Myeloablative Versus Reduced Intensity Allogeneic Stem Cell Transplantation for Relapsed / Refractory Hodgkin's Lymphoma in Recent Years. A Retrospective Analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation

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Key Words. Relapsed / Refractory Hodgkin's Lymphoma, Allogeneic Stem Cell Transplantation, Conditioning Regimen

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ABSTRACT

Purpose: To evaluate long-term outcome of myeloablative allogeneic stem cell transplantation (allo-SCT) (MAC) *vs* reduced-intensity allo-SCT (RIC) in patients with relapsed/refractory Hodgkin's lymphoma (HL) in recent years.

Patients and Methods: Three hundred and twelve patients (63 MAC and 249 RIC) with relapsed/refractory HL who received allo-SCT between 2006 and 2010 and were reported to the EBMT Database were included in the study.

Results: With a median follow-up for alive patients of 56 (26 – 73) months, there were no significant differences in non-relapse mortality (NRM) between MAC and RIC. Relapse rate (RR) was somewhat lower in the MAC group (41% *vs* 52% at 24 months, p=0.16). This lower RR translated into a marginal improvement in event-free survival (EFS) for the MAC group (48% *vs* 36% at 24 months, p=0.09) with no significant differences in overall survival (73% for MAC 62% for RIC at 24 months, p=0.13). Multivariate analysis after adjusting for disease status at the time of allo-SCT showed that the use of MAC was of borderline statistical significance for predicting a lower RR and EFS [HR 0.7, 95%CI (0.5 – 1.0), p=0.1] and [HR 0.7, 95%CI (0.5 – 1.0), p=0.07] respectively after allo-SCT.

Conclusion: With modern transplant practices, the NRM associated with MAC for HL has strongly decreased, resulting into non-significant improvement of EFS because of a somewhat better disease control compared to RIC transplants. The intensity of conditioning regimens should be considered when designing individual allo-SCT strategies or clinical trials in patients with relapsed/refractory HL.

n = 244 words

INTRODUCTION

Most patients with Hodgkin lymphoma (HL) achieve sustained remissions following first-line chemotherapy (CT) with or without consolidation radiotherapy (RT). [1,2] However, studies report that 5–10% are refractory to first-line therapy and up to 30% of patients will relapse. Autologous stem cell transplantation (ASCT) is considered to be the standard of care for patients with relapsed / refractory HL.[3-5]

Prognosis of patients relapsing after ASCT is poor.[6] Allogeneic stem cell transplant (allo-SCT) is the standard of care for young patients with chemosensitive disease at the time of transplant and a HLA compatible donor available.[7] The use of myeloablative conditioning protocols (MAC) was associated to an exceedingly high non-relapse mortality (NRM) of about 50% in the earlier days.[8,9] The Lymphoma Working Party (LWP) of the European Group for Blood and Marrow Transplantation (EBMT) demonstrated that reduced intensity conditioning protocols (RIC) were able to significantly decrease NRM after the procedure.[10] Nevertheless, the use of less intense CT has also been associated to a high relapse rate (RR) after transplant.[11-15]

The objective of this retrospective registry analysis was to analyze the long-term outcome of patients with relapsed / refractory HL being treated either with MAC *vs* RIC in recent years and the potential clinical benefit of MAC, assuming that the improvement in HLA typing molecular techniques, supportive measures and expertise in the transplant centers over time would have potentially decreased NRM after the procedure, thus potentially improving survival outcomes by the already known reduced RR in this setting.

PATIENTS AND METHODS

Data Source

EBMT is a voluntary organization comprising more than 500 transplant centers mainly from Europe. Accreditation as a member centre requires submission of minimal essential data (MED-A form) from all consecutive patients to a central registry in which patients may be identified by the diagnosis of underlying disease and type of transplantation. MED-A data is updated annually. Informed consent for transplantation and data collection was obtained locally according to regulations applicable at the time of transplantation. Since January 1 2003, all transplant centers have been required to obtain written informed consent prior to data registration with the EBMT following the Helsinki Declaration 1975.

Patient Eligibility

Inclusion criteria for this study were adult patients with relapsed / refractory HL who underwent allo-SCT from an HLA identical related donor (HLA id sib) or well-matched unrelated donor (WMUD, 10 out of 10 antigens) between January 2006 and December 2010 and were reported to the EBMT registry. Only first allo-SCT were included. Tandem and cord blood transplants were excluded as well as recipients of syngeneic transplants. Minimum data required for the inclusion of a patient were age, sex, histological diagnosis, date of diagnosis, details of prior high-dose therapy, disease status at transplantation, details of conditioning regimen, date of transplantation, donor relationship, date of follow-up, disease status at follow-up, date of disease progression or death, and cause of death.

Definitions

Histological diagnosis was based on local review. Disease status at transplantation was classified as chemosensitive disease including all patients who had shown at least a partial remission (PR) and chemoresistant disease including patients with primary refractory disease, refractory relapse or untreated relapse. Patients who survived more than 90 days after allo-SCT without evidence of tumor were classified as having experienced complete remission (CR). PR was defined as a ≥ 50% reduction of all pre-transplantation measurable disease for at least 1 month. Patients achieving less than 50% tumor reduction were considered non-responders. Intensity of conditioning regimens was defined as previously published.[16] In addition to that, details in terms of drugs used and total doses administered for each individual patient were specifically reviewed by the principal investigator of the study in order to double check the definition of MAC vs RIC.

Statistical analysis

Primary end points studied were overall survival (OS) and event free survival (EFS) after allo-SCT. OS was defined as the time from allo-SCT to death from any cause and EFS was defined as the time from allo-SCT to relapse or progressive disease or death from any cause, whatever came first. Probabilities of OS were calculated using the Kaplan-Meier estimate and compared using the log-rank test. Multivariate comparisons of OS times and estimations of hazard ratios were calculated using Cox regression models. Secondary endpoints were RR and NRM, and incidences of acute and chronic graft-versus-host disease (GVHD). RR was calculated as time from allo-SCT to relapse or progression, NRM was calculated as time from allo-SCT to death in the absence of prior relapse or progression. Relapse and NRM events were considered as competing risks. For cumulative incidence of chronic GVHD (cGVHD), death was considered as a competing risk. Cumulative incidence curves for relapse, cGVHD and NRM incidences were compared using the Gray's test. Multivariate analysis for relapse

and NRM incidences were performed using a competing risk proportional subdistribution hazards regression model. Median observation time was calculated by the reversed Kaplan-Meier estimate. Database follow up was closed in December 2015. All statistical analyses were performed using R 2.15.3 (R Foundation for Statistical Computing, Vienna, Austria, http://www.R- project.org). All statistical tests were 2-sided with a P value <0.05 considered to indicate a statistically significant result.

RESULTS

A group of 312 patients fulfilling the inclusion criteria were identified; 63 had received a MAC and the remaining 249, a RIC approach. Most important characteristics at the time of transplantation are shown in **Table 1a**. **Table 1b** indicates clinical characteristics of patients receiving allo-SCT as a first transplant (data included in supplemental files). Details of conditioning regimens are included in **Table 2**.

GVHD

There were no differences in the incidence of grades II-IV acute GVHD (aGVHD) and chronic GVHD (cGVHD) between both groups of patients. Multivariate analysis indicated that age of the recipient over 30 years, male sex, MAC protocols and the use of total body irradiation (TBI) in the conditioning regimen were independent adverse prognostic factors for the development of cGVHD (**Table 3a**).

NRM

NRM was 9%, 12% and 13% at 1, 2 and 5 years, respectively for the whole group of patients (**Figure 1a**), with no significant differences between MAC (5%, 11% and 13% at 1, 2 and 5 years) and RIC

patients (10%, 11% and 12% at 1, 2 and 5 years) (**Figure 1b**). The multivariate analysis adjusted on age did not show the presence of any independent adverse prognostic factor for NRM (**Table 3a**).

Relapse / Progression

One hundred and forty-five patients (53% of the whole group; 46% for MAC *vs* 55% for RIC) experienced disease relapse / progression. Median [interquartile range (IQR)] time to relapse was 8.7 (3.1 – 12.3) months in the MAC group *vs* 6.1 (3.5 – 14.3) months in the RIC group. Cumulative incidence of relapse was 38%, 50% and 59% at 1, 2 and 5 years, respectively (**Figure 1a**) [33%, 41% and 50% for MAC patients and 39%, 52% and 60% for RIC patients at 1,2 and 5 years (**Figure 1b**)]. Multivariate analysis indicates that disease status at the time of transplantation was the only significant risk factor for disease relapse (**Table 3a**)

Event-free survival

The estimated EFS was 53%, 39% and 30% at 1, 2 and 5 years, respectively (**Figure 2a**). Conditioning intensity did impact in EFS, which was better although non-significantly different in the MAC group (48% *vs* 36% at 24 months, p=0.09) (**Figure 2b**). Disease status had a major impact in the outcome of the procedure (**Figure 2c**). Multivariate analysis adjusted on disease status, age and use of TBI indicated that the use of MAC protocols was associated with a non-significant EFS benefit (**Table 3a**).

Overall survival

After a median follow-up for survivors of 56 months (IQR 26 to 73 months), 153 patients were alive, 36 (58%) in the MAC group and 116 (48%) in the RIC. one The estimated OS was 73%, 64% and 45% at

1, 2 and 5 years, respectively (**Figure 3a**). There were no significant OS differences between both groups of patients (73% for MAC 62% for RIC at 24 months, p=0.13) (**Figure 3b**). Chemosensitive disease at allo-SCT was the only independent prognostic factor for OS in the multivariate analysis after adjusting for age (**Table 3a, Figure 3c**).

Multivariate analysis for patients being treated with allo-SCT as first SCT

Multivariate analysis restricted to the population of patients treated with allo-SCT as first transplantation procedure (**Table 3b,** data included in supplemental files) indicated that MAC protocols were associated with a lower although non-significant RR that was translated into an improvement in both EFS and OS. The intensity of the conditioning regimen was not a prognostic factor for NRM (**Table 3b,** data included in supplemental files).

DISCUSSION

Despite the advent of novel potent pharmacological treatment options, [21-25] allo-SCT remains a reasonable treatment option for those patients who relapse or progress after an ASCT. Nevertheless, there are still many unsolved questions in this setting; the intensity of the conditioning regimen to optimize long-term results of the procedure is one of them. While MAC allo-SCT has been classically associated to an unacceptably high NRM, the major obstacle for a long-term remission in the RIC scenario is the high relapse risk. Since most of the analyses looking at the outcome after MAC allo-SCT deal with patients allografted more than 15 years ago; [8-10] the hypothesis of the present study was that advances in HLA typing and selection of the appropriate donor in the unrelated setting, better selection of the allotransplant candidates, better supportive measures, and more experienced clinical teams might have improved the outcome of MAC allo-SCT.

Several lines of evidence have demonstrated that in HL, conditioning intensity matters. In our previous study, the multivariate analysis restricted to the RIC group indicated that RR was higher in those patients receiving TBI-containing regimens.[10] In children and adolescents treated with a allo-SCT PFS after RIC was significantly lower than after MAC because of the higher RR after RIC; NRM was independent on the intensity of the conditioning regimen used.[17] Finally, excellent results with the combination of BEAM conditioning and alemtuzumab-based GVHD prophylaxis as first transplant in patients with relapsed / refractory HL have been reported by Thomson and Peggs.[18]

With all this background in mind, we decided to perform a second retrospective analysis in patients with relapsed/refractory HL looking at the long-term outcome of RIC *vs* MAC. In this study a more recent population of patients thus, more representative of our present clinical practice was included. Clinical characteristics of the allografted population of patients were not so different from our previous analysis. In both retrospective comparisons the RIC group was significantly older, the evolution of the underlying disease before transplant was also longer and a higher percentage of them had eventually failed a prior ASCT. While in the first retrospective comparison NRM at 1 year was 46% and 23% for MAC and RIC, respectively, in this second one, NRM at 1 year was remarkably low with 9% for both groups of patients. NRM after allo-SCT for HL has improved over time independently of the conditioning used, but this improvement is most evident in the MAC group. Of note, 21 of the 63 HL patients conditioned with MAC (33%) were treated with BEAM-Alemtuzumab that has been classically associated with a low NRM. [19] In contrast, and in keeping with our previous analysis where 57% of the RIC patients relapsed *vs* 30% in the MAC group, [10] HL relapse remains the most important cause of allo-SCT failure in patients being treated with a RIC. In the present analysis, disease relapse was also more frequent in the RIC group (55% *vs* 46%). Thus EFS was superior with MAC in the multivariate analysis although this difference was not statistically significant. Moreover, MAC patients also enjoyed a non-significant

improvement in OS. The analysis of those patients with relapsed/refractory disease that were treated with an allogeneic approach as first transplant, indicate a better EFS and OS for MAC recipients vs RIC recipients. RR was lower in the MAC group but did not reach statistical significance in the multivariate analysis.

Unfortunately, this analysis is hampered by its retrospective nature and the fact that both groups of patients are not comparable in terms of disease and patients' characteristics before allo-SCT. Still the decision on the intensity of the conditioning regimen to be used in this setting is not completely settled down. In the absence of prospective clinical trials, the possibility to modify the pre-existing conditioning protocols with the introduction of new drugs in order to increase the effectiveness but not the toxicity of the combination is a concept that could be taken into consideration.

The unique clinical benefit of an allo-SCT in the lymphoma setting is the combination of the effectiveness of high-dose chemotherapy with the graft-versus-lymphoma effect. Although retrospective studies [10-12,14] as well as prospective clinical trials [15] and evidence from DLI studies[20,21] have indicated the existence of a beneficial graft-versus-HL effect, its clinical impact seems to be limited. Fine-tuning of the efficacy of the conditioning regimen may help to set the stage for GVL activity becoming effective in HL. Novel targeted drugs could further optimize the outcome of HL allotransplants by improving disease status prior to and disease control post allo-SCT. [22-26]

In addition to the inherent pitfalls associated to the retrospective nature of this analysis, one has to acknowledge that the relapsed / refractory setting has changed in patients with HL with the advent of the new drugs. Brentuximab vedotin (BV) granted an accelerated approval by the FDA and the EMA in 2011 and 2012, respectively for those patients with HL relapsing after an ASCT; overall response rate of 76% with a PET negative CR of 34% in this population of patients. [22] Although the curative potential

of BV is still unknown, a 4-year follow up study indicates that there are long-term disease free survivors after stopping the drug. [23] More recently, the anti-PD1 ligands (nivolumab and pembrolizumab), have given interesting results in relapsed / refractory HL patients, even in those failing BV. [24,25] The decision to whether allograft every single patient with HL relapsing or progressing after an ASCT or to delay allotransplants to a later phase of the disease remains to be elucidated but, from a daily practice point of view, many centers are still allograting young patients with chemosensitive disease demonstrated after a short course of BV. This strategy most probably will improve results of the allogeneic procedure by taking patients into the transplant in better clinical conditions and also in a better disease status. [26]

In conclusion, this study suggests that with current transplant practices, the NRM associated with MAC has strongly decreased, resulting into a non-significant improvement in EFS. The intensity of conditioning regimens should be considered when designing individual allo-SCT strategies or clinical trials in patients with relapsed / refractory HL.

N = 2438 words

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Table 1a. Characteristics of the whole series of patients.

Table 1a. Whole series of patients.

Characteristic	Whole Group (n = 312)	MAC (n = 63)	RIC (n = 249)	P value
Sex				
Male	172 (55%)	38 (60%)	139 (54%)	NS
Female	140 (45%)	25 (40%)	114 (46%)	
Age at diagnosis, years (median, IQR)	28 (22 – 36)	26 (21 – 33)	27.8 (22 – 37)	NS
Age at allo-SCT, years (median, IQR)	31 (25 –40)	27.1 (24 – 36)	32 (25 – 41)	0.04
Dx –Allo-SCT, months (median, IQR)	32 (20 – 54)	21 (13 – 29)	35.6 (24 – 56)	0.0002
≥ 3 prior lines of therapy before allo-SCT	180 (57%)	25 (40%)	155 (62%)	0.08
Prior ASCT				
Yes	172 (55%)	17 (27%)	155 (62%)	
No	140 (44%)	46 (73%)	90 (38%)	0.00002
Stem cell source				
BM	37 (12%)	9 (14%)	28 (11%)	NS
PB	275 (88%)	54 (86%)	221 (89%)	
Type of donor				
HLA Id-sib	272 (87%)	61 (97%)	211 (85%)	0.01
MUD	40 (13%)	2 (3%)	38 (15%)	
Disease status at allo-SCT				
Sensitive Disease	151 (51%)	29 (46%)	132 (53%)	NS
Refractory Disease	153 (49%)	34 (54%)	118 (47%)	
Performance Status at allo-SCT				
0 – 1	224 (72%)	40 (63%)	184 (74%)	NS
≥ 2	65 (20%)	17 (27%)	48 (19%)	
Unknown	23 (8%)	6 (10%)	17 (7%)	
TBI in the conditioning regimen				
Yes	48 (15%)	16 (25%)	32 (13%)	0.02
No	264 (85%)	47 (75%)	217 (87%)	

Allo-SCT. Allogeneic stem cell transplantation; MAC. Myeloablative conditioning regimen; RIC. Reduced intensity conditioning regimen; Dx. Diagnosis; ASCT. Autologous stem cell transplantation; BM. Bone marrow; PB. Peripheral blood; HLA id sib. HLA identical sibling donor; WMUD. Well matched unrelated donor; TBI. Total body irradiation; NS. Not significant.

Table 2. Details of conditioning protocols.

Conditioning Regimen	MAC (n = 63)	RIC (n = 249)
BEAM	10 (17%)	0
BEAM-A	21 (33%)	0
BuCy +/- VP-16	16 (25%)	0
CyTBI	16 (25%)	0
FluBu +/- Others	0	50 (20%)
FluCy +/- Others	0	33 (13%)
FluMel +/- Others	0	134 (54%)
FluTBI (2 Gys)	0	32 (13%)

BEAM. BCNU, etoposide, ara-c and melphalan; A. Alemtuzumab; BuCy +/- VP-16. Busulfan and cyclophosphamide +/- etoposide; CyTBI. Cyclophosphamide and total body irradiation; FluBu. Fludaraine and busulfan; FluCy. Fludarabine and cyclophosphamide; FluMel. Fludarabine and melphalan; FluTBI. Fludarabine and total body irradiation.

Table 3a. Multivariate analysis for cGHVD, NRM, RR, EFS and OS: whole series of patients.

Chronic graft versus host disease

Variable	HR	95%CI	p value
Time from diagnosis to SCT over 20 months	1.54	0.96 – 2.48	0.07
Age over 30 years	0.65	0.43 – 0.98	0.03
Male vs Female	1.62	1.07 – 2.46	0.02
MAC vs RIC	0.55	0.32 – 0.95	0.03
TBI vs no TBI	2.21	1.33 – 3.7	0.002
Matched unrelated vs Identical sibling	0.55	0.27-1.11	0.098
Refractory disease vs sensitive disease	1.04	0.68-1.58	0.846

Non-Relapse Mortality

Variables	HR	95%CI	P value
TBI vs no TBI	1.84	0.80 – 4.25	0.15
Refractory disease vs sensitive disease	0.98	0.50 – 1.94	0.60
MAC vs RIC	0.79	0.33-1.89	0.60

Relapse Rate

Variables	HR	95%CI	P value
Refractory disease vs sensitive disease	1.92	1.36 – 2.71	0.0002
MAC vs RIC	0.72	0.47-1.09	0.127

Event Free Survival

Variables	HR	95%CI	P value
Refractory disease vs sensitive disease	1.65	1.21 – 2.25	0.001
MAC vs RIC	0.70	0.48 – 1.04	0.07
TBI vs no TBI	1.28	0.84-1.89	0.217

Overall Survival

Variable	HR	95%CI	p value
MAC vs RIC	0.72	0.47 – 1.10	0.13
Refractory disease vs sensitive disease	1.70	1.19 – 2.41	0.002
Male vs female	1.29	0.92-1.81	0.128

Stratified on age (cut off of 30 years)

HR. Hazard ratio; 95%CI. 95% confidence interval; MAC. Myeloablative conditioning regimen; RIC. Reduced intensity conditioning regimen; TBI. Total body irradiation.

Figure legends.

Figure 1. Non-relapse mortality and relapse incidence after allogeneic stem cell transplantation.

Figure 1a. Results from the whole group of patients included in the analysis (n = 312)

Figure 1b. Comparison between MAC (n = 63) and RIC (n = 249) groups.

Figure 2. Progression free survival after allogeneic stem cell transplantation.

Figure 2a. Results from the whole series.

Figure 2b. Comparison between MAC and RIC.

Figure 2c. Impact of disease status at the time of allo-SCT in the PFS after the procedure.

Figure 3. Overall survival after allogeneic stem cell transplantation.

Figure 3a. Results from the whole series.

Figure 3b. Comparison between MAC and RIC groups.

Figure 3c. Impact of disease status at allo-SCT in the OS after the procedure.

Figure 1a.

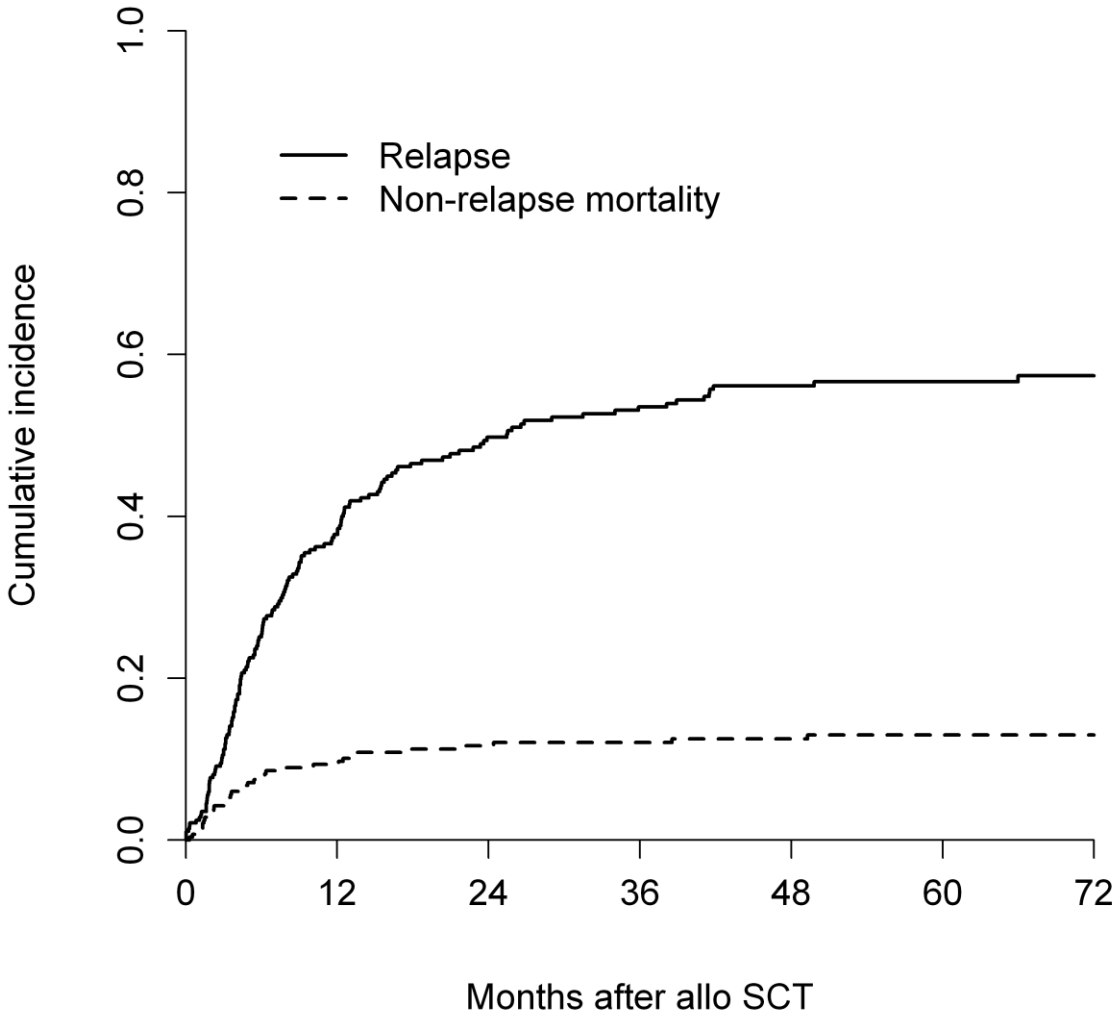

Relapse
Non-relapse mortality
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
Months after allo SCT

Figure 1b.

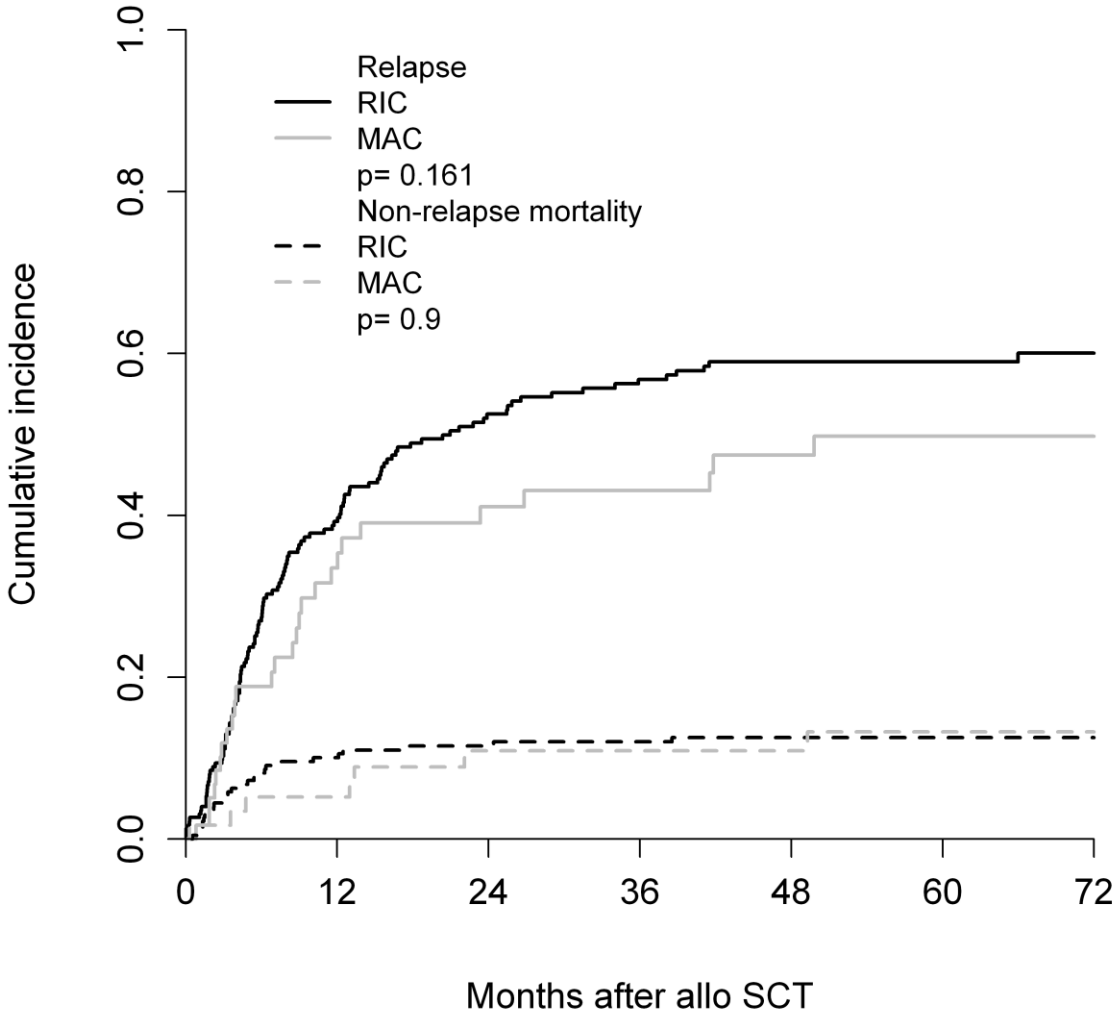

Relapse
RIC
MAC
p= 0.161
Non-relapse mortality
RIC
MAC
p= 0.9
Cumulative incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
Months after allo SCT

Figure 2a.

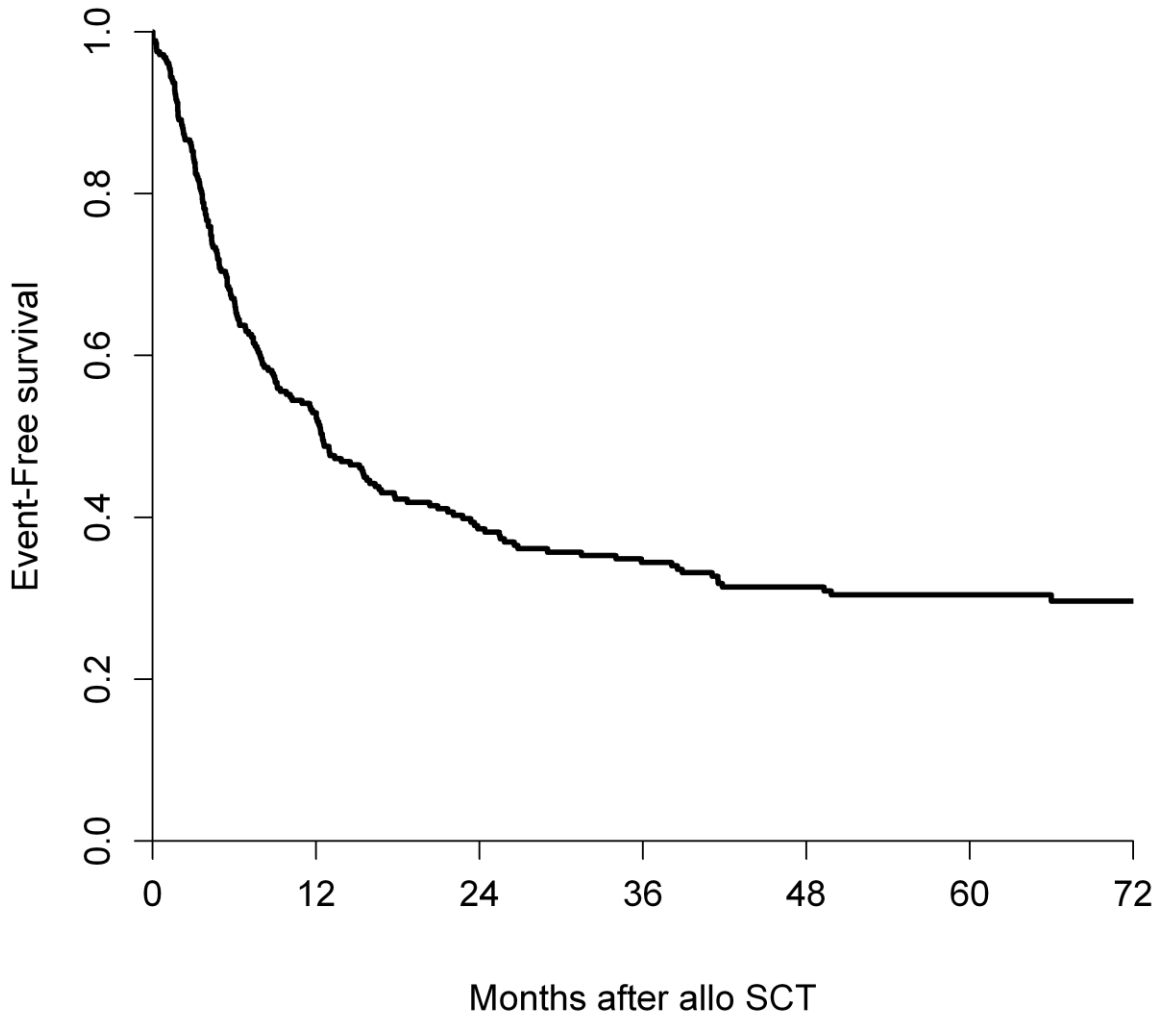

Event-Free survival
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
Months after allo SCT

Figure 2b.

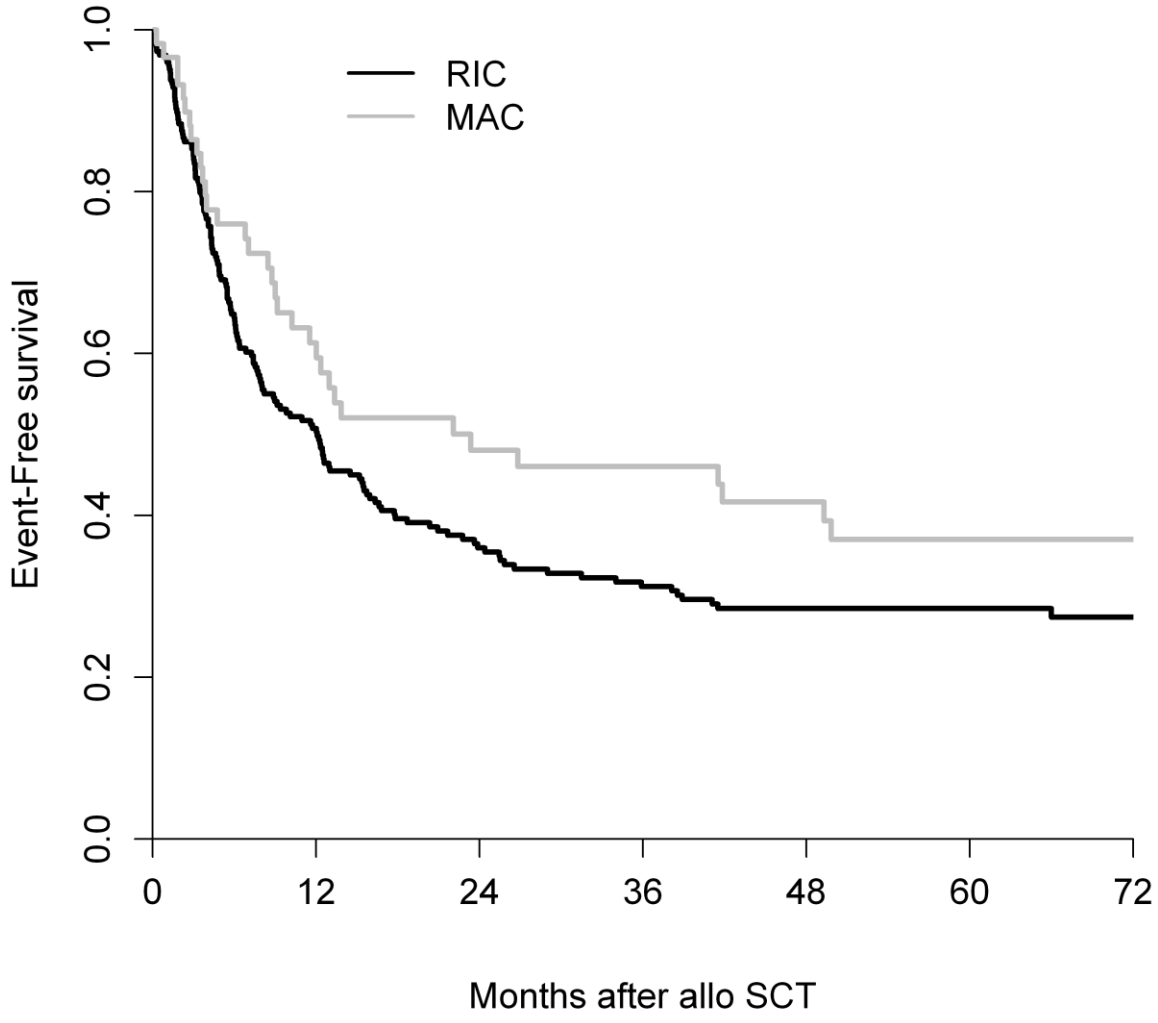

RIC
MAC
Event-Free survival
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
Months after allo SCT

Figure 2c.

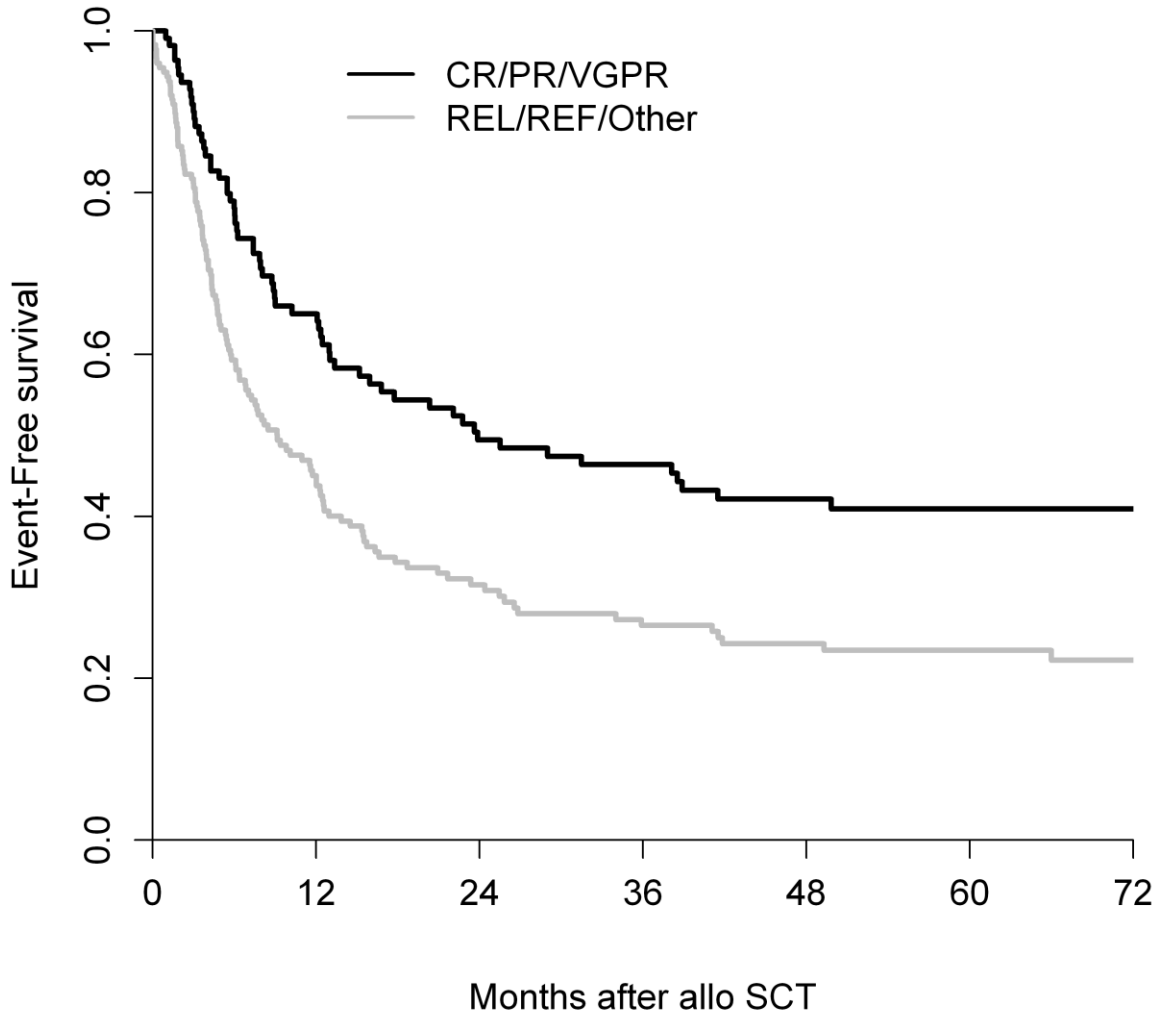

CR/PR/VGPR
REL/REF/Other
Event-Free survival
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
Months after allo SCT

Figure 3a.

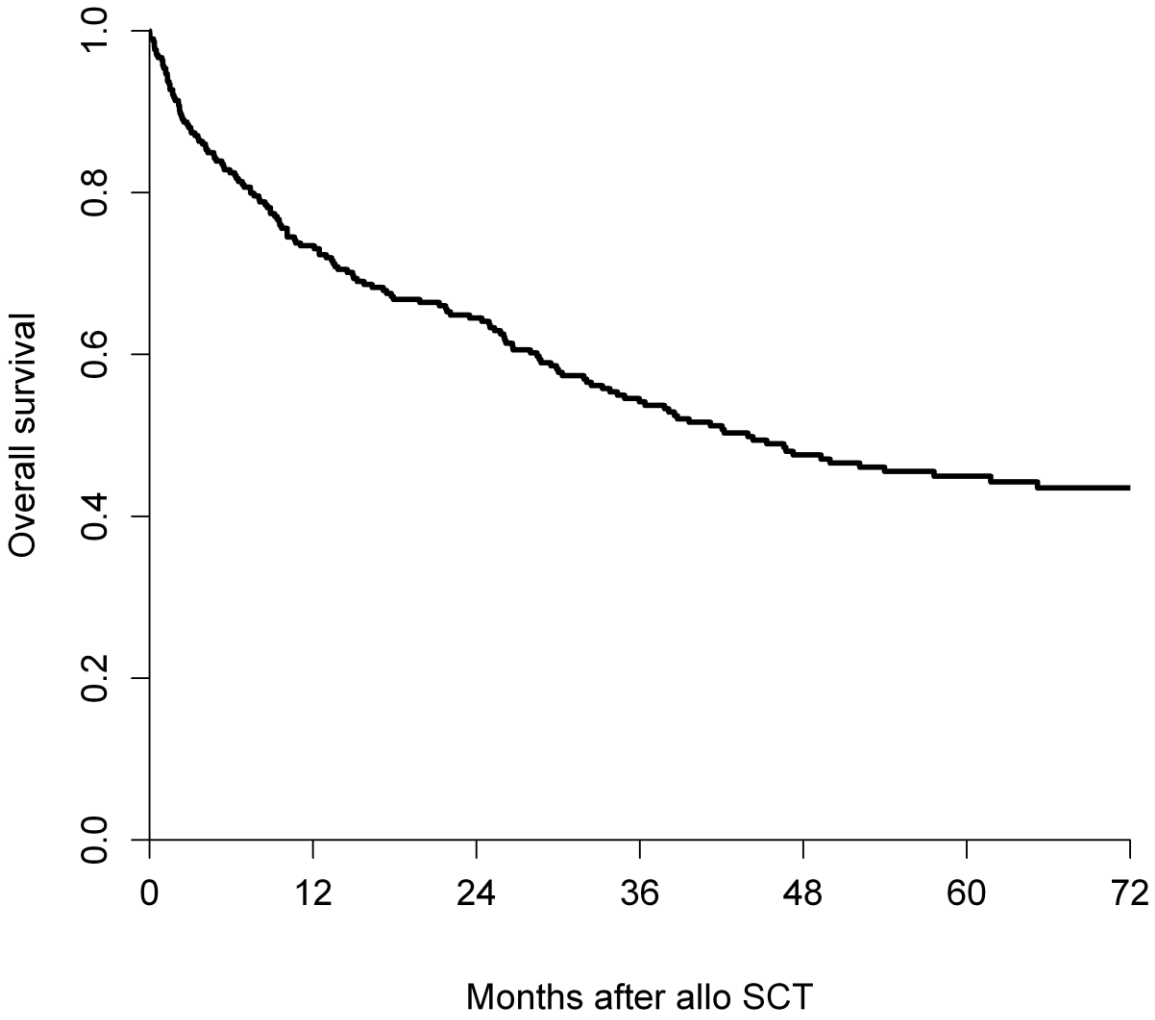

Overall survival
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
Months after allo SCT

Figure 3b.

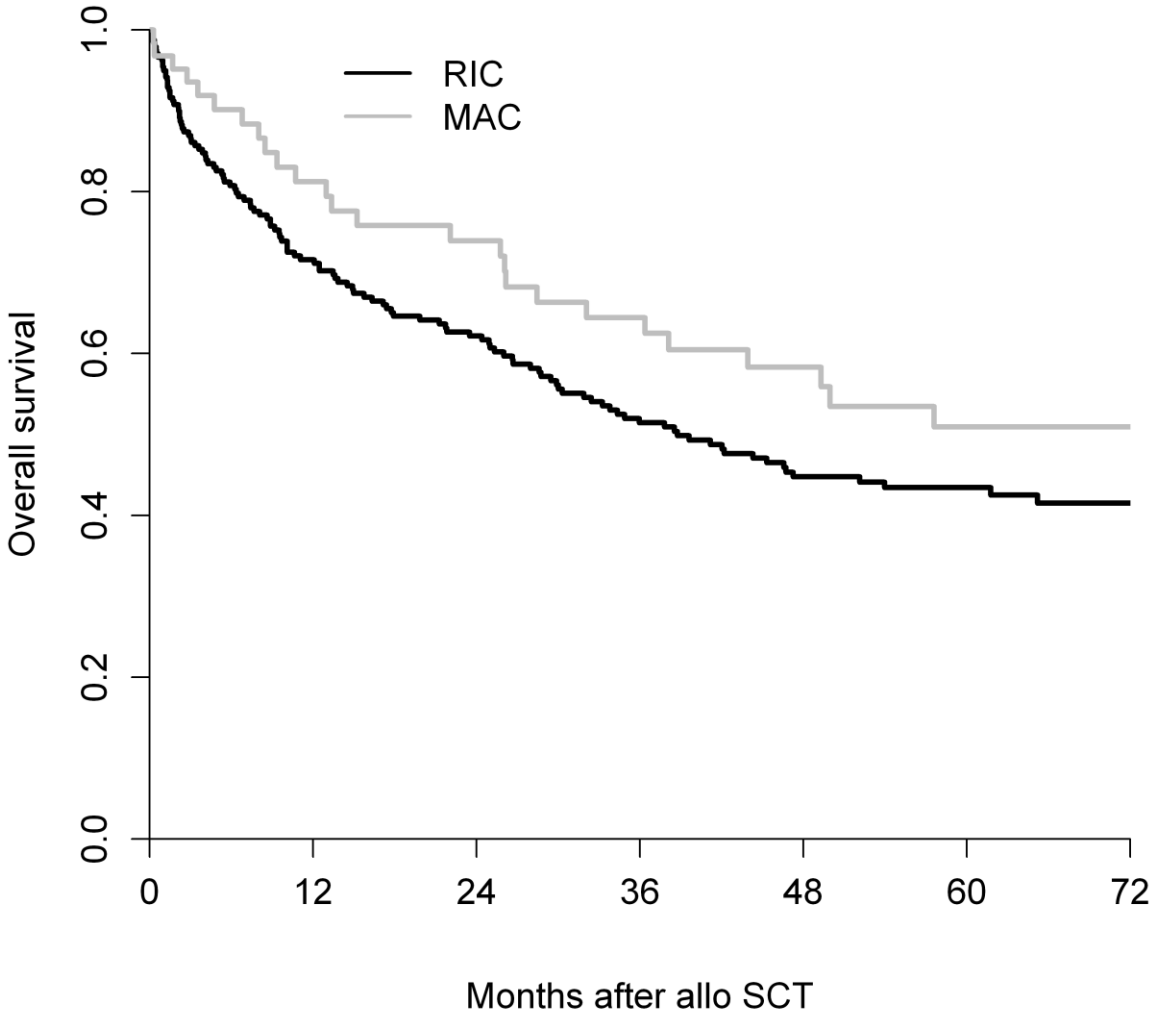
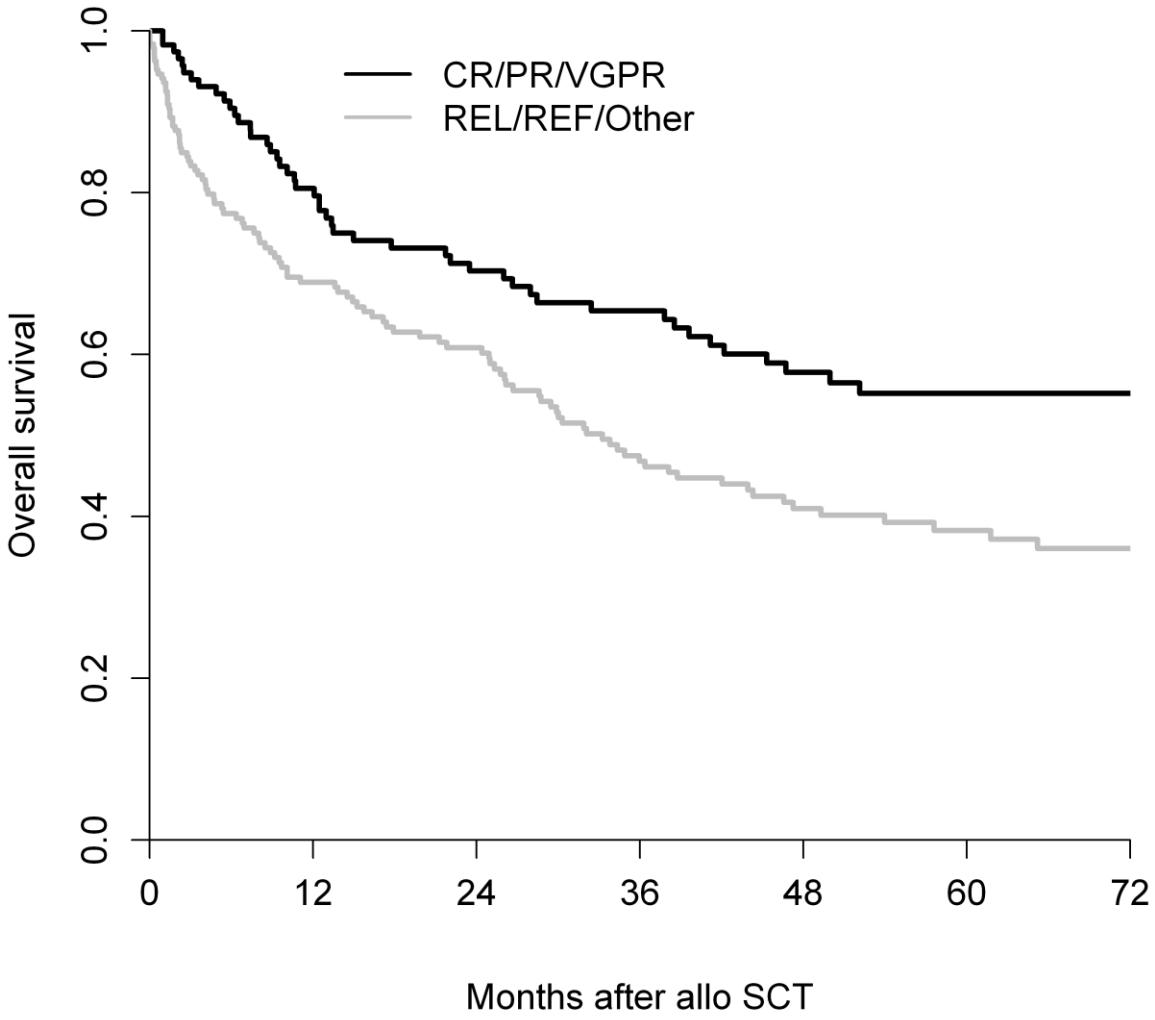

RIC
MAC
Overall survival
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
Months after allo SCT

Figure 3c.


CR/PR/VGPR
REL/REF/Other
Overall survival
0.0
0.2
0.4
0.6
0.8
1.0
0
12
24
36
48
60
72
Months after allo SCT