAP	06/11/2006	RITUXIMAB	09/03/2007	22/05/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	13/02/2007	3	2
5003101021038	ARM B / R-DHAP	06/10/2005	OBSERVATION	02/02/2006	05/12/2006	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	09/01/2006	3	5
5003101021605	ARM A / R-ICE	04/11/2003	OBSERVATION	04/02/2004	29/04/2004	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	03/02/2004	3	4
5003101071643	ARM B / R-DHAP	29/10/2007	OBSERVATION	20/03/2008	15/05/2008	FOLLOW UP PERIOD	DEATH		DEATH WITHOUT PROGRESSION	27/02/2008	3	2
5003101131072	ARM A / R-ICE	27/09/2007	OBSERVATION	26/12/2007	18/01/2008	FOLLOW UP PERIOD	OTHER	PATIENT RETURN IN ROUMANIA	UNCONFIRMED COMPLETE RESPONSE	24/12/2007	3	1
5003101601610	ARM B / R-DHAP	16/02/2004	OBSERVATION	17/05/2004	11/08/2004	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	24/05/2004	3	-
5003101621026	ARM A / R-ICE	31/05/2005	OBSERVATION	14/09/2005	22/03/2006	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	06/09/2005	3	3
5003101621615	ARM A / R-ICE	10/06/2004	OBSERVATION	16/09/2004	19/04/2005	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	21/09/2004	3	4
5003102341045	ARM A / R-ICE	30/03/2006	OBSERVATION	03/07/2006	09/09/2006	FOLLOW UP PERIOD	OTHER	RADIOTHERAPY TREATMENT	PARTIAL RESPONSE	21/06/2006	3	3
5003102361203	ARM B / R-DHAP	21/11/2003	OBSERVATION	19/02/2004	13/03/2004	FOLLOW UP PERIOD	PATIENT VOLONTARY WITHDRAWAL		NOT EVALUATED	18/02/2004	3	-
5003102411054	ARM B / R-DHAP	27/09/2006	OBSERVATION	08/01/2007	28/08/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	28/12/2006	3	6
5003102411069	ARM B / R-DHAP	05/07/2007	OBSERVATION	24/10/2007	21/01/2008	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	04/10/2007	3	3

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of induction cycles received	Nb of maintenance visits
5003102541052	ARM A / R-ICE	26/07/2006	OBSERVATION	12/10/2006	04/01/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	05/11/2006	3	1
5003104621053	ARM B / R-DHAP	02/08/2006	OBSERVATION	15/11/2006	22/01/2007	FOLLOW UP PERIOD	OTHER	INDUCTION RESPONSE WAS SD AND NOT RESOLVED AFTER TRANSPLANT	STABLE DISEASE	22/11/2006	3	2
5003601401006	ARM A / R-ICE	18/04/2007	OBSERVATION	11/07/2007	25/02/2008	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	03/07/2007	3	4
5003601601003	ARM A / R-ICE	07/03/2007	OBSERVATION	08/06/2007	31/08/2007	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	29/05/2007	3	6
5003601601005	ARM A / R-ICE	15/01/2008	OBSERVATION	16/04/2008	03/07/2008	FOLLOW UP PERIOD	OTHER	PROGRESSION OF DISEASE	PROGRESSIVE DISEASE	08/04/2008	3	2
5003601601602	ARM B / R-DHAP	05/12/2007	OBSERVATION	13/03/2008	23/05/2008	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	27/02/2008	3	2
5003602801011	ARM A / R-ICE	14/09/2006	OBSERVATION	22/12/2006	13/07/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	06/12/2006	3	3
5003602901601	ARM A / R-ICE	08/09/2004	OBSERVATION	27/12/2004	06/10/2005	FOLLOW UP PERIOD	OTHER	RELAPS	PROGRESSIVE DISEASE	21/03/2005	3	6
5003603201038	ARM A / R-ICE	09/10/2006	OBSERVATION	17/01/2007	11/04/2007	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	29/12/2006	3	5
5003603201213	ARM A / R-ICE	23/02/2007	OBSERVATION	29/05/2007	28/03/2008	FOLLOW UP PERIOD	DEATH		PROGRESSIVE DISEASE	23/05/2007	3	3
5003603701006	ARM A / R-ICE	14/10/2005	OBSERVATION	30/01/2006	13/03/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	09/01/2006	3	1
5003603801009	ARM B / R-DHAP	31/05/2006	OBSERVATION	07/09/2006	10/11/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	05/09/2006	3	2
5003603801608	ARM A / R-ICE	09/04/2008	OBSERVATION	03/07/2008	24/10/2008	FOLLOW UP PERIOD	OTHER	EARLY RELAPSE AFTER TRANSPLANTATION	PROGRESSIVE DISEASE	01/07/2008	3	2
5003604201056	ARM B / R-DHAP	22/04/2008	OBSERVATION	22/08/2008	15/04/2009	FOLLOW UP PERIOD	OTHER	PD	PROGRESSIVE DISEASE	12/08/2008	3	3
5003604901007	ARM B / R-DHAP	15/01/2008	OBSERVATION	18/06/2008	05/10/2008	FOLLOW UP PERIOD	OTHER	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 UPTATE DUE TO PET-CT RESULTS, THE TREATING PHYSICIAN SUSPECTED THAT *	PARTIAL RESPONSE	19/05/2008	3	2
5003606701003	ARM A / R-ICE	10/03/2005	OBSERVATION	07/06/2005	13/01/2006	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	08/06/2005	3	6
5003607201016	ARM A / R-ICE	09/05/2005	OBSERVATION	11/08/2005	16/12/2005	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	01/08/2005	3	3

Randomization Number	Arm of treatment	First Randomization Date	Arm of 2nd randomization	Date of 2nd randomization	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Transplantation date	Nb of induction cycles received	Nb of maintenance visits
5003607501403	ARM A / R-ICE	16/10/2006	OBSERVATION	07/02/2007	11/07/2007	FOLLOW UP PERIOD	OTHER	RELAPSE DISEASE	PROGRESSIVE DISEASE	02/02/2007	3	4
5003608701008	ARM B / R-DHAP	09/02/2006	OBSERVATION	19/05/2006	13/06/2006	FOLLOW UP PERIOD	OTHER	PROGRESSED AFTER STABLE DISEASE	PROGRESSIVE DISEASE	01/05/2006	3	3
5003610301209	ARM B / R-DHAP	17/03/2005	OBSERVATION	21/06/2005	14/03/2006	FOLLOW UP PERIOD	OTHER	PATIENT WITHDRAWN BY INVESTIGATOR AS IS NON COMPLIANT WITH ATTENDING FOR REVIEW	UNCONFIRMED COMPLETE RESPONSE	27/06/2005	3	2
5003610301613	ARM B / R-DHAP	01/03/2005	OBSERVATION	23/05/2005	07/09/2005	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	31/05/2005	3	4
5003610501031	ARM A / R-ICE	20/03/2008	OBSERVATION	08/07/2008	28/07/2008	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	11/06/2008	3	1
5003610701403	ARM B / R-DHAP	06/12/2007	OBSERVATION	28/03/2008	06/10/2008	FOLLOW UP PERIOD	OTHER	RECCURENT IN FU-PHASE 6 MONTHS AFTER TRANSPLANT	PROGRESSIVE DISEASE	03/03/2008	3	4
5003614301407	ARM B / R-DHAP	06/03/2008	OBSERVATION	21/07/2008	18/09/2008	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	20/06/2008	3	2
5003618301005	ARM B / R-DHAP	01/02/2006	OBSERVATION	19/05/2006	23/06/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	03/05/2006	3	4
5003618501025	ARM B / R-DHAP	05/12/2007	OBSERVATION	29/04/2008	08/01/2009	FOLLOW UP PERIOD	OTHER	PROGRESSION DURING MAINTENANCE	PROGRESSIVE DISEASE	10/04/2008	3	3
5003619301621	ARM A / R-ICE	01/12/2006	OBSERVATION	19/03/2007	18/10/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	08/03/2007	3	2
5003621201020	ARM A / R-ICE	28/07/2005	OBSERVATION	07/12/2005	26/04/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	17/11/2005	3	3
5003623501408	ARM B / R-DHAP	18/10/2007	OBSERVATION	25/01/2008	28/04/2008	FOLLOW UP PERIOD	OTHER	COMMENCING RADIOTHERAPY, CONSIDERED A NEW TREATMENT, PATIENT IS IN PARTIAL RESPONSE	PARTIAL RESPONSE	18/01/2008	3	2
N = 83												

6.2. Initial treatment

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

Randomization Number	Arm of 2nd randomization	Number of cycles of chemotherapy	Chemotherapy regimen	Specify other Chemotherapy regimen
5003603801601	RITUXIMAB	4	OTHER	B ALL GERMAN : PEDIATRIC PROTOCOL NHL-BFM95
5003603801608	OBSERVATION	6	OTHER	NHL-BFM 95 PROTOCOL FOR RISK GROUP 3
5003607201016	OBSERVATION	6	OTHER	B ALL GERMAN : HOELZER PROTO (BLOCK A1, B1, C1, A2, B2, C2) + INTRATHECAL MTX + ARAC + DEXAMETHASONE
5003617201209	OBSERVATION	8	OTHER	BEACOPP ESC.
N = 4				

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

Randomization Number	Arm of 2nd randomization	Radiotherapy	Specify dose of radiotherapy (Gy)
5003101061617	RITUXIMAB	LOCAL	40
5003101131058	RITUXIMAB	LOCAL	30
5003101251035	RITUXIMAB	LOCAL	40
5003101281033	RITUXIMAB	LOCAL	36
5003101481614	RITUXIMAB	LOCAL	40
5003102341641	RITUXIMAB	LOCAL	40
5003102491619	RITUXIMAB	LOCAL	30
5003102541640	RITUXIMAB	LOCAL	36
5003601301015	RITUXIMAB	LOCAL	30
5003601401604	RITUXIMAB	LOCAL	40
5003601601601	RITUXIMAB	LOCAL	30
5003601801017	RITUXIMAB	LOCAL	16
5003601881401	RITUXIMAB	-	48
5003601881601	RITUXIMAB	LOCAL	36
5003602201601	RITUXIMAB	LOCAL	36
5003602801605	RITUXIMAB	LOCAL	40
5003603201608	RITUXIMAB	LOCAL	36
5003603801203	RITUXIMAB	LOCAL	6
5003603801406	RITUXIMAB	LOCAL	40
5003603801601	RITUXIMAB	LOCAL	36
5003604301602	RITUXIMAB	LOCAL	40
5003604801205	RITUXIMAB	LOCAL	40
5003604901602	RITUXIMAB	LOCAL	4
5003606201605	RITUXIMAB	LOCAL	36
5003606301204	RITUXIMAB	LOCAL	30
5003607501401	RITUXIMAB	LOCAL	30
5003607701007	RITUXIMAB	LOCAL	36
5003607701405	RITUXIMAB	LOCAL	39.6
5003608301605	RITUXIMAB	OTHER	40

Randomization Number	Arm of 2nd randomization	Radiotherapy	Specify dose of radiotherapy (Gy)
5003612301623	RITUXIMAB	LOCAL	40
5003616301403	RITUXIMAB	LOCAL	36
5003617301616	RITUXIMAB	LOCAL	30
5003628201618	RITUXIMAB	LOCAL	36
5003630201040	RITUXIMAB	LOCAL	36
5003101071013	OBSERVATION	LOCAL	36
5003101071643	OBSERVATION	LOCAL	50
5003101141624	OBSERVATION	LOCAL	27
5003101251009	OBSERVATION	LOCAL	36
5003101251021	OBSERVATION	LOCAL	40
5003101391646	OBSERVATION	LOCAL	40
5003101431627	OBSERVATION	LOCAL	40
5003101621609	OBSERVATION	LOCAL	40
5003101621615	OBSERVATION	LOCAL	40
5003102541052	OBSERVATION	LOCAL	36
5003102541636	OBSERVATION	LOCAL	7.6
5003601201604	OBSERVATION	LOCAL	40
5003601401601	OBSERVATION	LOCAL	44
5003601601005	OBSERVATION	LOCAL	45
5003601801607	OBSERVATION	LOCAL	40
5003602901402	OBSERVATION	LOCAL	45
5003603201213	OBSERVATION	LOCAL	40
5003603701001	OBSERVATION	LOCAL	30.6
5003603801002	OBSERVATION	LOCAL	36
5003604301013	OBSERVATION	LOCAL	36
5003604701011	OBSERVATION	LOCAL	36
5003604801004	OBSERVATION	LOCAL	40
5003606201029	OBSERVATION	LOCAL	38
5003606301604	OBSERVATION	LOCAL	30
5003606501601	OBSERVATION	LOCAL	39.6
5003607201016	OBSERVATION	LOCAL	59
5003607201623	OBSERVATION	LOCAL	36
5003608701008	OBSERVATION	LOCAL	36
5003610201615	OBSERVATION	LOCAL	39.6
5003617201209	OBSERVATION	LOCAL	30
5003617201629	OBSERVATION	LOCAL	36
5003626501607	OBSERVATION	LOCAL	40
5003632201606	OBSERVATION	LOCAL	36
5003632201614	OBSERVATION	LOCAL	40
N = 68			

6.3. Progression/relapse diagnosis

Table 6.3-1 Nodal involvement (MITT)

	Arm of 2nd randomization					
	RITUXIMAB		OBSERVATION		All	
	N	%	N	%	N	%
Cervical right						
Normal	82	67	96	80	178	74
Involved	36	30	21	18	57	24
Not evaluated	4	3	2	2	6	2
.	0	0	1	1	1	0
Cervical left						
Normal	73	60	92	77	165	68
Involved	45	37	25	21	70	29
Not evaluated	4	3	2	2	6	2
.	0	0	1	1	1	0
Supraclavicular right						
Normal	106	87	105	88	211	87
Involved	14	11	11	9	25	10
Not evaluated	2	2	3	3	5	2
.	0	0	1	1	1	0
Supraclavicular left						
Normal	100	82	107	89	207	86
Involved	20	16	9	8	29	12
Not evaluated	2	2	3	3	5	2
.	0	0	1	1	1	0
Axillary right						
Normal	103	84	101	84	204	84
Involved	18	15	17	14	35	14
Not evaluated	1	1	1	1	2	1
.	0	0	1	1	1	0
Axillary left						
Normal	89	73	102	85	191	79
Involved	31	25	17	14	48	20
Not evaluated	2	2	1	1	3	1
Inguinal right						
Normal	98	80	105	88	203	84
Involved	23	19	13	11	36	15
Not evaluated	1	1	1	1	2	1
.	0	0	1	1	1	0
Inguinal left						
Normal	106	87	98	82	204	84
Involved	16	13	20	17	36	15
Not evaluated	0	0	1	1	1	0

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
.	0	0	1	1	1	0
Mediastinal						
Normal	79	65	80	67	159	66
Involved	40	33	39	33	79	33
Not evaluated	3	2	0	0	3	1
.	0	0	1	1	1	0
Pulmonary hilar						
Normal	101	83	106	88	207	86
Involved	18	15	13	11	31	13
Not evaluated	3	2	0	0	3	1
.	0	0	1	1	1	0
Para-aortic						
Normal	73	60	73	61	146	60
Involved	47	39	46	38	93	38
Not evaluated	2	2	0	0	2	1
.	0	0	1	1	1	0
Mesenteric						
Normal	81	66	86	72	167	69
Involved	39	32	34	28	73	30
Not evaluated	2	2	0	0	2	1
Iliac right						
Normal	101	83	106	88	207	86
Involved	19	16	13	11	32	13
Not evaluated	2	2	0	0	2	1
.	0	0	1	1	1	0
Iliac left						
Normal	97	80	104	87	201	83
Involved	23	19	15	13	38	16
Not evaluated	2	2	0	0	2	1
.	0	0	1	1	1	0
Splenic Hilar						
Normal	106	87	109	91	215	89
Involved	15	12	6	5	21	9
Not evaluated	1	1	3	3	4	2
.	0	0	2	2	2	1
Other nodal involvement						
No	109	89	108	90	217	90
Yes	11	9	8	7	19	8
.	2	2	4	3	6	2
TOTAL	122	100	120	100	242	100

Listing 6.3-1 Other nodal involvement localizations (MITT)

Randomization Number	Arm of 2nd randomization	Other nodal involvement	Other nodal involvement - localization
5003101031401	RITUXIMAB	Yes	LEFT POPLITEAL NODE
5003101051050	RITUXIMAB	Yes	RIGHT MAMMAR NODE
5003101051405	RITUXIMAB	Yes	LEFT EPITROCHLEEN NODE
5003101431622	RITUXIMAB	Yes	SUBCAPSULAR HEPATIC LESION
5003103161206	RITUXIMAB	Yes	EPIGASTRIC LODGE
5003601601601	RITUXIMAB	Yes	CELIAC
5003603201628	RITUXIMAB	Yes	RETROCRURAL BOTH SIDES
5003604901603	RITUXIMAB	Yes	OMENTUM
5003607701007	RITUXIMAB	Yes	HEPATIC
5003614501032	RITUXIMAB	Yes	COELIAC AXIS
5003617201021	RITUXIMAB	Yes	SUBCUTANEOUS LYMPH NODES
5003101051648	OBSERVATION	Yes	INTERBRONCHIAL
5003101161407	OBSERVATION	Yes	RIGHT-LATERO AND RETRO CAVA
5003604301013	OBSERVATION	Yes	LEFT LOWER LEG
5003606501409	OBSERVATION	Yes	SUBCUTANEOUS LYMPH NODES BEHIND MASTOID
5003610501031	OBSERVATION	Yes	OMENTUM
5003621501412	OBSERVATION	Yes	RIGHT INTERNAL MAMMARY
5003623501408	OBSERVATION	Yes	SPLENOMEGALY
5003626501607	OBSERVATION	Yes	PORLA LYMPH NODE
N = 19			

Table 6.3-2 Extra-nodal involvement (MITT)

	Arm of 2nd randomization					
	RITUXIMAB		OBSERVATION		All	
	N	%	N	%	N	%
Liver						
Normal	113	93	106	88	219	90
Involved	8	7	11	9	19	8
Not evaluated	1	1	2	2	3	1
.	0	0	1	1	1	0
Ascites						
Normal	119	98	115	96	234	97
Involved	2	2	1	1	3	1
Not evaluated	1	1	3	3	4	2
.	0	0	1	1	1	0
Pleural effusion						
Normal	115	94	110	92	225	93
Involved	5	4	5	4	10	4
Not evaluated	2	2	3	3	5	2
.	0	0	2	2	2	1
Lung						
Normal	110	90	98	82	208	86
Involved	11	9	20	17	31	13
Not evaluated	1	1	1	1	2	1
.	0	0	1	1	1	0
Spleen						
Normal	98	80	102	85	200	83
Involved	22	18	15	13	37	15
Not evaluated	2	2	2	2	4	2
.	0	0	1	1	1	0
Pericardium						
Normal	117	96	116	97	233	96
Involved	1	1	1	1	2	1
Not evaluated	4	3	2	2	6	2
.	0	0	1	1	1	0
Breast						
Normal	115	94	112	93	227	94
Involved	2	2	2	2	4	2
Not evaluated	5	4	5	4	10	4
.	0	0	1	1	1	0
Gonadal						
Normal	114	93	107	89	221	91
Involved	1	1	3	3	4	2
Not evaluated	7	6	9	8	16	7

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
.	0	0	1	1	1	0
Kidney						
Normal	116	95	109	91	225	93
Involved	5	4	7	6	12	5
Not evaluated	1	1	3	3	4	2
.	0	0	1	1	1	0
Adrenal						
Normal	117	96	114	95	231	95
Involved	4	3	2	2	6	2
Not evaluated	1	1	3	3	4	2
.	0	0	1	1	1	0
Thyroid						
Normal	117	96	109	91	226	93
Involved	1	1	2	2	3	1
Not evaluated	4	3	8	7	12	5
.	0	0	1	1	1	0
Skin						
Normal	114	93	112	93	226	93
Involved	6	5	3	3	9	4
Not evaluated	2	2	4	3	6	2
.	0	0	1	1	1	0
Bone						
Normal	107	88	101	84	208	86
Involved	10	8	12	10	22	9
Not evaluated	5	4	6	5	11	5
.	0	0	1	1	1	0
Tonsil						
Normal	98	80	100	83	198	82
Involved	11	9	4	3	15	6
Not evaluated	13	11	14	12	27	11
.	0	0	2	2	2	1
Cavum						
Normal	102	84	101	84	203	84
Involved	2	2	1	1	3	1
Not evaluated	18	15	16	13	34	14
.	0	0	2	2	2	1
Parotid						
Normal	103	84	103	86	206	85
Involved	2	2	0	0	2	1
Not evaluated	17	14	15	13	32	13

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
.	0	0	2	2	2	1
Orbit						
Normal	103	84	98	82	201	83
Involved	0	0	2	2	2	1
Not evaluated	19	16	18	15	37	15
.	0	0	2	2	2	1
Sinus						
Normal	99	81	99	83	198	82
Involved	2	2	1	1	3	1
Not evaluated	21	17	18	15	39	16
.	0	0	2	2	2	1
Oesophagus						
Normal	99	81	99	83	198	82
Involved	0	0	1	1	1	0
Not evaluated	23	19	18	15	41	17
.	0	0	2	2	2	1
Stomach						
Normal	94	77	93	78	187	77
Involved	5	4	8	7	13	5
Not evaluated	23	19	18	15	41	17
.	0	0	1	1	1	0
Duodenum						
Normal	97	80	96	80	193	80
Involved	2	2	5	4	7	3
Not evaluated	23	19	17	14	40	17
.	0	0	2	2	2	1
Colon						
Normal	94	77	99	83	193	80
Involved	4	3	1	1	5	2
Not evaluated	24	20	18	15	42	17
.	0	0	2	2	2	1
Caecum						
Normal	96	79	96	80	192	79
Involved	2	2	3	3	5	2
Not evaluated	24	20	19	16	43	18
.	0	0	2	2	2	1
Rectum						
Normal	98	80	99	83	197	81
Not evaluated	24	20	19	16	43	18
.	0	0	2	2	2	1

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Other extra nodal involvement						
No	108	89	109	91	217	90
Yes	14	11	11	9	25	10
TOTAL	122	100	120	100	242	100

Listing 6.3-2 Other extra-nodal involvement localizations (MITT)

Randomization Number	Arm of 2nd randomization	Other extra nodal involvement	Other extra nodal involvement - localization
5003101031001	RITUXIMAB	Yes	LEFT SHOULDER MUSCLE
5003101051050	RITUXIMAB	Yes	PANCREAS
5003102491619	RITUXIMAB	Yes	LARGE TUMORAL MASS (INCLUDING PROSTATE AND BLADDER)
5003601401402	RITUXIMAB	Yes	
5003601881401	RITUXIMAB	Yes	ANTERIOR TIBIAL MUSCLE
5003603801008	RITUXIMAB	Yes	NERVUS ULNARIS L. SINISTRI
5003603801404	RITUXIMAB	Yes	INFILTRATION OF MUSC. ILIACUS L. SIN
5003604301202	RITUXIMAB	Yes	RIGHT FLANK MASS
5003604701602	RITUXIMAB	Yes	PLEURA RIGHT
5003604901602	RITUXIMAB	Yes	PANCREAS
5003605301610	RITUXIMAB	Yes	
5003610501402	RITUXIMAB	Yes	LEFT INFRA TEMPERAL FOSSA SOFT TISSUE MASS
5003620501027	RITUXIMAB	Yes	LEFT CHEST / ABDOMINAL WALL MASS
5003622201014	RITUXIMAB	Yes	RIGHT UPPER LEG MEDIAL
5003101141624	OBSERVATION	Yes	PSOAS
5003101431627	OBSERVATION	Yes	RIGHT THIGH
5003101601610	OBSERVATION	Yes	Abdominal mass
5003601601003	OBSERVATION	Yes	
5003601601602	OBSERVATION	Yes	LEFT UPPER QUADRANT SMALL BOWEL
5003601881602	OBSERVATION	Yes	MUSCLE
5003603701001	OBSERVATION	Yes	MUSCLE HUMERUS PROX LEFT 7.5 X 6 CM
5003603801009	OBSERVATION	Yes	SOFT TISSUE - RIGHT ARM
5003607201623	OBSERVATION	Yes	FOSSA INFRASPINATA
5003607501403	OBSERVATION	Yes	ANTERIOR ABDOMINAL WALL INVASION RIGHT RECTUS MUSCLE
5003631201619	OBSERVATION	Yes	
N = 25			

Table 6.3-3 Codification of sites used for response evaluation at relapse diagnosis, sorted by most frequent (MITT)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Lesion Codification						
Para-aortic / Portal	36	12	41	15	77	13
Mediastinal / Paratracheal	37	12	35	13	72	13
Celiac / Mesenteric	28	9	30	11	58	10
Cervical / Post_cervical / Upper cervical / Pre_auricular : Left	27	9	20	7	47	8
Axillary : Left	22	7	13	5	35	6
Cervical / Post_cervical / Upper cervical / Pre_auricular : Right	18	6	15	6	33	6
Inguinal / Femoral / Retrocrural : Left	11	4	10	4	21	4
Axillary : Right	9	3	11	4	20	3
Inguinal / Femoral / Retrocrural : Right	14	5	6	2	20	3
External iliac / Iliac : Left	10	3	10	4	20	3
Spleen	11	4	8	3	19	3
Lung	3	1	12	4	15	3
External iliac / Iliac : Right	6	2	8	3	14	2
Liver	4	1	8	3	12	2
Soft Tissues	7	2	5	2	12	2
Skin	5	2	6	2	11	2
Tonsil / Waldeyer's ring	9	3	1	0	10	2
Pulmonary hilar	4	1	4	1	8	1
Kidney	5	2	3	1	8	1
Infraclavicular / Supraclavicular : Left	6	2	1	0	7	1
Bone	3	1	3	1	6	1
Infraclavicular / Supraclavicular : Right	3	1	2	1	5	1
Epitrochlear Right or Left / Other	4	1	1	0	5	1
Stomach	1	0	4	1	5	1
Splenic hilar	4	1	0	0	4	1
Adrenal	2	1	2	1	4	1
Breast	1	0	2	1	3	1
Gonadal	0	0	2	1	2	0
Cavum	1	0	1	0	2	0
Parotid	2	1	0	0	2	0
Sinus	1	0	1	0	2	0
Duodenum	1	0	1	0	2	0
Colon	2	1	0	0	2	0
Caecum	1	0	1	0	2	0
Ileon	2	1	0	0	2	0
Urinary Tract	2	1	0	0	2	0
Other extra-nodal involvement	1	0	1	0	2	0

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Ascites	0	0	1	0	1	0
Pleura	1	0	0	0	1	0
Thyroid	1	0	0	0	1	0
Oesophagus	0	0	1	0	1	0
TOTAL	305	100	270	100	575	100

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)

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Lesion Codification						
Para-aortic / Portal	36	12	43	16	79	14
Mediastinal / Paratracheal	37	12	34	13	71	12
Celiac / Mesenteric	28	9	28	10	56	10
Cervical / Post_cervical / Upper cervical / Pre_auricular : Left	27	9	20	7	47	8
Axillary : Left	22	7	13	5	35	6
Cervical / Post_cervical / Upper cervical / Pre_auricular : Right	18	6	15	6	33	6
Inguinal / Femoral / Retrocrural : Left	11	4	10	4	21	4
Axillary : Right	9	3	11	4	20	3
Inguinal / Femoral / Retrocrural : Right	14	5	6	2	20	3
External iliac / Iliac : Left	10	3	10	4	20	3
Spleen	11	4	8	3	19	3
Lung	3	1	12	4	15	3
External iliac / Iliac : Right	6	2	8	3	14	2
Soft Tissues	7	2	5	2	12	2
Liver	4	1	8	3	12	2
Skin	5	2	6	2	11	2
Tonsil / Waldeyer's ring	9	3	1	0	10	2
Kidney	5	2	3	1	8	1
Pulmonary hilar	4	1	4	1	8	1
Infraclavicular / Supraclavicular : Left	6	2	1	0	7	1
Bone	3	1	3	1	6	1
Stomach	1	0	4	1	5	1
Epitrochlear Right or Left / Other	4	1	1	0	5	1
Infraclavicular / Supraclavicular : Right	3	1	2	1	5	1
Splenic hilar	4	1	0	0	4	1
Adrenal	2	1	2	1	4	1

	Arm of 2nd randomization				All	
	RITUXIMAB		OBSERVATION			
	N	%	N	%	N	%
Breast	1	0	2	1	3	1
Not coded	2	1	1	0	3	1
Duodenum	1	0	1	0	2	0
Gonadal	0	0	2	1	2	0
Colon	2	1	0	0	2	0
Caecum	1	0	1	0	2	0
Ileon	2	1	0	0	2	0
Sinus	1	0	1	0	2	0
Other extra-nodal involvement	1	0	1	0	2	0
Cavum	1	0	1	0	2	0
Urinary Tract	2	1	0	0	2	0
Parotid	2	1	0	0	2	0
Thyroid	1	0	0	0	1	0
Pleura	1	0	0	0	1	0
Ascites	0	0	1	0	1	0
Oesophagus	0	0	1	0	1	0
Total	307	100	270	100	577	100

6.5. Follow-up

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

Randomization Number	Arm of 2nd randomization	Date of last contact
5003601301015	RITUXIMAB	18/03/2008
5003604701602	RITUXIMAB	21/08/2008
5003604901602	RITUXIMAB	28/06/2005
5003606301204	RITUXIMAB	23/06/2008
5003608301605	RITUXIMAB	13/09/2004
5003613301611	RITUXIMAB	25/05/2006
5003628201044	RITUXIMAB	12/06/2009
5003628201618	RITUXIMAB	03/06/2009
5003101131072	OBSERVATION	18/01/2008
5003102341045	OBSERVATION	09/06/2009
5003604301013	OBSERVATION	17/06/2009
5003604701011	OBSERVATION	18/05/2009
5003606201620	OBSERVATION	11/07/2008
5003607201623	OBSERVATION	29/07/2009
5003610301209	OBSERVATION	14/03/2006
5003622201607	OBSERVATION	04/01/2007
5003628201402	OBSERVATION	22/04/2009
5003632201614	OBSERVATION	24/05/2007
N = 18		

6.6. Efficacy results

6.6.1. Secondary criteria

Listing 6.6-1 Patients who died durin maintenance period (MITT)

Randomization Number	Date of 2nd randomization	Arm of 2nd randomization	Actual arm of maintenance	Transplantation date	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Date of death	Reason for death	Response at death	Nb of maintenance visits
5003101031001	21/10/2003	RITUXIMAB	RITUXIMAB	22/10/2003	18/11/2003	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	06/05/2004	LYMPHOMA	PROGRESSIVE DISEASE	1
5003101051050	16/10/2006	RITUXIMAB	RITUXIMAB	11/10/2006	13/01/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	19/02/2007	LYMPHOMA	PROGRESSIVE DISEASE	2
5003101131409	16/06/2006	RITUXIMAB	RITUXIMAB	14/06/2006	23/11/2006	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	09/06/2007	UNKNOWN	NOT EVALUATED	1
5003101281033	15/11/2005	RITUXIMAB	RITUXIMAB	04/10/2005	10/01/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	16/02/2006	LYMPHOMA	PROGRESSIVE DISEASE	1
5003101491042	09/05/2006	RITUXIMAB	RITUXIMAB	18/05/2006	31/07/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	05/02/2007	LYMPHOMA	PROGRESSIVE DISEASE	1
5003601401004	19/12/2006	RITUXIMAB	RITUXIMAB	15/12/2006	26/06/2007	FOLLOW UP PERIOD	TREATMENT TOXICITY		COMPLETE RESPONSE	26/08/2007	TOXICITY OF PROTOCOL TREATMENT / OF STUDY TREATMENT	COMPLETE RESPONSE	3
5003601401402	04/05/2005	RITUXIMAB	RITUXIMAB	10/05/2005	16/09/2005	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	14/11/2005	LYMPHOMA	PROGRESSIVE DISEASE	2
5003603801203	14/03/2005	RITUXIMAB	RITUXIMAB	01/03/2005	02/05/2005	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	25/10/2005	LYMPHOMA	PROGRESSIVE DISEASE	1
5003603801406	15/05/2008	RITUXIMAB	RITUXIMAB	13/05/2008	05/08/2008	FOLLOW UP PERIOD	OTHER	PR ; START OF NEW TREATMENT	PARTIAL RESPONSE	01/03/2009	LYMPHOMA	PROGRESSIVE DISEASE	1
5003604801006	09/03/2006	RITUXIMAB	RITUXIMAB	13/02/2006	16/05/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	10/11/2006	LYMPHOMA	NOT EVALUATED	1
5003604901005	09/05/2006	RITUXIMAB	RITUXIMAB	24/04/2006	27/07/2006	FOLLOW UP PERIOD	OTHER	BONE MARROW INVOLVEMENT	PROGRESSIVE DISEASE	11/01/2007	LYMPHOMA	PROGRESSIVE DISEASE	1
5003604901603	19/06/2008	RITUXIMAB	RITUXIMAB	18/06/2008	13/09/2008	FOLLOW UP PERIOD	DEATH		COMPLETE RESPONSE	13/09/2008	TOXICITY OF PROTOCOL TREATMENT / OF STUDY TREATMENT	COMPLETE RESPONSE	1
5003606201407	21/09/2006	RITUXIMAB	RITUXIMAB	13/09/2006	16/11/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	10/04/2007	TOXICITY OF NEW TREATMENT / OF ADDITIONNAL TREATMENT	PARTIAL RESPONSE	1
5003607501401	30/10/2006	RITUXIMAB	RITUXIMAB	18/10/2006	06/06/2007	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	25/08/2007	LYMPHOMA	PROGRESSIVE DISEASE	4
5003607701007	09/03/2006	RITUXIMAB	RITUXIMAB	14/03/2006	21/04/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	01/06/2006	LYMPHOMA	PROGRESSIVE DISEASE	1

Randomization Number	Date of 2nd randomization	Arm of 2nd randomization	Actual arm of maintenance	Transplantation date	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Date of death	Reason for death	Response at death	Nb of maintenance visits
5003616301615	22/12/2005	RITUXIMAB	RITUXIMAB	21/12/2005	01/09/2006	FOLLOW UP PERIOD	DEATH		COMPLETE RESPONSE	01/09/2006	TOXICITY OF PROTOCOL TREATMENT / OF STUDY TREATMENT	COMPLETE RESPONSE	4
5003630201040	09/03/2007	RITUXIMAB	RITUXIMAB	13/02/2007	22/05/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	21/12/2007	LYMPHOMA	PROGRESSIVE DISEASE	2
5003101071643	20/03/2008	OBSERVATION	OBSERVATION	27/02/2008	15/05/2008	FOLLOW UP PERIOD	DEATH		DEATH WITHOUT PROGRESSION	15/05/2008	TOXICITY OF PROTOCOL TREATMENT / OF STUDY TREATMENT	COMPLETE RESPONSE	2
5003102541052	12/10/2006	OBSERVATION	OBSERVATION	05/11/2006	04/01/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	07/05/2007	LYMPHOMA	PROGRESSIVE DISEASE	1
5003601601003	08/06/2007	OBSERVATION	OBSERVATION	29/05/2007	31/08/2007	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	23/04/2008	LYMPHOMA	PROGRESSIVE DISEASE	6
5003601601005	16/04/2008	OBSERVATION	OBSERVATION	08/04/2008	03/07/2008	FOLLOW UP PERIOD	OTHER	PROGRESSION OF DISEASE	PROGRESSIVE DISEASE	15/10/2008	LYMPHOMA	PROGRESSIVE DISEASE	2
5003602801011	22/12/2006	OBSERVATION	OBSERVATION	06/12/2006	13/07/2007	FOLLOW UP PERIOD	OTHER	PROGRESSION	PROGRESSIVE DISEASE	09/08/2007	TOXICITY OF NEW TREATMENT / OF ADDITIONNAL TREATMENT	PROGRESSIVE DISEASE	3
5003603201038	17/01/2007	OBSERVATION	OBSERVATION	29/12/2006	11/04/2007	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	20/09/2007	LYMPHOMA	PROGRESSIVE DISEASE	5
5003603201213	29/05/2007	OBSERVATION	OBSERVATION	23/05/2007	28/03/2008	FOLLOW UP PERIOD	DEATH		PROGRESSIVE DISEASE	28/03/2008	LYMPHOMA	PROGRESSIVE DISEASE	3
5003603701006	30/01/2006	OBSERVATION	OBSERVATION	09/01/2006	13/03/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	12/05/2006	LYMPHOMA	PROGRESSIVE DISEASE	1
5003603801009	07/09/2006	OBSERVATION	OBSERVATION	05/09/2006	10/11/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	31/03/2007	LYMPHOMA	PROGRESSIVE DISEASE	2
5003603801608	03/07/2008	OBSERVATION	OBSERVATION	01/07/2008	24/10/2008	FOLLOW UP PERIOD	OTHER	EARLY RELAPSE AFTER TRANSPLANTATION	PROGRESSIVE DISEASE	03/06/2009	LYMPHOMA	PROGRESSIVE DISEASE	2
5003607201016	11/08/2005	OBSERVATION	OBSERVATION	01/08/2005	16/12/2005	FOLLOW UP PERIOD	OTHER	PROGRESSIVE DISEASE	PROGRESSIVE DISEASE	07/03/2006	LYMPHOMA	PROGRESSIVE DISEASE	3
5003607501403	07/02/2007	OBSERVATION	OBSERVATION	02/02/2007	11/07/2007	FOLLOW UP PERIOD	OTHER	RELAPSE DISEASE	PROGRESSIVE DISEASE	23/10/2007	LYMPHOMA	NOT EVALUATED	4
5003608701008	19/05/2006	OBSERVATION	OBSERVATION	01/05/2006	13/06/2006	FOLLOW UP PERIOD	OTHER	PROGRESSED AFTER STABLE DISEASE	PROGRESSIVE DISEASE	14/10/2006	LYMPHOMA	PROGRESSIVE DISEASE	3
5003610501031	08/07/2008	OBSERVATION	OBSERVATION	11/06/2008	28/07/2008	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	01/09/2008	LYMPHOMA	PROGRESSIVE DISEASE	1
5003618301005	19/05/2006	OBSERVATION	OBSERVATION	03/05/2006	23/06/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	07/12/2006	LYMPHOMA	PROGRESSIVE DISEASE	4

Randomization Number	Date of 2nd randomization	Arm of 2nd randomization	Actual arm of maintenance	Transplantation date	Date of withdrawal	Treatment period at withdrawal	Reason for premature withdrawal	Other reason for premature withdrawal	Response at withdrawal	Date of death	Reason for death	Response at death	Nb of maintenance visits
5003618501025	29/04/2008	OBSERVATION	OBSERVATION	10/04/2008	08/01/2009	FOLLOW UP PERIOD	OTHER	PROGRESSION DURING MAINTENANCE	PROGRESSIVE DISEASE	08/01/2009	LYMPHOMA	PROGRESSIVE DISEASE	3
5003621201020	07/12/2005	OBSERVATION	OBSERVATION	17/11/2005	26/04/2006	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	14/07/2006	LYMPHOMA	PROGRESSIVE DISEASE	3
5003101601610	17/05/2004	OBSERVATION	NOT APPLICABLE	24/05/2004	11/08/2004	FOLLOW UP PERIOD	TRANSPLANTATION FAILURE		PROGRESSIVE DISEASE	12/08/2004	LYMPHOMA	PROGRESSIVE DISEASE	-
5003631201619	14/06/2006	OBSERVATION	NOT APPLICABLE	29/05/2006	-	-	-		-	14/10/2006	LYMPHOMA	PROGRESSIVE DISEASE	-
N = 36													

6.6.2. Non study or new treatment out of progression

Listing 6.6-2 New treatment out of progression - Chemotherapy (MITT)

Randomization Number	Arm of 2nd randomization	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003603801406	RITUXIMAB	Yes	12/08/2008	R-GFOX	4
N = 1					

Listing 6.6-3 New treatment out of progression - Radiotherapy (MITT)

Randomization Number	Arm of 2nd randomization	Radiotherapy	Date of radiotherapy	Site of radiotherapy	Dose of radiotherapy (Gy)
5003102341045	OBSERVATION	Yes	09/09/2006	MEDIASTINAL	40
5003104621053	OBSERVATION	Yes	22/01/2007	MEDIASTINUM	40
5003604901007	OBSERVATION	Yes	05/10/2008	MEDIASTINUM	40
5003623501408	OBSERVATION	Yes	02/06/2008	LEFT GROIN	-
N = 4					

6.6.3. Progression/relapse

Table 6.6-1 Progression/relapse n°1 – Extra-nodal involvement (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Bone marrow				
Not Done	10	37	7	26
Yes	5	19	5	19
No	12	44	15	56
Blood				
Not Done	1	4	0	0
Yes	2	7	4	15
No	24	89	23	85
Bone				
Not Done	0	0	4	15
Yes	6	22	4	15
No	21	78	19	70
Skin				
Yes	4	15	6	22
No	23	85	21	78
Liver				
Yes	7	26	7	26
No	20	74	20	74
Ascite				
Not Done	2	7	0	0
Yes	0	0	1	4
No	25	93	26	96

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Pleural effusion				
Not Done	2	7	0	0
Yes	2	7	1	4
No	23	85	26	96
Lung				
Yes	7	26	8	30
No	20	74	19	70
Spleen				
Yes	3	11	5	19
No	24	89	22	81
Pericardium				
Yes	1	4	0	0
No	26	96	27	100
Breast				
Not Done	1	4	2	7
Yes	0	0	1	4
No	26	96	24	89
Gonadal				
Not Done	3	11	0	0
Yes	0	0	2	7
No	24	89	25	93
Kidney				
Not Done	0	0	1	4
Yes	1	4	4	15
No	26	96	22	81
Adrenal				
Not Done	1	4	1	4
Yes	2	7	1	4
No	24	89	25	93
Thyroid				
Not Done	3	11	1	4
No	24	89	26	96
ORL area				
Not Done	4	15	1	4
Yes	1	4	1	4
No	22	81	25	93
Digestive area				
Not Done	3	11	1	4
Yes	2	7	5	19
No	22	81	21	78

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
CNS				
Not Done	7	26	0	0
Yes	2	7	2	7
No	18	67	25	93
Total	27	100	27	100

Table 6.6-2 Progression/relapse n°1 – Nodal involvement (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Cervical right				
Normal	7	21	11	38
Involved	2	6	1	3
Not evaluated	2	6	0	0
.	23	68	17	59
Cervical left				
Normal	6	18	10	34
Involved	3	9	2	7
Not evaluated	2	6	0	0
.	23	68	17	59
Supraclavicular right				
Normal	9	26	11	38
Not evaluated	2	6	1	3
.	23	68	17	59
Supraclavicular left				
Normal	8	24	10	34
Involved	2	6	1	3
Not evaluated	1	3	1	3
.	23	68	17	59
Axillary right				
Normal	9	26	10	34
Involved	0	0	2	7
Not evaluated	2	6	0	0
.	23	68	17	59
Axillary left				
Normal	8	24	7	24
Involved	1	3	5	17
Not evaluated	2	6	0	0
.	23	68	17	59

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Inguinal right				
Normal	8	24	9	31
Involved	2	6	3	10
Not evaluated	1	3	0	0
.	23	68	17	59
Inguinal left				
Normal	10	29	10	34
Involved	0	0	2	7
Not evaluated	1	3	0	0
.	23	68	17	59
Mediastinal				
Normal	9	26	6	21
Involved	1	3	4	14
Not evaluated	1	3	1	3
.	23	68	18	62
Pulmonary hilar				
Normal	9	26	7	24
Involved	1	3	2	7
Not evaluated	1	3	1	3
.	23	68	19	66
Para-ortic				
Normal	4	12	6	21
Involved	6	18	6	21
Not evaluated	1	3	0	0
.	23	68	17	59
Mesenteric				
Normal	8	24	9	31
Involved	3	9	3	10
.	23	68	17	59
Iliac right				
Normal	8	24	10	34
Involved	2	6	2	7
Not evaluated	1	3	0	0
.	23	68	17	59
Iliac left				
Normal	8	24	10	34
Involved	2	6	2	7
Not evaluated	1	3	0	0
.	23	68	17	59

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Splenic Hilar				
Normal	10	29	11	38
Involved	0	0	1	3
Not evaluated	1	3	0	0
.	23	68	17	59
Other nodal involvement				
No	8	24	7	24
Yes	1	3	4	14
.	25	74	18	62
TOTAL	34	100	29	100

Listing 6.6-4 Progression/relapse n°1 – Other nodal involvement (MITT)

Randomization Number	Arm of 2nd randomization	Other nodal involvement	Other nodal involvement - localization	Other nodal involvement
5003606201605	RITUXIMAB	Yes	INTERAORTOCAVAL	Abnormal / Involved
5003101161407	OBSERVATION	Yes	RIGHT CRURAL	Abnormal / Involved
5003101621609	OBSERVATION	Yes	SUB CLAVICULAR LEFT	Abnormal / Involved
5003605701601	OBSERVATION	Yes	KIDNEY HILUS LEFT	Abnormal / Involved
5003617301619	OBSERVATION	Yes	SUBMANDIBULAR RIGHT	Abnormal / Involved
N = 5				

Table 6.6-3 Progression/relapse n°1 – Details of extra-nodal involvement (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Liver				
Normal	6	22	8	30
Involved	1	4	2	7
Not evaluated	1	4	0	0
.	19	70	17	63
Ascites				
Normal	7	26	10	37
Not evaluated	2	7	0	0
.	18	67	17	63
Pleural effusion				
Normal	7	26	10	37
Not evaluated	2	7	0	0
.	18	67	17	63
Lung				
Normal	7	26	5	19

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Involved	1	4	4	15
Not evaluated	2	7	1	4
.	17	63	17	63
Spleen				
Normal	8	30	8	30
Involved	0	0	2	7
Not evaluated	1	4	0	0
.	18	67	17	63
Pericardium				
Normal	7	26	9	33
Not evaluated	2	7	1	4
.	18	67	17	63
Breast				
Normal	7	26	9	33
Not evaluated	2	7	1	4
.	18	67	17	63
Gonadal				
Normal	7	26	10	37
Not evaluated	2	7	0	0
.	18	67	17	63
Kidney				
Normal	8	30	7	26
Involved	0	0	3	11
Not evaluated	1	4	0	0
.	18	67	17	63
Adrenal				
Normal	8	30	9	33
Involved	0	0	1	4
Not evaluated	1	4	0	0
.	18	67	17	63
Thyroid				
Normal	6	22	10	37
Not evaluated	3	11	0	0
.	18	67	17	63
Skin				
Normal	6	22	9	33
Involved	2	7	1	4
Not evaluated	1	4	0	0
.	18	67	17	63

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Bone				
Normal	7	26	8	30
Involved	2	7	1	4
Not evaluated	1	4	1	4
.	17	63	17	63
Tonsil				
Normal	5	19	8	30
Not evaluated	4	15	2	7
.	18	67	17	63
Cavum				
Normal	5	19	8	30
Not evaluated	4	15	2	7
.	18	67	17	63
Parotid				
Normal	5	19	8	30
Not evaluated	4	15	2	7
.	18	67	17	63
Orbit				
Normal	5	19	8	30
Not evaluated	4	15	2	7
.	18	67	17	63
Sinus				
Normal	4	15	8	30
Involved	1	4	0	0
Not evaluated	4	15	2	7
.	18	67	17	63
Oesophagus				
Normal	6	22	10	37
Not evaluated	3	11	0	0
.	18	67	17	63
Stomach				
Normal	6	22	10	37
Not evaluated	3	11	0	0
.	18	67	17	63
Duodenum				
Normal	6	22	10	37
Not evaluated	3	11	0	0
.	18	67	17	63
Colon				
Normal	6	22	9	33

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Involved	0	0	1	4
Not evaluated	3	11	0	0
.	18	67	17	63
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)

Randomization Number	Arm of 2nd randomization	Progression/relapse number	Other extra-nodal involvement - localization
5003101491042	RITUXIMAB	1	BLADDER
5003628201044	RITUXIMAB	1	STERNOCLEIDOMASTOID MUSCLE (INFILTRATION)
5003101641618	OBSERVATION	1	ENDOMETRIUM
N = 3			

Table 6.6-4 Progression/relapse n°1 – Documentation (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Histological documentation				
Yes	21	45	27	59
No	26	55	19	41
Cytological documentation				
.	0	0	2	4
Not Done	2	4	0	0
Yes	8	17	16	35
No	37	79	28	61
Total	47	100	46	100

Listing 6.6-6 Progression/relapse n°1 - Chemotherapy (MITT)

Randomization Number	Arm of 2nd randomization	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003101021631	RITUXIMAB	Yes	14/06/2007	R-GEMOX	8
5003101031001	RITUXIMAB	Yes	11/03/2004	ONCOVIN + CELLTOP	-
5003101031401	RITUXIMAB	Yes	14/04/2005	MIV	2
5003101051050	RITUXIMAB	Yes	15/01/2007	CYCLOPHOSPHAMIDE + ETOPOSIDE	1
5003101071408	RITUXIMAB	Yes	29/11/2006	GEMOX	4
5003101071417	RITUXIMAB	Yes	09/08/2008	GEMOX	1
5003101251035	RITUXIMAB	Yes	17/07/2006	IVAM + 3 ETOPOSIDE/CYCLOPHOSPHAMIDE	5
5003101281033	RITUXIMAB	Yes	12/01/2006	DHAP	2
5003101431622	RITUXIMAB	Yes	03/04/2008	COP (1 CYCLE) DHAP (3 CYCLES) CARBO DHAP (1 CYCLE) GEMOX (1 CYCLE)	6
5003101491042	RITUXIMAB	Yes	04/08/2006	LOW DOSE CYCLOPHOSPHAMIDE, 18/09/06 : HOELZER BLOK A, 30/10/06 : HOELZER BLOK D, GEMCITABINE 15/01/07 AND 26/01/07	-
5003102341061	RITUXIMAB	Yes	10/01/2008	CYTARABINE, ETOPOSIDE, MITOXANTRONE, IFOSFAMIDE, METHOTREXATE	3
5003102341641	RITUXIMAB	Yes	12/11/2009	CHOP	3
5003102541640	RITUXIMAB	Yes	11/09/2007	RACVBP	3
5003103161041	RITUXIMAB	Yes	20/04/2007	ETOPOSIDE + IFOSFAMIDE	4
5003601401402	RITUXIMAB	Yes	19/09/2005	CHOR / CYTOSAR	4
5003601881401	RITUXIMAB	Yes	11/08/2007	DEXAMETHASONE / CYTARABINE / PLATINE	4
5003602201601	RITUXIMAB	Yes	01/04/2006	DHAP DOSE REDUCED	2
5003602801403	RITUXIMAB	Yes	24/03/2009	R-ESAP	1
5003602801605	RITUXIMAB	Yes	24/09/2008	R-GDP	5
5003603201628	RITUXIMAB	Yes	-	CHOP	5
5003603801203	RITUXIMAB	Yes	17/08/2005	ESHAP	1
5003603801406	RITUXIMAB	Yes	13/11/2008	P.O. ETOPOSIDE	3
5003604301602	RITUXIMAB	Yes	17/08/2006	2 CYCLES OF FLUDARABINE + 6 CYCLES OF CEOP	8
5003604801006	RITUXIMAB	Yes	07/06/2006	R-ICE	2
5003604801205	RITUXIMAB	Yes	10/08/2006	R-DHAP	4
5003606201407	RITUXIMAB	Yes	23/11/2006	GEMCITABINE / IRINOTECAN	2
5003606201605	RITUXIMAB	Yes	05/01/2006	GEMCITABINE / OXALIPLATIN	5

Randomization Number	Arm of 2nd randomization	Chemotherapy	Date of chemotherapy	Specify chemotherapy	Nb of cycles of chemotherapy
5003607501401	RITUXIMAB	Yes	19/06/2007	GEMCITABINE + CISPLATIN DEXAMETHASONE	2
5003607701007	RITUXIMAB	Yes	29/04/2006	DHAP	1
5003609301620	RITUXIMAB	Yes	26/11/2007	R-ICE	6
5003610201206	RITUXIMAB	Yes	21/06/2006	DHAP	2
5003617201021	RITUXIMAB	Yes	30/05/2007	R-BENDAMUSTIN	5
5003617201043	RITUXIMAB	Yes	24/09/2007	2 G VINCRISTIN FOLLOWED BY 6EM DEX OX	1
5003628201044	RITUXIMAB	Yes	05/08/2008	R-ICE, R-CHOP, GEMCITABINE / VINORELBINE	3
5003630201040	RITUXIMAB	Yes	16/06/2007	RITUXIMAB - GEMCITABINE - OXALIPLATIN	2
5003101021038	OBSERVATION	Yes	19/12/2006	GEMOX	4
5003101021605	OBSERVATION	Yes	28/05/2004	R-GEMOX	8
5003101141624	OBSERVATION	Yes	10/06/2009	ENDOXAN AND SOLUMEDROL FOLLOWING BY CHOP 1 CYCLE AND CVP	1
5003101161407	OBSERVATION	Yes	28/03/2007	DHAP (1 CYCLE) THEN DEXAMETHASONE + CYTARABINE + ETOPOSIDE (1 CYCLE) THEN CYCLOPHOSPHAMIDE + MITOXANTRONE + VINCRISTINE + DEXAMETHASONE	3
5003101621026	OBSERVATION	Yes	12/03/2007	RITUXIMAB - DEXAMETHASONE CISPLATINE CYTARABINE	6
5003101621609	OBSERVATION	Yes	13/11/2006	R CHOP	6
5003101621615	OBSERVATION	Yes	04/05/2005	DHAP	4
5003101641618	OBSERVATION	Yes	25/01/2007	GEMCITABINE - OXALIPLATIN	8
5003102411054	OBSERVATION	Yes	04/09/2007	RITUXIMAB + ETOPOSIDE + IFOSFAMIDE	2
5003102541052	OBSERVATION	Yes	10/01/2007	DHAP	1
5003601401006	OBSERVATION	Yes	05/03/2008	CYCLOPHOSPHAMIDE PER ORAL CONTINUOUS TREATEMENT TOGETHER WITH METHOTREXATE 2 DAYS / WEEK	-
5003601401603	OBSERVATION	Yes	28/11/2007	DOXORUBICIN (LIPOSOMAL) + GEMCITABIN TO 3/4-08 + ISOFOSFAMIDE 100 MG PO DAILY DOSE	6
5003601601003	OBSERVATION	Yes	16/11/2007	PALLIATIVE CYCLOPHOSPHAMIDE	3
5003601601005	OBSERVATION	Yes	11/09/2008	ORAL CYCLOPHOSPHAMIDE / ETOPOSIDE X 7 DAYS	1
5003601601602	OBSERVATION	Yes	14/08/2008	GEMATABINE W/ RITUXIMAB + DACETUZUMAB (INVESTIGATIONAL)	5
5003602801011	OBSERVATION	Yes	15/07/2007	HIGH DOSE MTX + ARA-C	1
5003603201038	OBSERVATION	Yes	-	SEE COPY	-
5003603801002	OBSERVATION	Yes	05/03/2010	R-MINE	1
5003603801602	OBSERVATION	Yes	13/10/2006	R-FND	4
5003603801608	OBSERVATION	Yes	03/11/2008	R-MEGA CHOP	3
5003604201056	OBSERVATION	Yes	18/06/2009	B-ALL	-
5003606201609	OBSERVATION	Yes	-	ICE	3
5003607301603	OBSERVATION	Yes	27/06/2006	VINCRISTINE 2 MG EVERY 2 OR 3 WEEKS / DEXAMETHASONE 40 MG DAILY FOR FOUR DAYS EVEREY THREE WEEKS	6
5003607501403	OBSERVATION	Yes	13/07/2007	GEMCYTABINE CISPLATIN	3
5003610501031	OBSERVATION	Yes	30/07/2008	GEMCITABINE, VINORELBINE	1
5003610701403	OBSERVATION	Yes	20/11/2008	R-ICE	2
5003614301407	OBSERVATION	Yes	24/06/2009	ICE	6
5003617301619	OBSERVATION	Yes	09/05/2007	GEMCITABINE ; IFOSFAMIDE ; PREDNISOLONE	4
5003618301005	OBSERVATION	Yes	05/07/2006	GEMCITABINE VINORELBINE	2
5003619301621	OBSERVATION	Yes	24/10/2007	R-VGF	4
5003621201020	OBSERVATION	Yes	28/04/2006	DEXAMETHASONE / CYTARABINE / METHOTREXATE	2
5003631201619	OBSERVATION	Yes	13/09/2006	ICE C IFOSFAMIDE 50%	1
N = 67					

Listing 6.6-7 Progression/relapse n°1 - Radiotherapy (MITT)

Randomization Number	Arm of 2nd randomization	Radiotherapy	Date of radiotherapy	Site of radiotherapy	Dose of radiotherapy (Gy)
5003101031001	RITUXIMAB	Yes	16/01/2004	LEFT ARM	47
5003101031401	RITUXIMAB	Yes	-	ENCEPHALON	45
5003101491042	RITUXIMAB	Yes	18/08/2006	BLADDER (TILL 01/09/2006) + 13/12/2006 - 02/01/2007, SITE : LATERAL LUMBAL FIELD, 30 GY	30
5003603801203	RITUXIMAB	Yes	16/05/2005	RIGHT INGUINA AND RIGHT ILIAC REGION	40
5003604801006	RITUXIMAB	Yes	04/09/2006		44
5003604901004	RITUXIMAB	Yes	29/04/2007	D8 AND APARASPINAL MASS	40
5003604901005	RITUXIMAB	Yes	17/07/2006	ILIAC BONE	36
5003605301610	RITUXIMAB	Yes	29/05/2006	LEFT NECK	30
5003609301620	RITUXIMAB	Yes	05/06/2008	PARANASAL SINUSES	36
5003612301623	RITUXIMAB	Yes	14/04/2008	BASE OF BRAIN	12
5003616501003	RITUXIMAB	Yes	18/04/2008	ENTIRE SPINE C2-L3 INCLUSIVE	30
5003628201044	RITUXIMAB	Yes	01/02/2009	CERVICAL MASS	-
5003101161407	OBSERVATION	Yes	-	RIGHT LEG	36
5003102411054	OBSERVATION	Yes	16/10/2007	LEFT ILIAC + LEFT INGUINAL	40
5003102411069	OBSERVATION	Yes	20/02/2008	CERVICO SUB CLAVICULAR GANGLION + WALDEYER RING	36
5003601601005	OBSERVATION	Yes	29/07/2008	LEFT PELVIC WALL	37
5003602901601	OBSERVATION	Yes	-	RIGHT ADRENAL	-
5003603201038	OBSERVATION	Yes	10/09/2007	TOTAL BODY	4
5003603701006	OBSERVATION	Yes	07/04/2006	THORAX WOUND	42
5003603801009	OBSERVATION	Yes	11/12/2006	RIGHT AXILLA AND RIGHT ARM	40
5003604301013	OBSERVATION	Yes	17/06/2009	RIGHT FOREARM	20
5003606701003	OBSERVATION	Yes	09/03/2006	MESENTERIC MASS	40
5003608701008	OBSERVATION	Yes	06/07/2006	AXILLA RIGHT	40
5003614301407	OBSERVATION	Yes	07/01/2010	PARA-AORTIC NODES	30
5003618301005	OBSERVATION	Yes	09/08/2006	RIGHT HEMIPELVIS	30
5003621201020	OBSERVATION	Yes	27/06/2006	TONSILLA RIGHT, ZONA LEG LEFT	8
5003621501412	OBSERVATION	Yes	09/11/2009	CHEST WALL	25
N = 27					

Listing 6.6-8 Progression/relapse n°1 - Immunotherapy (MITT)

Randomization Number	Arm of 2nd randomization	Immunotherapy	Date of immunotherapy	Specify immunotherapy
5003101021631	RITUXIMAB	Yes	14/06/2007	RITUXIMAB
5003101071408	RITUXIMAB	Yes	05/04/2007	IBRITUMOMAB TIUXETAN + RITUXIMAB
5003101251035	RITUXIMAB	Yes	17/07/2006	RITUXIMAB
5003101281033	RITUXIMAB	Yes	12/01/2006	RITUXIMAB
5003101431622	RITUXIMAB	Yes	09/04/2008	RITUXIMAB
5003102341641	RITUXIMAB	Yes	12/11/2009	RITUXIMAB
5003604801205	RITUXIMAB	Yes	10/08/2006	RITUXIMAB
5003609301620	RITUXIMAB	Yes	26/11/2007	RITUXIMAB (IN CONJUNCTION WITH CHEMOTHERAPY)
5003615501014	RITUXIMAB	Yes	12/03/2008	OFATUMOMAB
5003617201043	RITUXIMAB	Yes	26/09/2007	RITUXIMAB

Randomization Number	Arm of 2nd randomization	Immunotherapy	Date of immunotherapy	Specify immunotherapy
5003101021038	OBSERVATION	Yes	18/12/2006	RITUXIMAB (4 CYCLES)
5003101141624	OBSERVATION	Yes	10/06/2009	RITUXIMAB
5003101161407	OBSERVATION	Yes	28/03/2007	RITUXIMAB THEN ANTI CD20
5003101621615	OBSERVATION	Yes	27/08/2005	RITUXIMAB 8 CURES
5003101641618	OBSERVATION	Yes	25/01/2007	RITUXIMAB
5003601601602	OBSERVATION	Yes	14/08/2008	RITUXIMAB W/GEMCITABINE AND DACETUZUMAB (INVESTIGATIONAL)
5003602901601	OBSERVATION	Yes	17/01/2006	MABTHERA
5003603801602	OBSERVATION	Yes	13/10/2006	RITUXIMAB IN COMBINATION WITH FND
5003605701601	OBSERVATION	Yes	28/07/2006	RITUXIMAB (STOP : 04.08.2006)
5003606201609	OBSERVATION	Yes	-	RITUXIMAB EVERY 3 MONTHS
5003618301005	OBSERVATION	Yes	-	RITUXIMAB
5003621201020	OBSERVATION	Yes	08/05/2006	MABTHERA 2 CYCLES
N = 22				

Listing 6.6-9 Progression/relapse n°1 - Tranpslant (MITT)

Randomization Number	Arm of 2nd randomization	Transplantation	Date of transplantation	Conditioning Regimen
5003102341061	RITUXIMAB	Yes	26/05/2008	FLUDARABINE, ENDOXAN, IRRADIATION
5003102341641	RITUXIMAB	Yes	18/02/2010	IBRITUMOMAB TIUXETAN (ETUDE ZEVALLO)
5003102491619	RITUXIMAB	Yes	06/09/2007	FLUDARABINE BUSULFAN AND ATG
5003102541640	RITUXIMAB	Yes	21/04/2008	CPA, FLUDA, ATG, MPD, CYCLO
5003601881401	RITUXIMAB	Yes	11/12/2007	FLUDARABINE / BUSULFAN / SAL
5003602201601	RITUXIMAB	Yes	28/06/2006	FLUDARABIN / BUSULFAN / CYCLOPHOSPHAMID / ATG: ACC. DSHNHL-2004-R3 PROTOCOL (ARM B, WITHOUT RITUXIMAB)
5003602801605	RITUXIMAB	Yes	16/04/2009	FLUDARABIN, BUSULFAN, ANTITHYMOCYTE GLOBULIN
5003604701002	RITUXIMAB	Yes	30/12/2005	POMP
5003604801205	RITUXIMAB	Yes	22/12/2006	BU-CY
5003606201407	RITUXIMAB	Yes	19/03/2007	HD MELPHALAN
5003617201021	RITUXIMAB	Yes	13/11/2007	FLUDARABIN, BUSULFAN, CYCLOPHOSPHAMIDE, ATG
5003601601602	OBSERVATION	Yes	14/01/2009	CYCLOPHOSPHAMIDE, FLUDARABINE, METHOTREXATE
5003603201038	OBSERVATION	Yes	19/09/2007	MELPHALAN + FLUDARABIN
5003603801602	OBSERVATION	Yes	08/03/2007	TBI + ALEMTUZUMAB + CYCLOPHOSPHAMIDE
5003603801608	OBSERVATION	Yes	28/01/2009	FLAMSA + TBI
N = 15				

Listing 6.6-10 Progression/relapse n°1 – Other treatments (MITT)

Randomization Number	Arm of 2nd randomization	Other treatment	Date of other treatment	Specify other treatment
5003101021631	RITUXIMAB	Yes	07/02/2008	IBRITUMOMAB TIUXETAN
5003101031001	RITUXIMAB	Yes	23/12/2003	CORTICOIDES
5003101251035	RITUXIMAB	Yes	05/03/2007	MERCAPTOPURINE METHOTREXATE
5003102541640	RITUXIMAB	Yes	-	RADIOIMMUNOTHERAPY : IBRITUMOMAB TIUXETAN
5003103161041	RITUXIMAB	Yes	10/05/2007	HUMAN IMMUNOGLOBULIN
5003604701002	RITUXIMAB	Yes	08/06/2006	THORACOTOMY WITH RESECTION OF TUMOR - HISTOLOGY SHOWED NO VISIBLE LYMPHOMA ANYMORE
5003613701402	RITUXIMAB	Yes	01/12/2010	MABTHERA
5003630201040	RITUXIMAB	Yes	20/08/2007	RITUXIMAB - BENDAMUSTIN
5003101351012	OBSERVATION	Yes	10/08/2006	CORTICOIDS
5003102411069	OBSERVATION	Yes	01/02/2008	CORTICOTHERAPY
5003605701601	OBSERVATION	Yes	28/07/2006	IBRITUMOMAB TIUXETAN (STOP : 04.08.2006)
5003610301613	OBSERVATION	Yes	18/10/2005	SPLENECTOMY
5003621201020	OBSERVATION	Yes	09/05/2006	MTX HIGH DOSE 2 CYCLES
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)

Rituximab : Dose received (% of planned dose)		Actual arm of maintenance RITUXIMAB	
		N	%
Cycle 1	<75%	0	0
	[75-90%[	5	4
	[90-110%[	111	96
	[110-125%[	0	0
	>125%	0	0
	Total	116	100
Cycle 2	<75%	0	0
	[75-90%[	6	6
	[90-110%[	94	94
	[110-125%[	0	0
	>125%	0	0
	Total	100	100
Cycle 3	<75%	0	0
	[75-90%[	5	5
	[90-110%[	86	95
	[110-125%[	0	0
	>125%	0	0
	Total	91	100
Cycle 4	<75%	0	0
	[75-90%[	5	6
	[90-110%[	84	94
	[110-125%[	0	0
	>125%	0	0
	Total	89	100
Cycle 5	<75%	0	0
	[75-90%[	5	6
	[90-110%[	75	94
	[110-125%[	0	0
	>125%	0	0
	Total	80	100
Cycle 6	<75%	0	0
	[75-90%[	5	6
	[90-110%[	73	94
	[110-125%[	0	0
	>125%	0	0
	Total	78	100

6.7.2. Overview of toxicity profile

Table 6.7-2 Incidence of maintenance toxicities by grade and cycle (MSAP)

			Actual arm of maintenance																	
			RITUXIMAB									OBSERVATION								
			Grade									Grade								
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
	Cycle number																				
Grade allergy	1	N	1	109	0	1	0	0	0	0	6	116	0	88	0	0	0	0	0	31	119
		%	1	94	0	1	0	0	0	0	5	100	0	74	0	0	0	0	0	26	100
	2	N	1	95	0	1	0	0	0	0	4	100	1	92	0	0	1	0	1	23	116
		%	1	95	0	1	0	0	0	0	4	100	1	79	0	0	1	0	1	20	100
	3	N	1	87	0	1	0	0	0	0	3	91	1	72	0	0	1	0	1	29	102
		%	1	96	0	1	0	0	0	0	3	100	1	71	0	0	1	0	1	28	100
	4	N	1	85	0	1	0	0	0	0	3	89	0	63	0	0	0	0	0	25	88
		%	1	96	0	1	0	0	0	0	3	100	0	72	0	0	0	0	0	28	100
	5	N	1	76	0	1	0	0	0	0	3	80	0	48	0	0	0	0	0	19	67
		%	1	95	0	1	0	0	0	0	4	100	0	72	0	0	0	0	0	28	100
	6	N	1	75	0	0	1	0	0	1	2	78	0	34	0	0	0	0	0	14	48
		%	1	96	0	0	1	0	0	1	3	100	0	71	0	0	0	0	0	29	100

			Actual arm of maintenance																	
			RITUXIMAB									OBSERVATION								
			Grade									Grade								
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade auditory	**1**	**N**	7	103	1	4	2	0	0	2	6	116	0	88	0	0	0	0	0	31	119
		%	6	89	1	3	2	0	0	2	5	100	0	74	0	0	0	0	0	26	100
	2	**N**	5	91	0	3	2	0	0	2	4	100	0	93	0	0	0	0	0	23	116
		%	5	91	0	3	2	0	0	2	4	100	0	80	0	0	0	0	0	20	100
	3	**N**	5	83	1	2	2	0	0	2	3	91	0	73	0	0	0	0	0	29	102
		%	5	91	1	2	2	0	0	2	3	100	0	72	0	0	0	0	0	28	100
	4	**N**	4	82	0	2	2	0	0	2	3	89	0	63	0	0	0	0	0	25	88
		%	4	92	0	2	2	0	0	2	3	100	0	72	0	0	0	0	0	28	100
	5	**N**	2	75	1	1	0	0	0	0	3	80	0	48	0	0	0	0	0	19	67
		%	3	94	1	1	0	0	0	0	4	100	0	72	0	0	0	0	0	28	100
	6	**N**	3	73	1	2	0	0	0	0	2	78	0	34	0	0	0	0	0	14	48
		%	4	94	1	3	0	0	0	0	3	100	0	71	0	0	0	0	0	29	100
Grade blood	**1**	**N**	65	44	23	13	15	14	0	29	7	116	44	44	19	7	10	8	18	31	119
		%	56	38	20	11	13	12	0	25	6	100	37	37	16	6	8	7	15	26	100
	2	**N**	59	36	23	15	14	7	0	21	5	100	44	48	13	17	5	9	14	24	116
		%	59	36	23	15	14	7	0	21	5	100	38	41	11	15	4	8	12	21	100
	3	**N**	53	34	26	13	7	7	0	14	4	91	32	37	18	7	4	3	7	33	102
		%	58	37	29	14	8	8	0	15	4	100	31	36	18	7	4	3	7	32	100
	4	**N**	40	44	18	11	6	5	0	11	5	89	24	37	18	3	2	1	3	27	88
		%	45	49	20	12	7	6	0	12	6	100	27	42	20	3	2	1	3	31	100
	5	**N**	27	48	14	6	4	3	0	7	5	80	17	31	11	3	2	1	3	19	67
		%	34	60	18	8	5	4	0	9	6	100	25	46	16	4	3	1	4	28	100
	6	**N**	28	46	18	4	4	2	0	6	4	78	8	26	7	0	1	0	1	14	48
		%	36	59	23	5	5	3	0	8	5	100	17	54	15	0	2	0	2	29	100

			Actual arm of maintenance																	
			RITUXIMAB									OBSERVATION								
			Grade									Grade								
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade cardiovascular	1	N	2	108	1	1	0	0	0	0	6	116	3	87	1	2	0	0	0	29	119
		%	2	93	1	1	0	0	0	0	5	100	3	73	1	2	0	0	0	24	100
	2	N	1	95	0	1	0	0	0	0	4	100	4	90	2	2	0	0	0	22	116
		%	1	95	0	1	0	0	0	0	4	100	3	78	2	2	0	0	0	19	100
	3	N	1	87	0	1	0	0	0	0	3	91	3	70	1	2	0	0	0	29	102
		%	1	96	0	1	0	0	0	0	3	100	3	69	1	2	0	0	0	28	100
	4	N	1	85	1	0	0	0	0	0	3	89	1	62	0	1	0	0	0	25	88
		%	1	96	1	0	0	0	0	0	3	100	1	70	0	1	0	0	0	28	100
	5	N	3	74	2	1	0	0	0	0	3	80	1	47	0	0	0	1	1	19	67
		%	4	93	3	1	0	0	0	0	4	100	1	70	0	0	0	1	1	28	100
	6	N	4	72	3	1	0	0	0	0	2	78	0	34	0	0	0	0	0	14	48
		%	5	92	4	1	0	0	0	0	3	100	0	71	0	0	0	0	0	29	100
Grade coagulation	1	N	4	104	2	0	2	0	0	2	8	116	1	87	1	0	0	0	0	31	119
		%	3	90	2	0	2	0	0	2	7	100	1	73	1	0	0	0	0	26	100
	2	N	1	92	1	0	0	0	0	0	7	100	0	92	0	0	0	0	0	24	116
		%	1	92	1	0	0	0	0	0	7	100	0	79	0	0	0	0	0	21	100
	3	N	1	84	1	0	0	0	0	0	6	91	0	72	0	0	0	0	0	30	102
		%	1	92	1	0	0	0	0	0	7	100	0	71	0	0	0	0	0	29	100
	4	N	3	80	2	0	1	0	0	1	6	89	0	62	0	0	0	0	0	26	88
		%	3	90	2	0	1	0	0	1	7	100	0	70	0	0	0	0	0	30	100
	5	N	2	72	1	1	0	0	0	0	6	80	0	44	0	0	0	0	0	23	67
		%	3	90	1	1	0	0	0	0	8	100	0	66	0	0	0	0	0	34	100
	6	N	2	71	1	1	0	0	0	0	5	78	0	34	0	0	0	0	0	14	48
		%	3	91	1	1	0	0	0	0	6	100	0	71	0	0	0	0	0	29	100

			Actual arm of maintenance																	
			RITUXIMAB									OBSERVATION								
			Grade									Grade								
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade skin	1	N	7	103	4	3	0	0	0	0	6	116	10	80	8	2	0	0	0	29	119
		%	6	89	3	3	0	0	0	0	5	100	8	67	7	2	0	0	0	24	100
	2	N	9	87	9	0	0	0	0	0	4	100	6	88	3	3	0	0	0	22	116
		%	9	87	9	0	0	0	0	0	4	100	5	76	3	3	0	0	0	19	100
	3	N	5	83	3	2	0	0	0	0	3	91	8	65	4	4	0	0	0	29	102
		%	5	91	3	2	0	0	0	0	3	100	8	64	4	4	0	0	0	28	100
	4	N	3	83	3	0	0	0	0	0	3	89	6	57	1	3	2	0	2	25	88
		%	3	93	3	0	0	0	0	0	3	100	7	65	1	3	2	0	2	28	100
	5	N	3	74	2	1	0	0	0	0	3	80	5	43	2	3	0	0	0	19	67
		%	4	93	3	1	0	0	0	0	4	100	7	64	3	4	0	0	0	28	100
	6	N	2	74	1	1	0	0	0	0	2	78	3	31	2	1	0	0	0	14	48
		%	3	95	1	1	0	0	0	0	3	100	6	65	4	2	0	0	0	29	100
Grade gastrointestinal	1	N	21	89	14	7	0	0	0	0	6	116	25	65	12	11	1	1	2	29	119
		%	18	77	12	6	0	0	0	0	5	100	21	55	10	9	1	1	2	24	100
	2	N	12	84	8	4	0	0	0	0	4	100	15	79	11	4	0	0	0	22	116
		%	12	84	8	4	0	0	0	0	4	100	13	68	9	3	0	0	0	19	100
	3	N	10	78	8	2	0	0	0	0	3	91	10	63	9	0	1	0	1	29	102
		%	11	86	9	2	0	0	0	0	3	100	10	62	9	0	1	0	1	28	100
	4	N	4	82	3	1	0	0	0	0	3	89	4	59	2	0	1	1	2	25	88
		%	4	92	3	1	0	0	0	0	3	100	5	67	2	0	1	1	2	28	100
	5	N	1	76	0	1	0	0	0	0	3	80	3	45	2	1	0	0	0	19	67
		%	1	95	0	1	0	0	0	0	4	100	4	67	3	1	0	0	0	28	100
	6	N	2	74	1	1	0	0	0	0	2	78	2	32	2	0	0	0	0	14	48
		%	3	95	1	1	0	0	0	0	3	100	4	67	4	0	0	0	0	29	100

			Actual arm of maintenance																	
			RITUXIMAB									OBSERVATION								
			Grade									Grade								
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade hepatic	1	N	10	100	7	2	1	0	0	1	6	116	11	79	8	2	0	1	1	29	119
		%	9	86	6	2	1	0	0	1	5	100	9	66	7	2	0	1	1	24	100
	2	N	8	88	8	0	0	0	0	0	4	100	6	88	4	0	2	0	2	22	116
		%	8	88	8	0	0	0	0	0	4	100	5	76	3	0	2	0	2	19	100
	3	N	4	84	4	0	0	0	0	0	3	91	2	71	0	1	1	0	1	29	102
		%	4	92	4	0	0	0	0	0	3	100	2	70	0	1	1	0	1	28	100
	4	N	6	80	6	0	0	0	0	0	3	89	2	60	1	1	0	0	0	26	88
		%	7	90	7	0	0	0	0	0	3	100	2	68	1	1	0	0	0	30	100
	5	N	6	71	6	0	0	0	0	0	3	80	2	46	2	0	0	0	0	19	67
		%	8	89	8	0	0	0	0	0	4	100	3	69	3	0	0	0	0	28	100
	6	N	5	71	5	0	0	0	0	0	2	78	1	33	1	0	0	0	0	14	48
		%	6	91	6	0	0	0	0	0	3	100	2	69	2	0	0	0	0	29	100
Grade infection	1	N	11	99	3	5	2	0	1	3	6	116	10	80	5	2	3	0	3	29	119
		%	9	85	3	4	2	0	1	3	5	100	8	67	4	2	3	0	3	24	100
	2	N	8	88	3	5	0	0	0	0	4	100	15	79	5	3	6	1	7	22	116
		%	8	88	3	5	0	0	0	0	4	100	13	68	4	3	5	1	6	19	100
	3	N	12	76	4	4	3	1	0	4	3	91	5	68	0	4	1	0	1	29	102
		%	13	84	4	4	3	1	0	4	3	100	5	67	0	4	1	0	1	28	100
	4	N	16	70	3	11	1	0	1	2	3	89	6	57	2	3	0	1	1	25	88
		%	18	79	3	12	1	0	1	2	3	100	7	65	2	3	0	1	1	28	100
	5	N	11	66	3	7	1	0	0	1	3	80	3	45	1	2	0	0	0	19	67
		%	14	83	4	9	1	0	0	1	4	100	4	67	1	3	0	0	0	28	100
	6	N	9	66	2	5	2	0	0	2	3	78	4	30	0	4	0	0	0	14	48
		%	12	85	3	6	3	0	0	3	4	100	8	63	0	8	0	0	0	29	100

			Actual arm of maintenance																	
			RITUXIMAB									OBSERVATION								
			Grade									Grade								
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade viral infection	1	N	3	107	0	2	1	0	0	1	6	116	3	87	2	1	0	0	0	29	119
		%	3	92	0	2	1	0	0	1	5	100	3	73	2	1	0	0	0	24	100
	2	N	1	95	1	0	0	0	0	0	4	100	4	90	1	2	1	0	1	22	116
		%	1	95	1	0	0	0	0	0	4	100	3	78	1	2	1	0	1	19	100
	3	N	2	86	0	1	0	1	0	1	3	91	2	71	0	2	0	0	0	29	102
		%	2	95	0	1	0	1	0	1	3	100	2	70	0	2	0	0	0	28	100
	4	N	2	84	1	0	1	0	0	1	3	89	4	59	1	3	0	0	0	25	88
		%	2	94	1	0	1	0	0	1	3	100	5	67	1	3	0	0	0	28	100
	5	N	2	75	1	1	0	0	0	0	3	80	3	45	1	2	0	0	0	19	67
		%	3	94	1	1	0	0	0	0	4	100	4	67	1	3	0	0	0	28	100
	6	N	0	76	0	0	0	0	0	0	2	78	1	33	0	1	0	0	0	14	48
		%	0	97	0	0	0	0	0	0	3	100	2	69	0	2	0	0	0	29	100
Grade metabolic	1	N	12	98	7	2	2	1	0	3	6	116	8	81	5	2	1	0	1	30	119
		%	10	84	6	2	2	1	0	3	5	100	7	68	4	2	1	0	1	25	100
	2	N	10	86	6	3	1	0	0	1	4	100	9	84	7	1	1	0	1	23	116
		%	10	86	6	3	1	0	0	1	4	100	8	72	6	1	1	0	1	20	100
	3	N	7	81	3	4	0	0	0	0	3	91	6	65	5	0	1	0	1	31	102
		%	8	89	3	4	0	0	0	0	3	100	6	64	5	0	1	0	1	30	100
	4	N	11	75	8	3	0	0	0	0	3	89	6	55	6	0	0	0	0	27	88
		%	12	84	9	3	0	0	0	0	3	100	7	63	7	0	0	0	0	31	100
	5	N	8	69	8	0	0	0	0	0	3	80	4	44	4	0	0	0	0	19	67
		%	10	86	10	0	0	0	0	0	4	100	6	66	6	0	0	0	0	28	100
	6	N	8	67	8	0	0	0	0	0	3	78	1	33	1	0	0	0	0	14	48
		%	10	86	10	0	0	0	0	0	4	100	2	69	2	0	0	0	0	29	100

			Actual arm of maintenance																	
			RITUXIMAB									OBSERVATION								
			Grade									Grade								
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade neurology	1	N	7	103	5	1	0	0	1	1	6	116	7	83	3	4	0	0	0	29	119
		%	6	89	4	1	0	0	1	1	5	100	6	70	3	3	0	0	0	24	100
	2	N	10	86	8	2	0	0	0	0	4	100	8	86	2	5	1	0	1	22	116
		%	10	86	8	2	0	0	0	0	4	100	7	74	2	4	1	0	1	19	100
	3	N	4	84	3	1	0	0	0	0	3	91	9	64	6	3	0	0	0	29	102
		%	4	92	3	1	0	0	0	0	3	100	9	63	6	3	0	0	0	28	100
	4	N	4	82	3	1	0	0	0	0	3	89	7	56	4	3	0	0	0	25	88
		%	4	92	3	1	0	0	0	0	3	100	8	64	5	3	0	0	0	28	100
	5	N	7	70	4	1	2	0	0	2	3	80	6	42	5	1	0	0	0	19	67
		%	9	88	5	1	3	0	0	3	4	100	9	63	7	1	0	0	0	28	100
	6	N	5	71	3	2	0	0	0	0	2	78	4	30	3	1	0	0	0	14	48
		%	6	91	4	3	0	0	0	0	3	100	8	63	6	2	0	0	0	29	100
Grade pulmonary	1	N	8	102	4	2	1	1	0	2	6	116	8	82	7	1	0	0	0	29	119
		%	7	88	3	2	1	1	0	2	5	100	7	69	6	1	0	0	0	24	100
	2	N	6	90	3	3	0	0	0	0	4	100	7	87	4	2	0	1	1	22	116
		%	6	90	3	3	0	0	0	0	4	100	6	75	3	2	0	1	1	19	100
	3	N	7	81	5	2	0	0	0	0	3	91	2	71	0	2	0	0	0	29	102
		%	8	89	5	2	0	0	0	0	3	100	2	70	0	2	0	0	0	28	100
	4	N	6	80	4	1	0	1	0	1	3	89	2	61	1	1	0	0	0	25	88
		%	7	90	4	1	0	1	0	1	3	100	2	69	1	1	0	0	0	28	100
	5	N	7	70	5	2	0	0	0	0	3	80	0	48	0	0	0	0	0	19	67
		%	9	88	6	3	0	0	0	0	4	100	0	72	0	0	0	0	0	28	100
	6	N	6	70	4	2	0	0	0	0	2	78	0	34	0	0	0	0	0	14	48
		%	8	90	5	3	0	0	0	0	3	100	0	71	0	0	0	0	0	29	100

			Actual arm of maintenance																	
			RITUXIMAB									OBSERVATION								
			Grade									Grade								
			All Tox.	0	1	2	3	4	5	>=3	NE	Total	All Tox.	0	1	2	3	4	>=3	NE	Total
Grade renal	1	N	8	102	5	0	3	0	0	3	6	116	5	85	5	0	0	0	0	29	119
		%	7	88	4	0	3	0	0	3	5	100	4	71	4	0	0	0	0	24	100
	2	N	4	92	3	1	0	0	0	0	4	100	7	87	6	1	0	0	0	22	116
		%	4	92	3	1	0	0	0	0	4	100	6	75	5	1	0	0	0	19	100
	3	N	3	85	3	0	0	0	0	0	3	91	4	68	2	2	0	0	0	30	102
		%	3	93	3	0	0	0	0	0	3	100	4	67	2	2	0	0	0	29	100
	4	N	4	82	4	0	0	0	0	0	3	89	4	58	3	1	0	0	0	26	88
		%	4	92	4	0	0	0	0	0	3	100	5	66	3	1	0	0	0	30	100
	5	N	3	74	3	0	0	0	0	0	3	80	5	43	4	1	0	0	0	19	67
		%	4	93	4	0	0	0	0	0	4	100	7	64	6	1	0	0	0	28	100
	6	N	4	72	4	0	0	0	0	0	2	78	3	31	3	0	0	0	0	14	48
		%	5	92	5	0	0	0	0	0	3	100	6	65	6	0	0	0	0	29	100
Other Toxicity	1	N	28	82	16	10	1	0	1	2	6	116	26	63	17	9	0	0	0	30	119
		%	24	71	14	9	1	0	1	2	5	100	22	53	14	8	0	0	0	25	100
	2	N	18	78	10	7	1	0	0	1	4	100	23	71	14	9	0	0	0	22	116
		%	18	78	10	7	1	0	0	1	4	100	20	61	12	8	0	0	0	19	100
	3	N	16	72	12	4	0	0	0	0	3	91	12	61	6	6	0	0	0	29	102
		%	18	79	13	4	0	0	0	0	3	100	12	60	6	6	0	0	0	28	100
	4	N	13	73	11	1	1	0	0	1	3	89	10	53	5	5	0	0	0	25	88
		%	15	82	12	1	1	0	0	1	3	100	11	60	6	6	0	0	0	28	100
	5	N	12	66	7	4	1	0	0	1	2	80	8	39	4	3	1	0	1	20	67
		%	15	83	9	5	1	0	0	1	3	100	12	58	6	4	1	0	1	30	100
	6	N	12	64	8	3	1	0	0	1	2	78	4	29	3	1	0	0	0	15	48
		%	15	82	10	4	1	0	0	1	3	100	8	60	6	2	0	0	0	31	100

Listing 6.7-1 Other toxicities during maintenance (MSAP)

Randomization Number	Actual arm of maintenance	Other	Toxicity	Cycle number	Grade
5003101031001	RITUXIMAB	YES	BONE PAIN	1	2
5003101031621	RITUXIMAB	YES	CLIMATERIC SYNDROME POST CHEMOTHERAPY	6	2
5003101031634	RITUXIMAB	YES	RIGHT HIP PAIN	1	1
5003101031634	RITUXIMAB	YES	RIGHT HIP PAIN	2	1
5003101031634	RITUXIMAB	YES	SHOULDER PAIN	2	1
5003101031634	RITUXIMAB	YES	RIGHT HIP PAIN	3	1
5003101031634	RITUXIMAB	YES	SHOULDER PAIN	3	1
5003101031634	RITUXIMAB	YES	RIGHT HIP PAIN	4	1
5003101031634	RITUXIMAB	YES	SHOULDER PAIN	4	1
5003101051405	RITUXIMAB	YES	PLATELETS	1	1
5003101051405	RITUXIMAB	YES	PLATELETS	2	1
5003101071408	RITUXIMAB	YES	DORSAL LESIONS	3	2
5003101071417	RITUXIMAB	YES	ASTHENIA	1	1
5003101071417	RITUXIMAB	YES	ASTHENIA	2	1
5003101071417	RITUXIMAB	YES	ASTHENIA	3	1
5003101071417	RITUXIMAB	YES	ASTHENIA	4	1
5003101071417	RITUXIMAB	YES	ASTHENIA	5	1
5003101071417	RITUXIMAB	YES	CONSTITUTIONAL SYNDROME	5	2
5003101071417	RITUXIMAB	YES	ASTHENIA	6	1
5003101171633	RITUXIMAB	YES	ANOREXIA	2	2
5003101171633	RITUXIMAB	YES	ANOREXIA	3	1
5003101171633	RITUXIMAB	YES	ANOREXIA	4	1
5003101171633	RITUXIMAB	YES	ASTHENIA	4	1
5003101171637	RITUXIMAB	YES	ASTHENIA	1	1
5003101171644	RITUXIMAB	YES	ASTHENIA	1	1
5003101171644	RITUXIMAB	YES	ASTHENIA	2	1
5003101171644	RITUXIMAB	YES	ASTHENIA	3	1
5003101171644	RITUXIMAB	YES	COUGHT	4	1
5003101211642	RITUXIMAB	YES	PAIN-MUSCULO/NEURO (CRURALGIA)	2	2
5003101431608	RITUXIMAB	YES	ASTHENIA	1	1
5003101431608	RITUXIMAB	YES	ASTHENIA	3	2
5003101431608	RITUXIMAB	YES	ASTHENIA	5	9
5003101481614	RITUXIMAB	YES	NOSE INFECTION	5	2
5003101491042	RITUXIMAB	YES	FLUID RETENTION	1	2
5003102171419	RITUXIMAB	YES	CANKER OF RIGHT CHEEK (DUE TO PROTHESIS)	1	1
5003102441011	RITUXIMAB	YES	ASTHENIA	1	1
5003102441011	RITUXIMAB	YES	NERVOUS BREAKDOWN	1	1
5003102441011	RITUXIMAB	YES	ASTHENIA	2	1
5003102441011	RITUXIMAB	YES	NERVOUS BREAKDOWN	2	1
5003102441011	RITUXIMAB	YES	ASTHENIA	3	1
5003102441011	RITUXIMAB	YES	NERVOUS BREAKDOWN	3	1
5003102441011	RITUXIMAB	YES	ASTHENIA	4	1
5003102441011	RITUXIMAB	YES	NERVOUS BREAKDOWN	4	1
5003102441011	RITUXIMAB	YES	ASTHENIA	5	1

Randomization Number	Actual arm of maintenance	Other	Toxicity	Cycle number	Grade
5003102441011	RITUXIMAB	YES	ASTHENIA	6	1
5003102491619	RITUXIMAB	YES	MOOD ALTERATION (DEPRESSED FEELING)	1	1
5003102491619	RITUXIMAB	YES	HYPOMAGNESEMIA + XEROSTOMIA	1	1
5003102491619	RITUXIMAB	YES	FATIGUE	1	2
5003102491619	RITUXIMAB	YES	FATIGUE	2	2
5003102491619	RITUXIMAB	YES	FATIGUE	3	1
5003102491619	RITUXIMAB	YES	FATIGUE	5	1
5003102491619	RITUXIMAB	YES	FATIGUE	6	1
5003601501407	RITUXIMAB	YES	ALOPECIA GRADE 1	4	1
5003601501407	RITUXIMAB	YES	ALOPECIA GRADE 1	5	1
5003601501407	RITUXIMAB	YES	ALOPECIA GRADE 1	6	1
5003601881601	RITUXIMAB	YES	SWEATING	3	1
5003601881601	RITUXIMAB	YES	HYPOGAMMAGLOBULINEMIA	6	3
5003603801404	RITUXIMAB	YES	HERPES SIMPLEX LABIALIS	4	1
5003603801404	RITUXIMAB	YES	HERPES SIMPLEX LABIALIS	5	1
5003603801601	RITUXIMAB	YES	HEADACHE	1	1
5003603801601	RITUXIMAB	YES	HEADACHE	3	1
5003604301202	RITUXIMAB	YES	FATIGUE	1	2
5003604301202	RITUXIMAB	YES	FATIGUE	2	2
5003604301202	RITUXIMAB	YES	LOWER LEG CRAMP	6	1
5003604301602	RITUXIMAB	YES	FATIGUE	1	2
5003604301602	RITUXIMAB	YES	FATIGUE	4	2
5003604301602	RITUXIMAB	YES	FEVER	4	1
5003604701002	RITUXIMAB	YES	BONE PAIN	1	1
5003604701002	RITUXIMAB	YES	BONE PAIN	2	1
5003604701002	RITUXIMAB	YES	BONE PAIN	3	1
5003604701602	RITUXIMAB	YES	INFLAMMATION EYES	4	1
5003604701602	RITUXIMAB	YES	INFLAMMATION EYES	5	1
5003604701602	RITUXIMAB	YES	INFLAMMATION EYES	6	1
5003604901004	RITUXIMAB	YES	COUGH	1	1
5003604901004	RITUXIMAB	YES	ABDOMINAL PAIN	1	1
5003604901004	RITUXIMAB	YES	COUGH	2	1
5003604901005	RITUXIMAB	YES	FATIGUE	1	1
5003604901603	RITUXIMAB	YES	COMA DEPRESSED LEVEL OF CONCIOUSNESS	1	5
5003604901603	RITUXIMAB	YES	SUPERFICIAL BLEEDING AFTER REMUVAL OF PORTACATH	1	1
5003605701401	RITUXIMAB	YES	CONSTITUTIONAL : FATIGUE	1	1
5003605701401	RITUXIMAB	YES	CONSTITUTIONAL : FATIGUE	2	1
5003605701401	RITUXIMAB	YES	CONSTITUTIONAL : FATIGUE	3	1
5003605701401	RITUXIMAB	YES	CONSTITUTIONAL : FATIGUE	4	1
5003605701401	RITUXIMAB	YES	CONSTITUTIONAL : FATIGUE	5	2
5003605701401	RITUXIMAB	YES	PERONAEUS PARESIS LEFT	5	3
5003605701401	RITUXIMAB	YES	CONSTITUTIONAL : FATIGUE	6	2
5003606201019	RITUXIMAB	YES	FATIGUE	1	1
5003606201019	RITUXIMAB	YES	FATIGUE	2	1
5003606201019	RITUXIMAB	YES	FATIGUE	3	2

Randomization Number	Actual arm of maintenance	Other	Toxicity	Cycle number	Grade
5003606201019	RITUXIMAB	YES	FATIGUE	4	1
5003606201019	RITUXIMAB	YES	FATIGUE	5	2
5003606201019	RITUXIMAB	YES	FATIGUE	6	2
5003606201605	RITUXIMAB	YES	ABDOMINAL PAIN	5	1
5003606201605	RITUXIMAB	YES	ABDOMINAL PAIN	6	1
5003610201206	RITUXIMAB	YES	ALOPEZIA	1	2
5003610701014	RITUXIMAB	YES	LOSS OF APPETITE	1	2
5003610701014	RITUXIMAB	YES	PAIN BACK	1	1
5003610701014	RITUXIMAB	YES	LOSS OF APPETITE	2	2
5003610701014	RITUXIMAB	YES	PAIN BACK	2	1
5003610701014	RITUXIMAB	YES	NAUSEA	2	1
5003610701014	RITUXIMAB	YES	LOSS OF APPETITE	3	2
5003610701014	RITUXIMAB	YES	PAIN BACK	3	1
5003614501022	RITUXIMAB	YES	LEFT EAR PAIN	1	1
5003614501022	RITUXIMAB	YES	FATIGUE	1	1
5003614501022	RITUXIMAB	YES	MUSKULOSKELETAL PAIN	2	1
5003614501022	RITUXIMAB	YES	MUSKULOSKELETAL PAIN	3	1
5003614501032	RITUXIMAB	YES	FATIGUE	1	2
5003616301615	RITUXIMAB	YES	DENTAL - PERIODONTAL	4	3
5003616301615	RITUXIMAB	YES	DENTAL -TEETH	4	3
5003617301616	RITUXIMAB	YES	FATIGUE	2	2
5003617301616	RITUXIMAB	YES	FATIGUE	5	1
5003618201030	RITUXIMAB	YES	PAIN MUSCULO/SKELETAL	1	2
5003618201030	RITUXIMAB	YES	PAIN MUSCULO/SKELETAL	2	2
5003618201030	RITUXIMAB	YES	PAIN MUSCULO/SKELETAL	3	2
5003618301405	RITUXIMAB	YES	FATIGUE	1	2
5003618301405	RITUXIMAB	YES	HYPOMAGNESIUM	1	1
5003618301405	RITUXIMAB	YES	NEUTROPENIA	1	1
5003618301405	RITUXIMAB	YES	FATIGUE	2	1
5003618301405	RITUXIMAB	YES	HYPOMAGNESIUM	2	1
5003618301405	RITUXIMAB	YES	NEUTROPENIA	2	3
5003618301405	RITUXIMAB	YES	FATIGUE	3	1
5003618301405	RITUXIMAB	YES	NEUTROPENIA	3	1
5003618301405	RITUXIMAB	YES	FATIGUE	4	1
5003618301405	RITUXIMAB	YES	NEUTROPENIA	6	1
5003620501602	RITUXIMAB	YES	ASTHENIA	1	1
5003620501602	RITUXIMAB	YES	NEW MOLES (SKIN)	1	1
5003620501602	RITUXIMAB	YES	TINNITUS	5	2
5003622201014	RITUXIMAB	YES	LEUKOPENIA	1	3
5003630201621	RITUXIMAB	YES	FATIGUE	6	2
5003101021038	OBSERVATION	YES	CONSTITUTIONAL (WEIGHT LOSS)	4	9
5003101021038	OBSERVATION	YES	CONSTITUTIONAL (WEIGHT LOSS)	5	1
5003101051648	OBSERVATION	YES	CONSTITUTIONAL SYMPTOMS = FATIGUE	1	1
5003101051648	OBSERVATION	YES	CONSTITUTIONAL SYMPTOMS = FATIGUE	2	1
5003101051648	OBSERVATION	YES	CONSTITUTIONAL SYMPTOMS = FATIGUE	3	1

Randomization Number	Actual arm of maintenance	Other	Toxicity	Cycle number	Grade
5003101071643	OBSERVATION	YES	ASTHENIA	1	2
5003101071643	OBSERVATION	YES	MUCOSITIS	1	1
5003101071643	OBSERVATION	YES	ASTHENIA	2	2
5003101191632	OBSERVATION	YES	MUSCULAR PAIN	2	1
5003101191632	OBSERVATION	YES	MUSCULAR PAIN	5	9
5003101211628	OBSERVATION	YES	FATIGUE	2	2
5003101211630	OBSERVATION	YES	INSOMNIA	2	1
5003101251021	OBSERVATION	YES	ASTHENIA	1	1
5003101251021	OBSERVATION	YES	ARTICULAR PAIN	1	1
5003101251205	OBSERVATION	YES	ASTHENIA	1	1
5003101351012	OBSERVATION	YES	DEPRESSION	2	2
5003101351012	OBSERVATION	YES	DEPRESSION	3	2
5003101351012	OBSERVATION	YES	DEPRESSION	4	2
5003101351012	OBSERVATION	YES	DEPRESSION	5	2
5003101351012	OBSERVATION	YES	DEPRESSION	6	2
5003101431627	OBSERVATION	YES	ASTHENIA	2	1
5003101461629	OBSERVATION	YES	ASTHENIA	2	1
5003101461629	OBSERVATION	YES	IMPOTENCE	4	1
5003101621026	OBSERVATION	YES	PNEUMOPATHY INTERSTINAL	1	2
5003101621055	OBSERVATION	YES	PAIN PELVIS	2	2
5003101621055	OBSERVATION	YES	LEGS OEDEMA	2	2
5003101621055	OBSERVATION	YES	PAIN PELVIS	3	2
5003101621055	OBSERVATION	YES	LEGS OEDEMA	3	2
5003101621055	OBSERVATION	YES	PAIN PELVIS	5	2
5003101621055	OBSERVATION	YES	LEGS OEDEMA	5	2
5003101621609	OBSERVATION	YES	FATIGUE	1	2
5003101621609	OBSERVATION	YES	PAIN (SHOULDER)	1	2
5003101621609	OBSERVATION	YES	FATIGUE	2	1
5003101621609	OBSERVATION	YES	PAIN (SHOULDER)	2	1
5003101641618	OBSERVATION	YES	ASTHENIA	1	1
5003101641618	OBSERVATION	YES	LOSS OF APPETITE	1	1
5003101641618	OBSERVATION	YES	ASTHENIA	2	1
5003101641618	OBSERVATION	YES	ASTHENIA	3	1
5003101641618	OBSERVATION	YES	LOSS OF APPETITE	3	1
5003101641618	OBSERVATION	YES	ASTHENIA	4	1
5003101641618	OBSERVATION	YES	WEIGHT GAIN	4	1
5003101641618	OBSERVATION	YES	ASTHENIA	5	1
5003101641618	OBSERVATION	YES	ASTHENIA	6	1
5003102541636	OBSERVATION	YES	FATIGUE	1	1
5003102541636	OBSERVATION	YES	ANEREXIA	1	1
5003102541636	OBSERVATION	YES	FATIGUE	3	2
5003102541636	OBSERVATION	YES	FATIGUE	4	1
5003601601003	OBSERVATION	YES	TASTE ALTERATION	1	1
5003601601003	OBSERVATION	YES	ALOPECIA	1	1
5003601601005	OBSERVATION	YES	CHRONIC L LOWER EXTREMITY PAIN	1	1

Randomization Number	Actual arm of maintenance	Other	Toxicity	Cycle number	Grade
5003601601005	OBSERVATION	YES	FATIGUE	1	1
5003601601005	OBSERVATION	YES	CHRONIC L LOWER EXTREMITY PAIN	2	1
5003601601005	OBSERVATION	YES	FATIGUE	2	1
5003601601602	OBSERVATION	YES	FATIGUE	1	1
5003601601602	OBSERVATION	YES	PAIN RIGHT HIP/SHOULDER	1	1
5003601881602	OBSERVATION	YES	FEVER	1	1
5003601881602	OBSERVATION	YES	FEVER	2	1
5003602301009	OBSERVATION	YES	LYMPHATICS	1	1
5003602301009	OBSERVATION	YES	CONSTITUTIONAL	1	2
5003602301009	OBSERVATION	YES	LYMPHATICS	4	9
5003602301009	OBSERVATION	YES	CONSTITUTIONAL	4	9
5003602901402	OBSERVATION	YES	WEIGHT LOSS	1	1
5003603701001	OBSERVATION	YES	ALOPECIA	1	2
5003603701001	OBSERVATION	YES	WEAKNESS	1	2
5003603701001	OBSERVATION	YES	DYSGENSIA	1	2
5003603701001	OBSERVATION	YES	ALOPECIA	2	2
5003603701001	OBSERVATION	YES	WEAKNESS	2	1
5003603701001	OBSERVATION	YES	DYSGENSIA	2	1
5003603701001	OBSERVATION	YES	ALOPECIA	3	1
5003604901007	OBSERVATION	YES	RIGHT LOWER LIMB PAIN	1	1
5003605701601	OBSERVATION	YES	MUSCULOSKELETAL PAIN / BACK PAIN	1	2
5003605701601	OBSERVATION	YES	MUSCULOSKELETAL PAIN / BACK PAIN	2	2
5003605701601	OBSERVATION	YES	MUSCULOSKELETAL PAIN / BACK PAIN	3	2
5003605701601	OBSERVATION	YES	MUSCULOSKELETAL PAIN / BACK PAIN	4	2
5003605701601	OBSERVATION	YES	MUSCULOSKELETAL PAIN / BACK PAIN	5	3
5003605701601	OBSERVATION	YES	MUSCULOSKELETAL PAIN / BACK PAIN	6	1
5003606201029	OBSERVATION	YES	PNP	2	1
5003606201620	OBSERVATION	YES	FATIGUE	1	1
5003606201620	OBSERVATION	YES	FATIGUE	2	1
5003606201620	OBSERVATION	YES	PAIN (TRIGEMINUS)	3	2
5003606201620	OBSERVATION	YES	FATIGUE	3	1
5003606201620	OBSERVATION	YES	PAIN (TRIGEMINUS)	4	2
5003606201620	OBSERVATION	YES	FATIGUE	4	1
5003606201620	OBSERVATION	YES	PAIN (TRIGEMINUS)	6	2
5003606201620	OBSERVATION	YES	FATIGUE	6	1
5003606301207	OBSERVATION	YES	PAIN-PELVIC (INGUINAL HERNIA)	4	2
5003606501409	OBSERVATION	YES	COUGH	2	1
5003606501409	OBSERVATION	YES	SORE THROAT	2	1
5003606501409	OBSERVATION	YES	NIGHT SWEATS	2	1
5003606501409	OBSERVATION	YES	COUGH	3	1
5003606501409	OBSERVATION	YES	COUGH	5	2
5003606501601	OBSERVATION	YES	ANXIETY	1	2
5003606501601	OBSERVATION	YES	ANOREXIA	1	2
5003606501601	OBSERVATION	YES	URINARY URGENCY	1	2
5003606501601	OBSERVATION	YES	ANXIETY	2	2

Randomization Number	Actual arm of maintenance	Other	Toxicity	Cycle number	Grade
5003606501601	OBSERVATION	YES	ANXIETY	3	1
5003606501601	OBSERVATION	YES	ANXIETY	4	2
5003606501601	OBSERVATION	YES	ANXIETY	5	2
5003606701003	OBSERVATION	YES	BUCCAL INFECTION (CLINICAL)	1	1
5003607201016	OBSERVATION	YES	LOSS OF APPETITE	1	9
5003610701403	OBSERVATION	YES	HEADPAIN	1	1
5003610701403	OBSERVATION	YES	HEADPAIN	2	1
5003610701403	OBSERVATION	YES	PAIN VARIX NODE	2	1
5003612501011	OBSERVATION	YES	FATIGUE	1	1
5003612501011	OBSERVATION	YES	FATIGUE	2	1
5003612501011	OBSERVATION	YES	EYE PAIN	2	2
5003612501011	OBSERVATION	YES	FATIGUE	3	1
5003612501011	OBSERVATION	YES	FATIGUE	4	1
5003612501011	OBSERVATION	YES	PAIN FOOT	4	1
5003612501011	OBSERVATION	YES	FATIGUE	5	1
5003612501011	OBSERVATION	YES	FATIGUE	6	1
5003617201209	OBSERVATION	YES	FATIGUE	1	2
5003617201209	OBSERVATION	YES	FATIGUE	2	2
5003617201209	OBSERVATION	YES	FATIGUE	3	2
5003617201209	OBSERVATION	YES	FATIGUE	4	1
5003617201209	OBSERVATION	YES	FATIGUE	5	1
5003618301005	OBSERVATION	YES	PAIN-ABDOMIN	1	1
5003618501025	OBSERVATION	YES	LEFT ARM PAIN	1	1
5003619301621	OBSERVATION	YES	ORAL MUCOSA	1	1
5003619301621	OBSERVATION	YES	LETHARGY	1	2
5003619301621	OBSERVATION	YES	DRY COUGH	1	2
5003619301621	OBSERVATION	YES	LETHARGY	2	1
5003619301621	OBSERVATION	YES	DRY COUGH	2	1
5003619301621	OBSERVATION	YES	DRY COUGH	3	1
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

Randomization Number	First Randomization Date	Arm of treatment	Date of 2nd randomization	Arm of 2nd randomization	SAE diagnosis	SAE: date of start	AE/SAE: date of end	Outcome	Sponsor Causality
5003613301007	14/11/2006	ARM A / R-ICE	31/01/2007	RITUXIMAB	HYPOTENSIVE STATE. ATRIAL FIBRILLATION	21/11/2006	-	Unknown	Related
5003613301007	14/11/2006	ARM A / R-ICE	31/01/2007	RITUXIMAB	ACUTE RENAL IMPAIREMENT	03/01/2007	08/01/2007	Recovered without sequelae	Related
5003613301404	14/11/2006	ARM B / R-DHAP	08/02/2007	OBSERVATION	BRADYCARDIA	19/11/2006	-	Unknown	Related
5003613301404	14/11/2006	ARM B / R-DHAP	08/02/2007	OBSERVATION	FEVER, NAUSEA AND VOMITING	13/05/2007	-	Not yet recovered	Unrelated
5003613301404	14/11/2006	ARM B / R-DHAP	08/02/2007	OBSERVATION	VOMITING AND DIARRHEA INCREASED CREATININE LEVEL	23/05/2007	-	Not yet recovered	Related
N = 5									

Listing 6.7-3 Serious adverse events within 100 days after ASCT (MSAP)

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003101431622	ARM A / R-ICE	RITUXIMAB	MALE	49	INTERSTITIAL PNEUMOPATHY	19/09/2005	SEVERE	MILD	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	-
5003101431622	ARM A / R-ICE	RITUXIMAB	MALE	49	BRUTAL NEUTROPENIA APPEARANCE	10/10/2005	UNKNOWN	SEVERE	Yes	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	15
5003101491042	ARM A / R-ICE	RITUXIMAB	MALE	46	RESPIRATORY DISTRESS WITH SEPTICEMIA	26/05/2006	LIFE THREATENING	LIFE THREATENING	Yes	No	RECOVERED WITH SEQUELAE	3
5003101641623	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	PERSISTANT COUGH -> PULMONARY INFILTRATE ON CT SCAN	28/02/2006	MODERATE	NORMAL	No	Yes	ONGOING / PERSISTANT	1600
5003102341202	ARM A / R-ICE	RITUXIMAB	FEMALE	56	SEPTICAEMIA (STREPTOCOCCUS PNEUMONIAE)	28/01/2004	SEVERE	LIFE THREATENING	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	20
5003601401602	ARM A / R-ICE	RITUXIMAB	MALE	41	septicaemia	04/11/2004	LIFE THREATENING	LIFE THREATENING	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003601401602	ARM A / R-ICE	RITUXIMAB	MALE	41	HYPOTENSION	04/11/2004	LIFE THREATENING	-	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003601401602	ARM A / R-ICE	RITUXIMAB	MALE	41	GASTRO INTESTINAL SYMPTOMS (DIARRHEA)	04/11/2004	SEVERE	-	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003601601601	ARM B / R-DHAP	RITUXIMAB	FEMALE	53	CATHETER RELATED INFECTION	02/11/2004	SEVERE	MODERATE	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	4
5003604701015	ARM B / R-DHAP	RITUXIMAB	MALE	56	PANCYTOPENIA, COPROSTASIS	23/03/2008	MILD	MILD	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003604901004	ARM B / R-DHAP	RITUXIMAB	FEMALE	52	LINE SEPSIS - PSEUDOMONAS AERUGINOSA	21/06/2006	SEVERE	SEVERE	No	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	13
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	CMV INFECTION	19/07/2008	SEVERE	MODERATE	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	5
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	SUPERFICIAL BLEEDING AFTER REMUVAL OF PORTACATH	12/08/2008	MILD	MODERATE	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	1
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	THROMBOCYTOPENIA	17/08/2008	-	LIFE THREATENING	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003604901603	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	BRONCHOPNEUMONIA, EXTENSIVE DIFFUSE ALVEOLAR DAMAGE	04/09/2008	DEATH	-	Yes	No	FATAL / DEATH	9
5003605701401	ARM A / R-ICE	RITUXIMAB	FEMALE	30	HOSPITALIZATION DUE TO PNEUMONIA	14/02/2007	SEVERE	MILD	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	9
5003606201617	ARM A / R-ICE	RITUXIMAB	FEMALE	54	INFECTION, FEVER	12/01/2006	SEVERE	-	No	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	13
5003607501401	ARM B / R-DHAP	RITUXIMAB	MALE	54	FOLLOWING FIRST RITUXIMAB MAINTENANCE NEUTROPHILS 0.21 ABSOLUTE VALUE	03/01/2007	-	LIFE THREATENING	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	9
5003608701013	ARM A / R-ICE	RITUXIMAB	MALE	54	GASTROINTESTINAL BLEEDING (NEUTROPENIC COLITIS)	03/09/2007	SEVERE	LIFE THREATENING	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	4
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	ACQUIRED TYPE 4 RENAL TUBULAR ACIDOSIS CAUSING REFRACTORY HYPERKALEMIA GRADE 2 FROM 05/01/2007-06/01/2007 GRADE 3 FROM 06/01/2007-09/01/2007, DECREASE GRADE 2 09/012007-11/01/2007 THEN FULLY RESOLVED	05/01/2007	SEVERE	-	Yes	No	RECOVERED WITH SEQUELAE	6
5003101051056	ARM A / R-ICE	OBSERVATION	MALE	64	HEARING LOSS	03/04/2007	SEVERE	-	Yes	No	ONGOING / PERSISTANT	-
5003101051612	ARM A / R-ICE	OBSERVATION	MALE	36	Cardiac infarction	28/06/2004	SEVERE	MILD	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	4
5003101071643	ARM B / R-DHAP	OBSERVATION	FEMALE	58	SEPTICEMIA STAPHYLOCOCCUS EPIDERMIDIS PNEUMOPATHY	07/05/2008	LIFE THREATENING	SEVERE	Yes	No	FATAL / DEATH	8
5003101141624	ARM B / R-DHAP	OBSERVATION	FEMALE	64	CLOSTRIDIUM DIFFICILE INFECTION WITH THROMBOPENIA	13/12/2005	SEVERE	LIFE THREATENING	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	50
5003101621026	ARM A / R-ICE	OBSERVATION	MALE	64	PNEUMOPATHY INTERSTITIAL	15/11/2005	MODERATE	MODERATE	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	8
5003101621615	ARM A / R-ICE	OBSERVATION	MALE	64	HEPATITIS	14/10/2004	SEVERE	NORMAL	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	33
5003102411069	ARM B / R-DHAP	OBSERVATION	MALE	63	MALIGNANT CHICKEN POX INFECTION	23/11/2007	SEVERE	SEVERE	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	14

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003601801607	ARM B / R-DHAP	OBSERVATION	FEMALE	40	PERIPHERAL PARESIS OF NERVUS VII LEFT (PROBABLE ASSOCIATED WITH PREVIOUS HERPES ZOSTER)	14/05/2008	SEVERE	MILD	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	30
5003602901601	ARM A / R-ICE	OBSERVATION	MALE	63	SUBDURAL HEMATOMA. ON 12/01/05 THE PATIENT WAS ADMITTED FOR FURTHER THERAPY. ON THE 17/01/05 HE COMPLAINED ABOUT HEADACHES AND THUS UNDERWENT HEAD CT SCAN.	17/01/2005	SEVERE	NORMAL	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	34
5003603201053	ARM B / R-DHAP	OBSERVATION	MALE	52	DIARRHEA	24/03/2008	MODERATE	-	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003603701001	ARM B / R-DHAP	OBSERVATION	MALE	64	ANEMIA CAUSED BY INSUFFICIENT ERYTHROPOIESIS AFTER STEM CELL TRANSPLANTATION	13/06/2005	UNKNOWN	SEVERE	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003603701001	ARM B / R-DHAP	OBSERVATION	MALE	64	INFECTION (BACTEREMIA WITH PSEUDOMONAS AERUGINOSA, ENTEROCOCCUS GALLINARUM AND STAPH. EPIDERMIDIS)	20/04/2005	SEVERE	-	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	5
5003606301207	ARM A / R-ICE	OBSERVATION	MALE	37	DENTAL CARIES - REQURING FULL UPPER DENTAL CLEARANCE AND PARTIAL LOWER DENTAL CLEARANCE / DENTAL PREVIOUSLY REPORTED HISTORY OF DENTAL DECAY OVER MANY YEARS	20/02/2005	MODERATE	NORMAL	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	68
5003606301604	ARM B / R-DHAP	OBSERVATION	MALE	61	SOCIAL HOSPITAL ADMISSION	24/09/2004	MODERATE	LIFE THREATENING	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	10
5003606301604	ARM B / R-DHAP	OBSERVATION	MALE	61	ACUTE RENAL FAILURE SECONDARY TO PRE RENAL DEHYDRATATION WITH DIARRHOEA	11/10/2004	MODERATE	LIFE THREATENING	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003620501406	ARM A / R-ICE	OBSERVATION	MALE	44	DIARRHOEA AND VOMITING	12/12/2007	SEVERE	MILD	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	5
5003622501604	ARM A / R-ICE	OBSERVATION	MALE	47	CHEST INFECTION	10/01/2008	SEVERE	LIFE THREATENING	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	4
N = 37												

Listing 6.7-4 Serious adverse events more than 100 days after ASCT (MSAP)

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003101021601	ARM B / R-DHAP	RITUXIMAB	FEMALE	48	BRONCHI SUPER INFECTION DOCUMENTED : PYOCYANIC	10/01/2005	SEVERE	SEVERE	Yes	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	24
5003101031621	ARM A / R-ICE	RITUXIMAB	FEMALE	55	SEPTIC SHOCK WITH PNEUMONIA	06/07/2006	LIFE THREATENING	LIFE THREATENING	Yes	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	33
5003101031621	ARM A / R-ICE	RITUXIMAB	FEMALE	55	PULMONARY ASPERGILLOSIS	06/07/2006	LIFE THREATENING	LIFE THREATENING	Yes	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	50
5003101031621	ARM A / R-ICE	RITUXIMAB	FEMALE	55	BRONCHITIS TO PNEUMOCOCCUS	18/01/2007	SEVERE	MILD	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	64
5003101031621	ARM A / R-ICE	RITUXIMAB	FEMALE	55	PULMONARY INFECTION TO PSEUDOMONAS AERUGINOSA WITH HEMOPTYSIA	02/06/2007	SEVERE	MILD	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	72
5003101431608	ARM B / R-DHAP	RITUXIMAB	MALE	64	PULMONARY INFECTION WITH HAEMOPHILUS INFLUENZAE	16/03/2005	SEVERE	UNKNOWN	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	13
5003101431608	ARM B / R-DHAP	RITUXIMAB	MALE	64	SECONDARY MALIGNANCY : HEPATIC ADENOCARCINOMA	24/04/2007	LIFE THREATENING	NORMAL	No	No	FATAL / DEATH	361
5003102161604	ARM B / R-DHAP	RITUXIMAB	FEMALE	55	NOSE MELANOMA	15/03/2009	SEVERE	-	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	184
5003601401002	ARM A / R-ICE	RITUXIMAB	MALE	56	ACUTE NON-LYMPHOCYTIC LEUKEMIA = AML	15/06/2006	UNKNOWN	UNKNOWN	Yes	-	FATAL / DEATH	24
5003601401004	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	FEVER AND MENTAL DISTURBANCES. VARICELLA LESIONS IN THE SKIN. VARICELLA ZOSTER VIRUS SEEN IN BLISTERS.	26/06/2007	DEATH	NORMAL	Yes	Yes	FATAL / DEATH	61
5003601401602	ARM A / R-ICE	RITUXIMAB	MALE	41	MYOCARDITIS	06/08/2006	LIFE THREATENING	UNKNOWN	Yes	No	FATAL / DEATH	0
5003601401604	ARM B / R-DHAP	RITUXIMAB	FEMALE	62	PNEUMOCYSTIS JIROVECII	17/07/2006	SEVERE	SEVERE	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	19
5003602201601	ARM A / R-ICE	RITUXIMAB	FEMALE	55	HERPES ZOSTER INFECTION WITH INVOLVEMENT OF FACE , LEFT TRIGEMINUS	09/05/2005	MODERATE	NORMAL	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	122
5003604901004	ARM B / R-DHAP	RITUXIMAB	FEMALE	52	FEVER, SUSP. PNEUMONIA	04/02/2007	MODERATE	SEVERE	No	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	7
5003605701401	ARM A / R-ICE	RITUXIMAB	FEMALE	30	BACTERIAL PNEUMONIA	18/09/2007	MODERATE	NORMAL	Yes	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003605701401	ARM A / R-ICE	RITUXIMAB	FEMALE	30	PERONAEUS PARESIS LEFT AND CRUSH KIDNEY (GRADE 3) DUE TO RHABDOMYOLYSIS AFTER HEROIN INJECTION AND UNRESPONSIVE SYNDROME (TRAUMA)	17/10/2007	SEVERE	NORMAL	No	Yes	RECOVERED WITH SEQUELAE	9

Randomization Number	Actual arm of induction	Actual arm of maintenance	Sex	Age (years)	Adverse event description	Date of AE become serious	Non hematological toxicity grade	Hematological toxicity grade	Relation with study drugs	Action taken with study drug	AE outcome	Duration of AE serious (days)
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	NEUTROPENIC SEPSIS	21/06/2007	SEVERE	SEVERE	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	6
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	CHEST INFECTION	21/08/2007	MODERATE	-	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	11
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	LOWER RESPIRATORY TRACT INFECTION	01/02/2008	SEVERE	-	Yes	No	RECOVERED WITH SEQUELAE	7
5003610501402	ARM B / R-DHAP	RITUXIMAB	MALE	58	RESPIRATORY TRACT INFECTION WITH NEUTROPENIA	14/04/2008	LIFE THREATENING	SEVERE	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	14
5003616301615	ARM A / R-ICE	RITUXIMAB	MALE	63	CHRONIC COUGH, DRY NON PRODUCTIVE ASSOCIATED WITH FEBRILE ILLNESS FOR 2 WEEKS. DIAGNOSED WITH PNEUMONIA 14082006	15/08/2006	DEATH	MILD	Yes	No	FATAL / DEATH	17
5003618201030	ARM B / R-DHAP	RITUXIMAB	FEMALE	45	HERPES ZOSTER (OPHTALMIC NERVE RIGHT	19/05/2007	SEVERE	MILD	No	Yes	RECOVERED/ RECOVERED WITHOUT SEQUELAE	60
5003618201030	ARM B / R-DHAP	RITUXIMAB	FEMALE	45	INTERMITTEND HYPESTHESIA OF LEFT LEG, HAND AND LIPS, TONGUE. ON 02/09/2007 REDUCTION OF VISUAL FIELD LEFT WITH SPONTANEOUS REMISSION	03/09/2007	MILD	-	-	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	3
5003101141624	ARM B / R-DHAP	OBSERVATION	FEMALE	64	DISCONFORT WITH TREMOR THAN FAINTING AND FINALLY REGAIN CONSCIOUSNESS WITHOUT DEFICIENCY. REACTION TO METRONIDAZOL (CONFUSION) + CLOSTRIDIUM DIFFICILE INFECTION	29/01/2006	SEVERE	SEVERE	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	19
5003101541415	ARM B / R-DHAP	OBSERVATION	MALE	53	STREPTOCOCCUS PNEUMONIAE	14/07/2007	SEVERE	-	No	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	13
5003606301207	ARM A / R-ICE	OBSERVATION	MALE	37	HIGH GRADE UROTHELIAL CARCINOMA	20/03/2008	LIFE THREATENING	-	Yes	No	FATAL / DEATH	568
5003606301604	ARM B / R-DHAP	OBSERVATION	MALE	61	MYELODYSPLASTIC SYNDROME	05/02/2008	-	MODERATE	Yes	-	FATAL / DEATH	503
5003620501406	ARM A / R-ICE	OBSERVATION	MALE	44	GRADE 4 NEUTROPENIA, PROBABLY RITUXIMAB INDUCED, NO SEQUELAE, MORE INFORMATION TO FOLLOW, NEUT 0.13	13/03/2008	-	LIFE THREATENING	Yes	No	RECOVERED/ RECOVERED WITHOUT SEQUELAE	13
N = 28												

6.7.4. Laboratory tests

Table 6.7-3 Hemoglobin (MSAP)

Actual arm of maintenance=RITUXIMAB

	Hemoglobin (g/dl)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	116	13.28	1.736	13.55	7.9	17.4	116	0.00	0.000	0.00	0.0	0.0
C1 between D7 and D10	108	12.70	1.832	12.65	7.6	17.9	108	-0.63	1.472	-0.50	-3.5	5.0
C1 around D14	107	11.54	1.775	11.60	7.6	15.8	107	-1.75	1.403	-1.70	-5.6	2.6
C2 pre-cycle	115	11.21	1.481	11.40	7.0	15.1	115	-2.07	1.321	-1.90	-5.6	1.4
C2 between D7 and D10	103	11.10	1.483	11.20	7.3	14.8	103	-2.27	1.772	-2.40	-6.5	4.2
C2 around D14	103	10.24	1.385	10.30	7.6	14.8	103	-2.91	1.667	-3.00	-6.3	2.8
C3 pre-cycle	114	10.38	1.432	10.40	6.9	14.8	114	-2.92	1.691	-3.10	-7.0	2.0
C3 between D7 and D10	106	10.08	1.317	9.90	6.4	14.1	106	-3.28	2.092	-3.20	-8.3	4.4
C3 around D14	105	9.63	1.368	9.60	6.1	13.5	105	-3.69	2.036	-3.60	-8.7	2.6
FU n°1	115	10.99	1.303	11.10	6.3	13.8	115	-2.26	1.863	-2.30	-7.4	2.3
FU n°2	109	11.99	1.637	12.10	7.7	15.9	109	-1.27	2.046	-1.20	-5.8	4.6
FU n°3	101	12.49	1.586	12.60	8.2	16.0	101	-0.79	1.924	-0.50	-7.8	3.7
FU n°4	93	12.72	1.556	12.90	8.7	16.4	93	-0.68	1.973	-0.60	-5.8	8.5
FU n°5	90	12.76	1.653	12.85	7.6	17.3	90	-0.64	1.816	-0.60	-6.9	4.5
FU n°6	85	12.89	1.621	13.10	8.5	15.9	85	-0.57	1.776	-0.40	-5.5	3.6
FU n°7	79	12.72	2.030	13.10	1.3	16.0	79	-0.83	2.076	-0.40	-11.6	2.7
FU n°8	82	13.10	1.500	13.30	8.3	15.9	82	-0.36	1.607	-0.35	-4.5	4.3
FU n°9	72	13.44	1.440	13.50	9.8	16.2	72	-0.05	1.538	0.00	-4.9	3.4
FU n°10	58	13.24	1.710	13.60	7.1	16.0	58	-0.19	1.667	0.10	-5.7	3.8
FU n°11	54	13.36	1.663	13.35	9.3	16.1	54	0.00	1.558	0.10	-5.2	3.7
FU n°12	40	13.53	1.585	13.70	10.2	16.9	40	0.40	1.724	0.55	-3.8	5.1
FU n°13	24	13.52	1.363	13.10	11.0	16.0	24	0.40	1.394	0.45	-2.4	3.3
FU n°14	19	13.28	1.370	12.70	10.6	16.1	19	0.34	1.450	0.60	-2.4	2.6
FU n°15	9	13.30	2.292	13.00	8.7	16.5	9	0.81	3.053	1.40	-6.0	4.5

Actual arm of maintenance=OBSERVATION

	Hemoglobin (g/dl)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	119	13.11	1.870	13.40	8.2	17.1	119	0.00	0.000	0.00	0.0	0.0
C1 between D7 and D10	105	12.28	1.821	12.30	8.3	16.1	105	-0.71	1.432	-0.80	-4.9	2.5
C1 around D14	103	11.36	1.709	11.30	6.5	15.3	103	-1.67	1.536	-1.60	-6.5	2.1
C2 pre-cycle	115	11.08	1.548	10.90	8.1	14.6	115	-2.02	1.550	-2.10	-7.1	2.0
C2 between D7 and D10	101	11.03	1.639	11.00	7.2	16.2	101	-2.12	2.117	-2.40	-6.4	5.7
C2 around D14	99	10.08	1.573	9.90	6.7	15.6	99	-3.05	2.008	-3.00	-7.7	3.4
C3 pre-cycle	116	10.20	1.326	10.20	6.8	13.3	116	-2.92	1.790	-2.95	-8.1	2.3
C3 between D7 and D10	95	9.95	1.609	9.90	6.5	14.3	95	-3.09	2.282	-3.50	-9.0	2.9
C3 around D14	104	9.60	1.573	9.50	5.4	15.0	104	-3.64	2.303	-3.75	-8.9	3.1
FU n°1	103	10.87	1.308	11.00	7.1	14.2	103	-2.23	2.019	-2.50	-6.4	3.7
FU n°2	111	12.02	1.619	12.20	6.7	16.9	111	-1.15	2.198	-1.10	-6.9	4.4
FU n°3	79	12.19	1.960	12.30	3.5	15.9	79	-0.96	2.630	-1.10	-8.4	5.6
FU n°4	76	12.31	1.859	12.35	6.0	16.5	76	-0.76	2.382	-0.60	-8.7	5.2
FU n°5	56	12.88	1.553	12.95	7.6	16.1	56	0.04	2.038	0.00	-4.3	3.9
FU n°6	48	13.12	1.633	13.35	8.6	15.9	48	0.25	2.008	0.35	-4.5	5.7
FU n°7	69	13.18	1.292	13.40	9.9	15.7	69	0.15	2.162	0.40	-6.6	5.7
FU n°8	74	13.21	1.463	13.25	7.9	16.4	74	0.23	2.061	0.10	-6.4	5.7
FU n°9	72	13.24	1.489	13.30	7.3	16.2	72	0.29	2.329	0.35	-5.9	5.4
FU n°10	58	13.61	1.224	13.60	10.6	16.8	58	0.62	1.810	0.55	-3.9	5.7
FU n°11	50	13.51	1.301	13.65	9.2	15.7	50	0.54	1.977	0.65	-4.8	5.9
FU n°12	36	13.69	1.976	14.10	4.3	16.1	36	0.73	2.714	0.80	-11.5	4.5
FU n°13	18	13.87	1.740	14.05	8.1	15.8	18	0.93	2.439	1.05	-6.0	4.9
FU n°14	11	13.88	1.568	13.40	11.7	17.1	11	1.57	1.910	2.00	-1.3	3.8
FU n°15	5	13.62	0.540	13.40	13.0	14.4	5	1.20	2.558	0.30	-1.5	5.2

Table 6.7-4 Leukocytes (MSAP)

Actual arm of maintenance=RITUXIMAB

	Leukocytes (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	116	6.461	2.8987	5.850	2.30	21.10	116	0.000	0.0000	0.000	0.00	0.00
C1 between D7 and D10	107	7.519	7.1483	5.000	0.30	32.90	107	0.976	7.4333	-0.800	-11.80	24.03
C1 around D14	108	6.101	6.7334	3.450	0.11	38.20	108	-0.358	6.5623	-2.285	-11.51	29.72
C2 pre-cycle	114	7.869	8.8768	6.050	1.20	87.30	114	1.395	9.0837	-0.245	-10.20	81.50
C2 between D7 and D10	103	11.030	11.2918	5.800	0.40	48.10	103	4.612	11.5891	0.520	-11.60	42.70
C2 around D14	103	14.281	15.3269	9.200	0.50	88.50	103	7.821	15.3637	3.300	-11.00	83.10
C3 pre-cycle	113	7.217	7.9445	5.000	0.90	63.90	113	0.744	7.9342	-0.800	-9.67	57.77
C3 between D7 and D10	105	6.712	6.5808	4.000	0.13	26.40	105	0.208	7.0744	-1.200	-14.87	20.90
C3 around D14	104	11.739	13.3774	5.950	0.20	70.90	104	5.374	13.4734	0.100	-13.17	63.39
FU n°1	113	5.039	2.6109	4.580	1.00	17.40	113	-1.404	3.2740	-1.500	-14.20	10.80
FU n°2	108	4.385	2.1278	3.935	1.06	12.10	108	-2.057	2.9057	-2.025	-13.90	7.30
FU n°3	100	4.638	2.4587	4.000	1.02	18.60	100	-1.909	3.2281	-1.980	-13.80	14.10
FU n°4	92	4.974	2.2140	4.390	1.50	13.90	92	-1.624	3.0457	-1.365	-13.70	7.50
FU n°5	89	5.023	2.5140	4.700	0.10	15.50	89	-1.582	3.3534	-1.200	-13.60	8.55
FU n°6	83	5.056	2.2339	4.600	0.90	15.20	83	-1.707	2.8892	-1.300	-12.60	6.81
FU n°7	78	5.374	2.3579	5.090	0.30	14.99	78	-1.406	2.9675	-1.060	-12.50	4.80
FU n°8	82	5.724	2.1049	5.465	2.00	14.20	82	-0.787	3.3775	-0.500	-12.90	9.50
FU n°9	71	6.047	2.2495	5.760	0.10	13.00	71	-0.521	2.9930	-0.250	-10.20	8.79
FU n°10	58	6.013	2.6158	5.550	1.80	13.79	58	-0.695	4.0008	-0.950	-13.20	8.95
FU n°11	54	6.436	2.4280	6.150	2.70	16.30	54	-0.373	3.5816	0.090	-12.40	10.29
FU n°12	41	6.440	1.9975	6.540	2.40	10.41	41	-0.162	3.0200	-0.100	-9.64	4.80
FU n°13	24	5.419	1.6543	5.150	3.00	9.30	24	-1.300	2.4260	-1.250	-8.10	2.12
FU n°14	19	5.693	2.6017	5.600	2.37	13.18	19	-1.036	2.1673	-1.000	-7.00	2.30
FU n°15	9	5.280	1.2976	5.890	2.90	6.72	9	-0.033	1.4357	0.090	-2.20	2.01

Actual arm of maintenance=OBSERVATION

	Leukocytes (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	119	6.805	2.6503	6.320	1.32	15.10	119	0.000	0.0000	0.000	0.00	0.00
C1 between D7 and D10	105	8.672	9.2784	5.300	0.10	52.20	105	1.948	9.1962	-0.020	-12.60	47.10
C1 around D14	103	7.370	8.9353	4.200	0.20	56.10	103	0.605	9.2570	-2.000	-14.10	50.90
C2 pre-cycle	115	7.615	5.4613	6.400	1.60	37.40	115	0.829	5.6330	-0.300	-9.50	24.30
C2 between D7 and D10	101	11.081	12.5055	6.100	0.10	66.90	101	4.318	12.5204	-0.700	-10.10	61.90
C2 around D14	98	16.091	17.6852	10.750	0.60	121.90	98	9.371	17.7145	3.440	-8.50	114.20
C3 pre-cycle	116	6.375	3.2144	5.750	1.40	20.30	116	-0.494	3.4429	-0.400	-9.00	12.10
C3 between D7 and D10	95	8.946	11.0557	4.400	0.10	68.20	95	1.992	11.1999	-1.300	-11.40	63.20
C3 around D14	104	13.166	12.9999	8.750	0.20	56.20	104	6.313	13.1245	1.500	-13.30	48.40
FU n°1	103	5.504	2.5823	4.800	0.60	15.10	103	-1.094	3.2023	-0.420	-10.10	7.70
FU n°2	110	5.007	2.3475	4.785	1.10	12.40	110	-1.819	3.1885	-1.940	-10.30	7.80
FU n°3	78	4.876	2.5903	4.300	0.80	16.80	78	-1.908	3.1552	-1.800	-10.20	5.80
FU n°4	74	5.107	2.0072	4.900	0.45	10.40	74	-1.511	2.6202	-0.950	-9.70	5.20
FU n°5	55	5.476	2.0356	5.000	1.88	12.30	55	-1.532	2.9699	-1.200	-9.20	5.50
FU n°6	47	5.588	1.7895	5.600	1.40	11.50	47	-1.068	2.2224	-0.800	-6.40	4.90
FU n°7	68	6.152	2.2905	5.515	2.90	13.40	68	-0.674	2.4283	-0.300	-8.90	5.00
FU n°8	74	5.822	2.2554	5.550	0.81	14.47	74	-0.943	2.7836	-0.560	-10.13	5.60
FU n°9	71	6.388	2.2916	6.200	0.80	14.52	71	-0.710	2.8488	-0.400	-8.79	5.60
FU n°10	59	6.664	2.2588	6.250	2.40	14.40	59	-0.120	2.6298	0.030	-7.53	7.00
FU n°11	50	6.739	2.3381	6.410	3.10	12.90	50	-0.339	2.7477	-0.160	-8.64	5.30
FU n°12	36	6.215	2.4542	6.000	1.60	14.60	36	-0.768	3.3421	-0.390	-11.50	6.54
FU n°13	18	7.211	4.4084	6.450	3.30	23.00	18	0.761	4.4312	0.575	-6.21	14.80
FU n°14	11	6.455	2.6579	5.700	3.85	11.82	11	0.205	1.2194	-0.160	-1.40	2.53
FU n°15	5	5.780	1.8499	5.000	4.40	8.90	5	1.296	2.4129	0.900	-1.70	4.30

Table 6.7-5 Neutrophils (MSAP)

Actual arm of maintenance=RITUXIMAB

	Neutrophils (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	114	4.467	2.6364	3.888	0.13	18.78	114	0.000	0.0000	0.000	0.00	0.00
C1 between D7 and D10	93	6.814	7.2747	3.690	0.00	31.35	92	2.186	7.5473	-0.092	-9.57	24.84
C1 around D14	92	3.931	5.8070	2.031	0.00	33.23	91	-0.477	5.8184	-1.837	-10.70	27.55
C2 pre-cycle	106	5.395	7.1300	3.619	0.00	66.35	104	0.953	7.4266	-0.346	-11.16	61.65
C2 between D7 and D10	86	9.676	10.9496	5.057	0.00	42.33	85	5.231	11.1963	1.134	-11.91	40.06
C2 around D14	94	9.840	12.0576	5.623	0.00	69.03	92	5.513	12.1300	1.485	-9.77	65.30
C3 pre-cycle	100	5.019	7.0686	3.168	0.00	58.79	99	0.583	7.1579	-0.604	-10.13	54.07
C3 between D7 and D10	91	5.589	5.9592	3.237	0.00	25.34	90	1.132	6.5436	-0.179	-12.37	23.31
C3 around D14	87	7.993	10.0314	3.108	0.00	41.71	86	3.611	10.1394	-0.545	-12.40	38.45
FU n°1	104	2.603	2.1315	2.051	0.00	15.49	102	-1.904	3.0365	-1.785	-14.36	10.01
FU n°2	102	2.409	1.6980	2.011	0.17	10.15	101	-2.087	2.7114	-1.968	-12.59	6.80
FU n°3	95	2.806	2.2863	2.212	0.10	17.67	93	-1.681	3.0517	-1.509	-13.45	15.62
FU n°4	87	3.071	1.9677	2.550	0.12	10.98	87	-1.474	2.9402	-1.279	-13.08	6.50
FU n°5	82	3.057	1.9773	2.690	0.25	10.85	82	-1.578	3.0281	-1.078	-12.70	7.43
FU n°6	77	3.206	1.8456	3.025	0.55	13.07	77	-1.573	2.6542	-1.183	-12.32	4.04
FU n°7	75	3.261	1.9884	2.977	0.02	11.25	74	-1.514	3.2215	-1.297	-17.66	7.94
FU n°8	78	3.414	1.2797	3.395	0.69	6.89	78	-1.098	2.8582	-0.961	-12.79	5.15
FU n°9	66	3.860	1.8187	3.768	0.82	10.79	65	-0.752	2.5563	-0.648	-8.21	7.80
FU n°10	53	3.738	2.1400	3.350	0.51	9.74	52	-0.989	3.4156	-0.607	-13.09	5.63
FU n°11	50	3.843	2.1150	3.582	0.22	13.37	49	-0.872	3.4723	-0.364	-12.60	8.74
FU n°12	38	3.782	1.4554	3.430	1.01	7.60	37	-0.794	2.7659	-0.461	-9.06	4.80
FU n°13	23	3.185	1.2028	3.010	1.11	5.77	23	-1.478	2.0993	-1.405	-7.51	1.27
FU n°14	19	3.351	2.4006	2.793	1.10	11.73	19	-1.298	2.2173	-1.250	-8.00	2.73
FU n°15	8	2.744	0.9233	2.691	1.10	4.29	8	-0.736	1.4057	-1.173	-2.19	1.80

Actual arm of maintenance=OBSERVATION

	Neutrophils (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	115	4.827	2.1642	4.307	1.10	12.84	115	0.000	0.0000	0.000	0.00	0.00
C1 between D7 and D10	90	8.212	9.3220	5.319	0.01	51.58	90	3.459	9.3526	0.579	-11.09	47.73
C1 around D14	86	5.264	7.4021	2.561	0.00	44.79	85	0.309	7.8337	-1.415	-12.76	40.60
C2 pre-cycle	94	4.994	4.0378	4.388	0.12	24.29	91	0.241	4.3234	-0.598	-8.69	20.86
C2 between D7 and D10	75	10.172	13.0947	4.840	0.00	66.23	74	5.027	12.4578	0.322	-9.07	62.38
C2 around D14	76	10.894	16.0431	5.298	0.06	114.59	76	6.238	16.0235	1.354	-9.60	109.43
C3 pre-cycle	102	4.049	2.5356	3.549	0.20	12.96	100	-0.784	2.8014	-0.930	-7.80	6.60
C3 between D7 and D10	81	7.759	10.8678	3.312	0.01	67.52	80	2.762	10.9550	-0.730	-8.99	63.67
C3 around D14	88	10.205	11.2647	5.416	0.00	50.02	86	5.359	11.5692	0.311	-11.30	45.26
FU n°1	95	2.779	1.5642	2.640	0.09	7.71	92	-1.940	2.2977	-1.511	-9.72	3.72
FU n°2	103	2.669	1.7608	2.464	0.04	9.92	99	-2.168	2.6275	-1.944	-9.38	6.66
FU n°3	69	2.947	2.1403	2.530	0.01	12.94	67	-1.983	2.5039	-1.911	-8.34	5.65
FU n°4	69	3.008	1.3906	2.932	0.05	6.79	68	-1.750	2.1761	-1.360	-8.87	3.90
FU n°5	49	3.208	1.5657	2.900	0.22	8.32	48	-1.793	2.4946	-1.295	-9.16	1.99
FU n°6	44	3.426	1.1643	3.450	0.62	6.07	43	-1.317	1.6753	-0.950	-6.58	1.37
FU n°7	63	3.576	1.6054	3.341	1.11	8.71	61	-1.224	2.1330	-0.704	-8.87	2.66
FU n°8	70	3.355	1.7500	3.073	0.04	12.88	68	-1.385	2.4007	-1.236	-10.50	6.25
FU n°9	63	3.737	1.8843	3.534	0.20	11.47	60	-1.123	2.5931	-0.879	-9.43	4.85
FU n°10	54	3.761	1.6921	3.419	1.51	11.38	51	-0.854	2.4184	-0.799	-8.14	6.34
FU n°11	45	3.824	1.8885	3.724	1.36	11.18	43	-1.171	2.8100	-0.871	-9.54	6.14
FU n°12	34	3.296	1.7931	3.191	0.40	10.95	32	-1.779	2.8837	-0.991	-9.06	5.07
FU n°13	17	4.427	4.1627	3.432	1.72	19.78	15	-0.512	4.8318	-0.942	-7.02	14.20
FU n°14	10	3.662	1.9687	3.100	2.00	8.51	10	-0.896	1.6079	-0.473	-3.77	0.91
FU n°15	4	3.195	1.1322	3.020	2.02	4.72	4	0.132	1.9218	0.552	-2.54	1.96

Table 6.7-6 Platelets (MSAP)

Actual arm of maintenance=RITUXIMAB

	Platelets (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	116	242.3	89.07	226.5	25	683	116	0.0	0.00	0.0	0	0
C1 between D7 and D10	108	149.8	86.60	147.0	9	560	108	-90.2	103.84	-87.5	-575	258
C1 around D14	108	86.8	80.02	63.5	7	392	108	-155.6	98.43	-152.5	-427	152
C2 pre-cycle	115	353.9	198.15	305.0	95	1250	115	111.3	173.59	87.0	-187	977
C2 between D7 and D10	104	226.3	157.56	191.5	12	816	104	-14.8	160.60	-21.5	-564	658
C2 around D14	104	75.0	54.98	57.0	9	288	104	-169.3	93.13	-164.0	-511	37
C3 pre-cycle	114	243.9	115.72	226.0	28	606	114	1.9	125.05	1.0	-378	442
C3 between D7 and D10	105	167.6	131.56	151.0	1	570	105	-72.5	125.11	-84.0	-321	287
C3 around D14	105	56.6	59.50	39.0	1	428	105	-182.4	99.80	-179.0	-630	152
FU n°1	114	139.2	73.17	133.5	10	332	114	-103.0	90.63	-85.5	-497	84
FU n°2	109	158.5	69.83	153.0	21	457	109	-83.5	87.16	-78.0	-483	142
FU n°3	101	162.4	67.48	160.0	14	403	101	-76.9	84.07	-67.0	-508	64
FU n°4	93	172.4	71.11	164.0	24	386	93	-65.3	79.51	-52.0	-489	113
FU n°5	90	178.6	82.48	173.5	4	616	90	-60.2	94.63	-54.5	-458	443
FU n°6	85	185.1	65.63	179.0	14	366	85	-56.2	83.75	-36.0	-499	126
FU n°7	79	186.6	76.78	181.0	9	427	79	-56.0	92.42	-33.0	-489	186
FU n°8	82	203.7	75.99	194.5	25	376	82	-40.5	94.12	-33.5	-483	218
FU n°9	71	203.6	73.37	186.0	27	398	71	-43.2	89.17	-36.0	-476	200
FU n°10	59	204.7	72.58	192.0	90	564	59	-47.5	94.63	-29.0	-526	185
FU n°11	53	201.6	65.27	197.0	55	362	53	-57.0	103.43	-30.0	-500	183
FU n°12	40	195.9	74.96	190.5	35	418	40	-55.5	102.00	-25.5	-525	78
FU n°13	24	189.8	72.25	200.0	65	359	24	-52.5	73.13	-54.5	-151	77
FU n°14	19	188.1	99.18	184.0	56	416	19	-63.9	90.39	-68.0	-232	138
FU n°15	9	179.0	74.14	187.0	85	314	9	-58.9	79.43	-62.0	-141	77

Actual arm of maintenance=OBSERVATION

	Platelets (G/L)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	119	292.3	188.59	260.0	29	1878	119	0.0	0.00	0.0	0	0
C1 between D7 and D10	104	162.9	114.12	141.0	9	600	104	-132.7	196.76	-103.0	-1800	144
C1 around D14	103	95.5	84.89	66.0	6	435	103	-194.7	203.04	-162.0	-1840	166
C2 pre-cycle	115	334.2	169.53	303.0	60	831	115	42.8	197.66	49.0	-1047	482
C2 between D7 and D10	100	209.4	142.09	197.0	10	619	100	-82.3	221.66	-50.5	-1777	243
C2 around D14	98	67.5	56.92	49.5	6	311	98	-223.3	188.78	-193.0	-1655	150
C3 pre-cycle	116	292.1	162.65	275.5	39	1043	116	-1.1	172.55	2.0	-835	522
C3 between D7 and D10	95	150.4	113.68	130.0	2	477	95	-150.5	227.07	-115.0	-1847	122
C3 around D14	103	62.4	66.31	40.0	5	454	103	-216.9	127.39	-205.0	-647	134
FU n°1	103	124.7	75.10	114.0	11	340	103	-153.6	115.34	-134.0	-515	71
FU n°2	111	159.4	78.83	157.0	22	581	111	-133.8	157.47	-99.0	-1297	151
FU n°3	79	159.2	80.68	161.0	27	493	79	-130.7	186.50	-105.0	-1385	181
FU n°4	75	161.5	84.20	157.0	7	415	75	-115.2	127.71	-103.0	-665	185
FU n°5	55	172.6	79.17	169.0	38	474	55	-145.9	211.07	-97.0	-1404	106
FU n°6	48	181.1	72.01	178.5	34	337	48	-100.0	120.49	-91.0	-643	111
FU n°7	68	183.1	69.50	183.5	53	455	68	-111.7	188.60	-80.0	-1423	118
FU n°8	74	180.2	72.47	178.0	25	385	74	-113.6	196.59	-75.5	-1493	131
FU n°9	72	183.4	76.79	184.5	45	428	72	-119.1	194.68	-93.0	-1450	111
FU n°10	59	196.5	69.94	190.0	43	452	59	-83.6	114.06	-69.0	-408	155
FU n°11	50	191.1	64.78	186.0	84	387	50	-87.5	111.23	-76.0	-417	83
FU n°12	36	204.0	76.38	195.0	14	396	36	-82.1	125.89	-56.0	-382	116
FU n°13	18	176.4	60.63	177.5	105	285	18	-58.2	96.10	-59.5	-198	116
FU n°14	11	226.1	98.13	198.0	128	441	11	-34.9	124.27	-5.0	-277	139
FU n°15	5	181.8	33.61	183.0	132	223	5	11.0	129.42	22.0	-197	144

Table 6.7-7 LDH (MSAP)

Actual arm of maintenance=RITUXIMAB

	LDH (UI/l)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	114	420.4	312.85	315.5	117	1867	114	0.0	0.00	0.0	0	0
FU n°1	110	2.9	3.09	2.0	1	9	108	-418.5	321.06	-311.5	-1866	-116
FU n°2	107	2.3	2.45	1.0	1	9	106	-422.1	319.48	-323.0	-1866	-115
FU n°3	100	2.8	3.04	1.5	1	9	99	-407.5	309.46	-307.0	-1866	-116
FU n°4	90	2.6	2.82	1.0	1	9	89	-404.6	317.94	-309.0	-1866	-108
FU n°5	83	2.5	2.83	1.0	1	9	82	-405.3	327.47	-307.0	-1866	-116
FU n°6	78	2.6	2.93	1.0	1	9	77	-392.0	331.15	-290.0	-1866	-116
FU n°7	74	2.2	2.57	1.0	1	9	73	-385.8	313.11	-293.0	-1866	-116
FU n°8	81	2.1	2.49	1.0	1	9	80	-369.3	274.61	-298.5	-1866	-115
FU n°9	70	2.1	2.53	1.0	1	9	69	-357.8	279.19	-290.0	-1866	-115
FU n°10	58	2.1	2.59	1.0	1	9	58	-358.9	298.22	-279.5	-1866	-115
FU n°11	53	1.8	2.12	1.0	1	9	53	-362.5	309.75	-285.0	-1866	-115
FU n°12	41	2.1	2.63	1.0	1	9	41	-341.0	241.46	-282.0	-1497	-116
FU n°13	22	3.0	3.35	1.0	1	9	22	-326.9	284.54	-262.5	-1497	-116
FU n°14	18	1.8	1.86	1.0	1	9	18	-328.0	312.00	-239.5	-1497	-116
FU n°15	7	2.3	2.98	1.0	1	9	7	-247.6	88.60	-231.0	-415	-161

Actual arm of maintenance=OBSERVATION

	LDH (UI/l)											
	Actual values						Change from baseline					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Baseline	118	385.5	235.54	330.0	57	1681	118	0.0	0.00	0.0	0	0
FU n°1	102	3.1	3.12	2.0	1	9	102	-395.7	245.84	-330.3	-1672	-134
FU n°2	108	2.1	2.27	1.0	1	9	108	-383.3	237.57	-322.5	-1680	-134
FU n°3	76	2.5	2.73	1.0	1	9	76	-401.0	261.11	-329.5	-1680	-152
FU n°4	75	2.6	2.86	1.0	1	9	74	-399.4	267.90	-320.5	-1672	-142
FU n°5	56	1.7	1.81	1.0	1	9	56	-384.2	223.11	-325.0	-1000	-152
FU n°6	46	2.5	3.02	1.0	1	9	45	-405.9	293.56	-329.0	-1680	-142
FU n°7	66	1.9	2.29	1.0	1	9	65	-388.0	248.83	-332.6	-1680	-152
FU n°8	74	2.1	2.60	1.0	1	9	73	-402.4	248.15	-343.0	-1680	-154
FU n°9	70	1.8	2.06	1.0	1	9	69	-378.0	248.45	-325.0	-1680	-144
FU n°10	58	1.4	1.49	1.0	1	9	58	-393.5	258.77	-329.0	-1679	-152
FU n°11	49	1.7	1.93	1.0	1	9	49	-409.5	282.99	-329.0	-1680	-152
FU n°12	35	1.8	2.26	1.0	1	9	35	-422.1	318.57	-325.0	-1672	-154
FU n°13	19	2.4	2.97	1.0	1	9	19	-386.0	227.13	-331.6	-1000	-154
FU n°14	11	1.7	2.41	1.0	1	9	11	-401.9	246.57	-398.0	-1000	-161
FU n°15	5	1.0	0.00	1.0	1	1	5	-429.6	351.52	-276.0	-1000	-166

Table 6.7-8 Monoclonal componant at relapse diagnosis (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Monoclonal component				
Yes	4	4	3	3
No	96	96	101	97
Total	100	100	104	100

Table 6.7-9 Serologies at relapse diagnosis (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
HIV Serology				
NEGATIVE	108	93	107	90
NOT DONE	8	7	12	10
HCV Serology				
NEGATIVE	105	91	103	87
POSITIVE	4	3	0	0
NOT DONE	7	6	16	13
HBs Ag Serology				
NEGATIVE	108	93	105	88
POSITIVE	0	0	3	3
NOT DONE	8	7	11	9
Total	116	100	119	100
HBs vaccination				
No	32	30	34	30
Yes	4	4	12	11
Not Done	70	66	66	59
Total	106	100	112	100

6.7.5. Vital signs

Table 6.7-10 LVEF value at relapse diagnosis (MSAP)

		Actual arm of maintenance	
		RITUXIMAB	OBSERVATION
LVEF value (%)	N	86	82
	Mean	62.2	63.8
	Std	8.55	8.38
	Median	62.0	65.0
	Min	31	43
	Max	82	89

Table 6.7-11 Cardiac exams at relapse diagnosis (MSAP)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
ECG				
Normal	78	67	78	66
Abnormal	6	5	11	9
Not done	32	28	30	25
Total	116	100	119	100
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)

	Actual arm of maintenance			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Other exams baseline				
No	98	84	105	90
Yes	18	16	12	10
Total	116	100	117	100

Exploratory analysis

Frequency table of overall response rate after induction by Response after 1st line - Induction ITT

		Arm of treatment					
		ARM A / R-ICE		ARM B / R-DHAP		All	
		N	%	N	%	N	%
Response after first line	**Response after complete induction (including deaths for all patients)**						
CR/CRu	**CR/CRu/PR**	117	75	105	73	222	74
	Other	40	25	38	27	78	26
	Total	157	100	143	100	300	100
PR	**Response after complete induction (including deaths for all patients)**						
	CR/CRu/PR	21	49	30	61	51	55
	Other	22	51	19	39	41	45
	Total	43	100	49	100	92	100
SD	**Response after complete induction (including deaths for all patients)**						
	CR/CRu/PR	6	55	6	50	12	52
	Other	5	45	6	50	11	48
	Total	11	100	12	100	23	100
PD	**Response after complete induction (including deaths for all patients)**						
	CR/CRu/PR	7	26	6	24	13	25
	Other	20	74	19	76	39	75
	Total	27	100	25	100	52	100
Total		238	100	229	100	467	100

Response after complete induction (including deaths for all patients) by Treatment	**P-value (Chi-2)**
Response after 1st line (CR/CRu)	0.8289
Response after 1st line (PR)	0.2330
Response after 1st line (SD)	0.8274
Response after 1st line (PD)	0.8727

Frequency table of overall response rate after induction by Response after 1st line - Induction ITT

		Arm of treatment				All	
		ARM A / R-ICE		ARM B / R-DHAP			
		N	%	N	%	N	%
Response after first line	**Response after complete induction (including deaths for all patients)**						
CR/CRu/PR	**CR/CRu/PR**	138	69	135	70	273	70
	Other	62	31	57	30	119	30
	Total	200	100	192	100	392	100
Other	**Response after complete induction (including deaths for all patients)**						
	CR/CRu/PR	13	34	12	32	25	33
	Other	25	66	25	68	50	67
	Total	38	100	37	100	75	100
Total		238	100	229	100	467	100

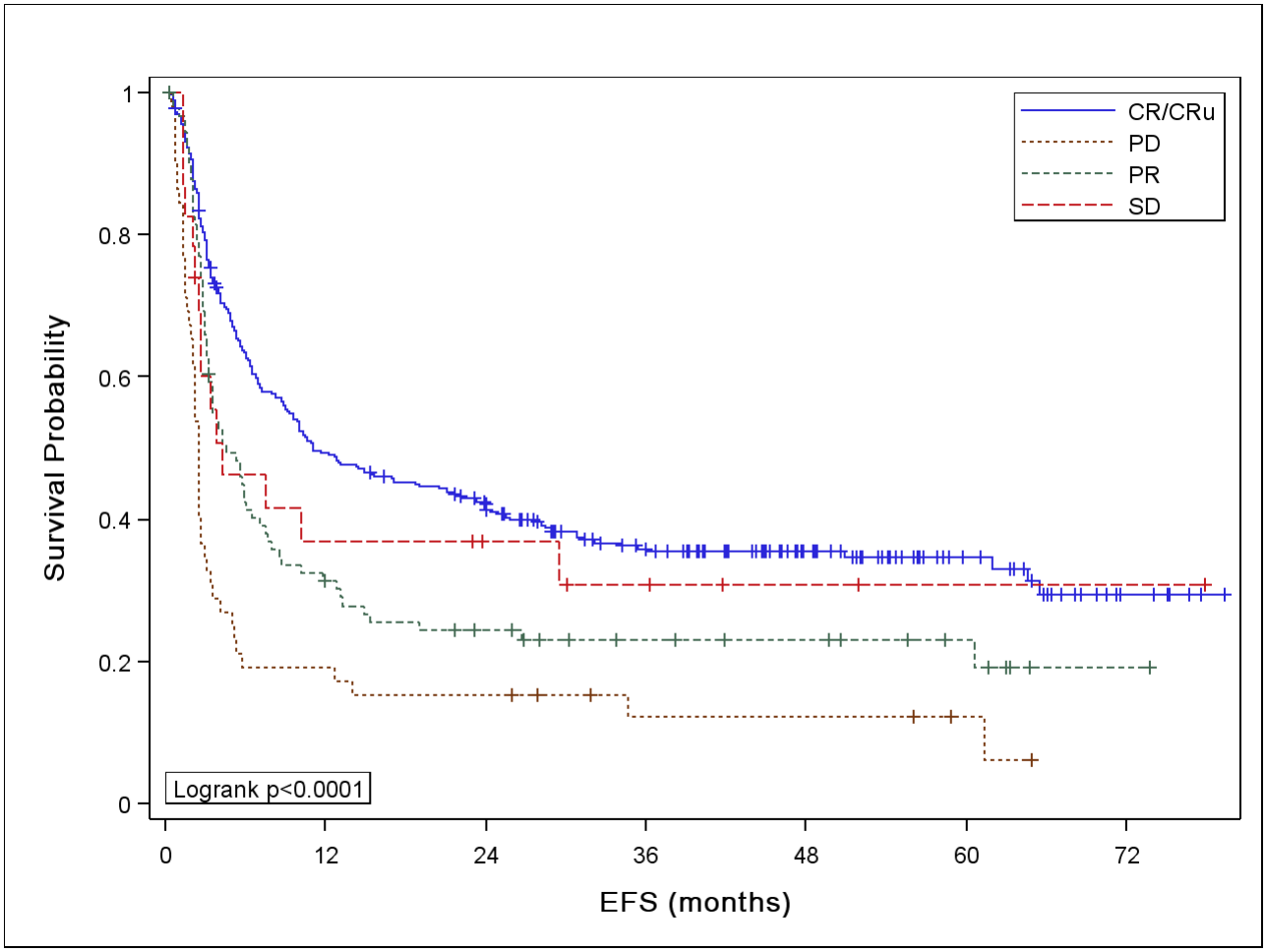
Response after complete induction (including deaths for all patients) by Treatment	P-value (Chi-2)
Response after 1st line (CR/CRu/PR)	0.7775
Response after 1st line (Other)	0.8703

Frequency table of complete response rate after induction by Response after 1st line - Induction ITT

		Arm of treatment				All	
		ARM A / R-ICE		ARM B / R-DHAP			
		N	%	N	%	N	%
Response after first line	**Response after complete induction (including deaths for all patients)**						
CR/CRu	**CR/CRu**	72	46	68	48	140	47
	Other	85	54	75	52	160	53
	Total	157	100	143	100	300	100
Other	**Response after complete induction (including deaths for all patients)**						
	CR/CRu	15	19	17	20	32	19
	Other	66	81	69	80	135	81
	Total	81	100	86	100	167	100
Total		238	100	229	100	467	100

Response after complete induction (including deaths for all patients) by Treatment	P-value (Chi-2)
Response after 1st line (CR/CRu)	0.7691
Response after 1st line (Other)	0.8376

Event-Free Survival according to Response after 1st line - induction ITT

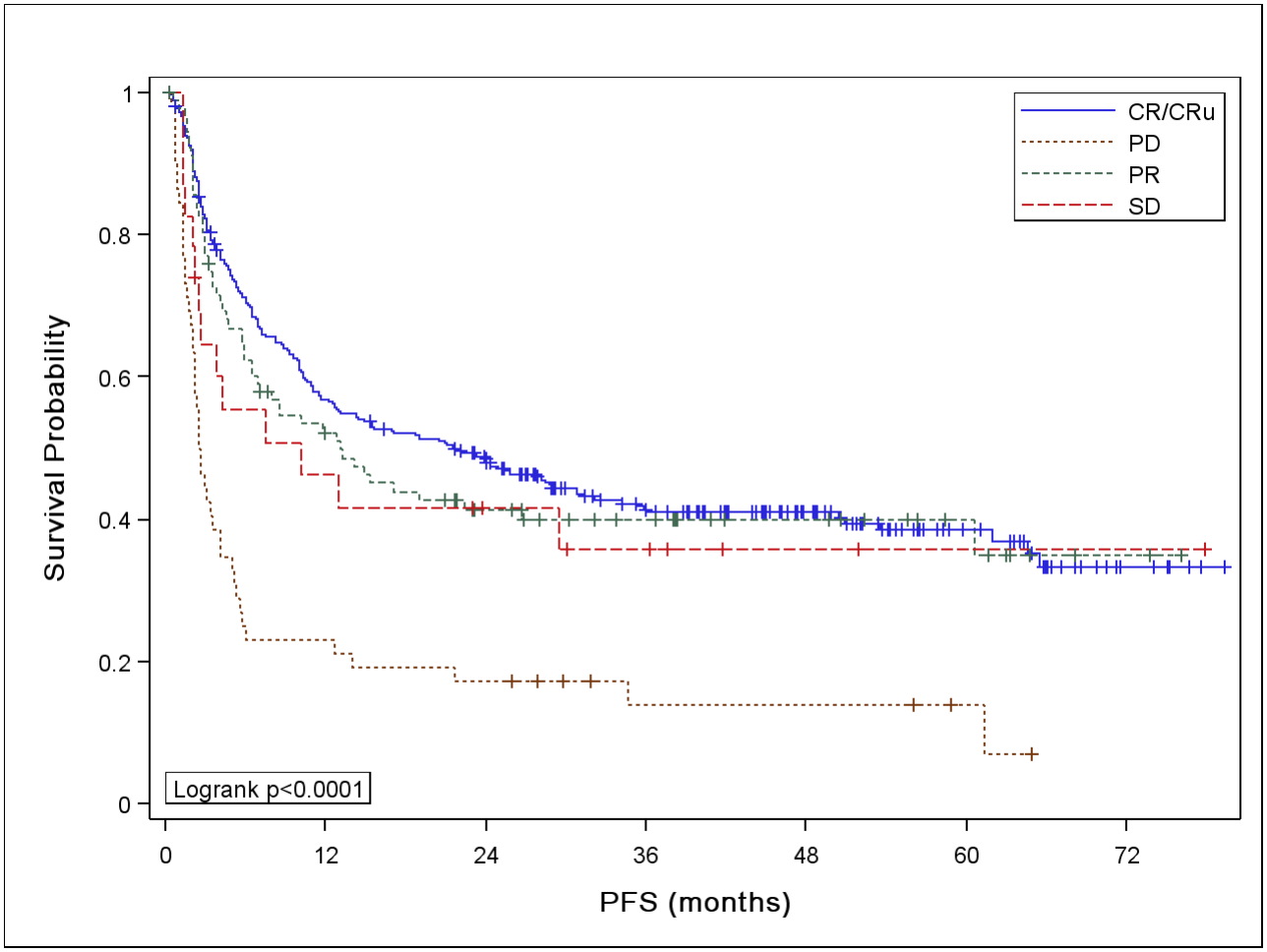


	Response after first line	N	Median	95% CI lower	95% CI Upper	Min	Max
EFS (months)	CR/CRu	300	11	9	21	0	79
EFS (months)	PR	92	5	3	7	0	74
EFS (months)	SD	23	4	3	-	1	78
EFS (months)	PD	52	3	2	3	0	65

Response after first line	Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	49.4	43.5	54.9	145
CR/CRu	24	42.1	36.4	47.7	117
CR/CRu	36	35.8	30.3	41.4	81
CR/CRu	48	35.4	29.9	41.0	51
CR/CRu	60	34.6	29.0	40.3	24
CR/CRu	72	29.5	22.5	36.8	6
PR	12	31.3	22.1	41.0	27
PR	24	24.4	16.0	33.7	19
PR	36	23.0	14.9	32.3	13
PR	48	23.0	14.9	32.3	10
PR	60	23.0	14.9	32.3	6
PR	72	19.2	10.3	30.1	1
SD	12	37.0	17.8	56.3	8

Response after first line	Time Point (months)	EFS (%)	95% CI Lower	95% CI Upper	Patients at risk
SD	24	37.0	17.8	56.3	6
SD	36	30.8	12.9	50.9	4
SD	48	30.8	12.9	50.9	2
SD	60	30.8	12.9	50.9	1
SD	72	30.8	12.9	50.9	1
PD	12	19.2	9.9	30.9	10
PD	24	15.4	7.2	26.4	8
PD	36	12.3	4.8	23.5	4
PD	48	12.3	4.8	23.5	4
PD	60	12.3	4.8	23.5	2
PD	72	6.2	0.7	20.6	0

Progression-Free Survival according to Response after 1st line - induction ITT

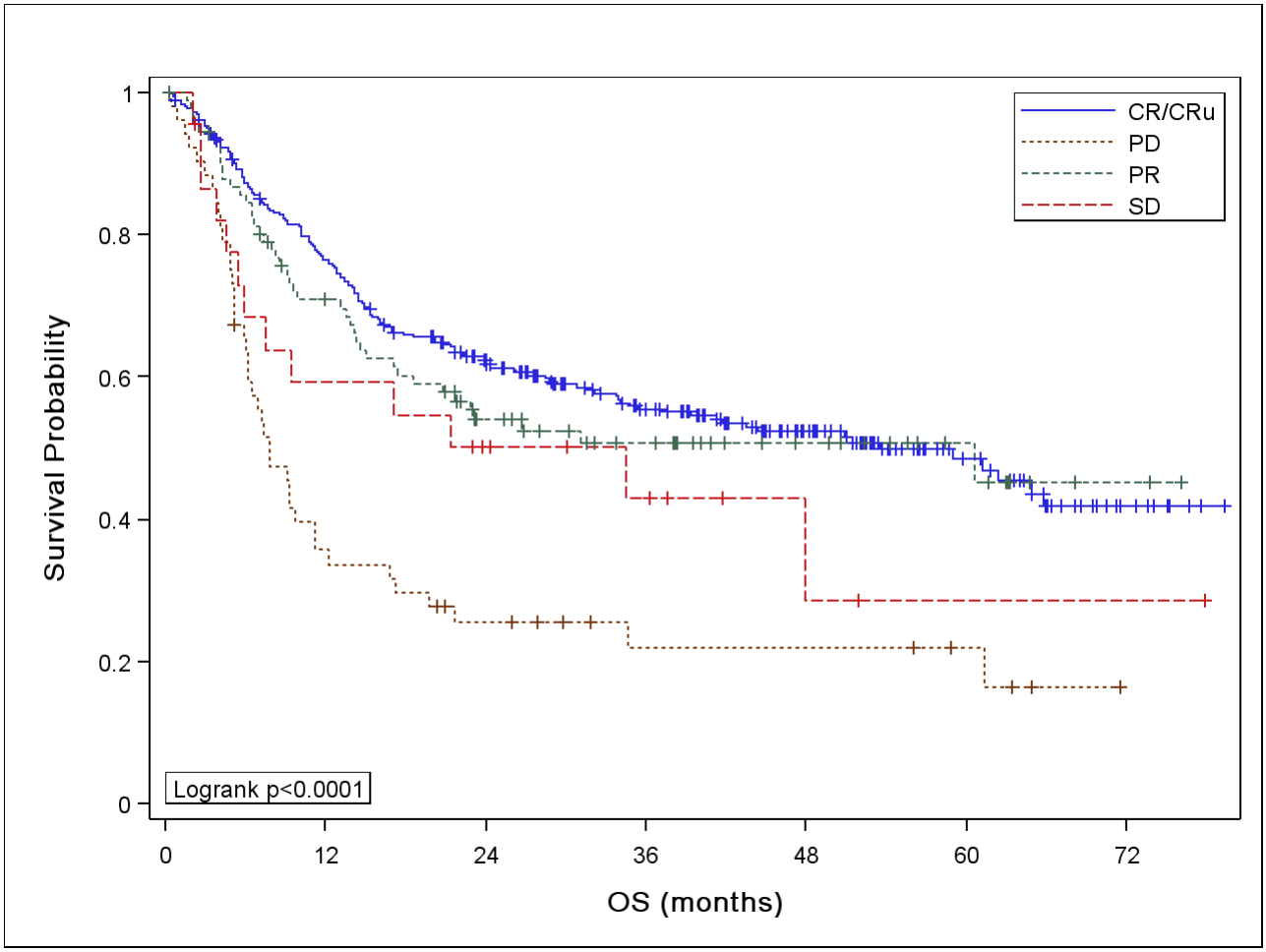


	Response after first line	N	Median	95% CI lower	95% CI Upper	Min	Max
PFS (months)	CR/CRu	300	21	13	31	0	79
PFS (months)	PR	92	13	7	61	0	76
PFS (months)	SD	23	10	3	-	1	78
PFS (months)	PD	52	3	2	4	0	65

Response after first line	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	56.8	51.0	62.2	167
CR/CRu	24	48.5	42.7	54.1	135
CR/CRu	36	41.4	35.6	47.1	93
CR/CRu	48	40.9	35.1	46.6	59
CR/CRu	60	38.4	32.3	44.4	27
CR/CRu	72	33.3	25.9	40.9	6
PR	12	52.2	41.4	61.9	44
PR	24	41.4	31.0	51.5	30
PR	36	39.9	29.5	50.0	21
PR	48	39.9	29.5	50.0	14
PR	60	39.9	29.5	50.0	8
PR	72	34.9	22.4	47.6	2

Response after first line	Time Point (months)	PFS (%)	95% CI Lower	95% CI Upper	Patients at risk
SD	12	46.2	25.1	65.0	10
SD	24	41.6	21.4	60.7	7
SD	36	35.6	16.3	55.6	5
SD	48	35.6	16.3	55.6	2
SD	60	35.6	16.3	55.6	1
SD	72	35.6	16.3	55.6	1
PD	12	23.1	12.8	35.2	12
PD	24	17.3	8.5	28.6	9
PD	36	13.8	5.7	25.6	4
PD	48	13.8	5.7	25.6	4
PD	60	13.8	5.7	25.6	2
PD	72	6.9	0.8	22.7	0

Overall Survival according to Response after 1st line - induction ITT

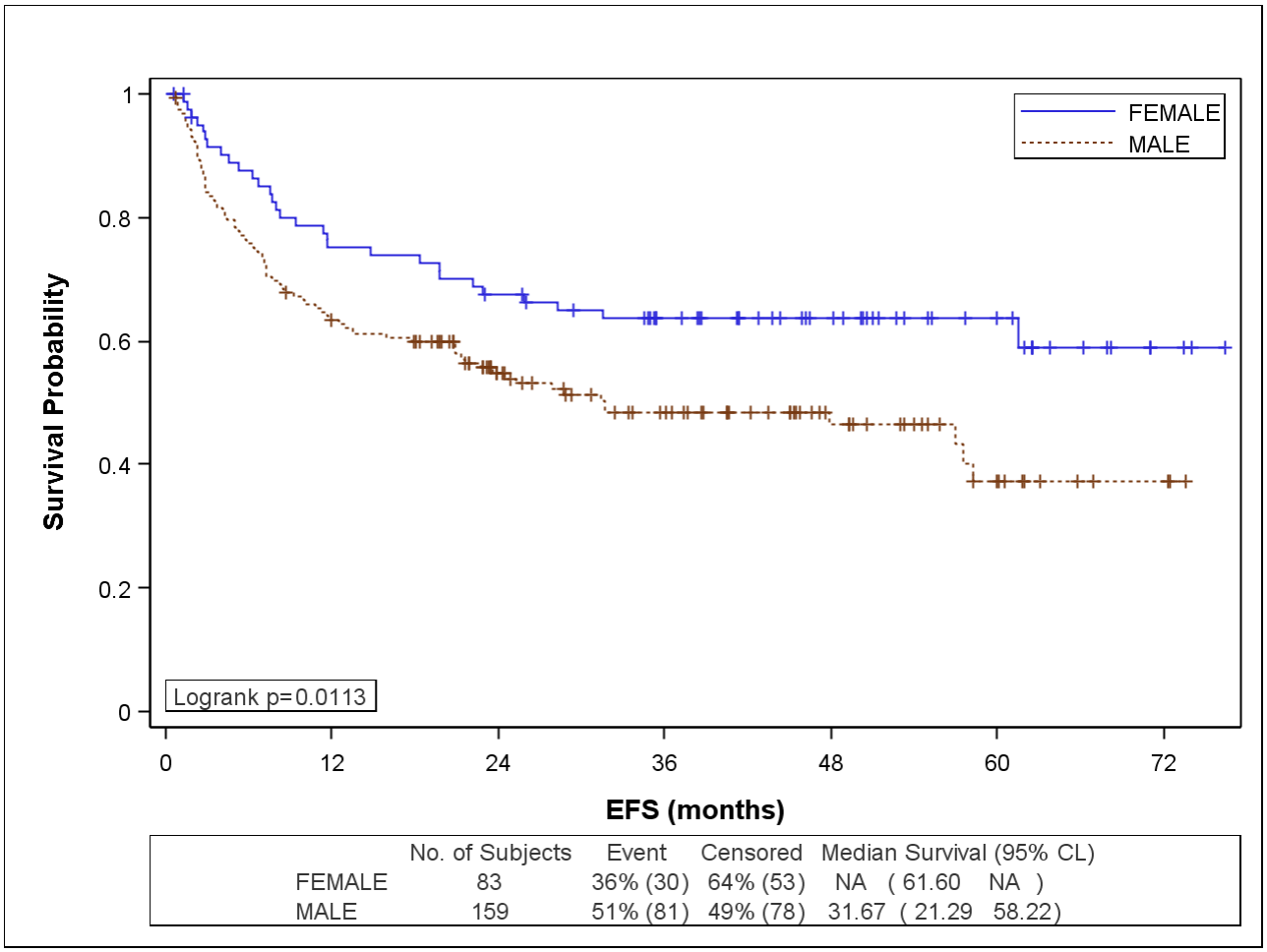


	Response after first line	N	Median	95% CI lower	95% CI Upper	Min	Max
OS (months)	CR/CRu	300	54	35	-	1	79
OS (months)	PR	92	61	17	-	0	76
OS (months)	SD	23	35	6	-	2	78
OS (months)	PD	52	8	6	11	0	71

Response after first line	Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
CR/CRu	12	76.6	71.3	81.0	224
CR/CRu	24	62.4	56.6	67.7	169
CR/CRu	36	55.5	49.4	61.1	123
CR/CRu	48	52.3	46.1	58.1	76
CR/CRu	60	48.4	41.4	54.9	34
CR/CRu	72	41.7	33.2	50.0	8
PR	12	70.8	60.2	79.1	60
PR	24	54.0	42.9	63.9	39
PR	36	50.8	39.5	61.0	27
PR	48	50.8	39.5	61.0	16
PR	60	50.8	39.5	61.0	9
PR	72	45.1	30.7	58.5	2

Response after first line	Time Point (months)	OS (%)	95% CI Lower	95% CI Upper	Patients at risk
SD	12	59.2	36.2	76.3	13
SD	24	50.1	28.3	68.5	9
SD	36	42.9	21.1	63.2	6
SD	48	28.6	6.9	55.7	2
SD	60	28.6	6.9	55.7	1
SD	72	28.6	6.9	55.7	1
PD	12	35.6	22.9	48.6	18
PD	24	25.4	14.4	38.0	11
PD	36	21.8	11.0	34.9	6
PD	48	21.8	11.0	34.9	6
PD	60	21.8	11.0	34.9	4
PD	72	16.3	6.0	31.2	0

Prognostic factors
Gender
2nd randomization : EFS (MITT)



Sex	N	Median	95% CI lower	95% CI Upper	Min	Max
MALE	159	32	21	58	1	74
FEMALE	83	-	62	-	1	76

Sex	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
MALE	12	63.3	55.2	70.2	98
MALE	24	54.8	46.6	62.3	65
MALE	36	48.3	39.7	56.3	45
MALE	48	46.4	37.5	54.9	25
MALE	60	37.1	25.6	48.7	11
MALE	72	37.1	25.6	48.7	3
FEMALE	12	75.0	64.0	83.1	60
FEMALE	24	67.5	56.1	76.6	53
FEMALE	36	63.6	52.0	73.1	41
FEMALE	48	63.6	52.0	73.1	28
FEMALE	60	63.6	52.0	73.1	15
FEMALE	72	59.0	44.8	70.7	3

Model with gender only:

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
SEXE	FEMALE	1	-0.53721	0.21486	6.2515	**0.0124**	0.584	0.384	0.890	Sex FEMALE

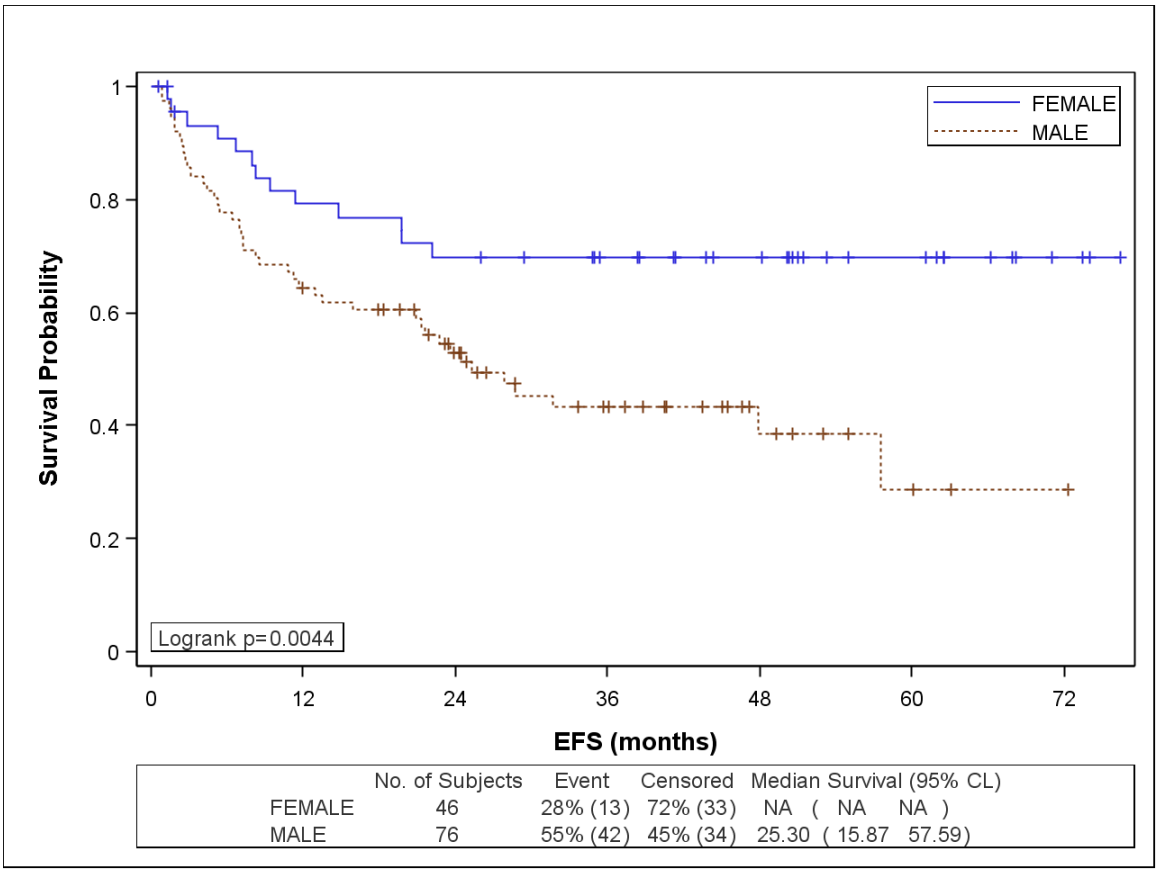
Model with gender and maintenance arm:

Analysis of Maximum Likelihood Estimates										
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
SEXE	FEMALE	1	-0.53532	0.21555	6.1682	**0.0130**	0.585	0.384	0.893	Sex FEMALE
brasrand2	RITUXIMAB	1	-0.02066	0.19056	0.0118	0.9137	0.980	0.674	1.423	Arm of 2nd randomization RITUXIMAB

Model with gender, maintenance arm and interaction:

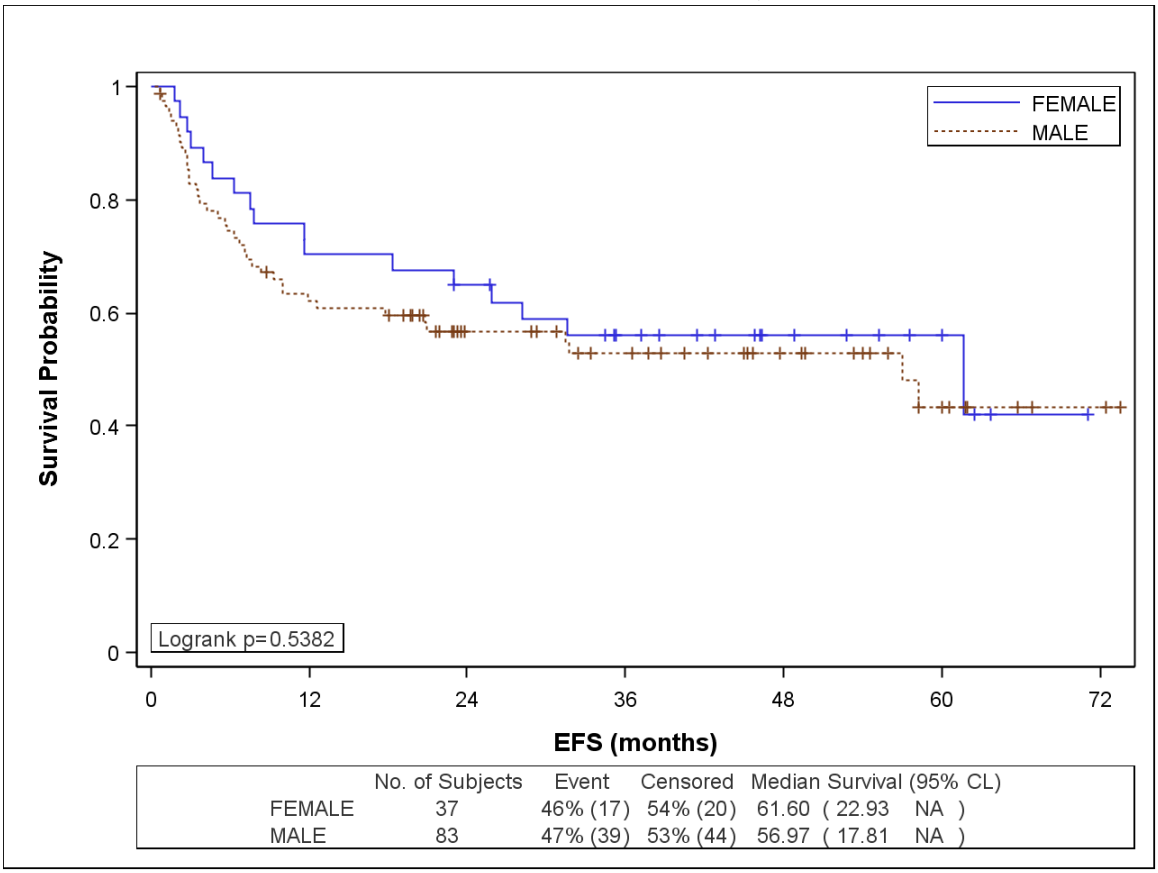
Analysis of Maximum Likelihood Estimates							
Parameter			DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
SEXE	FEMALE		1	-0.19064	0.29084	0.4296	0.5122
brasrand2	RITUXIMAB		1	0.16862	0.22290	0.5723	0.4494
SEXE*brasrand2	FEMALE	RITUXIMAB	1	-0.69997	0.43150	2.6315	0.1048

Arm of 2nd randomization=RITUXIMAB



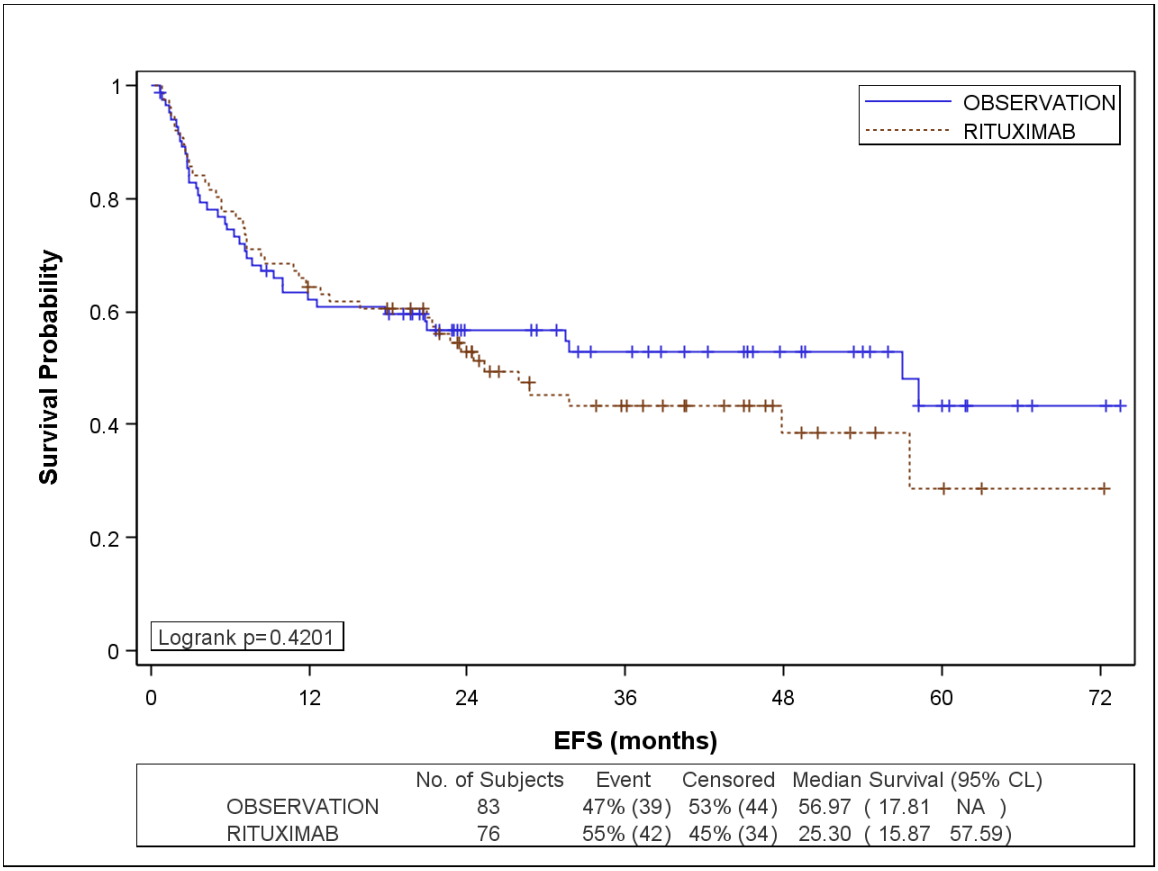
	No. of Subjects	Event	Censored	Median Survival (95% CL)
FEMALE	46	28% (13)	72% (33)	NA (NA NA)
MALE	76	55% (42)	45% (34)	25.30 (15.87 57.59)

Arm of 2nd randomization=OBSERVATION



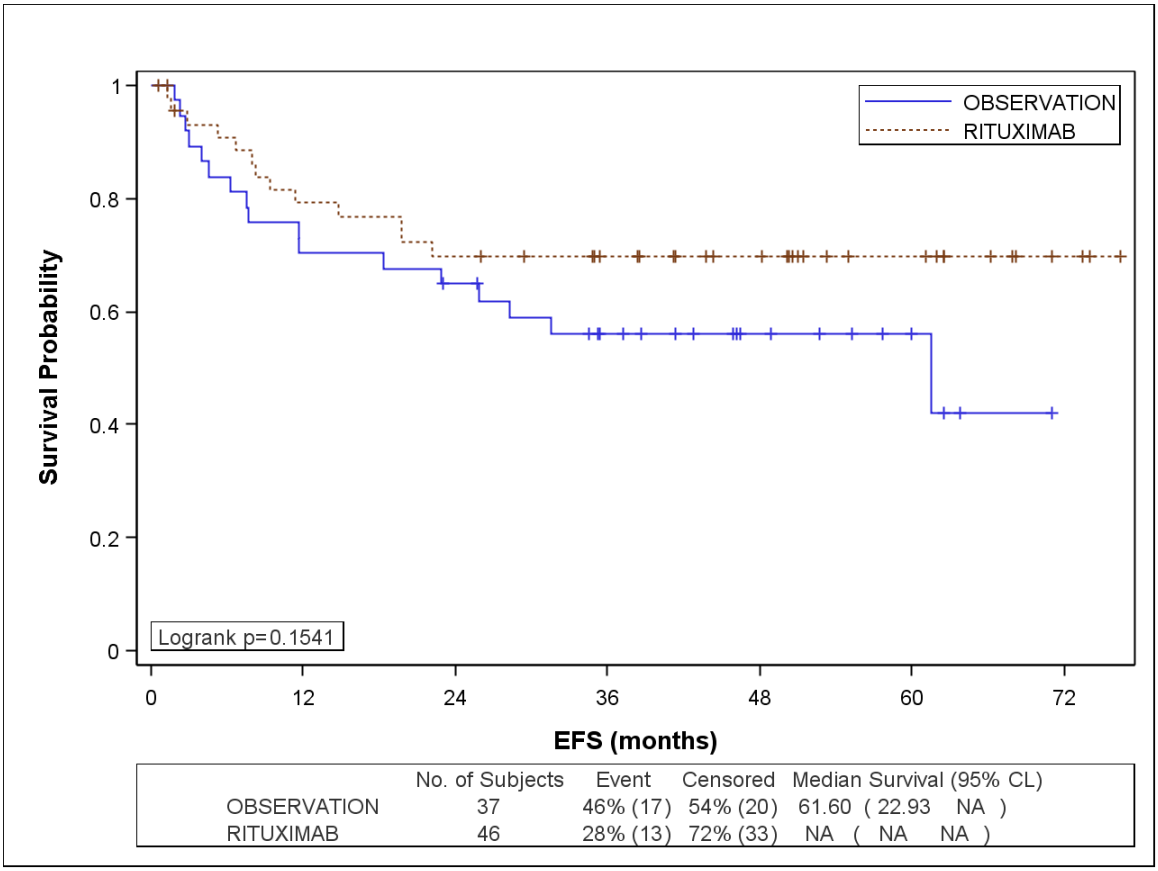
	No. of Subjects	Event	Censored	Median Survival (95% CL)
FEMALE	37	46% (17)	54% (20)	61.60 (22.93 NA)
MALE	83	47% (39)	53% (44)	56.97 (17.81 NA)

Sex=MALE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	83	47% (39)	53% (44)	56.97 (17.81 NA)
RITUXIMAB	76	55% (42)	45% (34)	25.30 (15.87 57.59)

Sex=FEMALE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	37	46% (17)	54% (20)	61.60 (22.93 NA)
RITUXIMAB	46	28% (13)	72% (33)	NA (NA NA)

Arm of 2nd randomization	Sex	N	Median	95% CI lower	95% CI Upper	Min	Max
RITUXIMAB	MALE	76	25	16	58	1	72
RITUXIMAB	FEMALE	46	-	-	-	1	76
OBSERVATION	MALE	83	57	18	-	1	74
OBSERVATION	FEMALE	37	62	23	-	2	71

Arm of 2nd randomization	Sex	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
RITUXIMAB	MALE	12	64.5	52.6	74.1	48
RITUXIMAB	MALE	24	52.9	40.9	63.6	32
RITUXIMAB	MALE	36	43.2	31.0	54.9	19
RITUXIMAB	MALE	48	38.4	24.7	52.0	8
RITUXIMAB	MALE	60	28.8	11.8	48.4	3
RITUXIMAB	MALE	72	28.8	11.8	48.4	1
RITUXIMAB	FEMALE	12	79.2	63.8	88.6	34
RITUXIMAB	FEMALE	24	69.8	53.8	81.2	30
RITUXIMAB	FEMALE	36	69.8	53.8	81.2	25
RITUXIMAB	FEMALE	48	69.8	53.8	81.2	19
RITUXIMAB	FEMALE	60	69.8	53.8	81.2	11
RITUXIMAB	FEMALE	72	69.8	53.8	81.2	3
OBSERVATION	MALE	12	62.1	50.7	71.6	50
OBSERVATION	MALE	24	56.8	45.3	66.8	33
OBSERVATION	MALE	36	53.0	41.1	63.5	26
OBSERVATION	MALE	48	53.0	41.1	63.5	17
OBSERVATION	MALE	60	43.4	28.0	57.8	8
OBSERVATION	MALE	72	43.4	28.0	57.8	2
OBSERVATION	FEMALE	12	70.3	52.8	82.3	26
OBSERVATION	FEMALE	24	64.9	47.3	77.9	23
OBSERVATION	FEMALE	36	56.0	38.5	70.4	16
OBSERVATION	FEMALE	48	56.0	38.5	70.4	9
OBSERVATION	FEMALE	60	56.0	38.5	70.4	4
OBSERVATION	FEMALE	72	42.0	16.5	65.9	0

Arm of 2nd randomization=RITUXIMAB

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Variable Label
SEXE	FEMALE	1	-0.88680	0.32082	7.6404	0.0057	0.412	0.220 0.773	Sex FEMALE

Arm of 2nd randomization=OBSERVATION

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Variable Label
SEXE	FEMALE	1	-0.17877	0.29101	0.3774	0.5390	0.836	0.473 1.479	Sex FEMALE

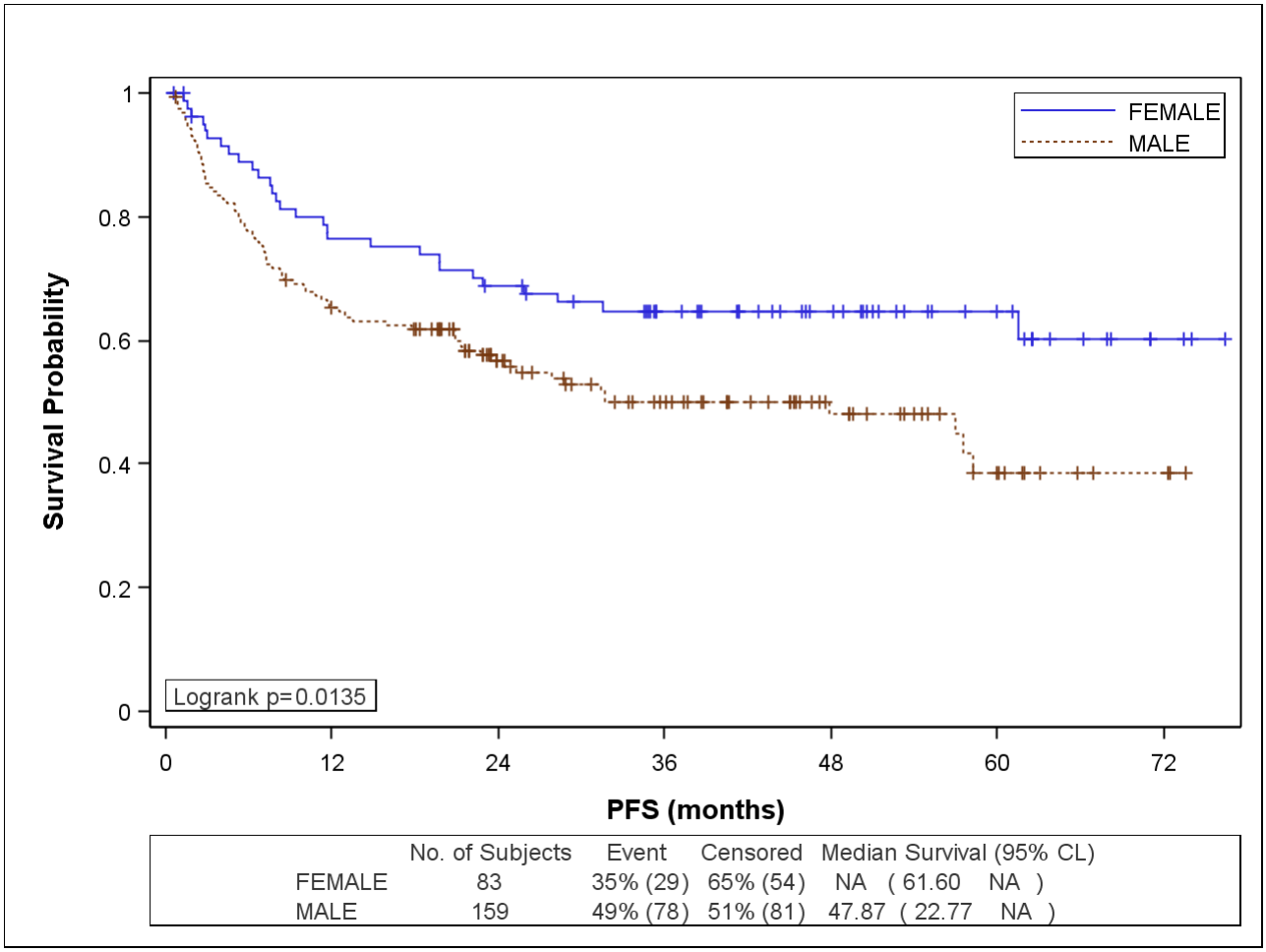
Sex=MALE

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Variable Label
brasrand2	RITUXIMAB	1	0.18015	0.22348	0.6498	0.4202	1.197	0.773 1.855	Arm of 2nd randomization RITUXIMAB

Sex=FEMALE

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Variable Label
brasrand2	RITUXIMAB	1	-0.52052	0.36927	1.9869	0.1587	0.594	0.288 1.225	Arm of 2nd randomization RITUXIMAB

Prognostic factors
Gender
2nd randomization : PFS (MITT)



Sex	N	Median	95% CI lower	95% CI Upper	Min	Max
MALE	159	48	23	-	1	74
FEMALE	83	-	62	-	1	76

Sex	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
MALE	12	65.2	57.2	72.0	101
MALE	24	56.7	48.4	64.1	66
MALE	36	50.0	41.4	58.0	45
MALE	48	48.1	39.0	56.6	25
MALE	60	38.5	26.6	50.2	11
MALE	72	38.5	26.6	50.2	3
FEMALE	12	76.3	65.4	84.2	61
FEMALE	24	68.8	57.4	77.7	54
FEMALE	36	64.8	53.2	74.2	41
FEMALE	48	64.8	53.2	74.2	28
FEMALE	60	64.8	53.2	74.2	15
FEMALE	72	60.2	45.9	71.8	3

Model with gender only:

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
SEXE	FEMALE	1	-0.53367	0.21869	5.9553	**0.0147**	0.586	0.382	0.900	Sex FEMALE

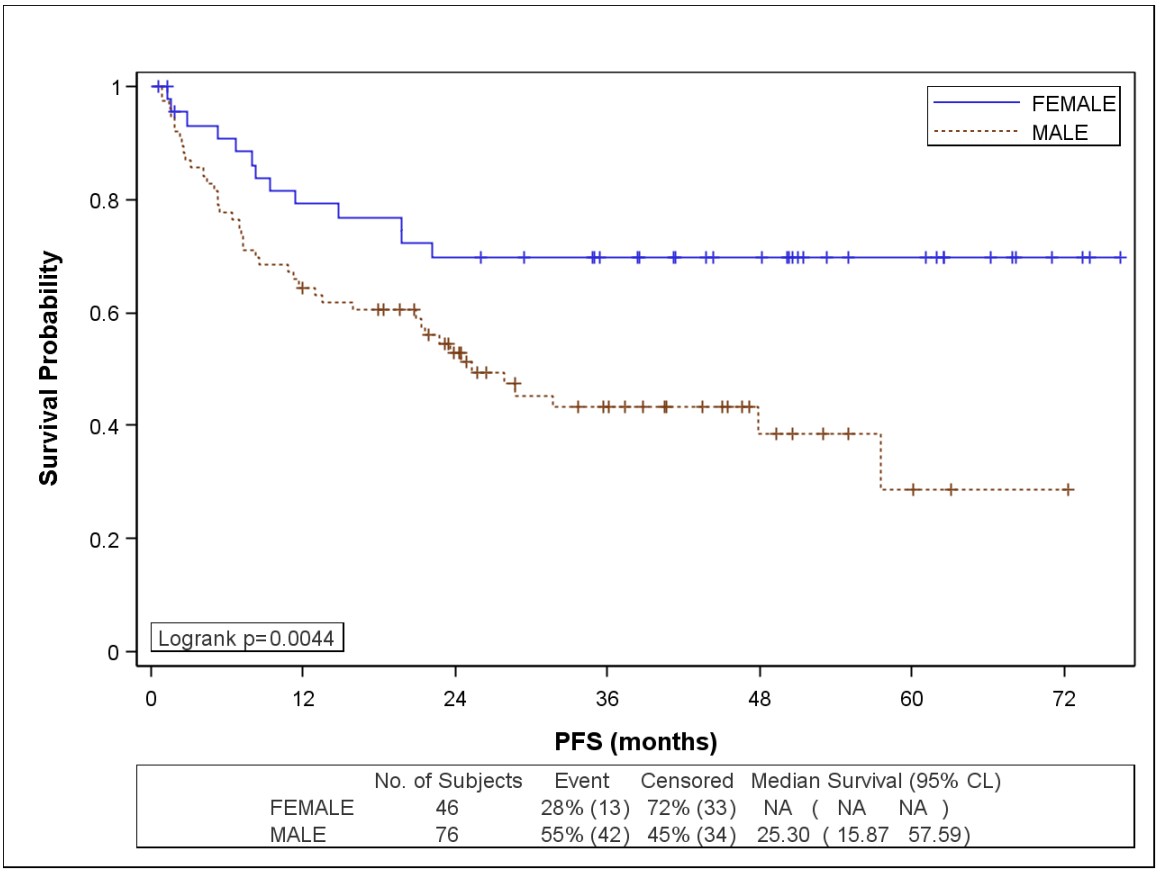
Model with gender and maintenance arm:

Analysis of Maximum Likelihood Estimates										
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
SEXE	FEMALE	1	-0.54152	0.21951	6.0861	**0.0136**	0.582	0.378	0.895	Sex FEMALE
brasrand2	RITUXIMAB	1	0.08406	0.19417	0.1874	0.6651	1.088	0.743	1.591	Arm of 2nd randomization RITUXIMAB

Model with gender, maintenance arm and interaction:

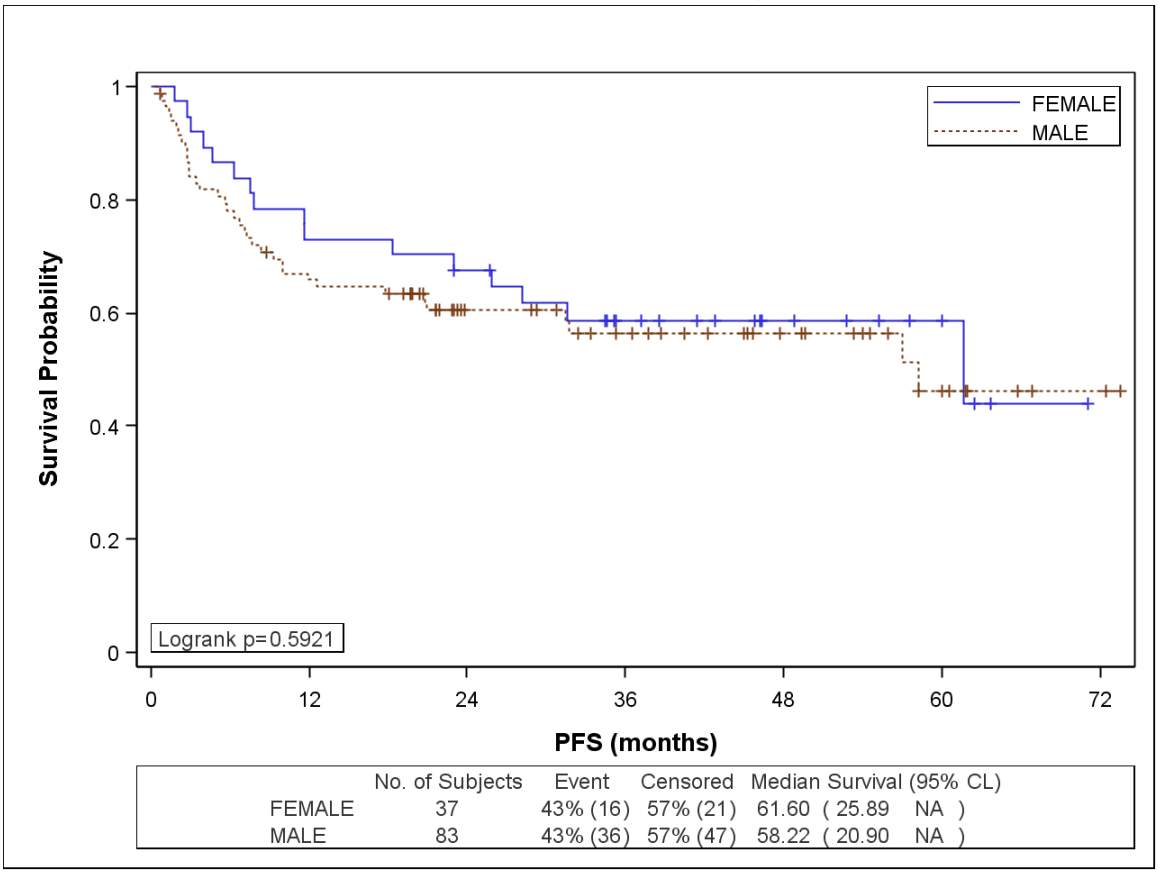
Analysis of Maximum Likelihood Estimates							
Parameter			DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
SEXE	FEMALE		1	-0.17025	0.30070	0.3206	0.5713
brasrand2	RITUXIMAB		1	0.28135	0.22765	1.5274	0.2165
SEXE*brasrand2	FEMALE	RITUXIMAB	1	-0.72785	0.43830	2.7577	0.0968

Arm of 2nd randomization=RITUXIMAB



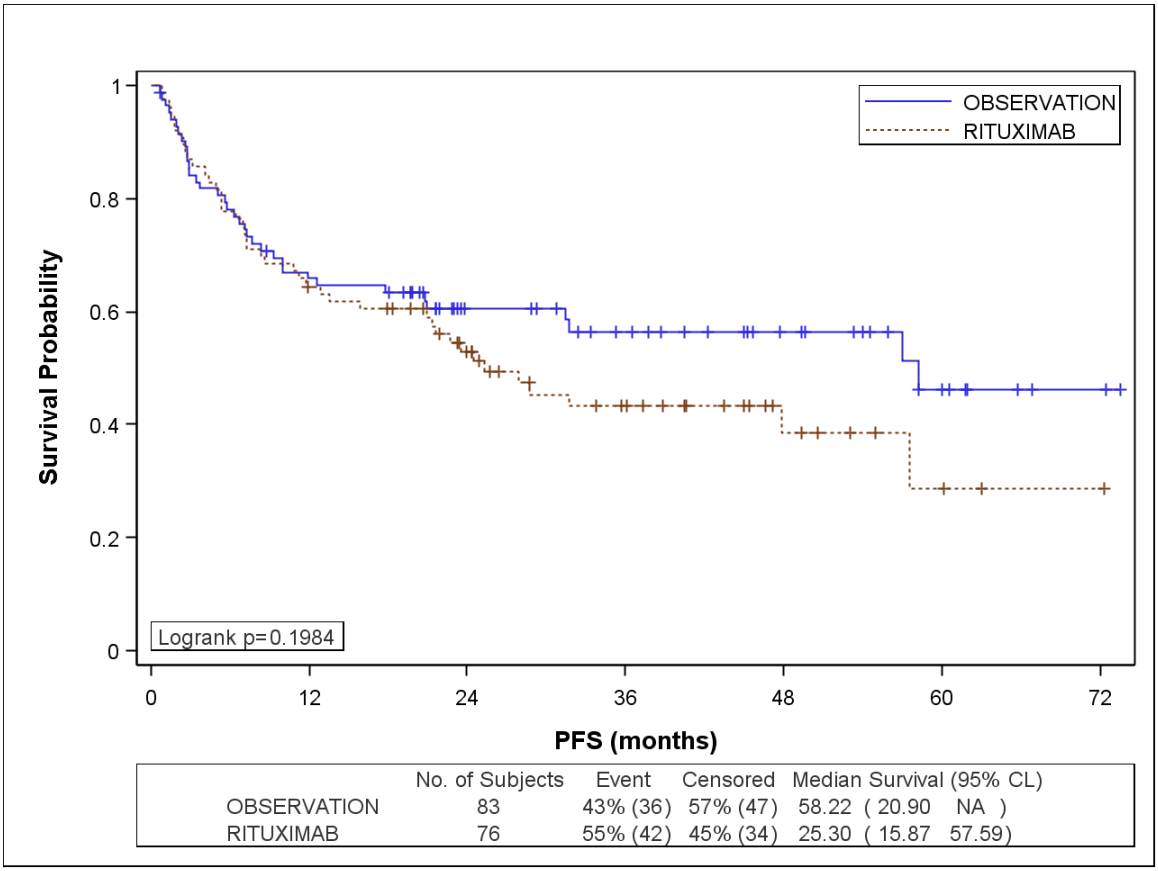
	No. of Subjects	Event	Censored	Median Survival (95% CL)
FEMALE	46	28% (13)	72% (33)	NA (NA NA)
MALE	76	55% (42)	45% (34)	25.30 (15.87 57.59)

Arm of 2nd randomization=OBSERVATION



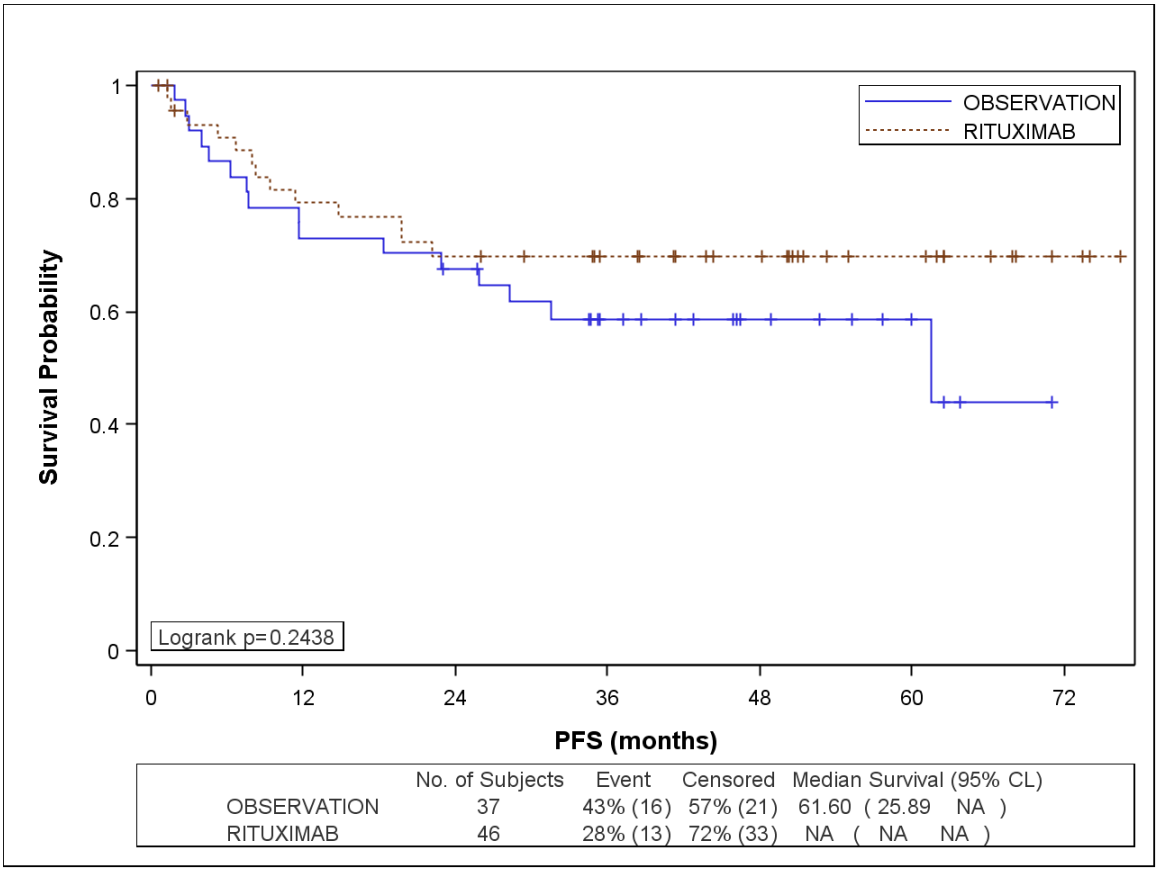
	No. of Subjects	Event	Censored	Median Survival (95% CL)
FEMALE	37	43% (16)	57% (21)	61.60 (25.89 NA)
MALE	83	43% (36)	57% (47)	58.22 (20.90 NA)

Sex=MALE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	83	43% (36)	57% (47)	58.22 (20.90 NA)
RITUXIMAB	76	55% (42)	45% (34)	25.30 (15.87 57.59)

Sex=FEMALE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	37	43% (16)	57% (21)	61.60 (25.89 NA)
RITUXIMAB	46	28% (13)	72% (33)	NA (NA NA)

Arm of 2nd randomization	Sex	N	Median	95% CI lower	95% CI Upper	Min	Max
RITUXIMAB	MALE	76	25	16	58	1	72
RITUXIMAB	FEMALE	46	-	-	-	1	76
OBSERVATION	MALE	83	58	21	-	1	74
OBSERVATION	FEMALE	37	62	26	-	2	71

Arm of 2nd randomization	Sex	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
RITUXIMAB	MALE	12	64.5	52.6	74.1	48
RITUXIMAB	MALE	24	52.9	40.9	63.6	32
RITUXIMAB	MALE	36	43.2	31.0	54.9	19
RITUXIMAB	MALE	48	38.4	24.7	52.0	8
RITUXIMAB	MALE	60	28.8	11.8	48.4	3
RITUXIMAB	MALE	72	28.8	11.8	48.4	1
RITUXIMAB	FEMALE	12	79.2	63.8	88.6	34
RITUXIMAB	FEMALE	24	69.8	53.8	81.2	30
RITUXIMAB	FEMALE	36	69.8	53.8	81.2	25
RITUXIMAB	FEMALE	48	69.8	53.8	81.2	19
RITUXIMAB	FEMALE	60	69.8	53.8	81.2	11
RITUXIMAB	FEMALE	72	69.8	53.8	81.2	3
OBSERVATION	MALE	12	65.8	54.4	74.9	53
OBSERVATION	MALE	24	60.4	48.8	70.2	34
OBSERVATION	MALE	36	56.5	44.5	66.9	26
OBSERVATION	MALE	48	56.5	44.5	66.9	17
OBSERVATION	MALE	60	46.2	30.0	61.0	8
OBSERVATION	MALE	72	46.2	30.0	61.0	2
OBSERVATION	FEMALE	12	73.0	55.6	84.4	27
OBSERVATION	FEMALE	24	67.6	50.0	80.1	24
OBSERVATION	FEMALE	36	58.8	41.1	72.8	16
OBSERVATION	FEMALE	48	58.8	41.1	72.8	9
OBSERVATION	FEMALE	60	58.8	41.1	72.8	4
OBSERVATION	FEMALE	72	44.1	17.1	68.3	0

Arm of 2nd randomization=RITUXIMAB

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
SEXE	FEMALE	1	-0.88581	0.32083	7.6229	**0.0058**	0.412	0.220	0.773	Sex FEMALE

Arm of 2nd randomization=OBSERVATION

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
SEXE	FEMALE	1	-0.16097	0.30091	0.2862	0.5927	0.851	0.472	1.535	Sex FEMALE

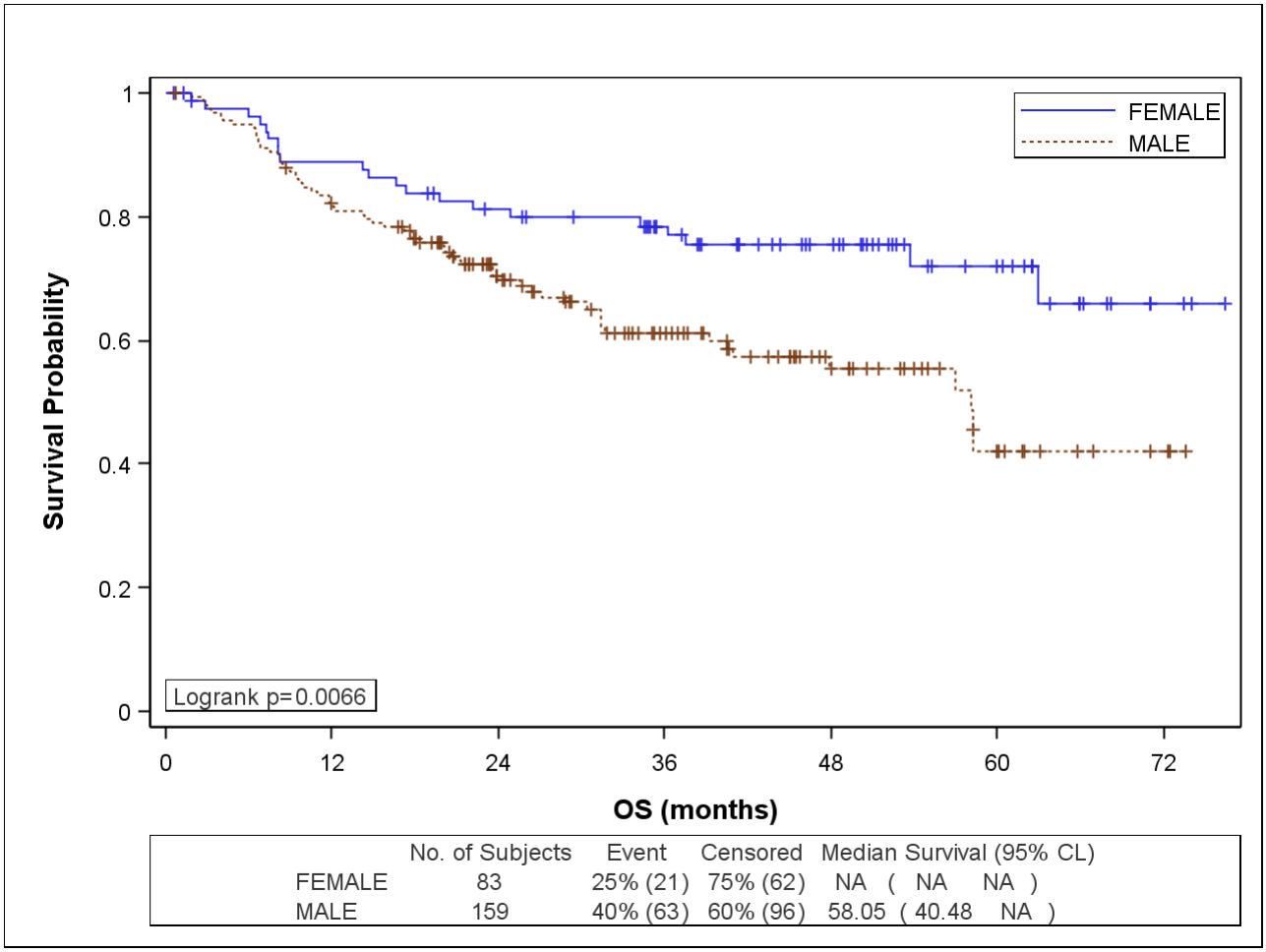
Sex=MALE

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
brasrand2	RITUXIMAB	1	0.29243	0.22825	1.6414	0.2001	1.340	0.856	2.096	Arm of 2nd randomization RITUXIMAB

Sex=FEMALE

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
brasrand2	RITUXIMAB	1	-0.43290	0.37427	1.3379	0.2474	0.649	0.311	1.351	Arm of 2nd randomization RITUXIMAB

Prognostic factors
Gender
2nd randomization : OS (MITT)



Sex	N	Median	95% CI lower	95% CI Upper	Min	Max
MALE	159	58	40	-	1	74
FEMALE	83	-	-	-	1	76

Sex	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
MALE	12	82.2	75.3	87.4	128
MALE	24	69.7	61.6	76.4	83
MALE	36	61.3	52.4	69.0	54
MALE	48	55.3	45.5	64.1	28
MALE	60	42.0	28.6	54.9	12
MALE	72	42.0	28.6	54.9	3
FEMALE	12	88.8	79.5	94.0	71
FEMALE	24	81.2	70.7	88.2	62
FEMALE	36	78.5	67.7	86.1	50
FEMALE	48	75.3	64.0	83.5	35
FEMALE	60	72.1	59.0	81.6	18
FEMALE	72	66.0	48.5	78.8	3

Model with gender only:

Analysis of Maximum Likelihood Estimates										
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
SEXE	FEMALE	1	-0.67898	0.25437	7.1247	0.0076	0.507	0.308	0.835	Sex FEMALE

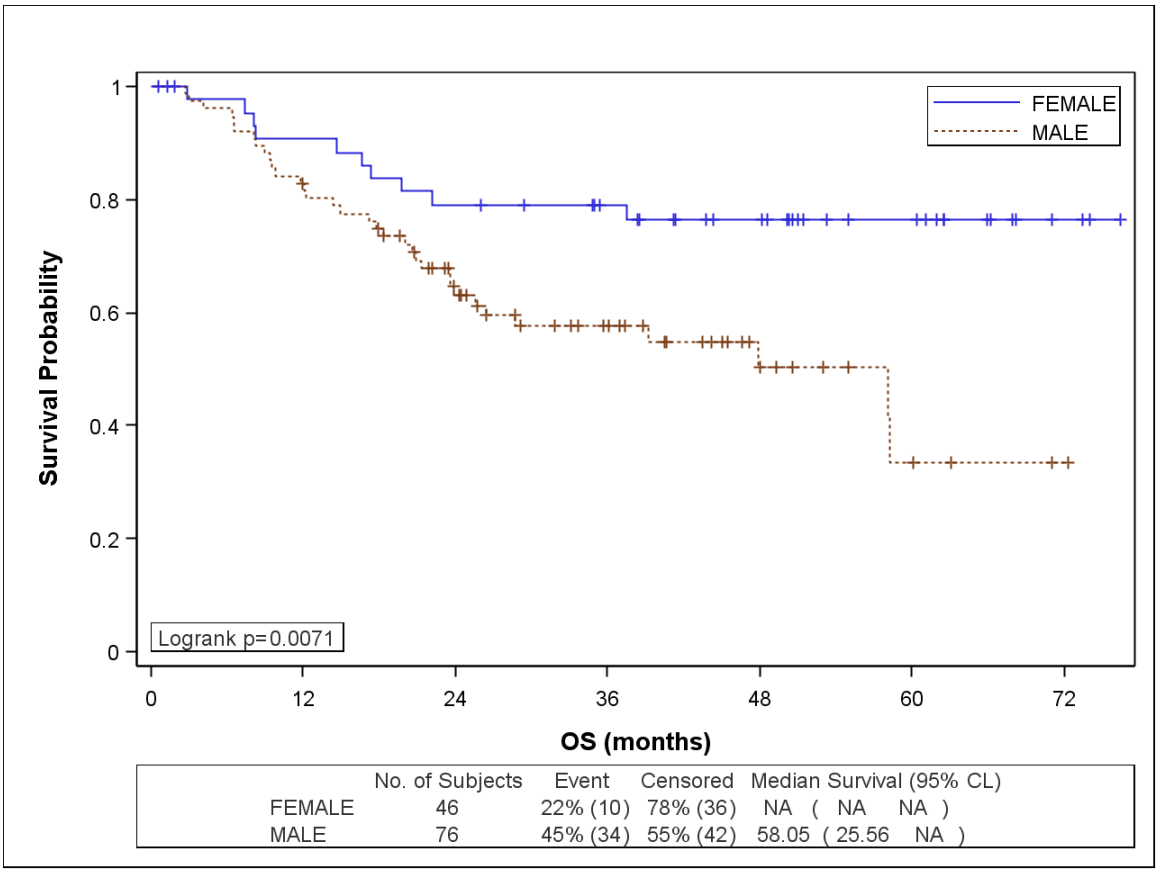
Model with gender and maintenance arm:

Analysis of Maximum Likelihood Estimates										
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Variable Label
SEXE	FEMALE	1	-0.69179	0.25547	7.3327	0.0068	0.501	0.303	0.826	Sex FEMALE
brasrand2	RITUXIMAB	1	0.12602	0.21938	0.3300	0.5657	1.134	0.738	1.744	Arm of 2nd randomization RITUXIMAB

Model with gender and maintenance arm:

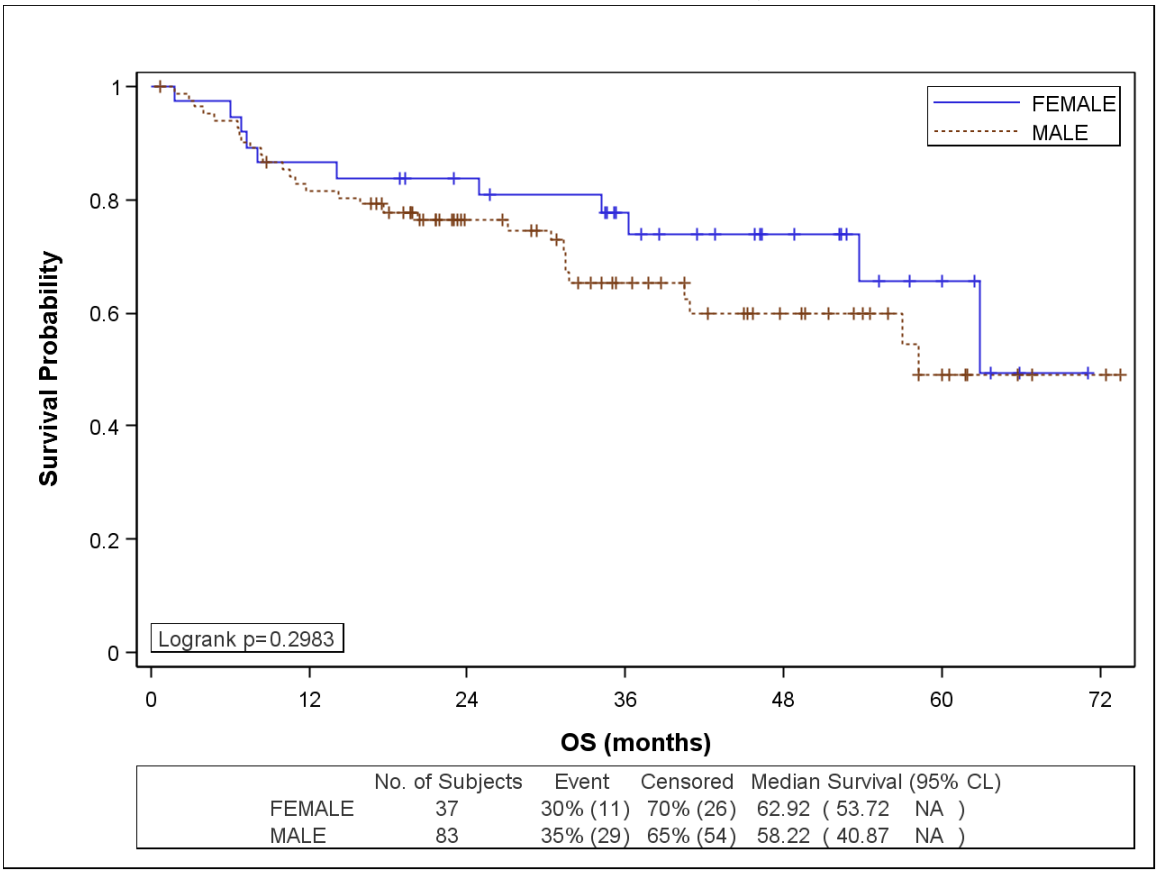
Analysis of Maximum Likelihood Estimates								
Parameter			DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq
SEXE	FEMALE		1	-0.34575	0.35476	0.9498	0.3298
brasrand2	RITUXIMAB		1	0.28894	0.25315	1.3028	0.2537
SEXE*brasrand2	FEMALE	RITUXIMAB	1	-0.65444	0.50590	1.6734	0.1958

Arm of 2nd randomization=RITUXIMAB



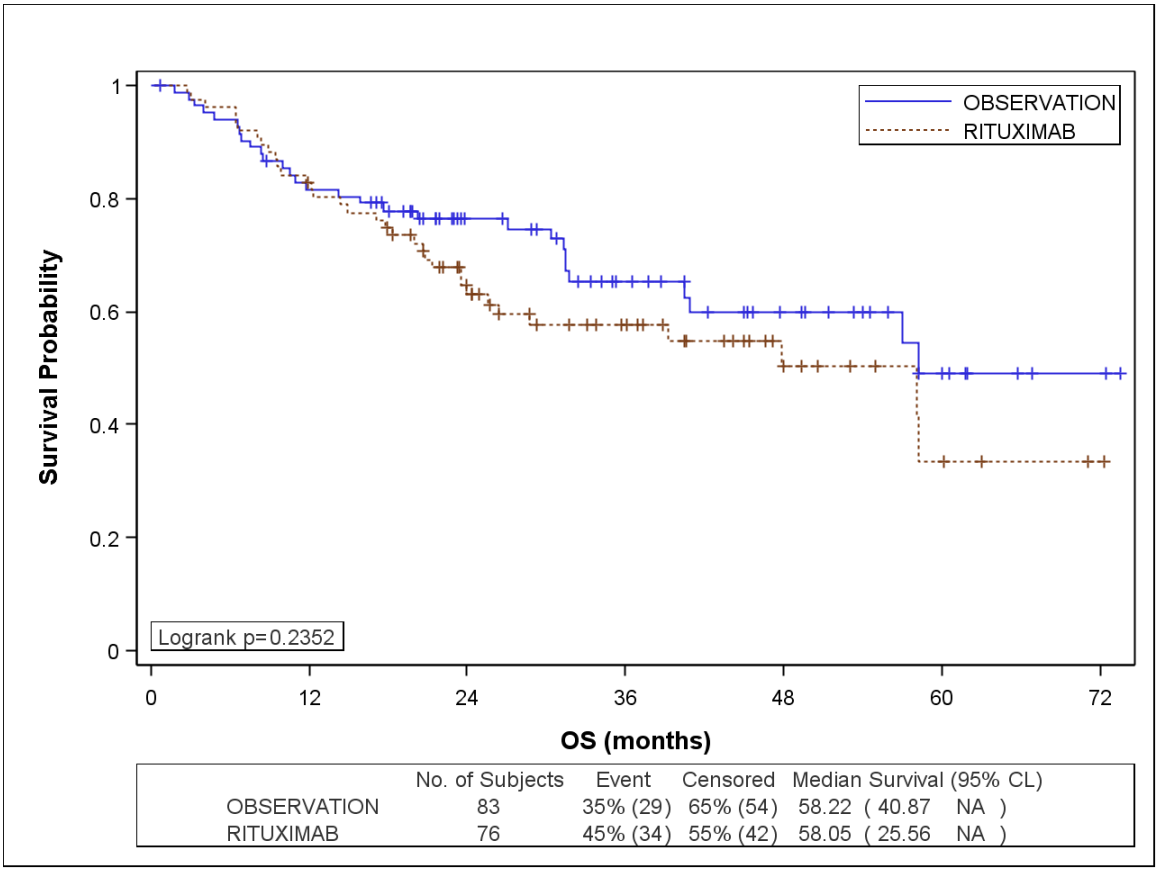
	No. of Subjects	Event	Censored	Median Survival (95% CL)
FEMALE	46	22% (10)	78% (36)	NA (NA NA)
MALE	76	45% (34)	55% (42)	58.05 (25.56 NA)

Arm of 2nd randomization=OBSERVATION



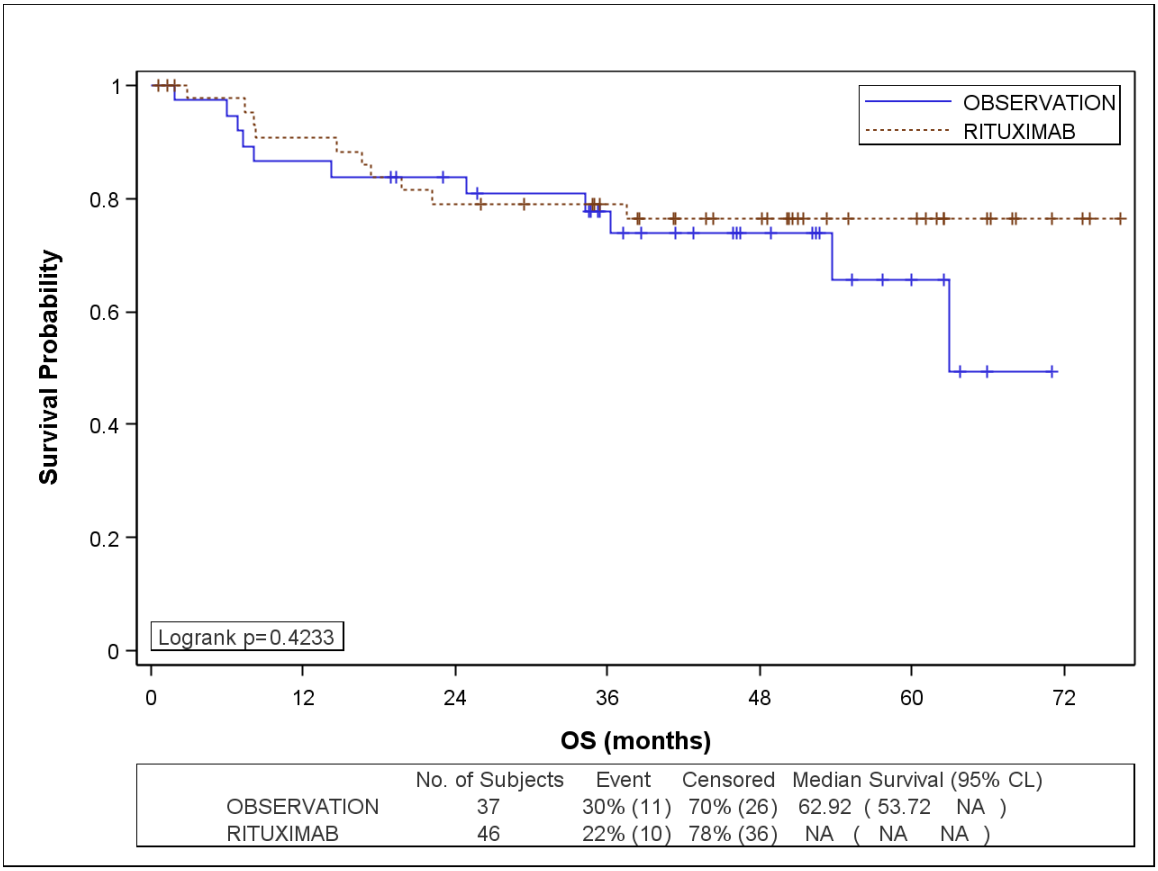
	No. of Subjects	Event	Censored	Median Survival (95% CL)
FEMALE	37	30% (11)	70% (26)	62.92 (53.72 NA)
MALE	83	35% (29)	65% (54)	58.22 (40.87 NA)

Sex=MALE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	83	35% (29)	65% (54)	58.22 (40.87 NA)
RITUXIMAB	76	45% (34)	55% (42)	58.05 (25.56 NA)

Sex=FEMALE



	No. of Subjects	Event	Censored	Median Survival (95% CL)
OBSERVATION	37	30% (11)	70% (26)	62.92 (53.72 NA)
RITUXIMAB	46	22% (10)	78% (36)	NA (NA NA)

Arm of 2nd randomization	Sex	N	Median	95% CI lower	95% CI Upper	Min	Max
RITUXIMAB	MALE	76	58	26	-	3	72
RITUXIMAB	FEMALE	46	-	-	-	1	76
OBSERVATION	MALE	83	58	41	-	1	74
OBSERVATION	FEMALE	37	63	54	-	2	71

Arm of 2nd randomization	Sex	Time Point (years)	Survival (%)	95% CI Lower	95% CI Upper	Patients at risk
RITUXIMAB	MALE	12	82.9	72.4	89.7	62
RITUXIMAB	MALE	24	63.0	50.8	73.0	39
RITUXIMAB	MALE	36	57.6	44.9	68.3	25
RITUXIMAB	MALE	48	50.2	35.4	63.4	10
RITUXIMAB	MALE	60	33.5	14.2	54.2	4
RITUXIMAB	MALE	72	33.5	14.2	54.2	1
RITUXIMAB	FEMALE	12	90.7	77.1	96.4	39
RITUXIMAB	FEMALE	24	79.1	63.6	88.5	34
RITUXIMAB	FEMALE	36	79.1	63.6	88.5	29
RITUXIMAB	FEMALE	48	76.3	60.4	86.5	22
RITUXIMAB	FEMALE	60	76.3	60.4	86.5	13
RITUXIMAB	FEMALE	72	76.3	60.4	86.5	3
OBSERVATION	MALE	12	81.6	71.4	88.5	66
OBSERVATION	MALE	24	76.5	65.6	84.3	44
OBSERVATION	MALE	36	65.1	52.3	75.3	29
OBSERVATION	MALE	48	59.9	46.1	71.3	18
OBSERVATION	MALE	60	49.0	31.2	64.6	8
OBSERVATION	MALE	72	49.0	31.2	64.6	2
OBSERVATION	FEMALE	12	86.5	70.5	94.1	32
OBSERVATION	FEMALE	24	83.8	67.4	92.4	28
OBSERVATION	FEMALE	36	77.7	60.2	88.2	21
OBSERVATION	FEMALE	48	74.0	55.6	85.7	13
OBSERVATION	FEMALE	60	65.8	41.9	81.7	5
OBSERVATION	FEMALE	72	49.3	17.3	75.2	0

Arm of 2nd randomization=RITUXIMAB

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Variable Label
SEXE	FEMALE	1	-0.95023	0.36531	6.7663	0.0093	0.387	0.189 0.791	Sex FEMALE

Arm of 2nd randomization=OBSERVATION

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Variable Label
SEXE	FEMALE	1	-0.36793	0.35591	1.0687	0.3012	0.692	0.345 1.390	Sex FEMALE

Sex=MALE

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Variable Label
brasrand2	RITUXIMAB	1	0.29959	0.25341	1.3977	0.2371	1.349	0.821 2.217	Arm of 2nd randomization RITUXIMAB

Sex=FEMALE

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	Variable Label
brasrand2	RITUXIMAB	1	-0.34876	0.43775	0.6347	0.4256	0.706	0.299 1.664	Arm of 2nd randomization RITUXIMAB

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			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	20.3524	3	0.0001
Score	21.4500	3	<.0001
Wald	20.6540	3	0.0001

Analysis of Maximum Likelihood Estimates									
Parameter		**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	**Variable Label**
brasrand2	**RITUXIMAB**	1	0.12762	0.20445	0.3896	0.5325	1.136	0.761 1.696	Arm of 2nd randomization RITUXIMAB
aaipi	**2-3**	1	0.78873	0.20596	14.6654	**0.0001**	2.201	1.470 3.295	Age-adjusted IPI 2-3
SEXE	**MALE**	1	0.60309	0.23156	6.7835	**0.0092**	1.828	1.161 2.878	Sex MALE

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			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	27.0463	7	0.0003
Score	28.1385	7	0.0002
Wald	27.1232	7	0.0003

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	
Arm of 2nd randomization RITUXIMAB	1	0.13214	0.20672	0.4086	0.5227	1.141	0.761	1.711
Age-adjusted IPI 2-3	1	0.74159	0.20798	12.7139	**0.0004**	2.099	1.396	3.156
Sex MALE	1	0.58717	0.23223	6.3926	**0.0115**	1.799	1.141	2.836
Prior treatment with Rituximab No	1	-0.17526	0.22847	0.5884	0.4430	0.839	0.536	1.313
Failure from diagnosis < 12 months	1	0.19620	0.23001	0.7276	0.3937	1.217	0.775	1.910
Response after complete induction PR	1	0.14102	0.20908	0.4549	0.5000	1.151	0.764	1.735
Arm of treatment ARM A / R-ICE	1	0.38543	0.20591	3.5038	0.0612	1.470	0.982	2.201

CORAL study
Cox models - maintenance population (excluding SD patients)
2nd randomization : OS

Number of Observations Read	234
Number of Observations Used	229

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	20.4930	3	0.0001
Score	21.8743	3	<.0001
Wald	20.8338	3	0.0001

Analysis of Maximum Likelihood Estimates									
Parameter		**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	**Variable Label**
brasrand2	**RITUXIMAB**	1	0.19196	0.22723	0.7137	0.3982	1.212	0.776 1.891	Arm of 2nd randomization RITUXIMAB
aaipi	**2-3**	1	0.89373	0.22754	15.4281	<.0001	2.444	1.565 3.818	Age-adjusted IPI 2-3
SEXE	**MALE**	1	0.63522	0.25860	6.0341	0.0140	1.887	1.137 3.133	Sex MALE

CORAL study
Cox models - maintenance population (excluding SD patients)
2nd randomization : OS

Number of Observations Read	234
Number of Observations Used	229

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	26.9752	7	0.0003
Score	28.3489	7	0.0002
Wald	27.1006	7	0.0003

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	
Arm of 2nd randomization RITUXIMAB	1	0.19336	0.22899	0.7130	0.3984	1.213	0.775	1.901
Age-adjusted IPI 2-3	1	0.84439	0.22978	13.5035	**0.0002**	2.327	1.483	3.650
Sex MALE	1	0.61535	0.25988	5.6067	**0.0179**	1.850	1.112	3.079
Prior treatment with Rituximab No	1	-0.24360	0.25747	0.8951	0.3441	0.784	0.473	1.298
Failure from diagnosis (< 12 months	1	0.18435	0.25763	0.5120	0.4743	1.202	0.726	1.992
Response after complete induction PR	1	0.13211	0.23275	0.3222	0.5703	1.141	0.723	1.801
Arm of treatment ARM A / R-ICE	1	0.41014	0.22914	3.2037	0.0735	1.507	0.962	2.361

CORAL study
PET scan in PR patients after induction

	N	%
PET scan after induction chemo		
NEGATIVE	7	8
POSITIVE	24	27
NOT DONE	58	65
Total	89	100

CORAL study
PET scan in PR patients after induction
List of PET positive and PR patients after induction

on	PET scan after induction chemo	PET scan at M3 post transplant	Transplantation date	Progression / Relapse	Date of Progression / Relapse	PFS (months) from 1st rando	PFS (months) from 2nd rando	Date of death	OS (months) from 1st rando
401	POSITIVE	NEGATIVE	26/11/2004	Yes	30/03/2005	6.9322	4.1068	30/11/2005	14.9815
650	POSITIVE	POSITIVE	11/10/2006	Yes	04/01/2007	5.7495	2.6283	19/02/2007	7.2608
013	POSITIVE	NOT DONE	21/12/2004	-	-	67.0883	62.5544	-	67.0883
642	POSITIVE	NOT DONE	27/12/2007	-	-	27.8275	24.4107	-	27.8275
633	POSITIVE	NOT DONE	04/10/2005	Yes	10/01/2006	5.8809	1.8398	16/02/2006	7.0965
637	POSITIVE	NEGATIVE	21/11/2005	-	-	49.6756	46.6530	-	49.6756
627	POSITIVE	POSITIVE	28/11/2005	-	-	50.6612	47.6715	-	50.6612
611	POSITIVE	NEGATIVE	17/05/2004	-	-	75.2033	72.3450	-	75.2033
610	POSITIVE	-	24/05/2004	Yes	11/08/2004	5.8152	2.8255	12/08/2004	5.8480
419	POSITIVE	NEGATIVE	15/07/2008	-	-	22.1766	17.9055	-	22.1766
645	POSITIVE	POSITIVE	21/06/2006	-	-	38.3409	35.2197	-	38.3409
641	POSITIVE	NOT DONE	28/11/2007	Yes	21/10/2009	25.5606	22.7680	-	32.0000
669	POSITIVE	NOT DONE	04/10/2007	Yes	21/01/2008	6.5708	2.9240	16/10/2008	15.4086
640	POSITIVE	-	26/07/2007	Yes	11/09/2007	5.3224	1.5113	-	35.5811
015	POSITIVE	-	14/02/2008	-	-	3.8768	1.2813	-	3.8768
607	POSITIVE	NEGATIVE	10/03/2008	-	-	29.6674	25.7248	-	29.6674
609	POSITIVE	NEGATIVE	14/11/2007	-	-	33.7413	30.7187	-	33.7413
607	POSITIVE	POSITIVE	19/05/2008	-	-	26.7433	21.6509	-	26.7433
407	POSITIVE	NOT DONE	13/09/2006	Yes	16/11/2006	5.3552	1.8398	10/04/2007	10.1191
603	POSITIVE	POSITIVE	08/06/2005	Yes	13/01/2006	10.1520	7.2279	-	54.3080
018	POSITIVE	NEGATIVE	16/09/2008	-	-	23.8850	19.6797	-	23.8850
613	POSITIVE	POSITIVE	31/05/2005	Yes	06/09/2005	6.2094	3.4825	29/07/2006	16.9199
402	POSITIVE	NEGATIVE	09/08/2007	Yes	14/09/2009	28.5175	24.5092	-	37.0595
621	POSITIVE	NEGATIVE	08/03/2007	Yes	07/09/2007	9.1992	5.6509	-	38.6037

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

GELA : **G**roupe d'**E**tude des **L**ymphomes de l'**A**dulte
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ABBREVIATIONS

AFSSAPS	**FRENCH HEALTH AUTHORITY**
GELA	**STUDY GROUP OF ADULTS' LYMPHOMA**
SAE	**SERIOUS ADVERSE EVENT**
AE	**ADVERSE EVENT**
SAR	**SERIOUS ADVERSE REACTION**
SUSAR	**SUSPECTED UNEXPECTED SERIOUS ADVERSE EVENT**
SMPC	**SUMMARY OF PRODUCT CHARACTERISTICS**
MEDDRA	**MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES**
SOC	**SYSTEM ORGAN CLASS**

TABLE OF CONTENTS

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.

R-ICE	Rituximab	375 mg/m²
	Etoposide	100 mg/m²
	Carboplatine	AUC (5) max 800mg
	Ifosfamide + Mesna	5 g/m²
	Lenograstim	

Arm B: 3 cycles of R-DHAP in 3–weekly intervals.

R-DHAP	Rituximab	375 mg/m²
	Cisplatine c.i.	100 mg/m²
	Cytarabine	2000 mg/m²/12 h
	Dexamethasone	40 mg/m²
	Lenograstim	

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

Carmustine	300 mg/m²
Etoposide	200 mg/m²
Cytarabine	200 mg/m²
Melphalan	140 mg/m²

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

Carboplatine: 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

Cisplatine: 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/m^2/12 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.

Amendment N°3 - June 18th, 2007

- The extension of the study up to 480 patients.
- Including of the updates of Mabthera® SmPC dated January 2007.

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:

Cancellation reason	**Nb of SAE**
Disease progression	10
Duplicate	6
Reporting out of protocol	10
Adverse event (non serious) according to the protocol	19
Patient not randomized	1
Existing at inclusion condition	1

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.

Causality by the investigator or by the sponsor	Listed in the reference document	Unlisted in the reference document	Total
Related	198	32	230
Unrelated	NA	NA	32

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.

Regimen	Total Number of subjects included	Nb SAR reports	Nb of patients Involved (%)
R-ICE +/- BEAM	**246**	**75**	**49 patients (19,9%)**
R-DHAP +/-BEAM	**235**	**104**	**67 patients (28.5%)**
TOTAL	**481**	**179**	**116**

Table I: SARs and number of patients involved during induction

During maintenance phase, 35 patients of 245 randomized, developed at least one SAR

Regimen	Total Number of subjects included	Nb SAE reports	Nb of patients involved (% of randomized to the arm subjects)
Rituximab	**124**	**35**	**23 subjects (18.5%)**
Observation	**121**	**16**	**12 subjects (13.2%)**
TOTAL	**245**	**51**	**35**

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

	Total	Arm R-ICE +/- BEAM, ASCT	Arm R-DHAP+/- BEAM, ASCT
Total of patients included		**246**	**235**
Blood and lymphatic system disorders	**21**	**8**	**13**
Febrile neutropenia [b)]		4	8
Neutropenia		-	2
Pancytopenia		1	-
Bicytopenia		2	1
Hematotoxicity		-	1
Thrombocytopenia		1	1
Cardiac disorders	**11**	**5**	**6**
Atrial fibrillation		1	1
Cardiac insufficiency [a)b)]		-	2
Cardiac failure		1	1
Cardiac arrest [a)b)]		1	1
Cardiac ischemia		1	-
Myocardial infarction		1	-
Bradycardia		-	1
Ear and labyrinth disorders	**1**	**0**	**1**
Tinnitus		-	1
Gastrointestinal disorders	**20**	**7**	**13**
Bowel obstruction		1	1
Colitis hemorrhagic		-	1
Diarrhea		2	1
Esophageal haemorrhage		1	-
Gastric ulcer haemorrhage		1	-
Gastrointestinal haemorrhage		1	3
Gastrointestinal disorders		-	1
Nausea and vomiting		-	3

	Total	Arm R-ICE +/- BEAM, ASCT	Arm R-DHAP+/- BEAM, ASCT
Perforation large intestine		1	-
Vomiting		-	2
Perforated bowel		-	1
General disorders and administration site conditions	**8**	**5**	**3**
Asthenia		1	-
Fever		4	1
Mucositis		-	2
Hepatobiliary disorders	**2**	**1**	**1**
Hepatitis		1	-
Acute cholecystitis		-	1
Immune system disorders	**1**	**-**	**1**
Drug hypersensitivity		-	1
Infections and infestations	**69**	**34**	**35**
Aspergillosis		1	-
Central line infection		3	1
Cellulitis		2	-
CMV Infection [a)b)]		-	1
Dental abscess		1	-
Diarrhea Clostridium difficile		-	2
Enterobacter septicemia		-	1
Escherichia Coli Infection		1	-
Gastrointestinal candidiasis		1	-
Herpes zoster		3	-
Klebsiella pneumoniae infection		1	-
Klebsiella sepsis		-	1
Infection		2	-
Infectious diarrhea		-	1
Lower respiratory tract infection		-	2
Neutropenic infection		2	3
Neutropenic sepsis [a)b)]		5	5
Pneumonia [a)b)]		2	5
Pneumonia streptococcal [b)]		1	1
Pseudomonas infection		-	1
Pseudomonal sepsis		-	1
Sepsis [a)b)]		1	-
Sinusitis aspergillus		-	1
Septic shock [a)b)]		6	1
Septicemia		1	1
Septicemia candida [a)b)]		-	1
Septicemia gram negative [a)b)]		1	1
Septicemia gram positive		-	1
Staphylococcal sepsis		-	2
Urinary tract infection		-	1
Upper respiratory tract infection		-	1

	Total	Arm R-ICE +/- BEAM, ASCT	Arm R-DHAP+/- BEAM, ASCT
Injury, poisoning and procedural complications	**1**	**1**	**0**
Subdural hematoma		1	-
Metabolism and nutrition disorders	**8**	**2**	**6**
Dehydration		2	2
Exsiccosis		-	1
Hyperglycemia		-	2
Hyponatremia [b)]		-	1
Musculoskeletal and connective tissue disorders	**1**	**0**	**1**
Bone pain		-	1
Nervous system disorders	**12**	**3**	**9**
Aphasia		-	1
Drug-induced encephalopathy		1	-
Embolic cerebral infarction [b)]		-	1
Epileptic seizure		-	1
Ischaemic stroke		-	1
Leukoencephalopathy [b)]		1	-
Neurotoxicity		-	1
Stroke		1	2
Vagal reaction		-	2
Psychiatric disorders	**1**	**1**	**0**
Confusion		1	-
Renal and urinary disorders	**10**	**2**	**8**
Renal failure		-	3
Acute renal failure		2	5
Respiratory, thoracic and mediastinal disorders	**8**	**3**	**5**
Respiratory failure [a)b)]		-	2
Respiratory insufficiency [b)]		-	1
Pulmonary embolism		3	2
Vascular disorders	**5**	**3**	**2**
Thrombosis		-	1
Hypotension		2	-
Collapse		-	1
Venoocclusive disease [b)]		1	-
Total	**179**	**75**	**104**

[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

	Arm R-ICE		Arm R-DHAP		Total
	Event's number	***% of all subjects in arm (N=246)***	**Event's number**	***% of all subjects in arm (N=235)***	**Total**
Blood and lymphatic system disorders	8	*3.3*	13	*5.5*	**21**
Cardiac disorders	5	*2.0*	6	*2.6*	**11**
Ear and labyrinth disorders	-	-	1	*0.4*	**1**
Gastrointestinal disorders	7	*2.8*	13	*5.5*	**20**
General disorders and administration site conditions	5	*2*	3	*1.3*	**8**
Hepatobiliary disorders	1	*0.4*	1	*0.4*	**2**
Immune system disorders	-	-	1	*0.4*	**1**
Infections and infestations	34	*13.8*	35	*14.4*	**69**
Injury, poisoning and procedural complications	1	*0.4*	-	-	**1**
Metabolism and nutrition disorders	2	*0.8*	6	*2.6*	**8**
Musculoskeletal and connective tissue disorders	-	-	1	*0.4*	**1**
Nervous system disorders	3	*1,2*	9	*3.8*	**12**
Psychiatric disorders	1	*0.4*	-	-	**1**
Renal and urinary disorders	2	*0.8*	8	*3.4*	**10**
Respiratory, thoracic and mediastinal disorders	3	*1.2*	5	*2.1*	**8**
Vascular disorders	3	*1.2*	2	*0.9*	**5**
Total	**75**		**104**		**179**

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.

	Total	**Arm Rituximab**	**Arm Observation**
Total of patients included		**124**	**121**
Blood and lymphatic system disorders	**5**	**3**	**2**
Anemia		-	1
Neutropenia		2	1
Thrombocytopenia		1	-

	Total	Arm Rituximab	Arm Observation
Cardiac disorders	**1**	**1**	**0**
Myocarditis [a)b)]		1	-
Ear and labyrinth disorders	**1**	**0**	**1**
Hearing Loss		-	1
Gastrointestinal disorders	**7**	**4**	**4**
Constipation		1	-
Dental caries		-	1*
Diarrhea		-	2
Faecaloma		1	
Gastrointestinal bleeding		1	-
Nausea		1	-
Nausea and vomiting		-	1*
General disorders and administration site conditions		**2**	**0**
Catheter related complication		1*	-
Mucositis		1	-
Hepatobiliary disorders	**1**	**0**	**1**
Hepatitis		-	1
Infections and infestations	**27**	**22**	**5**
Acute bronchopneumonia [a)b)]		1	-
Bacteraemia		-	1
Bacterial Pneumonia Unspecified		1	-
Bronchitis Pneumococcal		1	-
Bronchopneumonary infection		1	-
Catheter sepsis		1	-
Chest infection		1	1*
Clostridium difficile infection		-	1
CMV infection		1	
Haemophilus influenzae infection		1	-
Herpes zoster		1	-
Infection		1	-
Infection Bacillus Pyocyaneus		1	-
Lower respiratory tract infection		1	-
Neutropenic sepsis		1	-
Pneumonia [a)b)]		3	-
Pneumocystis jiroveci pneumonia [b)]		1	-
Pulmonary Aspergillosis		1	-
Respiratory tract infection		1	-
Septic shock		1	-
Septicemia		1	-
Septicemia streptococcal		1	-
Staphylococcus Epidermidis Septicemia		-	1*
Varicella		-	1

	Total	Arm Rituximab	Arm Observation
Investigation	**1**	**0**	**1**
Creatinine blood increase		-	1
Musculoskeletal and connective tissue disorders	**1**	**1**	**-**
Rhabdomyolysis		1*	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5**	**3**	**2**
Acute leukemia [a)b)]		1	-
Hepatic adenocarcinoma		1*	-
Melanoma limited to extremity		1*	-
Myelodysplastic syndrome [a)b)]		-	1
Urothelial carcinoma [a)b)]		-	1
Nervous system disorders	**4**	**2**	**2**
Leukoencephalopathy [a)b)]		1	-
Hypoesthesia		1*	-
Paresis		-	1
Loss of consciousness		-	1*
Renal and urinary disorders	**3**	**1**	**2**
Acute Renal failure		-	1
Renal Acidosis Tubular [b)]		1	-
Nephropathy toxic		-	1
Respiratory, thoracic and mediastinal disorders	**3**	**2**	**1**
Interstitial pneumonitis		1	-
Pulmonary infiltration		1	-
Pneumopathy		-	1
Social circumstances	**1**	**-**	**1**
Social stay hospitalization		-	1*
Total	**62**	**40**	**22**

[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.

SAE number	inclusion number	SAE occurrence	chemotherapy regimen	MedDRA LLT: reaction
002	5003101071002	Induction	R-DHAP	Septic shock
009	5003603201001	Induction	R-DHAP	Neutropenic sepsis
049	5003601601402	Induction	R-DHAP	Respiratory failure
160	5003607301622	Induction	R-DHAP	Septicemia Gram-Negative
173	5003619501010	Induction	R-DHAP	Respiratory failure
193	5003623501405	Induction	R-DHAP	Pneumonia
252	5003604701012	Induction	R-DHAP	Cardiac insufficiency
303 304	5003606301012	Induction	R-DHAP+ BEAM	Septicemia candida CMV infection
013	5003605301601	Induction	R-ICE	Cardiac arrest
175	5003619501013	Induction	R-ICE	Septic shock
082	5003101131030	Induction	R-ICE	Septic shock
083	5003603701004	Induction	R-ICE	Septic shock
159	5003616501005	Induction	R-ICE+BEAM	Sepsis
206	5003606301045	Induction	R-ICE+BEAM	Septic shock
127	5003601401602	Maintenance	Rituximab	Myocarditis
129	5003616301615	Maintenance	Rituximab	Pneumonia
190	5003601401004	Maintenance	Rituximab	Leukoencephalopathy
261	5003601401002	Maintenance	Rituximab	Acute leukemia
282	5003604901603	Maintenance	Rituximab	Acute Bronchopneumonia
292	5003606301604	Maintenance	Observation	Myelodysplastic syndrome
293	5003606301207	Maintenance	Observation	Urothelial carcinoma

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 **venooclusive 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, vinorelibine 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, carboplatine, 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 11 th -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 cisplatine. On day 1 of cycle 1, the patient received 550 mg rituximab, cisplatine 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 cisplatine 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 cisplatine 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 day6 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 cutaneus 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 cutaneus 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. La 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 **Pneumocystitis Jirovecii**. She was prescribed sulfamethoxazom 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, erindoprim, amlodipine 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 demyelinisation 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, cisplatine, 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 cysplatin 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 leukoencephalopathy 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

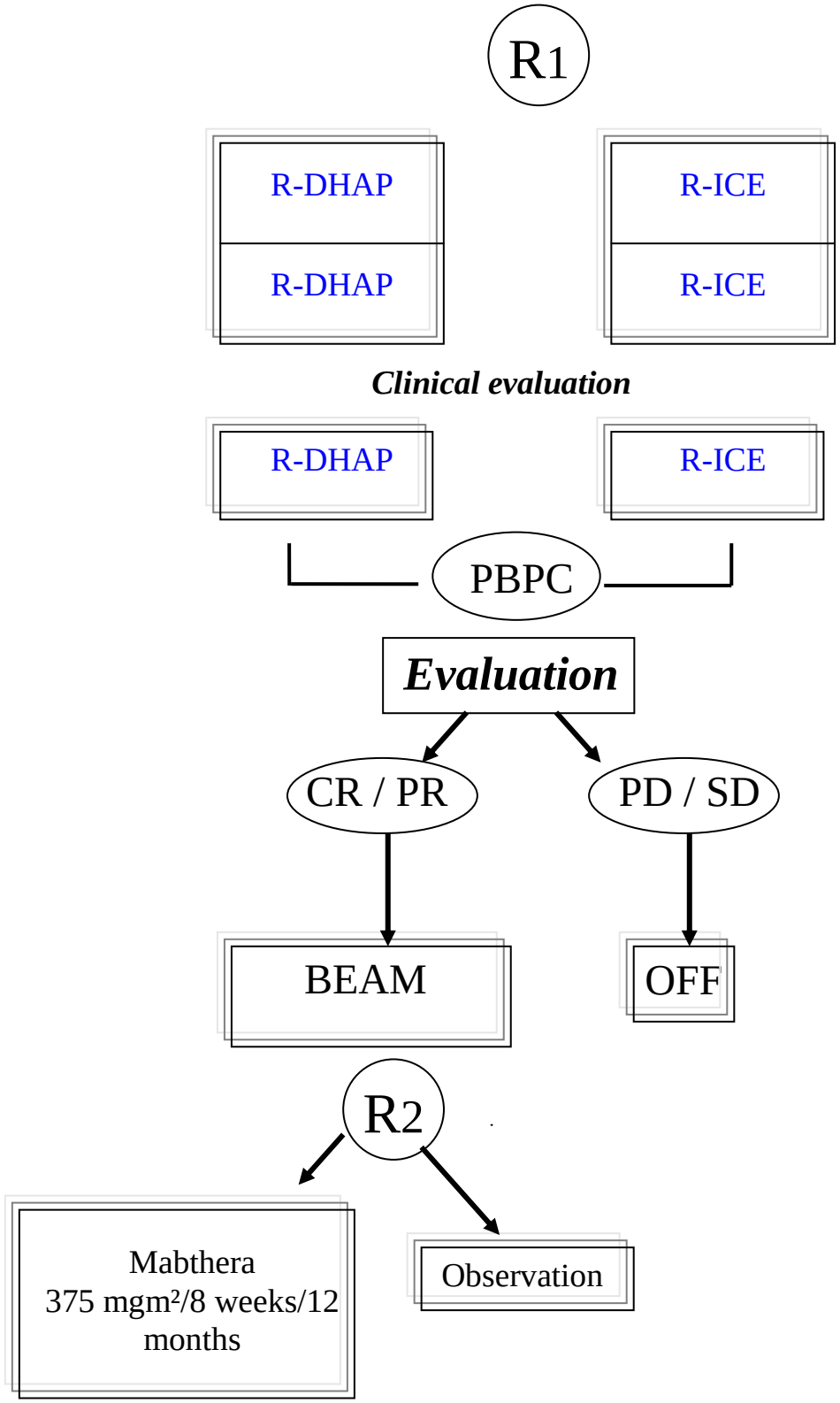
Appendix 5: DSMC recommendations dated 10 August 2007.

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 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 **Mabthera** maintenance therapy after transplantation.
Primary endpoints **Secondary 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.
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

Statistical analysis - Primary endpoints - Secondary endpoints	**Part I induction : Mobilization adjusted response rate** will be analyzed using chi-square test and a logistic regression to adjust for prognostic factors. **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 **- A arm**	**Induction : C**entral 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. **Maintenance :** Randomization to Rituximab post transplant vs. Observation will be done after restaging at the end of induction remission treatment. ➢ **Induction** : 3 cycles of RİCE in 3–weekly intervals. RICE Dose D-2 D1 D2 D3 D4 D5 D6 to D13 Rituximab 375 mg/m² (X) X Etoposide mg/m² 100 mg/m² X X X Carboplatine AUC (5) max 800mg X Ifosfamide + Mesna 5 g/m² X → (Continous infusion 24 h) G-CSF (SC) X **Rituximab D-2 first cycle only**
- B arm	➢ **Induction** : 3 cycles of R-DHAP, 3 weeks interval. R-DHAP Dose D-2 D1 D2 D3 D4 D5 D6 to D13 Rituximab 375 mg/m² X X Cisplatine c.i. 100 mg/m² X → Cytosine Arabinoside 2000 mg/m²/12 h XX Dexamethasone 40 mg X X X X G-CSF (sc) X **Rituximab D-2 first cycle only**
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. BEAM Dose D-6 D-5 D-4 D-3 D-2 D-1 D0 BCNU 300mg/m² X Etoposide 200 mg/m² X X X X Cytarabine twice daily 200 mg/m²/12h XX XX XX XX Melphalan 140 mg/m² X G R A F T
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 recruitement	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



Induction Phase

Blood and lymphatic system disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
SWITZERLAND	5003603701001	50	MALE	64	R-DHAP	BICYTOPENIA	28/01/2005	0	Recovered without sequelae
GERMANY	5003630201055	295	FEMALE	62	R-ICE	BICYTOPENIA	17/04/2008	0	Recovered without sequelae
GERMANY	5003630201055	299	FEMALE	62	R-ICE	BICYTOPENIA	12/06/2008	0	Recovered without sequelae
SWITZERLAND	5003603701001	56	MALE	64	R-DHAP	FEBRILE NEUTROPENIA	22/03/2005	0	Recovered without sequelae
AUSTRALIA	5003603301401	70	MALE	62	R-DHAP+ BEAM	FEBRILE NEUTROPENIA	14/12/2004	6	Recovered without sequelae
AUSTRALIA	5003605301610	76	MALE	60	R-DHAP+ BEAM	FEBRILE NEUTROPENIA	28/02/2005	7	Recovered without sequelae
AUSTRALIA	5003605301610	80	MALE	60	R-DHAP+ BEAM	FEBRILE NEUTROPENIA	14/03/2005	21	Recovered without sequelae
FRANCE	5003101251205	81	MALE	54	R-ICE + BEAM	FEBRILE NEUTROPENIA	20/08/2004	5	Recovered without sequelae
CZECH REPUBLIC	5003604801006	115	MALE	53	R-DHAP + BEAM	FEBRILE NEUTROPENIA	16/02/2006	71	Recovered without sequelae
CZECH REPUBLIC	5003603801203	132	FEMALE	53	R-ICE	FEBRILE NEUTROPENIA	09/12/2004	3	Recovered without sequelae
SWITZERLAND	5003604701012	178	MALE	62	R-DHAP	FEBRILE NEUTROPENIA (*)	30/04/2007	5	Ongoing at death
UNITED KINGDOM	5003612501012	183	FEMALE	55	R-ICE	FEBRILE NEUTROPENIA	17/05/2007	8	Recovered without sequelae
BELGIUM	5003101621055	268	FEMALE	64	R-ICE + BEAM	FEBRILE NEUTROPENIA	26/10/2006	1	Recovered without sequelae
UK	5003614501022	301	MALE	37	R-DHAP	FEBRILE NEUTROPENIA	17/12/2007	32	Recovered without sequelae
AUSTRALIA	5003606301012	302	FEMALE	64	R-DHAP + BEAM	FEBRILE NEUTROPENIA	16/01/2008	1	Recovered without sequelae
CZECH REPUBLIC	5003602801204	46	MALE	61	R-DHAP	HEMATOTOXICITY	12/01/2005	2	Recovered without sequelae
UNITED KINGDOM	5003620501602	174	FEMALE	60	R-DHAP	NEUTROPENIA	22/03/2007	10	Recovered without sequelae
UNITED KINGDOM	5003615501004	196	FEMALE	64	R-DHAP	NEUTROPENIA	20/11/2006	14	Recovered without sequelae
UNITED KINGDOM	5003612501011	170	FEMALE	41	R-ICE	PANCYTOPENIA	03/04/2007	13	Recovered without sequelae
UNITED KINGDOM	5003615501004	195	FEMALE	64	R-DHAP	THROMBOCYTOPENIA	23/10/2006	2	Recovered without sequelae
NEW ZEALAND	5003621301014	214	FEMALE	59	R-ICE	THROMBOCYTOPENIA	01/11/2007	5	Recovered without sequelae

Cardiac disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
BELGIUM	5003101281017	35	MALE	60	R-ICE	ATRIAL FIBRILLATION	25/11/2004	1	Recovered without sequelae
FRANCE	5003102411054	142	MALE	64	R-DHAP	ATRIAL FIBRILLATION	26/10/2006	10	Recovered without sequelae
AUSTRALIA	5003613301404	147	FEMALE	60	R-DHAP	BRADYCARDIA	19/11/2006	0	Unknown
NEW ZEALAND	5003605301601	13	MALE	61	R-ICE	CARDIAC ARREST (*)	20/06/2004	15	Died
AUSTRALIA	5003606301012	228	FEMALE	64	R-DHAP + BEAM	CARDIAC ARREST (*)	21/01/2008	6	Ongoing at death
BELGIUM	5003101601404	84	FEMALE	66	R-ICE	CARDIAC FAILURE	30/07/2005	0	Recovered without sequelae
FRANCE	5003101161028	262	MALE	59	R-DHAP	CARDIAC FAILURE	22/08/2005	14	Not reported
FRANCE	5003101141402	86	MALE	63	R-DHAP	CARDIAC INSUFFICIENCY	21/06/2005	9	Recovered without sequelae
SWITZERLAND	5003604701012	252	MALE	62	R-DHAP	CARDIAC INSUFFICIENCY (*)	30/04/2007	5	Died
GERMANY	5003622201210	114	MALE	54	R-ICE	CARDIAC ISCHEMIA	08/03/2006	3	Recovered without sequelae
FRANCE	5003101051612	14	MALE	37	R-ICE + BEAM	MYOCARDIAL INFARCTION	28/06/2004	1	Recovered without sequelae

Ear and labyrinth disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
BELGIUM	5003101641047	119	MALE	45	R-DHAP	TINNITUS	04/05/2006	1	Recovered without sequelae

(*) Suspected Unexpected Serious Adverse Reaction

Induction Phase

Gastrointestinal disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
NEW ZEALAND	5003605301010	209	MALE	55	R-ICE	BOWEL OBSTRUCTION	24/09/2007	8	Recovered without sequelae
CZECH REPUBLIC	5003601801607	239	FEMALE	40	R-DHAP + BEAM	COLITIS HEMORRHAGIC	14/03/2008	4	Recovered without sequelae
UNITED KINGDOM	5003612501012	168	FEMALE	55	R-ICE	DIARRHEA	27/03/2007	2	Recovered without sequelae
UNITED KINGDOM	5003612501019	212	FEMALE	51	R-DHAP	DIARRHEA	10/10/2007	0	Recovered without sequelae
SWEDEN	5003601401602	272	MALE	42	R-ICE + BEAM	DIARRHEA	04/11/2004	28	Recovered without sequelae
BELGIUM	5003102491616	15	MALE	46	R-ICE	ESOPHAGEAL HEMORRHAGE	02/07/2004	0	Recovered without sequelae
SWEDEN	5003601401605	184	FEMALE	57	R-ICE	GASTRIC ULCER HAEMORRHAGE	10/10/2006	7	Recovered without sequelae
BELGIUM	5003101281017	37	MALE	60	R-ICE	GASTROINTESTINAL BLEEDING	25/11/2004	1	Recovered without sequelae
USA	5003601601402	34	FEMALE	65	R-DHAP	GASTROINTESTINAL DISORDER	26/11/2004	0	Recovered without sequelae
FRANCE	5003101071417	169	FEMALE	56	R-DHAP	GASTROINTESTINAL HAEMORRHAGE	30/03/2007	9	Recovered without sequelae
NEW ZEALAND	5003607301603	39	MALE	65	R-DHAP + BEAM	GASTROINTESTINAL HEMORRHAGE	12/09/2004	4	Recovered without sequelae
CZECH REPUBLIC	5003601801603	58	MALE	41	R-DHAP	GASTROINTESTINAL HEMORRHAGE	15/02/2005	1	Recovered without sequelae
SWITZERLAND	5003603701001	55	MALE	64	R-DHAP	NAUSEA AND VOMITING	08/03/2005	5	Recovered without sequelae
AUSTRALIA	5003617301616	109	MALE	44	R-DHAP	NAUSEA AND VOMITING	06/03/2006	4	Recovered without sequelae
GERMANY	5003603201050	216	MALE	61	R-DHAP	NAUSEA AND VOMITING	24/09/2007	12	Recovered with sequelae
AUSTRALIA	5003603301401	69	MALE	62	R-DHAP + BEAM	OBSTRUCTION BOWEL	21/12/2004	13	Recovered with sequelae
USA	5003601601602	221	MALE	45	R-DHAP	PERFORATED BOWEL	11/12/2007	0	Recovered without sequelae
GERMANY	5003606201605	27	MALE	42	R-ICE	PERFORATION LARGE INTESTINE	16/06/2004	12	Recovered without sequelae
FRANCE	5003102181031	133	MALE	63	R-DHAP	VOMITING	27/06/2005	2	Recovered without sequelae
BELGIUM	5003101641623	145	FEMALE	62	R-DHAP	VOMITING	24/05/2005	11	Recovered without sequelae

General disorders and administration site conditions

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
SWITZERLAND	5003607701405	242	MALE	49	R-ICE	ASTHENIA	06/05/2008	2	Recovered without sequelae
SWEDEN	5003601401601	5	MALE	58	R-DHAP	FEVER	13/01/2004	8	Recovered without sequelae
AUSTRALIA	5003609301608	41	MALE	43	R-ICE	FEVER	26/12/2004	1	Recovered without sequelae
UNITED KINGDOM	5003615501018	203	FEMALE	49	R-ICE	FEVER	10/09/2007	6	Recovered without sequelae
AUSTRALIA	5003620301011	210	MALE	42	R-ICE	FEVER	15/10/2007	22	Recovered without sequelae
FRANCE	5003101251205	18	MALE	54	R-ICE	HYPERTHERMIA	15/07/2004	4	Recovered without sequelae
AUSTRALIA	5003603301401	72	MALE	62	R-DHAP + BEAM	MUCOSITIS	11/12/2004	3	Recovered without sequelae
FRANCE	5003101071643	286	FEMALE	59	R-DHAP + BEAM	MUCOSITIS	29/02/2008	2	Recovered without sequelae

Hepatobiliary disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
BELGIUM	5003102541016	31	MALE	54	R-DHAP	ACUTE CHOLECYSTITIS	07/11/2004	3	Recovered without sequelae
BELGIUM	5003102541625	96	MALE	25	R-ICE	HEPATITIS	31/07/2005	15	Recovered with sequelae

Immune system disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
GERMANY	5003604201028	107	MALE	65	R-DHAP	DRUG HYPERSENSITIVITY	02/02/2006	1	Recovered without sequelae

(*) Suspected Unexpected Serious Adverse Reaction

Line-listing 03 July 2003 to 02 July 2011

Induction Phase

Infections and infestations

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
BELGIUM	5003101281017	36	MALE	60	R-ICE	ASPERGILLOSIS	03/12/2004	9	Recovered without sequelae
AUSTRALIA	5003609301608	33	MALE	43	R-ICE	CELLULITIS	19/11/2004	1	Recovered without sequelae
USA	5003601601005	232	FEMALE	53	R-ICE	CELLULITIS	15/02/2008	6	Recovered without sequelae
UNITED KINGDOM	5003624501017	198	MALE	52	R-ICE	CENTRAL LINE INFECTION	19/08/2007	9	Recovered without sequelae
AUSTRALIA	5003620301017	235	MALE	59	R-ICE	CENTRAL LINE INFECTION	24/03/2008	Not reported	Recovered without sequelae
IRELAND	5003610501031	248	MALE	54	R-ICE	CENTRAL LINE INFECTION	02/05/2008	0	Not reported
ISRAEL	5003604901004	099	FEMALE	53	R-DHAP + BEAM	CATHETER SEPSIS	21/06/2006	33	Recovered without sequelae
AUSTRALIA	5003606301012	304	FEMALE	64	R-DHAP + BEAM	CMV INFECTION (*)	21/01/2008	6	Died
AUSTRALIA	5003606301207	60	MALE	37	R-ICE + BEAM	DENTAL ABSCESS	01/12/2004	10	Recovered without sequelae
GERMANY	5003603201034	277	MALE	33	R-DHAP	DIARRHEA, CLOSTRIDIUM DIFFICILE	01/09/2006	8	Recovered without sequelae
GERMANY	5003603201034	279	MALE	33	R-DHAP	DIARRHEA, CLOSTRIDIUM DIFFICILE	27/02/2007	145	Recovered without sequelae
FRANCE	5003101091025	131	FEMALE	61	R-DHAP	ENTEROBACTER SEPTICEMIA	04/07/2005	6	Recovered without sequelae
FRANCE	5003101051068	270	MALE	64	R-ICE	ESCHERICHIA COLI INFECTION	15/08/2007	40	Recovered without sequelae
GERMANY	5003630201055	296	FEMALE	62	R-ICE	GASTROINTESTINAL CANDIDIASIS	27/04/2008	0	Recovered without sequelae
SWITZERLAND	5003605701601	61	FEMALE	62	R-ICE	HERPES ZOSTER	04/05/2005	10	Recovered without sequelae
GERMANY	5003602201601	68	FEMALE	56	R-ICE	HERPES ZOSTER	09/05/2005	5	Recovered without sequelae
NEW ZELAND	5003605301010	202	MALE	55	R-ICE	HERPES ZOSTER	02/09/2007	9	Recovered without sequelae
ISRAEL	5003605901003	79	FEMALE	48	R-ICE	INFECTION	17/06/2005	53	Recovered without sequelae
SWEDEN	5003601401002	137	MALE	56	R-ICE + BEAM	INFECTION	09/07/2004	3	Recovered without sequelae
GERMANY	5003603201034	280	MALE	33	R-DHAP + BEAM	INFECTIOUS DIARRHEA	08/03/2007	154	Recovered without sequelae
SWEDEN	5003601401006	275	FEMALE	62	R-ICE	KLEBSIELLA PNEUMONIAE INFECTION	08/07/2007	24	Recovered without sequelae
UNITED KINGDOM	5003623501408	308	MALE	53	R-DHAP	KLEBSIELLA SEPSIS	25/01/2008	7	Recovered without sequelae
AUSTRALIA	5003604301607	22	MALE	62	R-DHAP	LOWER RESPIRATORY TRACT INFECTION	14/09/2004	0	Recovered without sequelae
AUSTRALIA	5003617301619	106	FEMALE	19	R-DHAP	LOWER RESPIRATORY TRACT INFECTION	16/02/2006	2	Recovered without sequelae
ISRAEL	5003602901401	42	MALE	60	R-ICE	NEUTROPENIC INFECTION	20/12/2004	0	Recovered without sequelae
UNITED KINGDOM	5003620501602	187	FEMALE	60	R-DHAP	NEUTROPENIC INFECTION	28/05/2007	77	Recovered without sequelae
UK	5003618501025	225	MALE	59	R-DHAP	NEUTROPENIC INFECTION	19/12/2007	2	Recovered without sequelae
GERMANY	5003630201055	297	FEMALE	62	R-ICE	NEUTROPENIC INFECTION	27/04/2008	0	Recovered without sequelae
UK	5003620501602	306	FEMALE	59	R-DHAP + BEAM	NEUTROPENIC INFECTION	28/06/2007	1	Recovered without sequelae
GERMANY	5003603201001	9	MALE	50	R-DHAP	NEUTROPENIC SEPSIS (*)	11/05/2004	0	Died
USA	5003601601401	20	MALE	59	R-ICE	NEUTROPENIC SEPSIS	03/05/2004	0	Recovered without sequelae
GERMANY	5003631201011	43	FEMALE	61	R-DHAP	NEUTROPENIC SEPSIS	23/12/2004	11	Recovered without sequelae
NEW ZEALAND	5003604301618	112	MALE	55	R-ICE	NEUTROPENIC SEPSIS	07/03/2006	0	Recovered without sequelae
UNITED KINGDOM	5003612501011	180	FEMALE	41	R-ICE	NEUTROPENIC SEPSIS	20/04/2007	0	Recovered without sequelae
UNITED KINGDOM	5003623501408	219	MALE	53	R-DHAP	NEUTROPENIC SEPSIS	29/11/2007	13	Recovered without sequelae
UNITED KINGDOM	5003617501026	224	FEMALE	59	R-DHAP	NEUTROPENIC SEPSIS	19/12/2007	8	Recovered without sequelae
UNITED KINGDOM	5003614501032	245	MALE	53	R-DHAP	NEUTROPENIC SEPSIS	16/04/2008	6	Recovered without sequelae
UNITED KINGDOM	5003614501002	289	MALE	27	R-ICE	NEUTROPENIC SEPSIS	25/09/2006	10	Recovered without sequelae
GERMANY	5003630201055	298	FEMALE	62	R-ICE	NEUTROPENIC SEPSIS	08/06/2008	0	Recovered without sequelae
BELGIUM	5003101541415	278	MALE	54	R-DHAP	STREPTOCOCCUS PNEUMONIAE PNEUMONIA	14/07/2007	122	Recovered without sequelae
ISRAEL	5003602901201	8	FEMALE	31	R-ICE	PNEUMONIA	07/04/2004	1	Recovered without sequelae
GERMANY	5003603201001	10	MALE	50	R-DHAP	PNEUMONIA	19/04/2004	8	Recovered with sequelae
GERMANY	5003601201201	28	FEMALE	32	R-DHAP	PNEUMONIA	01/05/2004	0	Recovered without sequelae
ISRAEL	5003602901002	52	MALE	64	R-ICE	PNEUMONIA	05/02/2005	0	Recovered without sequelae
BELGIUM	5003102541034	95	MALE	27	R-DHAP	PNEUMONIA	04/10/2005	23	Recovered without sequelae
ISRAEL	5003604901004	141	FEMALE	52	R-DHAP	PNEUMONIA	08/01/2006	12	Recovered without sequelae
UNITED KINGDOM	5003623501405	193	MALE	58	R-DHAP	PNEUMONIA (*)	26/07/2007	5	Died
ISRAEL	5003602901002	53	MALE	64	R-ICE	PNEUMONIA STREPTOCOCCAL (*)	17/02/2005	10	Recovered without sequelae
GERMANY	5003603201205	67	MALE	59	R-DHAP	PSEUDOMONAL SEPSIS	14/01/2005	32	Recovered without sequelae

(*) Suspected Unexpected Serious Adverse Reaction

Induction Phase

FRANCE	5003102181031	140	MALE	63	R-DHAP	PSEUDOMONAS INFECTION	04/08/2005	3	Recovered without sequelae
UNITED KINGDOM	5003616501005	159	FEMALE	59	R-ICE + BEAM	SEPSIS (*)	16/02/2007	2	Died
FRANCE	5003101071002	2	MALE	64	R-DHAP	SEPTIC SHOCK (*)	31/10/2003	10	Died
BELGIUM	5003102491616	17	MALE	46	R-ICE	SEPTIC SHOCK	17/07/2004	2	Recovered without sequelae
FRANCE	5003101131030	82	FEMALE	48	R-ICE	SEPTIC SHOCK (*)	16/08/2005	2	Died
SWITZERLAND	5003603701004	83	MALE	64	R-ICE	SEPTIC SHOCK (*)	21/08/2005	7	Died
FRANCE	5003102161413	175	MALE	49	R-ICE	SEPTIC SHOCK (*)	03/11/2006	7	Died
GERMANY	5003607201045	206	MALE	48	R-ICE + BEAM	SEPTIC SHOCK (*)	12/08/2007	40	Died
FRANCE	5003101051068	269	MALE	64	R-ICE	SEPTIC SHOCK	05/09/2007	4	Recovered without sequelae
SWEDEN	5003601401602	48	MALE	42	R-ICE + BEAM	SEPTICAEMIA	04/11/2004	5	Recovered without sequelae
AUSTRALIA	5003603301401	71	MALE	62	R-DHAP + BEAM	SEPTICEMIA	13/12/2004	5	Recovered with sequelae
AUSTRALIA	5003606301012	303	FEMALE	64	R-DHAP+ BEAM	SEPTICEMIA CANDIDA (*)	21/01/2008	6	Died
AUSTRALIA	5003603301201	16	FEMALE	49	R-ICE	SEPTICEMIA GRAM-NEGATIVE	12/07/2004	51	Recovered without sequelae
NEW ZEALAND	5003607301622	160	FEMALE	65	R-DHAP	SEPTICEMIA GRAM-NEGATIVE (*)	25/01/2007	36	Died
AUSTRALIA	5003603301401	23	MALE	61	R-DHAP	SEPTICEMIA GRAM-POSITIVE	04/10/2004	0	Recovered without sequelae
GERMANY	5003631201012	240	FEMALE	59	R-DHAP	SINUSITIS ASPERGILLUS	24/05/2005	91	Recovered without sequelae
AUSTRALIA	5003606301606	24	FEMALE	41	R-DHAP	STAPHYLOCOCCAL SEPSIS	04/09/2004	1	Recovered without sequelae
FRANCE	5003102411054	265	MALE	64	R-DHAP + BEAM	STAPHYLOCOCCAL SEPSIS	14/01/2007	17	Recovered without sequelae
AUSTRALIA	5003606301604	19	MALE	61	R-DHAP	UPPER RESPIRATORY TRACT INFECTION	26/07/2004	13	Recovered without sequelae
GERMANY	5003601201201	29	FEMALE	32	R-DHAP	URINARY TRACT INFECTION	17/05/2004	0	Recovered without sequelae

Injury, poisoning and procedural complications

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
ISRAEL	5003602901601	73	MALE	63	R-ICE	SUBDURAL HEMATOMA	17/01/2005	72	Recovered without sequelae

Metabolism and nutrition disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
AUSTRALIA	5003603301201	6	FEMALE	49	R-ICE	DEHYDRATION	17/04/2004	2	Recovered without sequelae
USA	5003601601402	32	FEMALE	65	R-DHAP	DEHYDRATION	08/11/2004	1	Recovered without sequelae
CZECH REPUBLIC	5003603801203	47	FEMALE	53	R-ICE	DEHYDRATION	09/12/2004	0	Recovered without sequelae
CZECH REPUBLIC	5003602801204	51	MALE	61	R-DHAP	DEHYDRATION	03/02/2005	3	Recovered without sequelae
GERMANY	5003603201050	215	MALE	61	R-DHAP	EXSICCOSIS	03/09/2007	0	Recovered without sequelae
USA	5003601601602	229	MALE	45	R-DHAP	HYPERGLYCEMIA	21/01/2008	0	Improved
FRANCE	5003102411054	264	MALE	64	R-DHAP	HYPERGLYCEMIA	06/11/2006	6	Recovered without sequelae
FRANCE	5003101071643	285	FEMALE	59	R-DHAP + BEAM	HYPONATREMIA (*)	22/02/2008	1	Recovered without sequelae

Musculoskeletal and connective tissue disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
AUSTRALIA	5003619301006	138	FEMALE	53	R-DHAP	BONE PAIN	12/06/2006	0	Recovered without sequelae

Nervous system disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
FRANCE	5003101431204	12	MALE	56	R-DHAP	APHASIA	13/02/2004	20	Recovered with sequelae
IRLAND	5003610501031	243	MALE	54	R-ICE	DRUG-INDUCED ENCEPHALOPATHY	04/05/2008	1	Recovered without sequelae
SWITZERLAND	5003604701012	251	MALE	62	R-DHAP	EMBOLIC CEREBRAL INFARCTION (*)	03/05/2007	8	Ongoing at death

(*) Suspected Unexpected Serious Adverse Reaction

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	5003603801013	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	26/10/2007	35	Recovered with 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	5003631201012	44	FEMALE	58	R-DHAP	RENAL FAILURE	26/12/2004	7	Recovered with 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	5003616301403	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
USA	5003601601402	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

Appendix 3: **Related Serious Adverse Reactions**

Maintenance phase

Blood and lymphatic system disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
SWITZERLAND	5003603701001	075	MALE	64	Observation	ANEMIA	13/06/2005	59	Recovered without sequelae
FRANCE	5003101431622	090	MALE	50	Rituximab	NEUTROPENIA	10/10/2005	54	Recovered without sequelae
UNITED KINGDOM	5003607501401	150	MALE	55	Rituximab	NEUTROPENIA	03/01/2007	49	Recovered without sequelae
UNITED KINGDOM	5003620501406	233	MALE	45	Observation	NEUTROPENIA	13/03/2008	120	Recovered without sequelae
ISRAEL	5,0036E+12	259	FEMALE	62	Rituximab	THROMBOCYTOPENIA	17/08/2008	32	Ongoing at death

Cardiac disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
SWEDEN	5003601401602	127	MALE	43	Rituximab	MYOCARDITIS (*)	06/08/2006	299	Died

Ear and Labyrinth disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
FRANCE	5003101051056	223	MALE	65	Observation	HEARING LOSS	03/04/2007	76	Ongoing

Gastrointestinal disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
UNITED-KINGDOM	5003620501406	222	MALE	44	Observation	DIARRHEA	12/12/2007	97	Recovered without sequelae
GERMANY	5003603201053	237	MALE	52	Observation	DIARRHEA	24/03/2008	18	Recovered without sequelae
SWITZERLAND	5003604701015	236	MALE	56	Rituximab	FAECALOMA	23/03/2008	53	Recovered without sequelae
SWITZERLAND	5003608701013	204	MALE	54	Rituximab	GASTROINTESTINAL BLEEDING	03/09/2007	55	Recovered without sequelae
AUSTRALIA	5003601301015	267	FEMALE	58	Rituximab	NAUSEA	12/03/2008	67	Recovered with sequelae

General disorders and administration site condition

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
AUSTRALIA	5003601301015	266	FEMALE	58	Rituximab	MUCOSITIS	18/02/2008	44	Recovered without sequelae

(*) Suspected Unexpected Serious Adverse Reaction

Appendix 3: **Related Serious Adverse Reactions**

Maintenance phase

Hepatobilary disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
BELGIUM	5003101621615	026	MALE	65	Observation	HEPATITIS	14/10/2004	25	Recovered without sequelae

Infections and infestations

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
ISRAEL	5003604901603	282	FEMALE	62	Rituximab	ACUTE BRONCHOPNEUMONIA (*)	04/09/2008	50	Died
SWITZERLAND	5003603701001	256	MALE	64	Observation	BACTERAEMIA	20/04/2005	9	Recovered without sequelae
SWITZERLAND	5003605701401	205	FEMALE	31	Rituximab	BACTERIAL PNEUMONIA, UNSPECIFIED	18/09/2007	47	Recovered without sequelae
FRANCE	5003101031621	207	FEMALE	57	Rituximab	BRONCHITIS PNEUMOCOCCAL	18/01/2007	374	Recovered without sequelae
FRANCE	5003101031621	208	FEMALE	58	Rituximab	BRONCHOPULMONARY INFECTION	02/06/2007	509	Recovered without sequelae
USA	5003601601601	030	FEMALE	53	Rituximab	CATHETER RELATED INFECTION	02/11/2004	1	Recovered without sequelae
IRELAND	5003610501402	199	MALE	59	Rituximab	CHEST INFECTION	21/08/2007	0	Recovered without sequelae
FRANCE	5003101141624	092	FEMALE	65	Observation	CLOSTRIDIUM DIFFICILE INFECTION	13/12/2005	64	Recovered without sequelae
ISRAEL	5003604901603	257	FEMALE	62	Rituximab	CMV INFECTION	19/07/2008	3	Recovered without sequelae
FRANCE	5003101431608	166	MALE	65	Rituximab	HAEMOPHILUS INFLUENZAE INFECTION	16/03/2005	14	Recovered without sequelae
GERMANY	5003618201030	185	FEMALE	46	Rituximab	HERPES ZOSTER	19/05/2007	72	Recovered without sequelae
GERMANY	5003606201617	155	FEMALE	55	Rituximab	INFECTION	12/01/2006	8	Recovered without sequelae
FRANCE	5003101021601	089	FEMALE	49	Rituximab	INFECTION BACILLUS PYOCYANEUS	10/01/2005	32	Recovered without sequelae
IRELAND	5003610501402	231	MALE	60	Rituximab	LOWER RESPIRATORY TRACT INFECTION	01/02/2008	51	Recovered without sequelae
IRELAND	5003610501402	188	MALE	59	Rituximab	NEUTROPENIC SEPSIS	21/06/2007	23	Recovered without sequelae
SWEDEN	5003601401604	126	FEMALE	62	Rituximab	PNEUMOCYSTIS JIROVECI PNEUMONIA (*)	17/07/2006	33	Recovered without sequelae
AUSTRALIA	5003616301615	129	MALE	64	Rituximab	PNEUMONIA (*)	15/08/2006	90	Died
ISRAEL	5003604901004	157	FEMALE	53	Rituximab	PNEUMONIA	04/02/2007	83	Recovered without sequelae
SWITZERALND	5003605701401	158	FEMALE	30	Rituximab	PNEUMONIA	14/02/2007	1	Recovered without sequelae
FRANCE	5003101031621	134	FEMALE	57	Rituximab	PULMONARY ASPERGILLOSIS	06/07/2006	178	Recovered without sequelae
IRLAND	5003610501402	244	MALE	60	Rituximab	RESPIRATORY TRACT INFECTION	14/04/2008	124	Not reported
FRANCE	5003101031621	124	FEMALE	57	Rituximab	SEPTIC SHOCK	06/07/2006	178	Recovered without sequelae
BELGIUM	5003101491042	121	MALE	46	Rituximab	SEPTICEMIA	26/05/2006	14	Recovered with sequelae
FRANCE	5003102341202	088	FEMALE	57	Rituximab	SEPTICEMIA STREPTOCOCCAL	28/01/2004	10	Recovered without sequelae
FRANCE	5003102411069	218	MALE	63	Observation	VARICELLA	23/11/2007	57	Recovered without sequelae

Investigations

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
AUSTRALIA	5003613301404	307	FEMALE	61	Observation	CREATININE BLOOD INCREASED	23/05/2007	Not reported	Not yet recovered

(*) Suspected Unexpected Serious Adverse Reaction

Appendix 3: **Related Serious Adverse Reactions**

Maintenance phase

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
SWEDEN	5003601401002	261	MALE	58	Rituximab	ACUTE LEUKEMIA (*)	15/06/2006	371	Died
AUSTRALIA	5003606301604	292	MALE	65	Observation	MYELODYSPLASTIC SYNDROME (*)	05/02/2008	1281	Died
AUSTRALIAN	5003606301207	293	MALE	40	Observation	UROTHELIAL CARCINOMA (*)	20/03/2008	1215	Died

Nervous system disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
SWEDEN	5003601401004	190	FEMALE	63	Rituximab	LEUKOENCEPHALOPATHY (*)	26/06/2007	54	Died
CZECH REP	5003601801607	246	FEMALE	41	Observation	PARESIS	14/05/2008	36	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
AUSTRALIA	5003606301604	063	MALE	62	Observation	ACUTE RENAL FAILURE	11/10/2004	22	Recovered without sequelae
AUSTRALIA	5003606301604	062	MALE	62	Observation	NEPHROPATHY TOXIC	11/10/2004	22	Recovered with sequelae
IRELAND	5003610501402	153	MALE	59	Rituximab	RENAL ACIDOSIS TUBULAR (*)	05/01/2007	18	Recovered with sequelae

Respiratory, thoracic and mediastinal disorders

Country	Inclusion number	SAE number	Gender	Age	Induction Arm	MedDRA LLT	Onset Date	Latency last administration (D)	Outcome
FRANCE	5003101431622	087	MALE	50	Rituximab	INTERSTITIAL PNEUMONITIS	19/09/2005	33	Recovered without sequelae
BELGIUM	5003101621026	143	MALE	64	Observation	PNEUMOPATHY	15/11/2005	122	Recovered without sequelae
BELGIUM	5003101641623	110	FEMALE	63	Rituximab	PULMONARY INFILTRATION	28/02/2006	54	Recovered without sequelae

(*) Suspected Unexpected Serious Adverse Reaction

Appendix 4: Unrelated Serious adverse events

Gastrointestinal disorders

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
SWEDEN	5003601401001	001	FEMALE	48	ABDOMINAL PAIN	19/11/2003	Induction	R-DHAP	Recovered without sequelae
AUSTRALIA	5003606301207	059	MALE	37	DENTAL CARIES	20/02/2005	Maintenance	Observation	Recovered without sequelae
GERMANY	5003603201627	172	MALE	49	GASTRIC PERFORATION	31/03/2007	Induction	R-ICE	Died
CZECH REPUBLI(	5003601801603	040	MALE	41	GASTROINTESTINAL HEMORRHAGE	26/12/2004	Induction	R-DHAP	Recovered without sequelae
AUSTRALIA	5003613301404	182	FEMALE	61	NAUSEA AND VOMITING	13/05/2007	Maintenance	Observation	Not yet recovered

General disorders and administration site condition

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
ISRAEL	5003604901603	258	FEMALE	62	CATHETER SITE BLEEDING	12/08/2008	Maintenance	Rituximab	Recovered without sequelae

Hepatobilary disorders

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
GERMANY	5003630201055	300	FEMALE	62	ACUTE CHOLECYSTITIS	16/06/2008	Induction	R-ICE	Recovered without sequelae

Infections and infestations

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
UNITED KINGDOI	5003619501010	161	FEMALE	45	CHEST INFECTION	22/02/2007	Induction	R-DHAP	Recovered without sequelae
AUSTRALIA	5003622501604	238	MALE	48	CHEST INFECTION	10/01/2008	Maintenance	Observation	Recovered without sequelae
AUSTRALIA	5003609301018	249	MALE	38	CHEST INFECTION	08/06/2008	Induction	R-DHAP	Recovered without sequelae
GERMANY	5003610201612	098	FEMALE	57	PULMONARY ASPERGILLOSIS	13/07/2005	Induction	R-ICE	Died
GERMANY	5003603201027	101	MALE	54	SEPTIC SHOCK	25/01/2006	Induction	R-DHAP	Died
FRANCE	5003101071643	290	FEMALE	59	STAPHYLOCOCCUS EPIDERMIDIS SEPTICEMIA	07/05/2008	Maintenance	Observation	Died

Injury, poisonning and procedural complications

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
AUSTRALIA	5003604301013	227	MALE	41	POST LUMBAR PUNCTURE SYNDROME	11/01/2008	Induction	R-ICE	Recovered without sequelae

Investigations

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
UNITED KINGDOI	5003612501019	220	FEMALE	51	CREATININE BLOOD INCREASED	06/09/2007	Induction	R-DHAP	Recovered without sequelae

Appendix 4: Unrelated Serious adverse events

Musculoskeletal and connective tissue disorders

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
FRANCE	5003101021601	021	FEMALE	48	BACK PAIN	06/10/2003	Induction	R-DHAP	Recovered without sequelae
SWITZERLAND	5003605701401	213	FEMALE	31	RHABDOMYOLYSIS	17/10/2007	Maintenance	Rituximab	Recovered with sequelae

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
FRANCE	5003101051603	274	FEMALE	58	CARCINOMA OF ESOPHAGUS	09/02/2006	Induction	R-ICE	Died
FRANCE	5003101431608	263	MALE	67	HEPATIC ADENOCARCINOMA	24/04/2007	Maintenance	Rituximab	Died
ISRAEL	5003605901003	281	FEMALE	50	HODGKIN'S LYMPHOMA	03/10/2007	Induction	R-ICE	Recovered without sequelae
FRANCE	5003102161604	305	MALE	61	MELANOMA LIMITED TO EXTREMITY	15/03/2009	Maintenance	Rituximab	Recovered without sequelae

Nervous system disorders

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
GERMANY	5003618201030	201	FEMALE	46	HYPOESTHESIA	03/09/2007	Maintenance	Rituximab	Recovered without sequelae
FRANCE	5003101141624	102	FEMALE	65	LOSS OF CONSCIOUSNESS	29/01/2006	Maintenance	Observation	Recovered without sequelae
BELGIUM	5003101281017	038	MALE	60	SYNCOPE	25/11/2004	Induction	R-ICE	Recovered without sequelae

Psychiatric disorders

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
SWITZERLAND	5003604701015	211	MALE	56	DEPRESSION MENTAL	15/10/2007	Induction	R-DHAP	Recovered without sequelae

Renal and urinary disorders

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
FRANCE	5003101031019	045	FEMALE	58	RENAL FAILURE	01/01/2005	Induction	R-DHAP	Recovered without sequelae
UNITED KINGDOI	5003615501201	144	MALE	56	UROLITHIASIS	17/11/2006	Induction	R-ICE	Recovered with sequelae

Respiratory, thoracic and mediastinal disorders

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
GERMANY	5003610201612	097	FEMALE	57	DYSPNEA	12/05/2005	Induction	R-ICE	Recovered with sequelae
UNITED KINGDOI	5003614501013	197	MALE	35	RESPIRATORY DISORDER	20/07/2007	Induction	R-DHAP	Died

Skins and subcutaneous tissue disorders

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
FRANCE	5003101071643	284	FEMALE	58	SKIN REACTION	06/12/2007	Induction	R-DHAP	Recovered without sequelae

Appendix 4: Unrelated Serious adverse events

Social circumstances

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
AUSTRALIA	5003606301604	064	MALE	62	SOCIAL STAY HOSPITALIZATION	24/09/2004	Maintenance	Observation	Recovered without sequelae

Surgical and medical procedures

Country	Inclusion number	SAE number	Gender	Age	MedDRA LLT	Onset Date	Treatment Period	Arm	Outcome
AUSTRALIA	5003619301006	139	MALE	54	PARTIAL HEPATECTOMY	05/09/2006	Induction	R-DHAP	Recovered without sequelae

Appendix 5

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 Clínic– 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 an other (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 polmunary infection. The DSMC concluded that given the complete recovery under Rituximab, the SUSAR is not cleary 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.

Appendix 6

UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

Cattedra di Oncologia Medica II
Direttore prof. Massimo Federico

Modena, March 3rd, 2010

Pr. Christian Gisselbrecht
Hopital Saint Louis – Centre Hayem
1, Avenue Claude Vellefaux
75010 Paris

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 "manitenance 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

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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; infomation 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