Nordic MCL3 study: Y-90-ibritumomab-tiuxetan added to BEAM/C in non-CR patients before transplant in mantle cell lymphoma

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Nordic Mantle Cell Lymphoma-3 study: Zevalin-BEAM/C conditioning followed by autologous stem cell transplantation in first line therapy - No benefit of Zevalin

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Abstract

Purpose: Since in previous Nordic MCL2 study based on high-dose immunochemotherapy with stem cell support, the response duration was significantly shorter for patients not in CR before the transplant, the main objective of the present MCL3 study was to improve outcome for this patient cohort by adding radioimmunotherapy with ^{90}Y-Ibritumomab-Tiuxetan (Zevalin) to the high-dose regimen.

Materials and Methods: Newly diagnosed stage II-IV MCL patients < 66 years received rituximab(R)- maxi-CHOP alternating with R-high-dose Ara-C (6 cycles total), followed by high-dose BEAM or BEAC and autologous stem cell transplantation. Intensification with Zevalin (0.4 mCi/kg) was given to patients in CRu/PR one week prior to high-dose therapy. Follow-up included CT-scans and minimal residual disease (MRD) measurement. Patients who developed solely molecular relapse received 4 weekly doses of rituximab.

Results: 160 consecutive MCL patients were included from 2005-2009. Overall response rate pre-transplant was 97% (CR: 51%, CRu: 17%, PR: 29%). After a median follow-up of 4.4 years the 4-year overall survival (OS), event free survival (EFS), and progression-free survival (PFS) were 78, 62 and 71%, respectively, similar to the MCL2 trial. Zevalin did not improve response duration for patients in CRu/PR. Inferior PFS, EFS- and OS were predicted by PET-positivity pre-transplant and MRD post-transplant. Zevalin added no acute toxicity. However, a trend towards higher MDS/AML rate was observed among Zevalin recipients.

Discussion: Late intensification with Zevalin did not improve outcome of patients in only CRu/PR before transplant. A positive PET prior to transplant was an even better predictor for outcome than detection of MRD after transplant

INTRODUCTION

Mantle cell lymphoma (MCL) comprises 5-10% of non-Hodgkin`s lymphomas (NHL) and often has an aggressive clinical course. At diagnosis, the disease is typically in stage III-IV with universal lymphadenopathy and bone marrow involvement[1]. Other extranodal sites like the gastrointestinal tract are often involved[2]. In addition to a characteristic immunophenotype, the hallmark chromosomal translocation t(11:14) leading to aberrant expression of cyclin-D1 can be found in most cases[3]. The importance of an effective induction regimen containing both Ara-C and rituximab has gained support based on results from phase-II and III trials[4-7] . MCL is known to be highly radiosensitive and anti-CD20 targeted radioimmunotherapy (RIT) with ^{90}Y-Ibritumomab-Tiuxetan (Zevalin) or ^{131}I-tositumomab (Bexxar) has been shown is effective and well tolerated[8-10]. Since myelosuppression is the major toxicity of these strategies, standard dose RIT plus myeloablative chemotherapy followed by stem cell rescue has been tested with promising results in MCL and other NHL [8,11] .

The Nordic phase-II MCL2 study which included 160 patients showed a strong correlation between the response pre-transplant and long-term PFS and OS. Hence, in the present study (MCL3), responders who did not achieve a CR after induction immunochemotherapy were

offered late intensification with standard dose Zevalin (0.4 mCi/kg) prior to high-dose treatment with BEAM or BEAC (Z-BEAM/C). The main objective was to improve duration of response in this patient subset.

PATIENTS and METHODS

Patients, diagnostic work-up and follow-up

The Nordic Lymphoma Group has conducted three successive phase II trials since 1996, including the present MCL3 study which recruited 160 patients from 2005 to 2009. The eligibility criteria were identical: Previously untreated stage II-IV MCL patients <66 years. The diagnostic specimens should fulfill the WHO criteria for MCL[3] regarding immunophenotype, cyclinD1 overexpression or t(11;14) by central pathology review. Patients underwent standard clinical and laboratory work-up including CT scans of chest and abdomen, bone marrow biopsy and aspirates for histology and flow cytometry. Blood and bone marrow aspirates were sent to a central laboratory (Leukemia Marker Laboratory, Department of Hematology, Rigshospitalet, Copenhagen, Denmark) for identification of disease- or patient-specific molecular markers. Mantle cell lymphoma international index (MIPI) score and MIPI-B (B: biologic) scores[12] were assessed at inclusion. The complete work-up was repeated after the fifth cycle of induction therapy and three months after the transplant. A PET/CT scan should be done after cycle 5 whenever feasible, especially for patients who had not achieved CR by regular CT scan, but should not influence treatment choice or response evaluation. PET scans were centrally reviewed in Sweden, Finland and Norway and in Denmark by experts at 4 large university

clinics. The scans were scored according to the Deauville[13] criteria with a five-point scale, where scores of 4 or 5 were considered positive. Follow-up visits were done every 6 months for 5 years with clinical examination, CT-scans, and blood and bone marrow samples. After 5 years, patients in remission continued annual follow-up with clinical assessment and blood samples. The Nordic MCL3 protocol was approved by all relevant Medicines Agencies and Ethics Committees. Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT00514475).

Treatment

Induction therapy for the MCL2 and MCL3 trials consisted of a total of 6 cycles of alternating maxi-CHOP-rituximab and high-dose Ara-C-rituximab administered every third week with G-CSF support[5]. Patients responding after five cycles underwent stem cell mobilization and peripheral blood stem cell harvest after the sixth cycle (Ara-C-rituximab). For in-vivo purging an extra dose of rituximab was administered at day 9 in cycle 6. A minimum of 2 x 10^6 CD34+ cells/kg was required to proceed to high-dose therapy with stem cell support. Responders who only achieved CRu or PR after cycle 5 were offered late intensification with standard dose of Zevalin (^{90}Y-Ibritumomab-Tiuxetan 0.4 mCi/kg, max. 32 mCi) one week before start of high-dose chemotherapy. Rituximab 250 mg/m2 was given both one week before and just prior to Zevalin. As described for MCL2[5], BEAM or BEAC conditioning was then given followed by stem cell infusion. During follow-up, patients who converted to PCR positivity without signs of clinical relapse were offered preemptive treatment with rituximab 375 mg/m2 weekly for 4 weeks.

Detection of minimal residual disease

As described elsewhere [16,17] fresh samples of blood and bone marrow was shipped overnight from all centers to the central laboratory in Copenhagen. Briefly, DNA was extracted and used for PCR primer design and standard nested PCR amplification of patient specific clonally rearranged immunoglobulin heavy chain genes (IGHV) and/or Bcl-1/IGHV rearrangement (translocation 11;14). Blood and bone marrow analyses were then performed after the fifth cycle of induction treatment, 3 and 6 months after transplant and then every 6 months in order to detect minimal residual disease and molecular relapse. PCR-positive follow-up samples were sequenced in order to secure identity with the original IGHV sequence/t(11;14).

Response criteria, end points and statistics

Response, EFS, PFS, OS and response duration were assessed according to NCI criteria[14]. Response duration was calculated for responding patients who completed the therapy, from the date of first documentation of response until the date of relapse or progression of lymphoma. Survival analyses were performed according to the Kaplan-Meier method[15] and differences between subgroups were analyzed by the log-rank test. Multivariate Cox regression analysis was performed to assess the effect of prognostic factors on outcome.

RESULTS

Between 2005 and 2009, 162 previously untreated patients 18-65 years of age were recruited. The inclusion and exclusion criteria were the same as for the previously reported MCL2 trial[5]. At

central pathology review only one case was excluded as non-MCL lymphoma. Another patient was excluded due to a concomitant renal cell carcinoma, leaving 160 evaluable patients. The characteristics of the MCL3 and MCL2 patients are shown in table 1 and are highly similar, with a median age of 58 years and the majority in stage IV with bone marrow infiltration, and a typical distribution between MIPI risk groups and pattern of Ki67 expression (table 1).

Study-terminating events, event-free and overall survival

A consort diagram is given in Figure 1. With a median observation time of 4.4 years, study-terminating events have occurred in 67 patients (42%), in 48 (30%) due to lack of response, relapse or progression, in 6 (4%) due to harvest failure, in 3 (2%) due to toxicity and in 10 (6%) due to death from other causes than MCL during treatment or after. The 4-year EFS for the MCL3 cohort was 62%. Forty-one patients have died, 30 of lymphoma and 11 of other causes: One sudden death after induction cycle 1, three from transplant complications (BEAM/C: 2, Z-BEAM/C: 1), three from secondary MDS/AML and four from other causes during follow-up (one each of: suicide, accident, large bowel cancer, infection). The 4-year OS rate was 78%. Both the EFS and OS curves for MCL3 and MCL2 were superimposable (Figure 2).

Response and progression free survival

At the first response evaluation after 5 cycles of therapy, prior to transplant, 155 patients (97%) had responded to the induction treatment, similarly to 96% in the MCL2 cohort[5]. Eighty-two (51%) had achieved CR, 26 (16%) CRu and 47 (29%) PR. Of the 155 responders, 146 proceeded

to transplant, whereas 9 did not (6 harvest failure, 3 toxicity). After the transplant, the number of patients in CR had increased to 119 (82%), 13 (9%) remained in CRu, 6 (4%) in PR, 4 (3%) had progressed and 4 (3%) had died. A total of 52 patients have relapsed or progressed during induction or follow-up. The 4-year- PFS was 71%, identical to that of the MCL2 study (Figure 2). No relapses have so far occurred among 34 patients observed in remission beyond five years after transplant.

Impact of Zevalin

Compared to MCL2, there was no improvement in response duration for the CRu/PR cohort despite the fact that 96% of the patients (64 of 67 patients in CRu or PR) eligible for Zevalin according to protocol did actually receive it (Figure 1). Twenty-seven of the 67 patients (40%) in CRu/PR have later relapsed or progressed, compared to only 16 of the 79 patients (20%) in CR with a projected 4-year response duration of 58% and 81%, respectively (P=0.001, Figure 3). Regarding toxicity, we did not observe unexpected severe adverse events related to Z-BEAM/C treatment and engraftment in terms of recovery time of absolute neutrophil (ANC) or platelet counts, which did not differ significantly from those of regular BEAM/C (not shown). However, there was a slight trend of higher incidence of secondary MDS or AML among those who did receive Zevalin (4 of 65), including one treated with Zevalin outside protocol after failed stem cell harvest), compared to only one of the 82 transplanted without Zevalin (P=0.17).

PET-scan prior to transplant predicts outcome

PET/CT was performed in 125 patients after cycle 5 of the induction treatment and 18 patients (14%) were scored PET positive. As expected, patients who were in PR by regular CT were more often PET positive compared to patients in CRu (36% vs 8%). Only one patient in CR had a positive PET-scan. Thirteen of 18 PET-positive patients (72%) have progressed/relapsed, compared to 26 of 107 (23%) PET-negative patients ($p<0.0001$). With a median observation time of 4.4 years the 4-year PFS of the PET positive cohort was 27%, significantly worse than the 78% of the PET negative group. This translated into inferior OS for patients who had a positive PET-scan before transplant (Figure 4).

Detection of minimal residual disease before and after transplant

Prior to the transplant 47 of 99 patients (47%) were MRD positive in blood and/or bone marrow, compared to only 18 of 107 (17%) patients tested after transplant. Of patients tested at both time-points, 26 of the MRD positive cases had converted to MRD-negative posttransplant, suggesting that high-dose therapy improved the quality of the remission. Patients who were MRD positive prior to transplant had a significantly shorter PFS than patients who were MRD negative (Figure 5). After the transplant, a positive MRD was shown to be an even stronger predictor of outcome: Among the 18 patients who were MRD positive post-transplant, 12 (67%) have relapsed, compared to only 16 out of 89 patients (18%) in the MRD

negative group (P < 0.0001). Interestingly, 10 of the 14 PET positive patients who had a PCR primer were also MRD positive before transplant and 8 of these patients have relapsed.

Prognostic factors

Similar to the MCL2 study population, MIPI and MIPI-B were strong predictors for outcome[16]. The 5-year survival of MIPI low and intermediate risk groups did not differ significantly (82 and 72%, respectively) while it was 50% for the MIPI high risk patients (not shown). Of MIPI-B variables (age, WHO, WBC, LDH, Ki-67) only WHO performance status was shown to be an independent prognostic factor for EFS and LDH for OS in a multivariate analyses (Table 2). In addition, blastoid type of MCL was significant for inferior EFS, PFS and OS. In patients with available MRD primer and PET-scan performed, MIPI-B, a positive PET pretransplant and detectable MRD post-transplant were independent variables for EFS, PFS and OS (Table 3). A positive pre-transplant PET proved to be a stronger predictor for OS (HR 13.79, 95% CI 4.07-46.8, p < 0.0001) than post-transplant MRD (HR 4.76, 95% CI 1.46-15.5, p < 0.001).

DISCUSSION

We have demonstrated that –despite the major improvement in the treatment of younger MCL patients reported for MCL2[5,6] , patients who do not achieve a CR after induction treatment have a poorer outcome. In order to improve this, we here in the MCL3 study offered such patients late intensification with Z-BEAM/C. Compared to the excellent historic control of the Nordic MCL2 patients, we did not succeed in reaching this objective. We confirm that the optimal

remission achieved before the transplant, assessed with both PET-scans and minimal residual disease, is the most important factor for the outcome.

Because MCL is highly radiosensitive and expresses surface CD20, targeting radiation directly to the malignant cells with Zevalin is an attractive strategy. Continued exposure to radiation would prevent the tumor cells from DNA damage repair[17]. Wang and colleagues[9] found a response rate of 31% and favorable safety profile in heavily pretreated MCL patients who received Zevalin as single agent. As frontline treatment, Zevalin consolidation after 4 cycles of R-CHOP improved response rates in the ECOG trial E1499[10], and ^{131}I-tositumomab (Bexxar) followed by CHOP chemotherapy led to a response rate of 86% with 67% CR[18]. Yttrium-90 is a pure β-emitting isotope with energy and path length theoretically yielding a higher cross-fire effect on macroscopic tumors than on single tumor cells. Based on this, we selected patients with residual disease visible on CT before transplant for Zevalin treatment (CRu and PR). Since the treatment was followed by stem cell rescue, Zevalin was not expected to increase hematological toxicity. Accordingly, Gopal et al[19] treated 16 patients with relapsed MCL with high-dose Bexxar plus chemotherapy followed by autologous stem cell support, and found no unexpected grade III/IV toxicities, and 3-year PFS and OS of 61% and 93%, respectively. Standard dose Zevalin (0.4 mCi/kg) added to high-dose BEAM, similar to our strategy, was first evaluated in a phase II trial for patients with relapsed aggressive NHL[8] and shown to be well tolerated with median time to WBC and platelet engraftment of 11 and 12 days, and median 2-year PFS and OS of 70% and 89%, respectively. A recent randomized study that compared high-dose BEAM with Z-BEAM in

43 patients with relapsed or refractory aggressive lymphoma[11] reported a trend towards a higher rate of mucositis and serious infections in the Z-BEAM arm but no difference in engraftment kinetics. There was a statistically significant benefit of Zevalin-BEAM over BEAM in regards to PFS (59% vs 30%) and OS (91% vs 62%) at two years. In contrast, the CRu/PR patients of our prospective study did not benefit from late intensification with standard dose Zevalin-BEAM/C, compared to the MCL2 patients. This was also the case in PR patients with a PET-positive mass, where crossfire might be expected to play a role.

Secondary MDS or AML is a well known complication of extensive exposure to chemotherapy,[20,21] including high-dose therapy with autologous stem cell transplantation where a cumulative incidence of 5-10% has been reported[22]. There has been concern that Zevalin, especially in heavily pretreated patients, may predispose for MDS/AML. However, Czuczman et al[23] investigating the incidence of MDS or AML in 746 patients with non-Hodgkin`s lymphoma treated with Zevalin across 5 studies, found 19 (2.5%) MDS/AML cases with a median follow-up of 4.4 years, a rate not higher than expected in a patient population heavily pretreated with cytotoxic agents. Our incidence of MDS/AML of 4 of 65 is 6% (3 patients who received Z-BEAM/C and one receiving Zevalin alone after failure to harvest stem cells), but with wide confidence interval (95% confidence interval: 0.2-12%). In contrast only one patient in MCL3 and one in MCL2 who received BEAM without Zevalin, developed MDS/AML. These figures are too low to draw any conclusions, but warrant further critical attention about the risk of MDS following RIT, especially when combined with high-dose chemotherapy.

There is not yet consensus on the use of FDG PET scan in MCL. In the most recent update of the International Working Group response criteria[24] sufficient evidence was not found to recommend PET for staging, response evaluation or post-therapy surveillance in this lymphoma subtype. Recent reports, however, suggest a relevance of PET in response assessment[25-27]. In our prospective study a positive PET scan pretransplant was associated with a median PFS of less than 3 years, significantly shorter than in the PET negative cohort. The PET positive PR group is of particular interest: According to the revised response criteria[28] in routinely FDG avid lymphoma including MCL, any PET negative residual mass is compatible with CR. Accordingly, the outcome of our PET negative patients did not differ irrespective being in PR, CR or CRu. In multivariate analysis a positive pre-transplant PET-scan proved to be more important than CT-scan and MIPI-B, and also to post-transplant MRD in predicting PFS, EFS and particularly OS. In retrospective studies[26,27], a positive post-treatment PET-scan also predicted early relapse. Our prospective PET based results strongly suggest a value of this modality in the evaluation of response in MCL.

Minimal residual disease monitoring has been shown in our previous Nordic MCL2 study to be of value to predict prognosis in MCL[6]. Furthermore, preemptive rituximab treatment of molecular relapse often converts patients to MRD negative and may delay clinical relapse[29]. Pott and colleagues[30] first showed that molecular remission posttransplant in MCL was highly predictive for outcome, with a median PFS of 92 months in the MRD negative group compared

to 21 months in the MRD positive group ($p < 0.001$). MRD monitoring has since been performed in the European MCL Network trials and has contributed to a better understanding of quality of remission and risk of relapse[31]. In the MCL Younger study the rate of MRD negativity in the bone marrow rose from 50% to 75% after consolidation with high-dose therapy[32]. These results correspond well to our data from MCL3, where 56% of patients were MRD negative before the transplant compared to 86% after. In a multivariate analysis MRD post-transplant independently contributed to predict PFS, EFS and OS. Hence, our data are in line with results from the MCL Younger study, suggesting that the tumor reduction achieved by high-dose consolidation contributes to long-term disease-free survival in MCL.

In conclusion late intensification with Zevalin added to BEAM/C before the transplant did not improve duration of response for patients only in CRu or PR compared to a historic control group (MCL2) and a trend was noted that Zevalin might contribute to a higher rate of MDS or AML. In addition to standard clinical response assessment, a positive PET-scan prior to transplant and detection of MRD in bone marrow or blood before or after transplant predicted higher rates of relapse and shorter PFS. For patients with less than a complete response prior to transplant, intervention at that time point may be too late to change the course of disease. High-risk patients can be identified up front by the MIPI and MIPI-B scores, and new strategies are warranted to improve the induction treatment in such patients.

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Legends Figure 1

Consort diagram of patients flow

Legends Figure 2

Survival. Event-free (A), progressions-free (B) and overall survival (C) of patients in MCL2 and MCL3 based on intention-to-treat of all included patients.

Legends Figure 3

Response duration in MCL2 and MCL3 of patients in CR, CRu and PR prior to transplant including all patients who completed therapy.

Legends Figure 4

Progression-free (A) and overall survival (B) for patients according to results of PET-scan prior to transplant

Legends Figure 5

Progression-free survival of patients according to results of MRD analysis before (A) and after (B) transplant

Figure 1

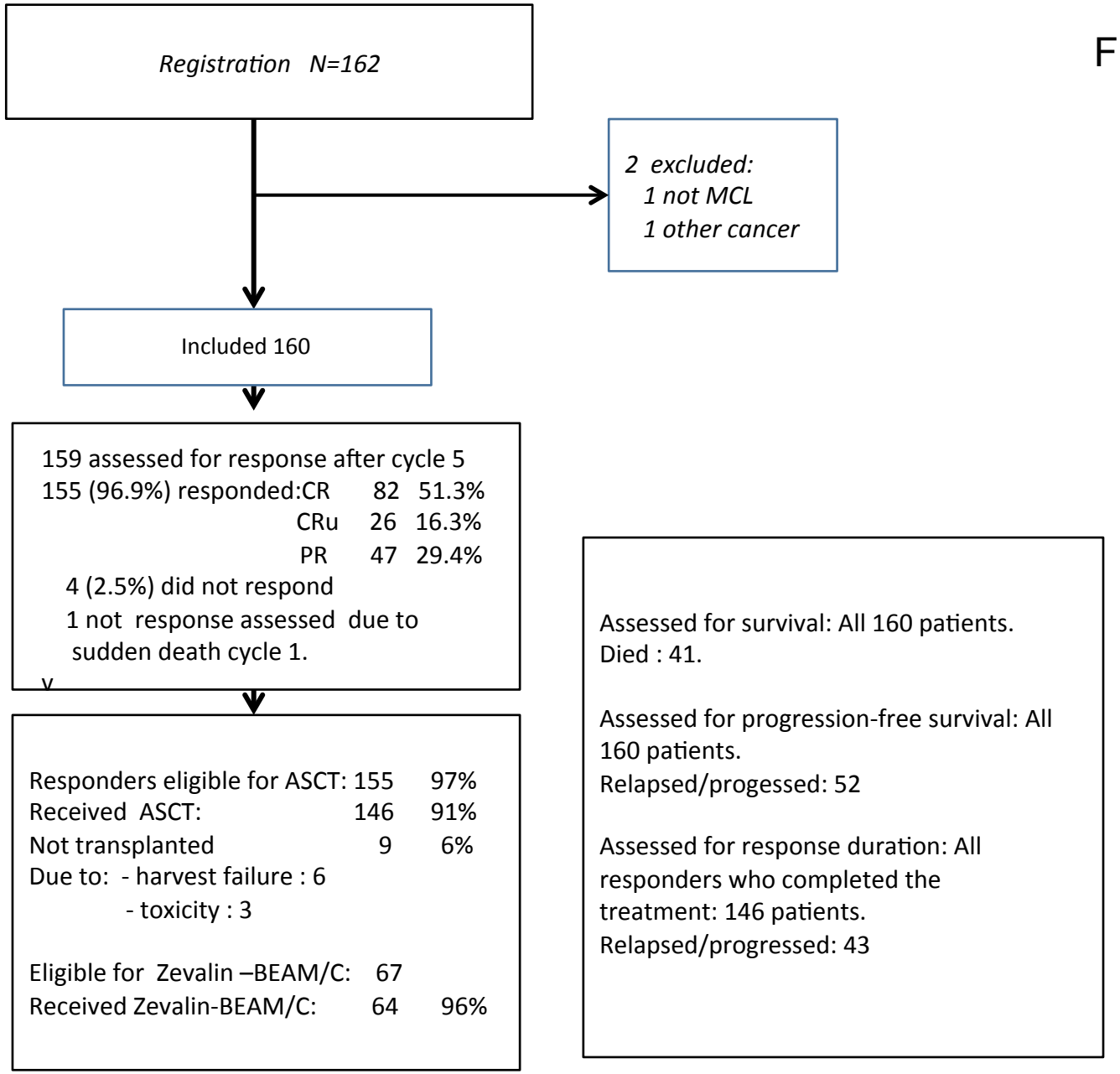
Registration N=162
2 excluded:
1 not MCL
1 other cancer
Included 160
159 assessed for response after cycle 5
155 (96.9%) responded:CR 82 51.3%
CRu 26 16.3%
PR 47 29.4%
4 (2.5%) did not respond
1 not response assessed due to sudden death cycle 1.
Responders eligible for ASCT: 155 97%
Received ASCT: 146 91%
Not transplanted 9 6%
Due to: - harvest failure : 6
- toxicity : 3
Eligible for Zevalin –BEAM/C: 67
Received Zevalin-BEAM/C: 64 96%
Assessed for survival: All 160 patients.
Died : 41.
Assessed for progression-free survival: All 160 patients.
Relapsed/progessed: 52
Assessed for response duration: All responders who completed the treatment: 146 patients.
Relapsed/progressed: 43

Figure 2

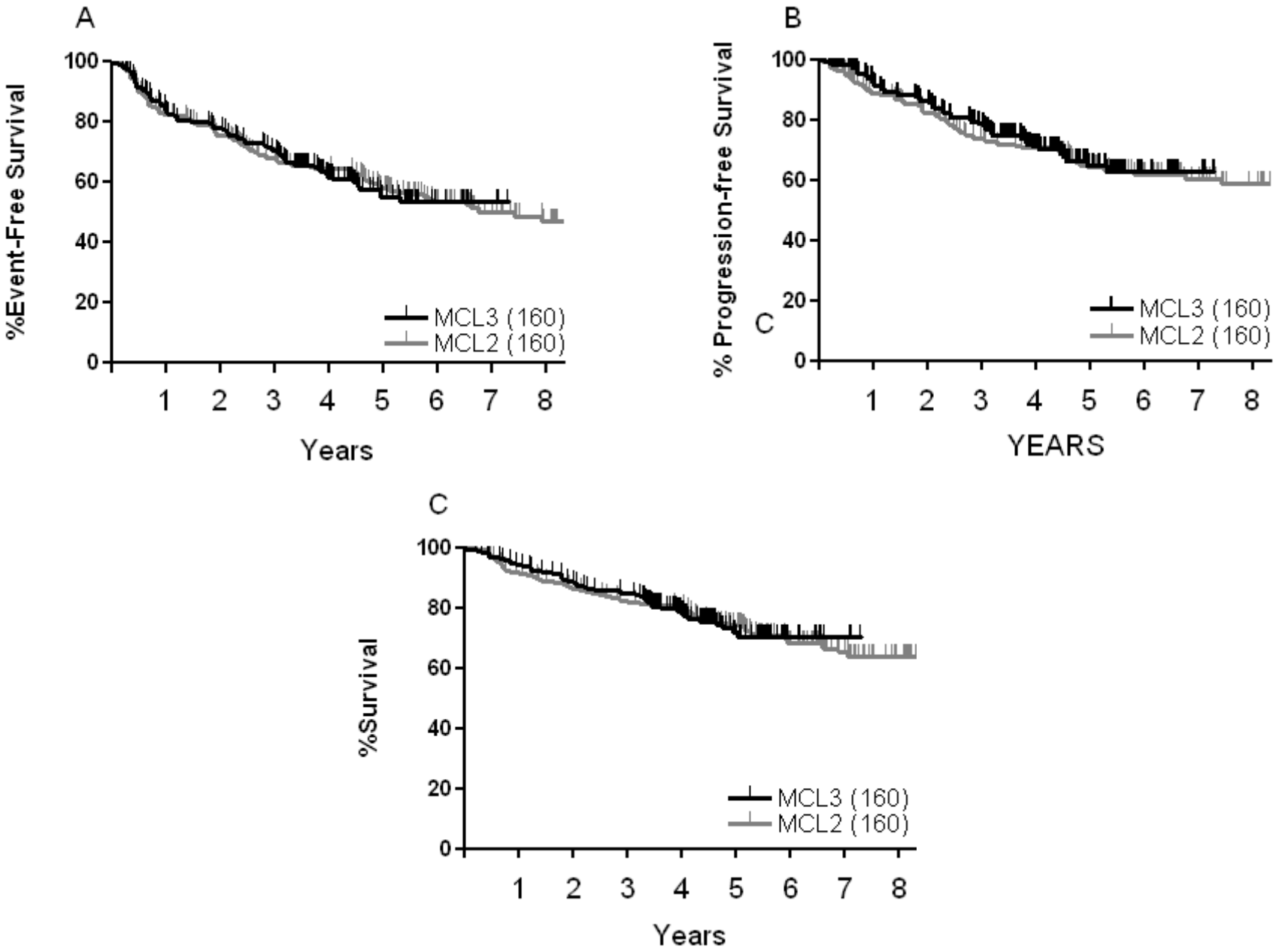
A
%Event-Free Survival
100
80
60
40
20
0
1
2
3
4
5
6
7
8
Years
MCL3 (160)
MCL2 (160)
B
% Progression-free Survival
C
YEARS
C
%Survival

Figure 3

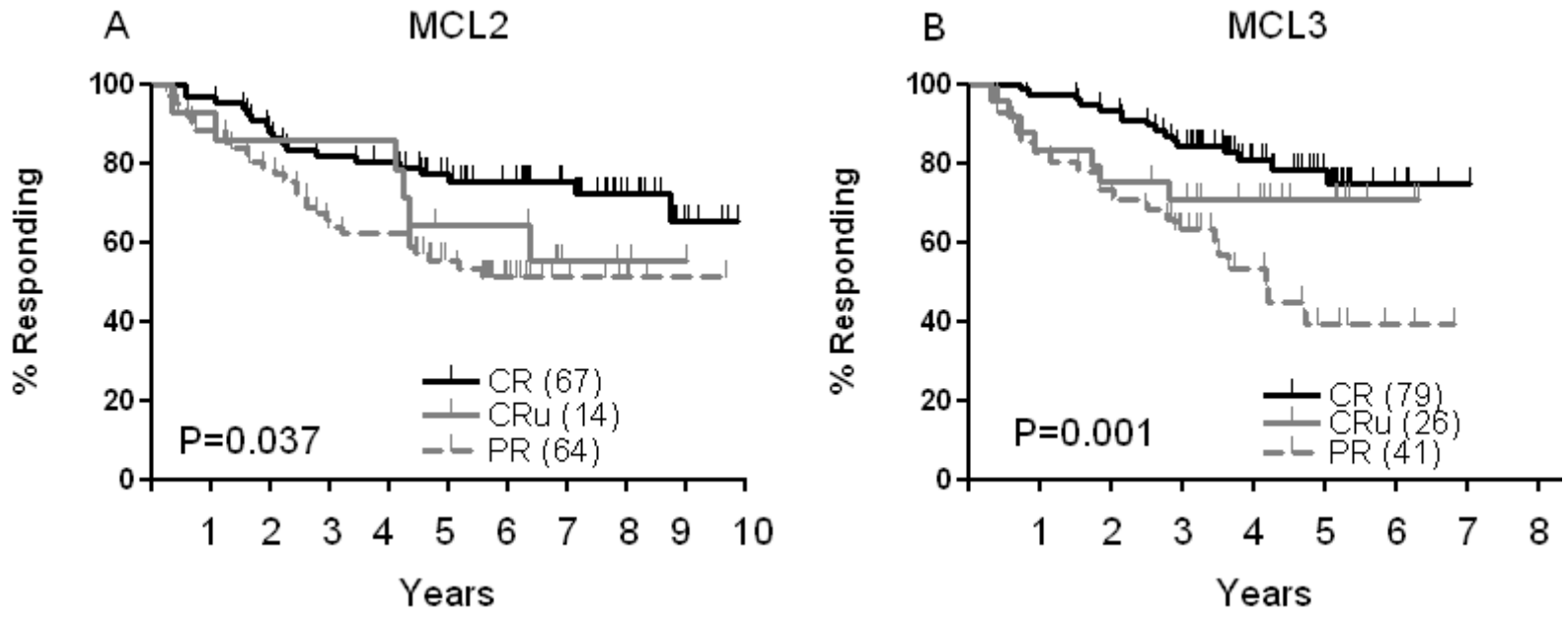
A
MCL2
% Responding
100
80
60
40
20
0
1 2 3 4 5 6 7 8 9 10
Years
P=0.037
CR (67)
CRu (14)
PR (64)
B
MCL3
% Responding
100
80
60
40
20
0
1 2 3 4 5 6 7 8
Years
P=0.001
CR (79)
CRu (26)
PR (41)

Figure 4

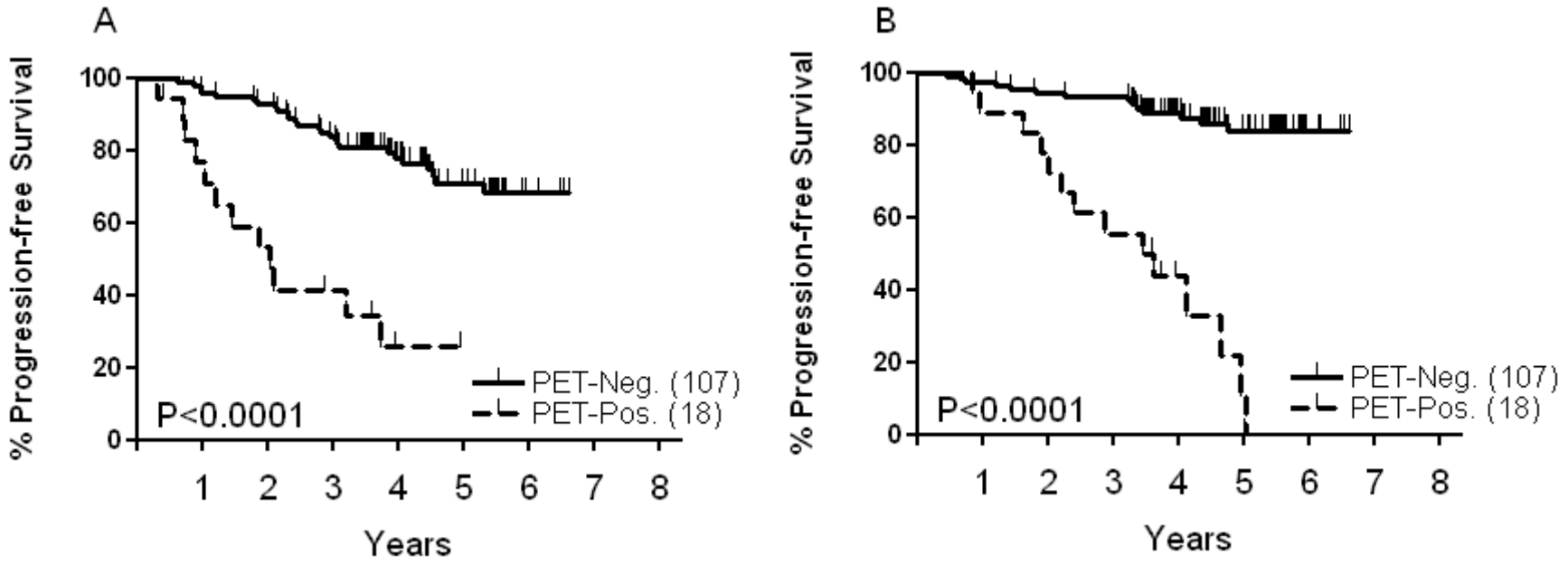
A
% Progression-free Survival
100
80
60
40
20
0
1
2
3
4
5
6
7
8
Years
P<0.0001
PET-Neg. (107)
PET-Pos. (18)
B
% Progression-free Survival
100
80
60
40
20
0
1
2
3
4
5
6
7
8
Years
P<0.0001
PET-Neg. (107)
PET-Pos. (18)

Figure 5

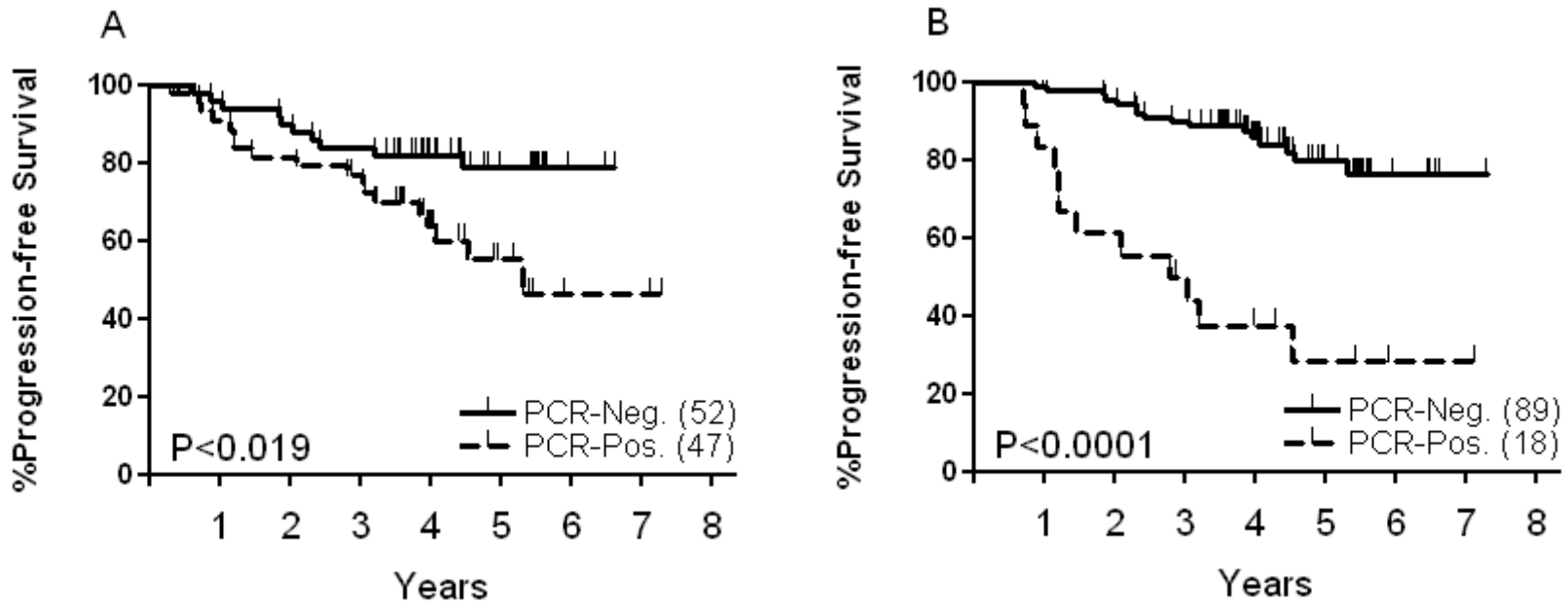
A
%Progression-free Survival
100
80
60
40
20
0
1
2
3
4
5
6
7
8
Years
P<0.019
PCR-Neg. (52)
PCR-Pos. (47)
B
%Progression-free Survival
100
80
60
40
20
0
1
2
3
4
5
6
7
8
Years
P<0.0001
PCR-Neg. (89)
PCR-Pos. (18)

Table 1. Characteristics of patients in MCL3 compared to MCL2				
Variable	**Category**	**MCL3**	**MCL2**	**p value**
Male sex		129 (80%)	113 (71%)	0.05
Median age (range)		58 (28-65)	56 (32-65)	
Stage IV		139 (88%)	136 (85%)	0.37
MIPI score	Low	77 (48%)	80 (51%)	0.75
	Intermediate	49 (31%)	41 (26%)	
	High	33 (21%)	37 (23%)	
Cytologic variant	Blastoid	28 (18%)	31 (19%)	0.36
	Common	128 (82%)	129 (81%)	
% Ki-67	0-9	11 (9%)	10 (8%)	0.94
	10-29	61 (49%)	60 (50%)	
	>29	53 (42%)	50 (42%)	

Table 2. Multivariate analysis of 142 patients with available Ki-67 value according to outcome										
		Event-free survival			Progression-free survival			Survival		
Variable	Score	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age	Value	0.99	0.96-1.03	0.776	0.99	0.96-1.03	0.804	1.01	0.96-1.06	0.670
WHO Perform	0-1/2-4	2.84	1.28-6.29	0.010	2.13	0.95-4.77	0.065	1.68	0.66-4.29	0.275
Sex	M/F	1.19	0.64-2.24	0.582	1.12	0.63-2.26	0.575	0.82	0.36-1.89	0.647
Stage	II/III-IV	0.57	0.17-1.91	0.363	0.64	0.19-2.13	0.464	0.54	0.12-2.46	0.424
Cytology	Common /Blastoid	1.78	0.96-3.30	0.067	2.11	1.15-3.88	0.015	3.43	1.74-6.77	<0.001
KI-67	0-30/30+	1.17	0.61-2.23	0.638	1.22	0.63-2.35	0.558	1.44	0.66-3.13	0.361
LDH	Normal/elevated	1.36	0.76-2.41	0.298	1.42	0.80-2.53	0.228	2.34	1.17-4.69	0.017
Wbc	0-11/11+	1.43	0.81-2.54	0.218	1.51	0.85-2.67	0.161	1.62	0.83-3.18	0.157

Table 3. Multivariate analysis of 82 patients with available MRD and PET data and who completed transplant

		Event-free survival			Progression-free survival			Survival		
Variable	Score	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
MIPI-B	Value	2.15	1.27-3.65	0.004	2.29	1.33-3.95	0.003	3.52	1.69-7.31	0.001
PET response pre-Tx	Pos/neg	6.00	2.37-15.19	<0.001	6.82	2.63-17.70	<.001	13.79	4.07-46.8	<.0001
CT response pre-Tx	CR/PR	1.99	0.81-4.92	0.134	2.20	0.87-5.61	0.097	3.66	0.89-15.1	0.073
MRD post-Tx	Pos/neg	4.58	1.92-10.89	0.001	4.98	2.07-12.01	<0.001	4.76	1.46-15.5	0.001