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Risk of Progression and Survival in Multiple Myeloma Relapsing After Therapy with IMiDs and Bortezomib: A Multicenter International Myeloma Working Group Study

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Abstract

Promising new drugs are being evaluated for treatment of multiple myeloma (MM), but their impact should be measured against the expected outcome in patients failing current therapies. However, the natural history of relapsed disease in the current era remains unclear. We studied 286 patients with relapsed MM, who were refractory to bortezomib and were relapsed, refractory, or ineligible, to an IMiD (Immunomodulatory Drug), with measurable disease and ECOG PS of 0, 1 or 2. The date patients satisfied the entry criteria was defined as time zero (T_0). The median age at diagnosis was 58 years and time from diagnosis to T_0 was 3.3 years. Following T_0, 213 (74%) patients had a treatment recorded with one or more regimens (median=1; range 0-8). The first regimen contained bortezomib in 55 (26%) patients and an IMiD in 70 (33%). A minor response

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or better was seen to at least one therapy after T_0 in 94 patients (51%) including >=partial response in 69 (38%). The median overall survival and event free survival from T_0 were 9 and 5 months respectively. This study confirms the poor outcome once patients become refractory to current treatments. The results provide context for interpreting ongoing trials of new drugs.

Keywords

multiple Myeloma; relapse; natural history; survival

INTRODUCTION

Survival of patients with multiple myeloma (MM) has improved during the past decade with the introduction of Immunomodulatory Drugs (IMiDs; thalidomide and lenalidomide), and the proteasome inhibitor bortezomib.(1-10) However, MM remains incurable and new therapies are required for continued disease control. In fact, several new drugs are currently undergoing evaluation, and many appear promising based on initial results.(5, 11) One of the difficulties in interpreting the early results of these newer therapies from the small single arm studies has been the lack of information about natural history of MM in the relapsed patient population. While this type of information is available for patients receiving the older therapies, such data is lacking for patients relapsing after the new therapies. However, this information can be beneficial for development of new therapies as early and accurate identification of the most promising treatments can allow prioritization of current clinical trials. Hence, the International Myeloma Working Group (IMWG) undertook this current study with the aim of determining the outcome of patients who have become refractory to bortezomib and at least one of the IMiDs. We also wanted to assess the types of therapy administered in this patient group and the response rates and duration of response to these treatments, to establish a context for assessing the results of ongoing trials with new drugs in myeloma.

PATIENTS AND METHODS

Patients were identified by review of medical records at multiple centers from across United States, Europe, and Asia. Patients had to be refractory to bortezomib (administered either alone or in combination with other agents), defined as no response (less than partial response) while receiving therapy with a prior bortezomib-containing regimens or progression on or within 60 days of a bortezomib-containing regimen. In addition, patients should have relapsed and/or were refractory, intolerant, or ineligible (in the opinion of the treating physician) to receive treatment with an immunomodulatory drug (IMiD; thalidomide OR lenalidomide). The date they met this criteria was defined as time zero (T_0). Given the goal of using this data as a benchmark for assessing future clinical trial results, we only included patients who would typically be considered for participation in a clinical trial. Hence, patients had to have ECOG performance status of 0, 1, or 2 as well as measurable disease at T_0 (defined conventionally as a serum M protein ≥1.0 g/dL or 24 hour urine M-protein excretion ≥200 mg or bone marrow plasma cells ≥30%). Patients with prior allogeneic stem cell transplantation were excluded from the study.

Clinical and laboratory data pertaining to the time of diagnosis and from the time of individual relapses were obtained from clinical records. The dates of initiation and discontinuation of each treatment regimen as well as the reason for discontinuation were identified, with specific attention to confirm use and discontinuation of IMiDs and bortezomib due to emergence of resistance or toxicity. Detailed data collection sheets were developed, that were used at all the study sites for uniformity of data collection. The data were sent to a centralized area (Cancer Research And Biostatistics, Seattle, WA) for analysis in a de-identified fashion. Institutional Review Boards from each site approved the study and the use of patient medical records and was conducted in accordance with the principles of the Declaration of Helsinki.

The response categories were defined according to the EBMT or IMWG criteria, and the response rate was defined as the proportion of patients achieving at least a partial response, from among those patients with valid response data. Patients who did not receive a myeloma regimen following time zero were not included in the response rate analysis. The response rate and best response were calculated for each regimen used after T_0. Duration of response was defined as the length of time between the date a patient first achieved a partial response or greater response level, following time zero and the earlier of the dates at which criteria for progression (defined by EBMT or IMWG criteria) were met or the date of death. Patients who did not have a documented progression after achieving at least a partial response and who were still alive at last contact were censored for duration of response at the date of last contact. Patients who did not achieve a partial response or better following T_0, and patients for whom the date of such response was missing, were excluded from the duration of response analysis. Duration of response was estimated using the Kaplan-Meier method with the median duration of response summarized.

Overall survival (OS) was defined as the length of time between T_0 and the date of death. Patients without a recorded death date were censored for OS at their last contact date. Progression-free survival (PFS) was defined as the length of time between T_0 until the earlier of the date at which criteria for progression were met or the date of death. Patients who did not have a documented progression after T_0 and who did not have a recorded death date were censored for PFS at their last contact date. OS and PFS were estimated using the Kaplan-Meier method with the median survival durations summarized. A Cox regression analysis was performed to determine which prognostic factors at T_0 and/or at baseline were correlated with improved OS or PFS from T_0. Prognostic factors were dichotomized, where appropriate, using standard myeloma cutoffs. Prognostic factors with univariate p-values < 0.100 were considered for inclusion in the multivariate model. The multivariate model used a stepwise selection with an entry level of $p<0.10$; with backwards elimination set at $p<0.05$.

Time to Next Treatment (TNT) was defined as the length of time between the start of the first regimen following T_0 and the start of the second regimen following T_0. Patients who started both a first and second regimen following T_0, who do not have recorded start dates for these regimens, were excluded from this analysis. Patients who did not start a second regimen following T_0 were censored for time to next treatment at the date of last contact. TNT was estimated using cumulative incidence methodology, with the median TNT summarized. Death preceding the start of a second regimen following T_0 was treated as a

competing risk. Additional TNT estimates were generated for subsequent regimens where a sufficient number of patients have recorded start dates for the required treatment regimens. All analyses were performed using SAS version 9.1.3.

RESULTS

Complete data were available on 286 patients (from among 300 patients enrolled) and were included in the current analysis. These included patients from 14 sites (107 pts from 3 US sites; 115 from 5 European sites; and 64 from 1 Asian site. The median (range) age for the patient group was 58 years (30, 85) at diagnosis and 62 (35, 87) at time zero, and 176 (62%) were male. The median estimated follow up for the entire cohort from diagnosis was 5.8 years (95% CI; 5.1, 6.3) and the median time from diagnosis to T_0 was 3.3 years (range, 0.2-18.7). The baseline characteristics from diagnosis and from T_0 are as shown in Table 1. In terms of prior therapy, by definition all patients had previous therapy with bortezomib and were considered refractory to bortezomib. With respect to prior IMiD exposure, 205 and 79 patients respectively met the entry criteria based on their previous treatment with thalidomide or lenalidomide. The eligibility reasons for the thalidomide patients were: 81 relapse, 23 refractory, 69 intolerant, 11 both relapse and refractory, 5 both refractory and intolerant, 5 both relapse and intolerant and 1 person was missing this information. The eligibility reasons for the Lenalidomide patients were: 37 relapse, 20 refractory, 9 intolerant, 8 both refractory and relapse, 1 both refractory and intolerant and 4 relapse and intolerant. The drug that patients were relapsing on or refractory to immediately prior to (or closest to) T_0 was bortezomib in 73% and an IMiD in 27%.

Initial therapy following time zero

We first examined the types of therapy that were employed immediately following T_0. Only 213 patients (74%) had a treatment identified in the medical records following T_0 and the median time to first treatment following T_0 was 0.5 months. The drugs utilized (alone or in combinations) for the initial treatment of the relapsed refractory disease are detailed in Table 2. Interestingly, in this group of patients who met the criteria for having bortezomib refractory disease, 55 patients (25%) received a bortezomib containing treatment regimen immediately following T_0. Bortezomib alone or with dexamethasone was the most common bortezomib based regimen used (41%) followed by the combination of bortezomib, lenalidomide or thalidomide, and dexamethasone (17%). Thalidomide or lenalidomide was included in the initial treatment in 70 patients (32%). As would be expected, corticosteroids were part of the treatment in 157 (74%) patients, including 17 (8%) patients receiving steroids as single agents. Alkylating agents (melphalan and cyclophosphamide) was the most common class of drugs employed at this stage of the disease with 97 (46%) patients receiving a regimen that contained one of these drugs. Interestingly, 22 (11%) and 25 (12%) of patients received cisplatin and etoposide respectively, likely a reflection of use of regimens such as DT-PACE.

Nearly a quarter of patients achieved a partial response or better to the first regimen used after T_0 (50/213, 24%) including a very good partial response (VGPR) or better in 7% of the patients. Another 22 (7%) patients had a minor response and 36 (10%) had stable disease as

their best response to the treatment. Nearly half of the patients (104; 49%) had progressive disease to the first line of therapy following T_0 or a response was not assessable. The response rates and categories of responses observed are as detailed in Table 3. We also analyzed responses by regimen based on whether patients received a regimen containing the newer drugs (bortezomib, lenalidomide or thalidomide) or not. The response rate to the first treatment regimen was 24% among the 106 patients treated with a regimen containing a bortezomib, lenalidomide or thalidomide compared to 25% among the 107 patients receiving a regimen not containing one of these three drugs (Table 2). The breakdown of the response rates and the response categories for the newer drug containing regimen and those without these three drugs are provided in supplementary tables 1 and 2. The primary reasons for discontinuing the regimens are detailed in supplementary table 3. The most common reason for discontinuation of a treatment regimen was lack of response or disease progression followed by adverse event or completion of planned course of treatment. A clear reason for discontinuation could not be ascertained for about 17% of the regimens.

Subsequent therapies

The subsequent drugs used for treatment within the different lines of therapy are detailed in Table 2, along with the best responses by regimen number (for the first five regimens) in Table 3. The median time to next treatment following the first regimen after T_0 was 0.5 months. Interestingly, bortezomib and the IMiDs continued to be used in the subsequent regimens in a significant proportion of patients. Overall, 75 (35%), 51 (24%) and 63 (30%) patients received bortezomib, thalidomide or lenalidomide at some point after T_0. The breakdown of the response categories for the newer drug containing regimen and those without these three drugs are provided in supplementary tables 1 and 2. Overall, 94 (44%) of patients had a minimal response or better including a partial response or better in 69 (32%) patients at some point during the post T_0 period. The median times to achieving any degree of response are shown in Figure 1. The primary reasons for discontinuing the regimens are detailed in supplementary table 3 (supplementary data).

We also examined the frequency of use of high dose therapy and stem cell transplantation in this population. There were 44 patients who received a transplant after time zero, the median time to transplant was 96 days (approximately 3 months) with the first transplant received after 5 days and the last one received after 936 days (approximately 2 years and 5 months). Half of the patients who received a transplant after T_0 received it between 37 days and 203 days. Among the 44 patients receiving a transplant after T_0, this was the first transplant in 16 patients (i.e., no transplants done before T_0).

Survival outcomes

The median event free survival (EFS) for the entire cohort was 5 months (95% CI; 4, 6) from T_0 and the median overall survival (OS) was 9 months (95% CI; 7, 11) from T_0 (Figure 2A). The overall survival from diagnosis for the entire cohort was 56 months (95% CI; 44, 72). When considering only the patients considered refractory at T_0 (n=90) the median EFS and OS from T_0 was 5 months (95% CI; 4,8) and 10 months (95% CI; 7,14) respectively (Figure 2B). We also examined the overall survival from T_0 based on whether the patients first met criteria for bortezomib refractoriness or the IMiD criteria for inclusion in the study.

The median OS from T_0 was 9 months (95% CI; 7,11) for patients meeting the bortezomib criteria first, compared to 9 months (95% CI; 7,13) for patients meeting criteria for IMiDs first (P=0.44). We also separately examined the outcome from the date they became refractory to bortezomib. The median overall survival from the time they were considered refractory to bortezomib (as defined for the purposes of the study) was 11 months (95% CI; 10,14). Similarly, the median overall survival from the date patients were considered to be relapsed/ refractory/ ineligible to an IMiD was 22 months (95% CI; 15, 26) for lenalidomide patients and 16 months (95% CI; 14, 22) for thalidomide patients. The median OS from the time they were refractory to anyone of the novel agent was 10 months (95% CI: 7, 14).

The per regimen outcome of patients on this study is detailed in Table 4, which provides patient disposition data in terms of treatment status and survival at various time points from T_0. The number of patients in each successive treatment regimen who died during that regimen, received another treatment, or are still receiving that regimen are shown in the Table. The median event-free survival (in months) for each regimen is shown in Table 4.

We also examined outcome on the basis of whether a transplant was performed following T_0. The median overall survival following T_0 among the 43 patients who had at least one transplant after T_0 was 15 months (95% CI; 14, 18) compared to 7 months (95% CI; 6, 9) for patients without a transplant post T_0 (Figure 3A). As the transplanted patients had a guaranteed survival time till they got to transplant, we also did a landmark analysis comparing patients who had a transplant within 3 months of T_0 with patients who survived at least 3 months, but did not have a transplant during that time period, and found that the OS from T_0 was comparable between the groups (Figure 3B). A similar analysis was performed using different time points after T_0 for landmark (6, 9 and 12 months) and as with the previous analysis, no differences were seen in the OS from T_0 based on whether a transplant was performed or not. Since transplant is often applied in a delayed fashion with comparable results as an early transplant, we separately examined the outcome of 16 patients who had received their first transplant after T_0 as these patients likely represent those who opted for a delayed transplant. The median EFS and OS for these 16 patients were 13 months (95% CI; 10, 21) and 18 months (95% CI; 13, 44) respectively.

Prognostic Factors

We performed additional analyses to identify prognostic factors predicting event free survival and overall survival following T_0. Factors impacting the OS and EFS from T_0 identified in a univariate analysis are shown in Table 5. In a multivariate model employing step wise selection that included most of these variables only B2M > 5.5 mg/L at T_0 (HR: 3.58; P=0.047) and an albumin < 3.5 mg/dL at T_0 (HR: 5.62; P=0.009) were independently significant for overall survival. Given that B2M and serum albumin, the two components of ISS, was prognostic for survival in this patients group, we examined the outcome based on ISS stage at T_0. As shown in Figure 4A, the ISS stage was prognostic for overall survival following T_0, with median survivals of 12, 8, and 4 months for ISS stages 1, 2, and 3 respectively. However, the ISS stage did not predict event free survival in this group.

We also specifically examined the prognostic value of cytogenetic features such as hypodiploidy, t(4,14), or del 17p on metaphase cytogenetics or FISH. High risk patients

were identified by the presence of any of these three abnormalities identified at either diagnosis or at T_0. Those with none of the abnormalities on cytogenetics/ FISH at either of the time points were considered as the standard risk. Patients with any of the high-risk abnormalities had both an inferior EFS as well as OS (Figure 4B) from T_0. We also examined the prognostic value of serum creatinine; an elevated creatinine at T_0 predicted for poorer EFS and OS from T_0 (Figure 4C). Given that nearly 20% of the patients survive beyond 2 years, we specifically compared the baseline characteristics of those who survived beyond 2 years to those who died within 3 months of reaching T0. The results of the comparison, which is detailed in Supplementary table 4, demonstrated significant differences between the two groups in terms of lower B2M and less patients with ISS stage 3 both at diagnosis and at T0, normal creatinine at T0, and at least a partial response or better prior to T0 among the group with longer survival.

Given the differences in terms of speed of drug approval process and availability in different countries, we also separately examined the outcomes among patients seen at the centers in United States. Among the 107 patients from US sites, the median time from diagnosis to T_0 was 4 years and these patients had a median of 3 therapies by T_0. Of these patients, 99 (93%) had at least one therapy documented post T_0 and the median (95% CI) EFS and OS from T_0 was 5 (4,6) and 13 (10,16) respectively.

DISCUSSION

New developments in therapy over the past decade have changed the treatment paradigm for myeloma and resulted in significant improvement in survival.(9, 10, 12) However, myeloma remains incurable and new treatments are currently being studied. The results of the new drugs, especially those from the single arm trials, should be interpreted in the context of the expected outcomes in this group of patients. However, the rapid pace of development in the area of myeloma therapy has precluded a good understanding of the outcome among patients who have exhausted the currently available therapies. The natural history of relapsed myeloma has been studied previously, but before the new drugs became available. Specifically, one study included 578 patients with newly diagnosed MM who were followed up and monitored throughout their clinical course at a single institution between 1985 and 1998.(13) The overall survival (OS) for the 578 patients at 1, 2, and 5 years was 72%, 55%, and 22%, respectively; the median OS from initial therapy was 28.4 months. The median OS of 355 patients who had relapsed at the time of the analysis was 17.1 months from initiation of the second therapy, and 84% died within 5 years. This study revealed decreasing response duration with increasing number of salvage regimens, likely reflecting acquired drug resistance and an increasing proliferative rate of the myeloma cells. The median survival of patients who had 3 previous therapies in the initial trials of bortezomib for similar patients was 12 months compared to the 5 months seen in this study demonstrating clinically relevant activity for the drug.(14) Similarly, the overall survival of heavily pre-treated patients in the initial study of thalidomide demonstrated a 58% overall survival at 12 months, again demonstrating improvement over historical data.(15) However, with the improved survival due to the widespread use of IMiDs and bortezomib this data is not reflective of the current practice.

It is important to understand the clinical course of patients, who have become refractory to one or more of these agents and hence our study was focused on patients considered refractory to bortezomib and at least one of the IMiDs. However, these drug scan be used in combination with a variety of agents, giving rise to multitude of regimens and detailed information regarding the specific combinations these drugs were part of is not available. In the current study, we specifically enrolled patients who would be considered eligible for a clinical trial, by restricting to patients with good performance status and those with measurable disease at the time point where they would be considered refractory to bortezomib and to one of the IMiDs. The definitions for refractory disease were based on the recommendations of the ASH/FDA Panel on clinical endpoints in myeloma.(16) Patients eligible for clinical trials generally have better survival outcomes irrespective of diseases being studied(17, 18) and does limit the generalizability of the results to myeloma patient population as a whole; but at the same time allows better comparison with the current clinical trials. We also required only failure of either one of the IMiDs to be eligible for the study, taking into account the varied availability/ accessibility of the two drugs in different parts of the world. By incorporating patients from several large centers from different geographical regions, similar to what is often seen in the large multicenter trials, we hoped to overcome the effect of heterogeneity of clinical practice. By using a uniform approach, we have therefore sought to minimize the heterogeneity in reporting that can happen in a multicenter study such as this.(19, 20)

One of the most striking aspects of our finding has been the response rates seen in this patient population with the first regimen employed after they become refractory to the new drugs. The overall response seen in a third of the patients can be due to several factors. With the advent of the new drugs, older drugs such as alkylators are increasingly being relegated to later stages of disease. It has been shown in the setting of transplant, that patients relapsing after IMiD therapy can obtain comparable response duration with delayed transplant as with early transplant suggesting preservation of sensitivity of tumor cells to alkylators.(21) In fact, alkylators were the most common drugs employed for treatment of patients once they stopped responding the newer drugs in the current study. In addition, transplant is increasingly being used later in the disease course as well as second transplants as salvage therapy. In fact in the current study nearly 20% of patients received a transplant after T_0, a third of which were first time transplants. Finally, many of the new drugs can be used again in patients who initially responded but had stopped responding to it, with variable degree of responses.(22) Bortezomib has activity with retreatment (22-25) and lenalidomide has significant activity in thalidomide refractory population.(6) As in this study, many of the current clinical trials include a similar mix of patients and the response rates seen in these phase 2 trials and phase 3 trials utilizing standard of care for control arm should be considered in the context of these findings. In contrast to previous studies, we do not see a progressive decline in response rates and duration of response.(13) This may be a reflection of increasing treatment choices that are available compared to a decade ago when alkylating agents and steroids formed the basis of myeloma treatment.(26) Also, some degree of selection bias leading to patients with better performance status as well as patients with more indolent disease being considered for multiple therapies cannot be excluded.

Despite the initial responses of over 30% in this group of relapsed and refractory patients, the median EFS of 5 months and OS of 9 months highlight the limited durability of these responses and the poor overall outcome among patients who are no longer responding to the existing newer therapies. This is consistent with recent reports showing poor outcome of patients refractory to IMiDs even in the context of SCT.(27) Another important finding from the study was the continued value of conventional prognostic factors in this patient group. Interestingly, the ISS staging parameters such as B2M and albumin at T_0 best predicted survival outcome in this group of patients and should be taken into account when comparing results between different trials and could be incorporated as stratification factors in clinical trials of new drugs.(28) Unfortunately, limited data was available with respect to cytogenetic and FISH features in the current study. However, examination of the available data suggests retained prognostic value for these characteristics. Patients with high risk genetic abnormalities such as t(4;14), t(14;16) and hypodiploidy had shorter duration of responses and poorer overall survival compared to the other patients.(29-31) Similar to previous studies in the context of newly diagnosed disease, the presence of renal insufficiency predicted to poorer survival. This might to some extent reflect the lack of enrollment in clinical trials of patients with compromised renal function. Clearly the results presented here have some drawbacks, particularly the inability to study patients who are refractory to individual IMiDs, the prognostic value of all genetic risk factors in the context of specific therapies and the variations across different geographical areas based on clinical practices and drug availability. An ongoing study is recruiting additional patients to extend the current analyses.

In conclusion, the current study provides valuable insights into the natural history of myeloma after it become non-responsive to the current therapies. Clearly there are some disadvantages with the current study in terms of only including ‘trial eligible’ patients and lack of uniform availability of modern prognostic factors such as cytogenetic and FISH abnormalities. However, the results provide an important reference point for comparison of the results of the ongoing phase 2 and possibly phase 3 trials of new drugs in myeloma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix

DISCLOSURES Authors Contributions: All authors (except JC, JH, JF and AH) provided patient data and were involved in manuscript preparation. JC, JH, JF and AH were involved in the statistical analysis.

CONFLICTS OF INTEREST

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David Siegel	No COI. Speakers Bureau for Celgene and Millenium
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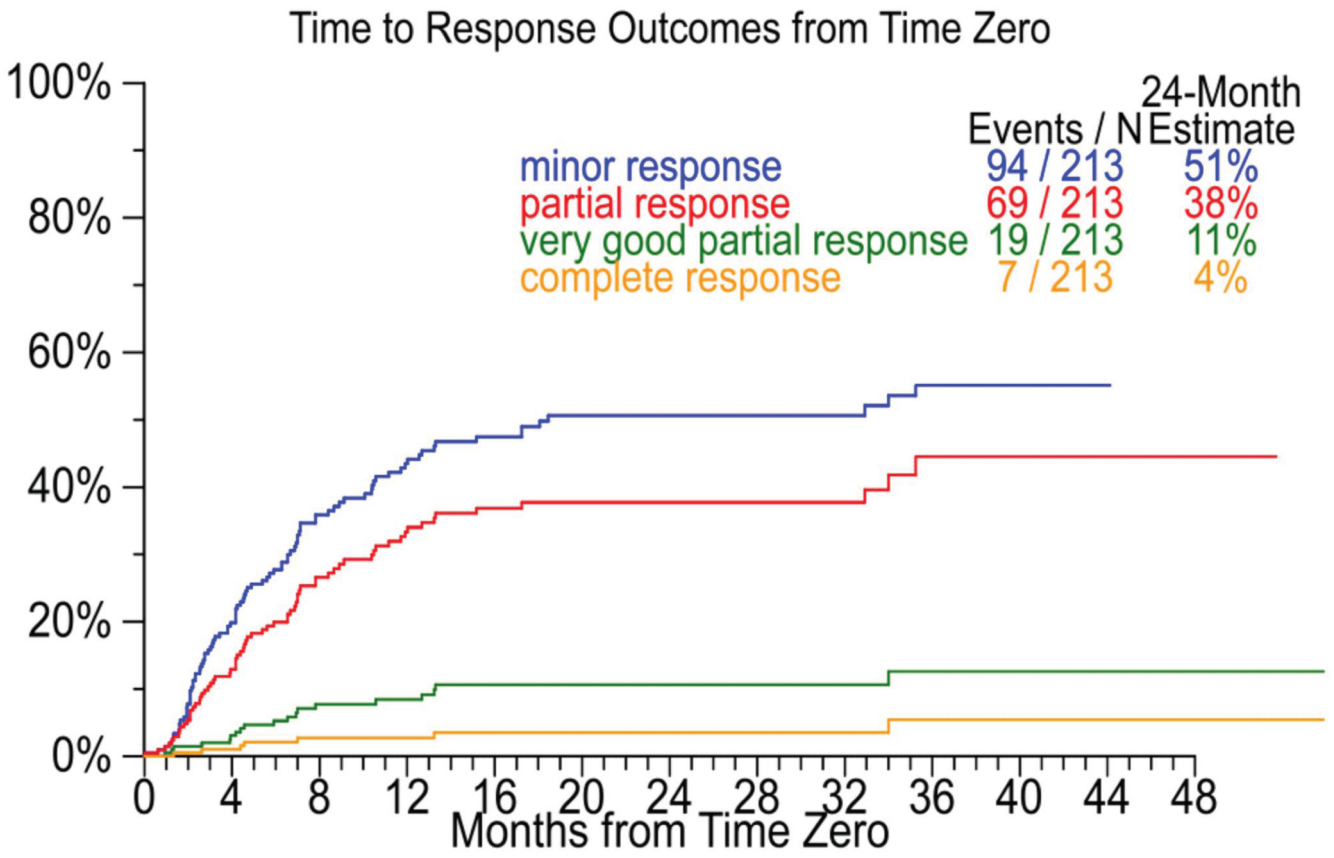
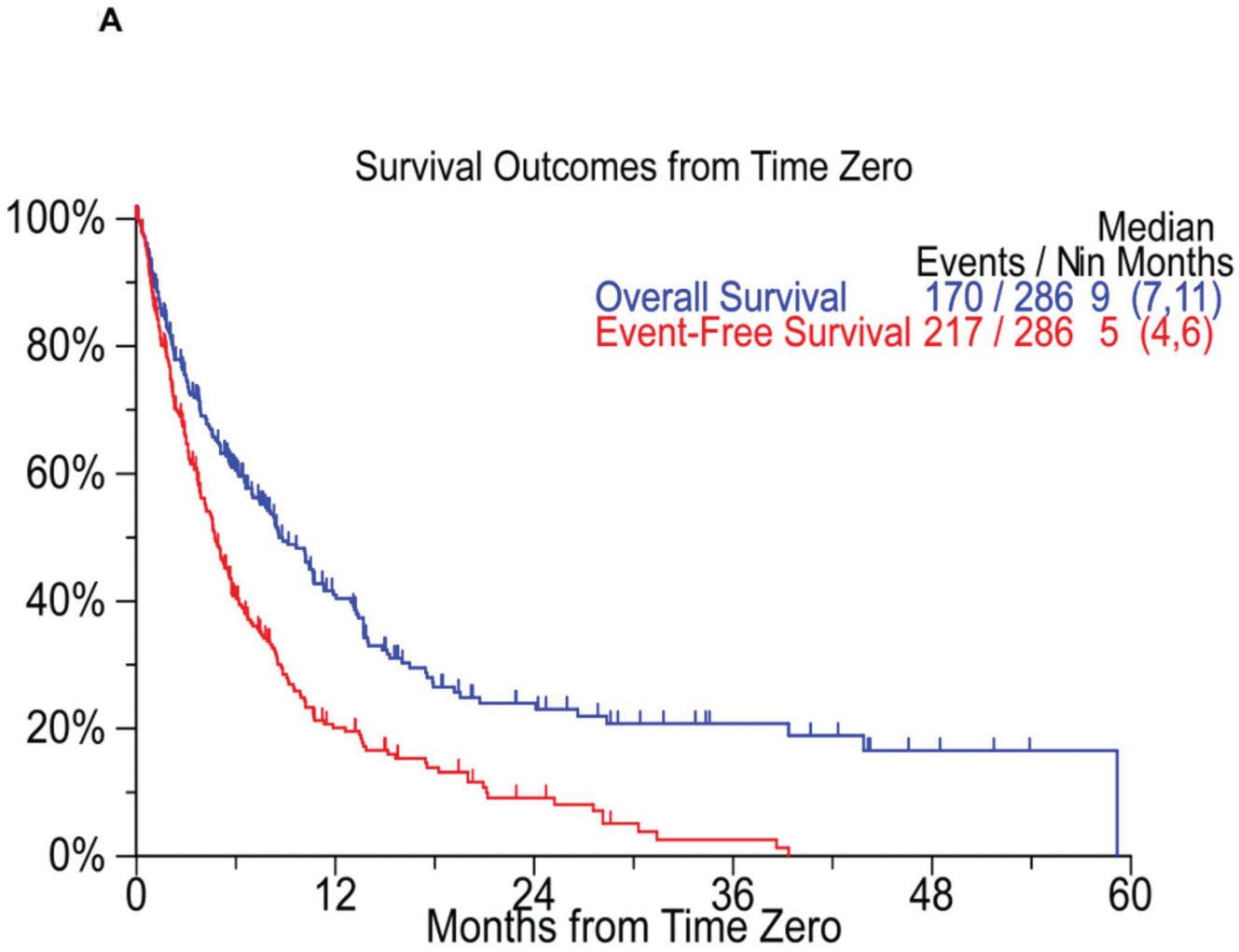


Figure 1.

Figure shows the time to response at any time after time zero (T_0) for the different categories of responses among 213 patients who received at least one treatment after T_0.



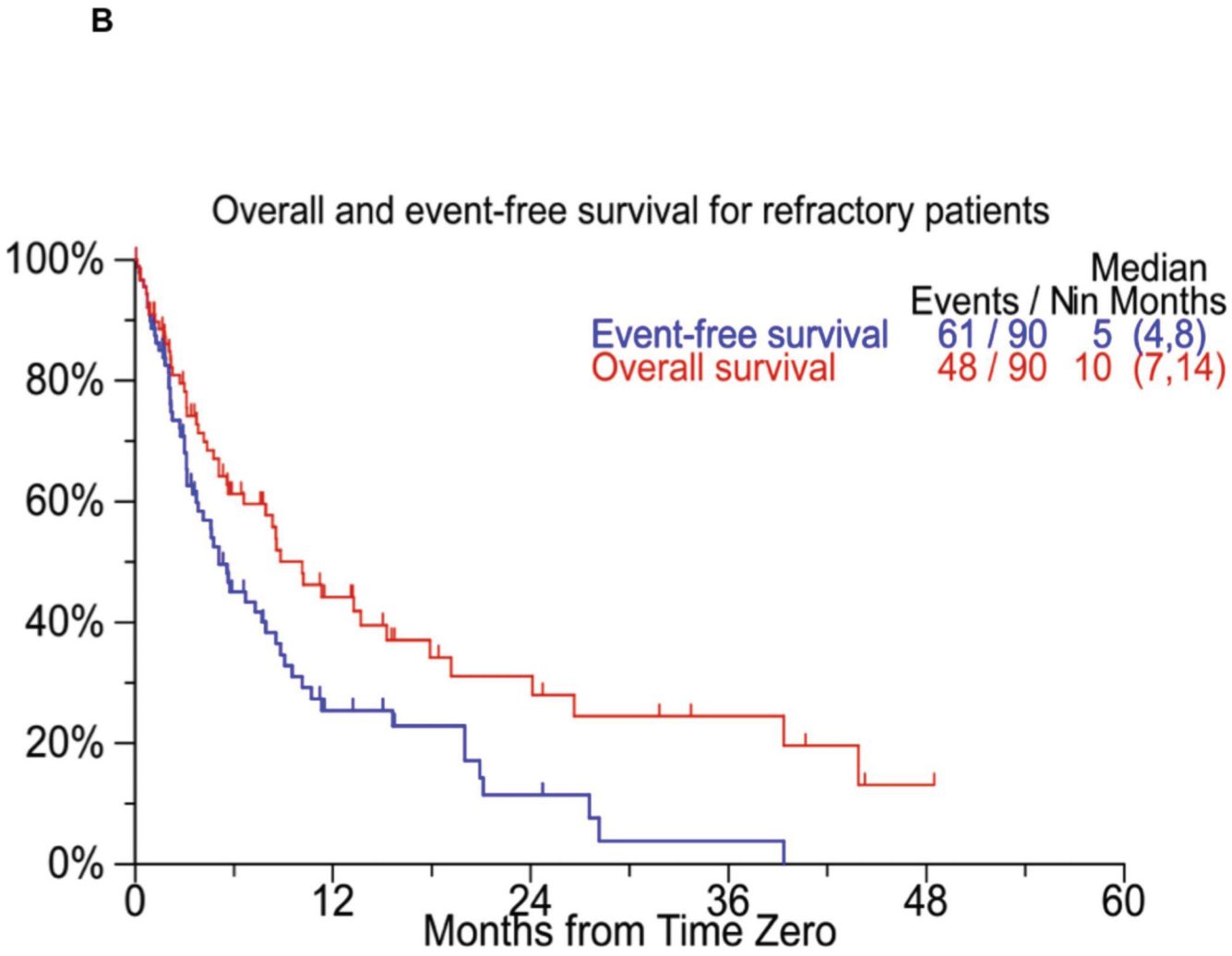
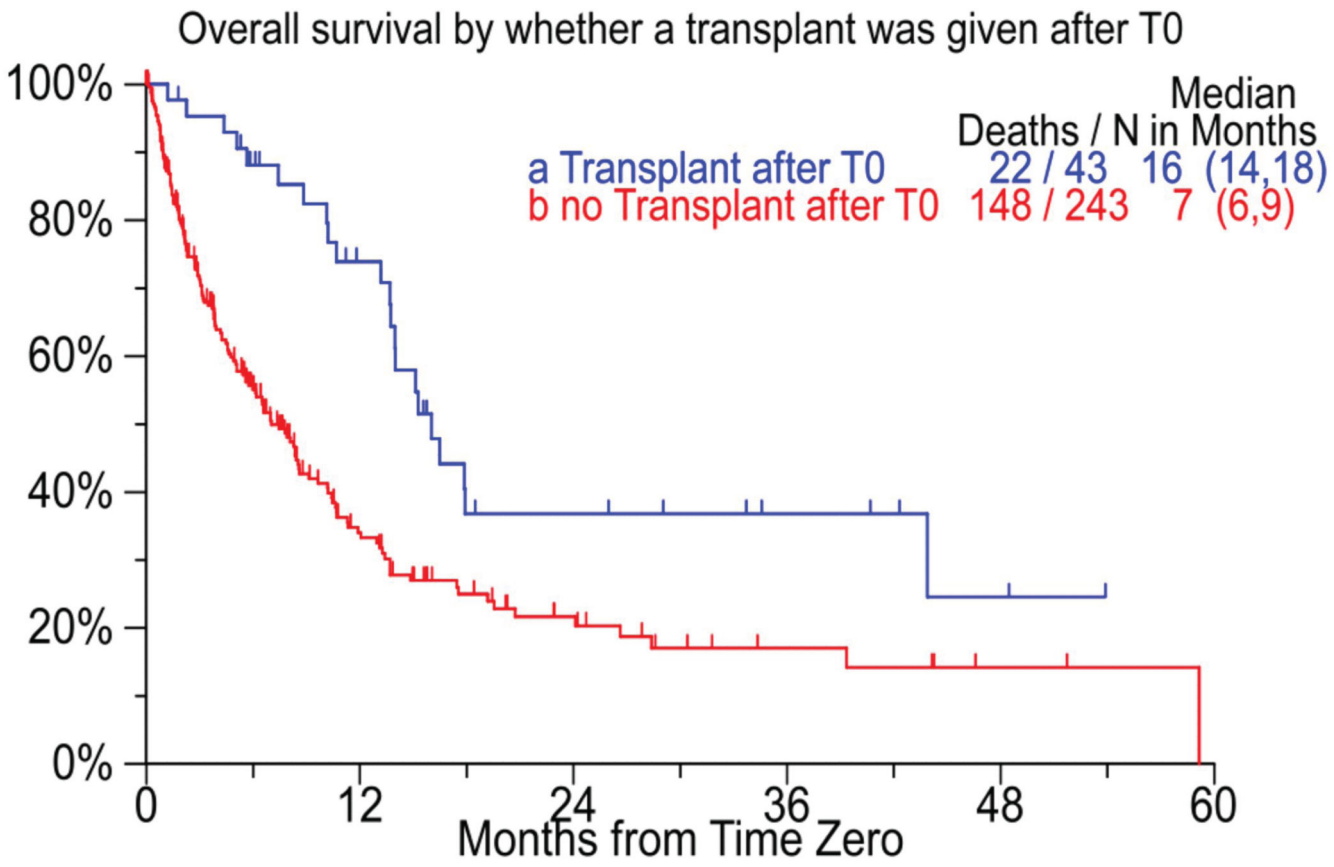


Figure 2.

Panel A shows the Kaplan Meier curves for event free survival (red curve, median 5 months) and overall survival (blue curve, median 9 months) from T_0 all patients (n=286) enrolled on the study. ***Panel B*** shows the Kaplan Meier curves for event free survival (blue curve, median 5 months) and overall survival (red curve, median 10 months) from T_0 for refractory patients (n=90).

A



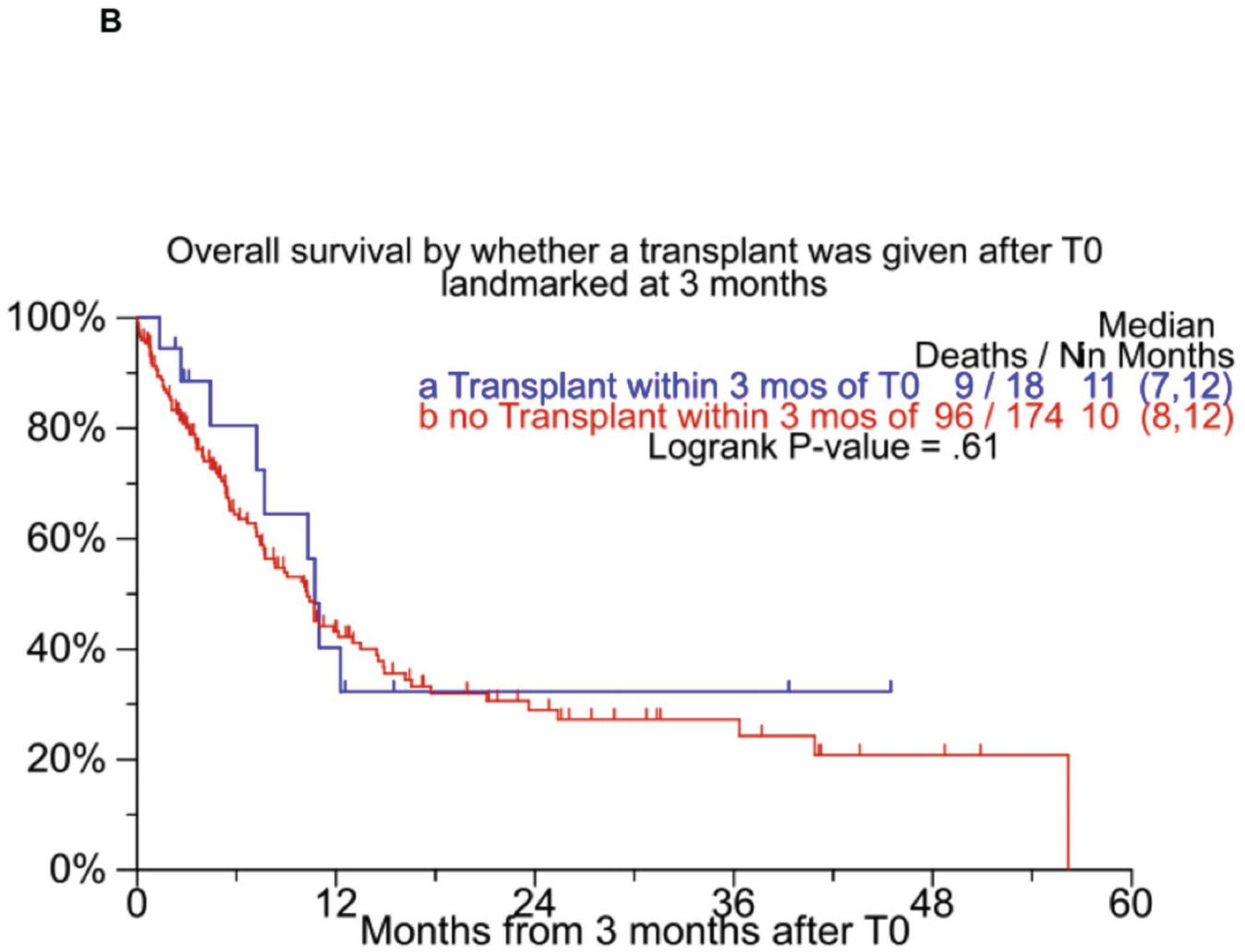
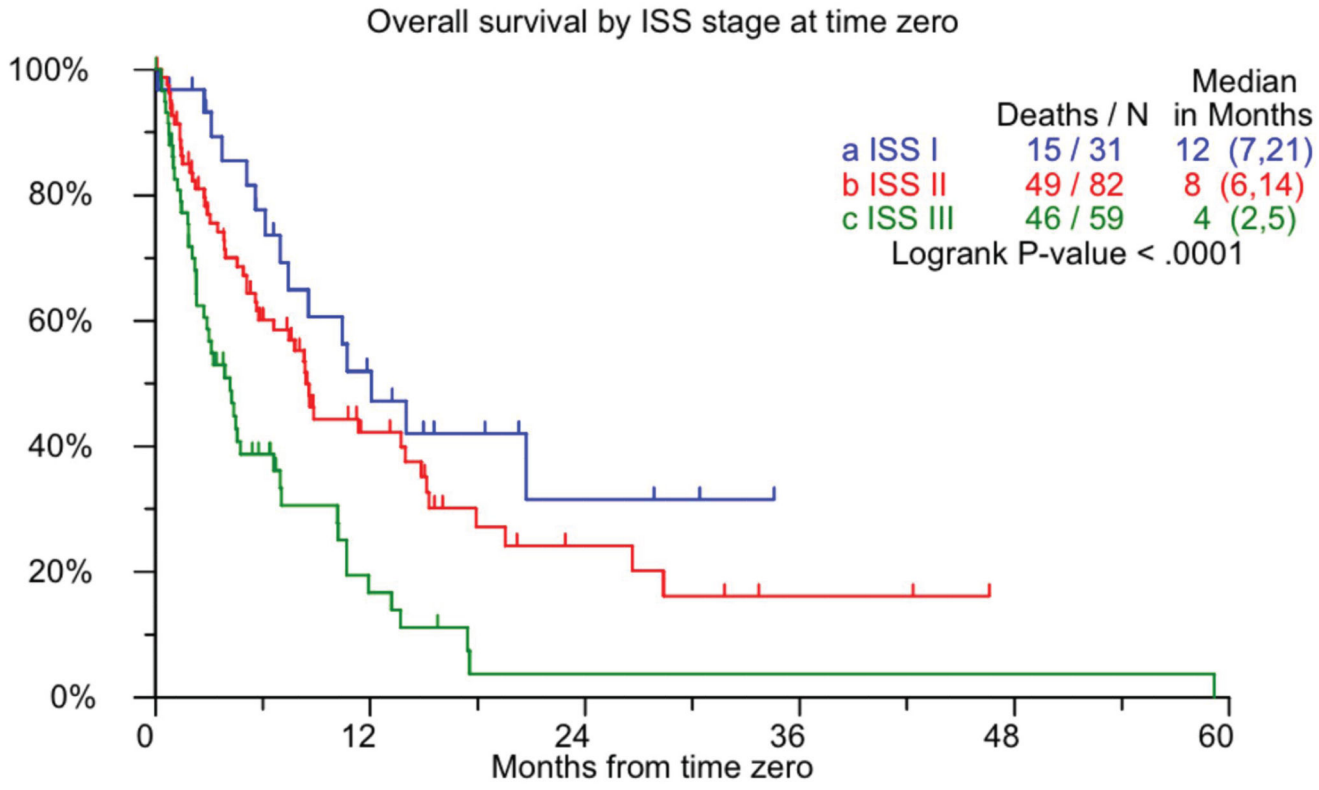


Figure 3.

Panel A shows the overall survival among patients who did or did not receive an autologous stem cell transplant at any time after T_0. ***Panel B*** shows a similar comparison, but is landmarked at 3 months by considering only transplants done within 3 months from T_0.

A



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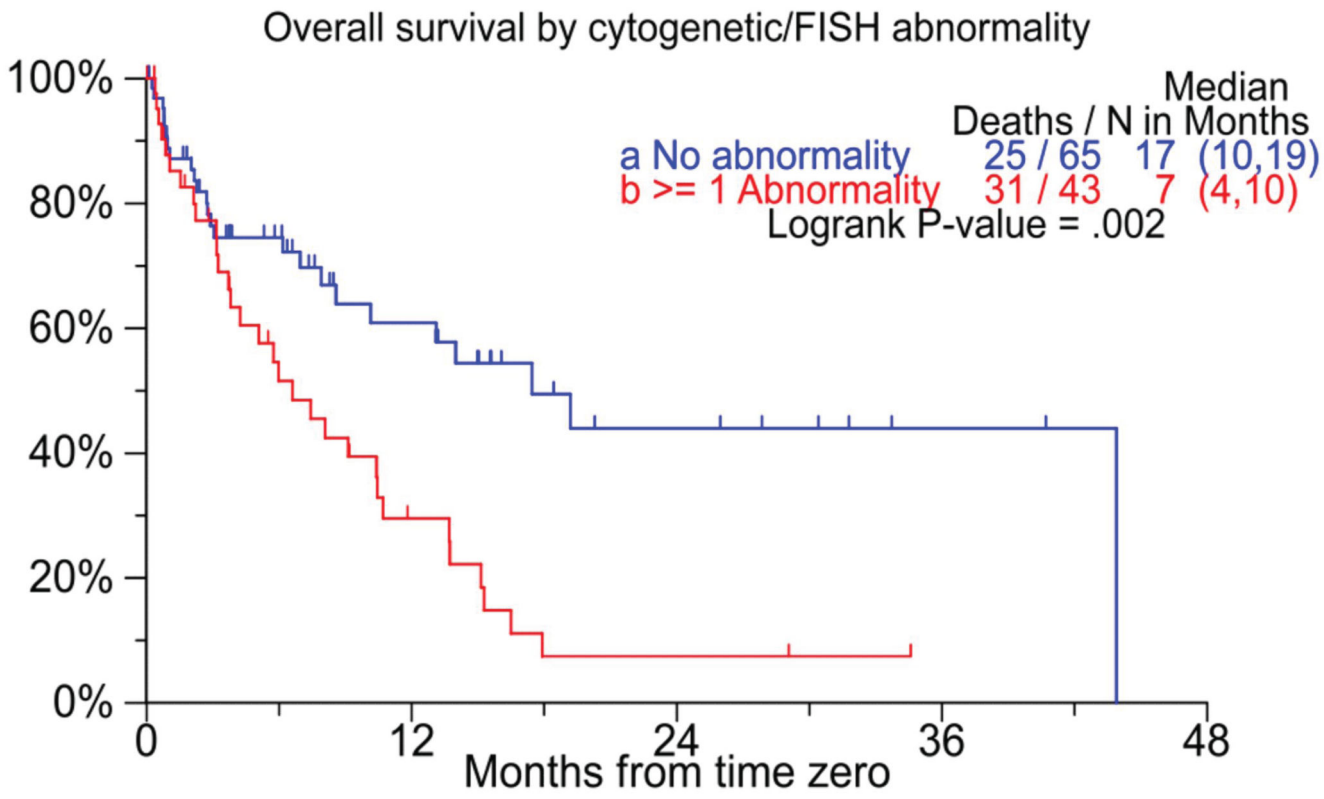

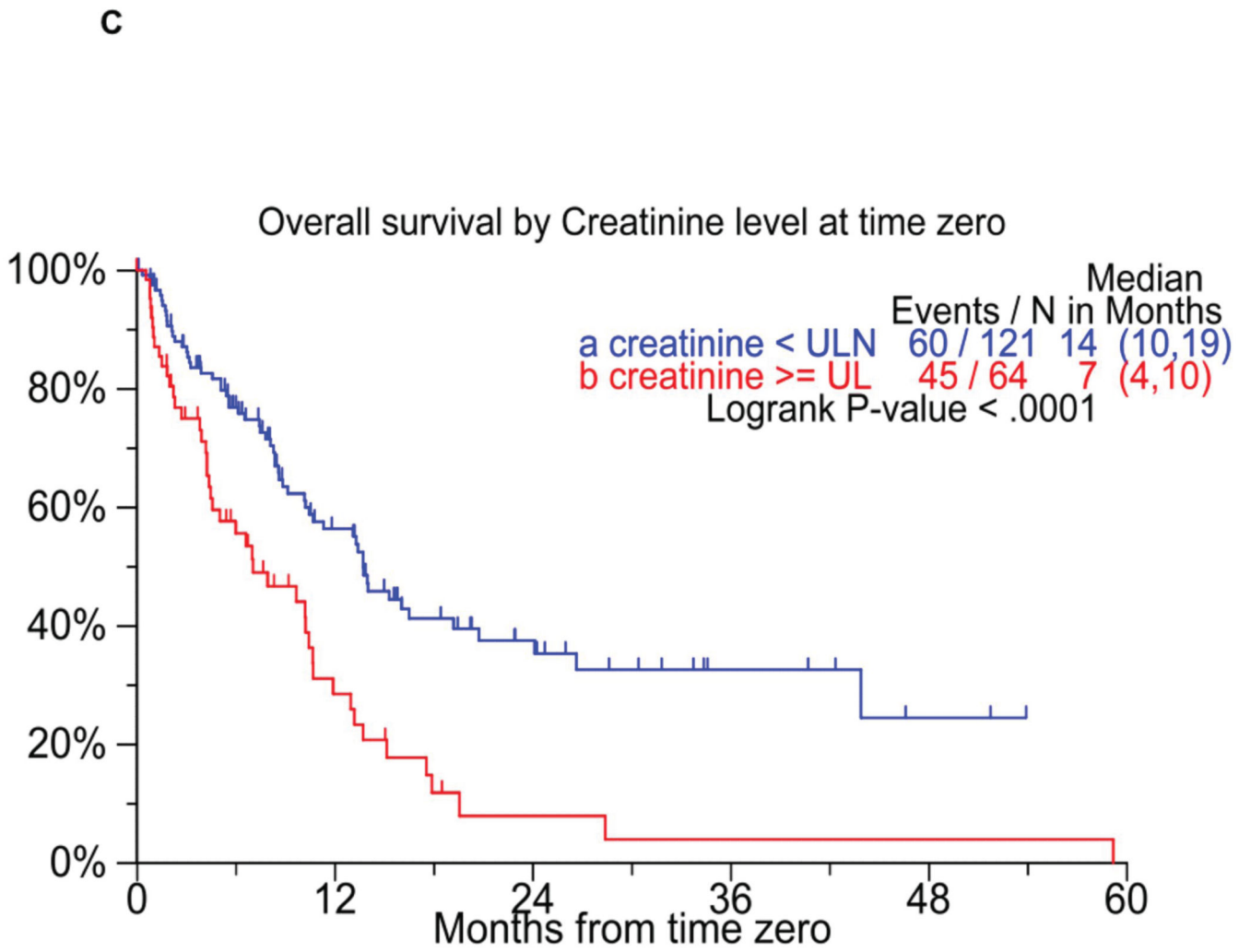

Figure 4.

Panel A shows the overall survival by ISS stage at T_0. ***Panel B*** compares the overall survival following T_0 among patients with with either t(4;14) or hypodiploidy, compared to the remaining patients. ***Panel C*** shows the overall survival among patients with elevated creatinine at T_0, compared to the remaining patients.

Table 1

Baseline characteristics at diagnosis and at Time zero (T0)

Factor		**n/N (%)**
Male		176/286 (62%)
Age >= 65 years at diagnosis		69/284 (24%)
Serum heavy chain at diagnosis	None	27/250 (11%)
	IgG	155/250 (62%)
	IgA	60/250 (24%)
Durie Salmon stage at diagnosis	Stage 1	14/216 (6%)
	Stage 2a	47/216 (22%)
	Stage 3a	152/216 (70%)
International Staging System (ISS) at diagnosis	Stage 1	63/208 (30%)
	Stage 2	87/208 (42%)
	Stage 3	58/208 (28%)
Diagnosis Creatinine > ULN		84/212 (40%)
No bone lesions at diagnosis		63/256 (25%)
>= 4 bone lesions at diagnosis		102/256 (40%)
Diagnosis FISH	All abnormalities	63/95 (66%)
	del 17p, t(4;14), t(14;16)	21/95 (22%)
	13q-	41/95 (43%)
	t(11;14)	9/95 (9%)
Diag. cytogenetic abnormalities		50/132 (38%)
Time zero (T_0)		
Age >= 65 yr at time zero		115/284 (40%)
International Staging System (ISS) at T_0	Stage 1	31/172 (18%)
	Stage 2	82/172 (48%)
	Stage 3	59/172 (34%)
FISH at T_0	All abnormalities	30/38 (79%)
	del 17p, t(4;14), t(14;16)	9/38 (26%)
	13q-	13/38 (34%)
	t(11;14)	3/38 (8%)
T_0 cytogenetic abnormalities		23/47 (49%)
At least 1 transplant prior to T_0		178/286 (62%)
>= 2 transplants prior to T_0		42/286 (15%)

n- Number with Factor, N- Number with Valid Data for Factor

Table 2

Response rate by regimen number, following time zero (T_0)

Drugs included in the regimen	Regimen number following time zero (T_0)				
	1	**2**	**3**	**4**	**5**
Number of patients	213	90	49	27	18
BCNU (Carmustine)	4 (2)	1 (1)	2 (4)	1 (4)	0 (0)
Bortezomib	55 (26)	22 (24)	19 (39)	7 (26)	8 (44)
Cisplatin	22 (10)	6 (7)	3 (6)	0 (0)	2 (11)
Cyclophosphamide	66 (31)	22 (24)	10 (20)	6 (22)	3 (17)
Corticosteroids (part of combination)	140 (66)	47 (52)	26 (53)	20 (74)	9 (50)
Corticosteroids alone	17 (8)	6 (7)	2 (4)	1 (4)	0 (0)
Doxorubicin	43 (20)	11 (12)	6 (12)	1 (4)	3 (17)
Etoposide	25 (12)	4 (4)	3 (6)	0 (0)	2 (11)
Lenalidomide	41 (19)	13 (14)	8 (16)	6 (22)	3 (17)
Melphalan	31 (15)	15 (17)	9 (18)	7 (26)	0 (0)
Thalidomide	29 (14)	15 (17)	7 (14)	3 (11)	2(11)
Vincristine	18 (8)	3 (3)	2 (4)	2 (7)	1 (6)
Best response (>=PR) %	51/213 (24%)	17/90 (19%)	12/49 (24%)	6/27 (22%)	1/18 (6%)
Best response (>=MR) %	73.213 (34%)	25/90 (28%)	14/49 (29%)	8/27 (30%)	3/18 (17%)
Best Response with a regimen containing bortezomib, lenalidomide or thalidomide %(number of patients)	25/106 (24%)	6/42 (14%)	7/27 (26%)	1/14 (7%)	0/10 (0%)
Best Response with a regimen without bortezomib, lenalidomide or thalidomide %(number of patients)	26/107 (24%)	11/48 (23%)	5/22 (23%)	5/13 (38%)	1/8 (13%)
Median duration of treatment (mos.)	1.9	1.3	1.4	1.7	1.9

PR: partial response; MR: Minor response

Table 3

Best response to regimen, by regimen number, for the initial regimens following time zero

Regimen / Factor	1st	2nd	3rd	4th	5th
Number of patients	213	90	49	27	18
Complete response	4/213 (2%)	1/90 (1%)	0/49 (0%)	1/27 (4%)	0/18 (0%)
Very good partial response	10/213 (5%)	2/90 (2%)	1/49 (2%)	2/27 (7%)	0/18 (0%)
Partial response	36/213 (17%)	14/90 (16%)	11/49 (22%)	3/27 (11%)	1/18 (6%)
Minor response	22/213 (10%)	8/90 (9%)	3/49 (6%)	2/27 (7%)	2/18 (11%)
Stable disease	36/213 (17%)	16/90 (18%)	8/49 (16%)	6/27 (22%)	4/18 (22%)
Progression	48/213 (23%)	25/90 (28%)	15/49 (31%)	5/27 (19%)	3/18 (17%)
No or Unknown response	56/213 (26%)	24/90 (27%)	11/49 (22%)	8/27 (30%)	8/18 (44%)

n/N (%): n- Numlber with Factor, N- Number with Valid Data for Factor

Table 4

Patient experience by regimen (from initiation of each regimen)

	Regimen number since time zero				
	First (n=213)	**Second (n=91)**	**Third (n=49)**	**Fourth (n=27)**	**Fifth (n=18)**
1 mos.	14/7/127/65	3/7/47/33	3/3/27/16	0/0/17/10	1/0/9/8
2 mos.	30/19/93/71	9/15/30/36	6/11/17/15	1/3/9/14	2/3/5/8
3 mos.	40/36/64/73	13/22/24/31	9/14/1214	2/4/9/12	2/5/4/7
4 mos.	44/46/52/71	15/26/17/32	9/16/9/15	2/9/7/9	2/5/4/7
5 mos.	48/59/36/70	17/31/12/30	9/16/8/16	2/12/5/8	2/5/3/8
6 mos.	52/67/29/65	19/35/6/30	12/18/6/13	3/13/5/6	4/5/1/8
9 mos.	60/74/13/66	20/42/4/24	13/21/4/11	4/18/0/5	4/7/0/7
12 mos.	64/80/6/63	21/45/2/22	13/23/2/11	4/18/0/5	4/7/0/7
15 mos.	68/84/5/56	22/46/2/20	13/24/1/11	4/18/0/5	4/7/0/7
18 mos.	68/84/5/56	22/47/2/19	13/27/0/9	4/18/0/5	4/7/0/7
21 mos.	68/86/4/55	22/48/1/19	13/27/0/9	4/18/0/5	4/7/0/7
24 mos.	68/87/3/55	22/48/0/20	13/27/0/9	4/18/0/5	4/7/0/7
Median EFS	3.2 mos.	2.6 mos.	2.2 mos.	4.6 mos.	3.6 mos.

XX/XX/XX =cumulative number of patients receiving regimen who died during treatment/cumulative number of patients started a new regimen/ number of patients who were still on regimen/cumulative number of patients still alive who went off regimen and did not start another regimen

Table 5

Univariate analysis of prognostic factors for OS and EFS from T_0

		OS from Time Zero		EFS from Time Zero	
Variable	**n/N (%)**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
At Diagnosis					
Serum heavy chain: None	27/250 (11%)	1.73 (1.03,2.89)	0.038	1.51 (0.94,2.42)	0.085
Serum heavy chain: G	155/250 (62%)	0.62 (0.45,0.86)	0.005	0.68 (0.51,0.91)	0.010
Serum heavy chain: A	60/250 (24%)	1.40 (0.98,2.01)	0.064	1.27 (0.92,1.76)	0.148
B2M >= 3.5 mg/L	123/226 (54%)	1.59 (1.12,2.26)	0.009	1.58 (1.15,2.16)	0.004
Platelet < 150,000/uL	50/229 (22%)	1.57 (1.06,2.32)	0.024	1.20 (0.83,1.72)	0.325
FISH t(4;14)	9/95 (9%)	2.14 (0.90,5.10)	0.086	2.15 (0.97,4.74)	0.058
Hypodiploidy	14/132 (11%)	1.86 (1.01,3.41)	0.045	1.53 (0.85,2.77)	0.158
At Time zero					
Age >= 65 yr	115/284 (40%)	1.34 (0.98,1.82)	0.063	1.11 (0.84,1.46)	0.471
Serum heavy chain: None	23/176 (13%)	1.86 (1.10,3.14)	0.021	1.50 (0.91,2.46)	0.114
Serum heavy chain: G	108/176 (61%)	0.49 (0.33,0.74)	<.001	0.58 (0.41,0.83)	0.002
Serum heavy chain: A	41/176 (23%)	1.69 (1.09,2.61)	0.020	1.54 (1.04,2.27)	0.029
Albumin < 3.5 g/dL	152/279 (54%)	1.73 (1.26,2.37)	<.001	1.47 (1.12,1.93)	0.006
B2M >= 3.5 mg/L	108/173 (62%)	2.36 (1.55,3.60)	<.001	1.71 (1.20,2.44)	0.003
B2M > 5.5 mg/L	59/173 (34%)	2.20 (1.50,3.25)	<.001	1.55 (1.09,2.21)	0.015
ISS Stage 3	59/172 (34%)	2.24 (1.52,3.31)	<.001	1.57 (1.10,2.24)	0.013
Creatinine > ULN	64/185 (35%)	2.19 (1.48,3.25)	<.001	1.50 (1.06,2.11)	0.022
FISH t(14;16)	3/38 (8%)	5.04 (0.97,26.16)	0.054	2.43 (0.54,10.98)	0.250
Time zero cytogenetic abnormalities	23/47 (49%)	3.71 (1.43,9.66)	0.007	1.82 (0.93,3.55)	0.080
Time zero hypodiploidy	12/47 (26%)	3.57 (1.52,8.38)	0.003	3.77 (1.72,8.27)	<.001
At least 1 transplant prior to time zero	178/286 (62%)	1.17 (0.85,1.61)	0.331	1.29 (0.98,1.71)	0.072

HR- Hazard Ratio, 95% CI- 95% Confidence Interval, P-value from Wald Chi-Square Test in Cox Regression