

ORIGINAL ARTICLE

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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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 following, refractory to or ineligible to receive, an IMiD (immunomodulatory drug), had measurable disease, and ECOG PS of 0, 1 or 2. The date patients satisfied the entry criteria was defined as time zero (T₀). The median age at diagnosis was 58 years, and time from diagnosis to T₀ was 3.3 years. Following T₀, 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 or better was seen to at least one therapy after T₀ in 94 patients (44%) including ≥partial response in 69 (32%). The median overall survival and event-free survival from T₀ 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.

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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 the natural history of MM in the relapsed patient population. Although this type of information is available for patients receiving the older therapies, such data are lacking for patients relapsing after the new therapies. 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 the 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), or progression on therapy, or progression within 60 days of stopping a bortezomib-containing regimen, as per published consensus criteria. 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 IMiD (thalidomide or lenalidomide). We used either one of the IMiDs instead of both IMiDs, taking into consideration the differences in availability of the two drugs in different parts of the world. The date the patient met this criteria was defined as time zero (T₀). Given the goal of using these 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 T₀ (defined conventionally as a serum M protein ≥1.0 g/dl or 24 h urine M-protein excretion ≥200 mg or bone

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²⁰See Appendix

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marrow plasma cells $\geq 30\%$). 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 confirmation of use and discontinuation of IMiDs and bortezomib due to emergence of resistance or toxicity. Detailed data collection sheets were developed, which 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, USA) for analysis in a de-identified manner. 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.

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 before and 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 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. Cox regression analysis was performed to determine which prognostic factors at T_0 and/or at baseline 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) after T_0 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 TNT 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 carried out 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. This included patients from nine sites (107 patients from three US sites; 115 from five European sites; and 64 from one 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. The median number of regimens

Table 1 Baseline characteristics at diagnosis and at time zero (T_0)

Factor	N/n (%)
Male	176/286 (62)
Median age at diagnosis (range)	58 (30–85)
<i>Serum heavy chain at diagnosis</i>	
None	27/250 (1)
IgG	155/250 (62)
IgA	60/250 (24)
<i>Durie Salmon stage at diagnosis</i>	
Stage 1	14/216 (6)
Stage 2a	47/216 (22)
Stage 3a	152/216 (70)
<i>ISS at diagnosis</i>	
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)
<i>Diagnosis FISH</i>	
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)
Diagnosis cytogenetic abnormalities	50/132 (38)
<i>Time zero (T_0)</i>	
Median age at T_0 (range)	62.5 (35–87)
<i>ISS at T_0</i>	
Stage 1	31/172 (18)
Stage 2	82/172 (48)
Stage 3	59/172 (34)
<i>FISH at T_0</i>	
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)
Median number of regimens before T_0 (range)	4 (1,13)
At least 1 transplant before T_0	178/286 (62)
≥ 2 transplants before T_0	42/286 (15)

Abbreviations: FISH, fluorescence *in situ* hybridization; ISS, International staging system; n, number with factor; N, number with valid data for factor.

Table 2 Response rate by regimen number, following time zero (T₀)

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
Corticosteroids (part of combination)	140 (66)	47 (52)	26 (53)	20 (74)	9 (50)
Cyclophosphamide	66 (31)	22 (24)	10 (20)	6 (22)	3 (17)
Bortezomib	55 (26)	22 (24)	19 (39)	7 (26)	8 (44)
Doxorubicin	43 (20)	11 (12)	6 (12)	1 (4)	3 (17)
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)
Etoposide	25 (12)	4 (4)	3 (6)	0 (0)	2 (11)
Cisplatin	22 (10)	6 (7)	3 (6)	0 (0)	2 (11)
Corticosteroids alone	17 (8)	6 (7)	2 (4)	1 (4)	0 (0)
Vincristine	18 (8)	3 (3)	2 (4)	2 (7)	1 (6)
BCNU (Carmustine)	4 (2)	1 (1)	2 (4)	1 (4)	0 (0)
Best response (≥PR) (%)	50/213 (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 (months)	1.9	1.3	1.4	1.7	1.9

Abbreviations: MR, minor response; PR, partial response.

before T₀ was 4 (range, 1–13); 81 (41%) patients had three regimens or less before reaching T₀ and 45 (16%) patients had received >6 regimens by the time they reached T₀. The details of the initial therapy in terms of the drugs used are included in Supplementary Table 1. In terms of prior therapy, by definition all patients had previous therapy with bortezomib and were considered refractory to bortezomib. Among them, 188 patients had relapsed on therapy while the remaining patients had either not responded or had relapsed within 60 days of discontinuing the drug. With respect to the IMiDs, 205 and 79 patients, respectively, were refractory to or ineligible for treatment with thalidomide or lenalidomide. Among the thalidomide treated patients, 135 patients had relapsed on therapy and/or were refractory, 69 patients had gone off for toxicity and were considered as intolerant, and one person was missing this information. For the lenalidomide patients, 70 had relapsed on therapy and/or were refractory, and nine were intolerant. The drug that patients were relapsing on or refractory to immediately before (or closest to) T₀ was bortezomib in 73% and an IMiD in 27%.

Initial therapy following time zero

We first examined the types of therapy that were used immediately following T₀. Only 213 patients (74%) had a treatment identified in the medical records following T₀ and the median time to first treatment following T₀ was 0.5 months. The drugs used (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 (26%) received a bortezomib-containing treatment regimen immediately following T₀. 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 used 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 the use of regimens such as DT-PACE.

Nearly a quarter of patients achieved a partial response or better to the first regimen used after T₀ (50/213, 24%) including a very good partial response 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 T₀ 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 bortezomib, lenalidomide or thalidomide compared with 25% among the 107 patients receiving a regimen not containing one of these three drugs (Table 3). Specifically, 12 (22%) of the 55 patients receiving bortezomib as part of the first regimen after T₀ had a response of partial response or better. The breakdown of the response rates and the response categories for a newer drug-containing regimen and those without these three drugs is provided in Supplementary Tables 2–4. The primary reasons for discontinuing the regimens are detailed in Supplementary Table 5. 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

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, number with factor; N, number with valid data for factor.

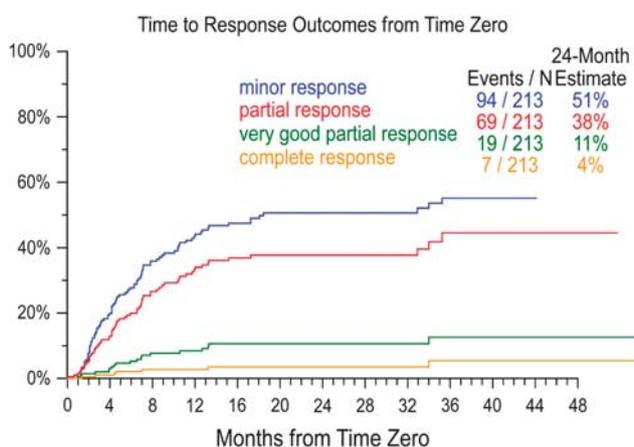


Figure 1 Figure shows the time to response at any time after time zero (T_0) for the different categories of responses among 213 patients who received at least one treatment after T_0 .

responses by regimen number (for the first five regimens) in Table 3. The median TNT 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 2 and 3. 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 5 (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 (~3 months) with the first transplant received after 5 days and the last one received after 936 days (~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 (that is, no transplants were carried out before T_0).

Survival outcomes

The median event-free survival for the entire cohort was 5 months (95% CI; 4, 6) from T_0 and the median OS was

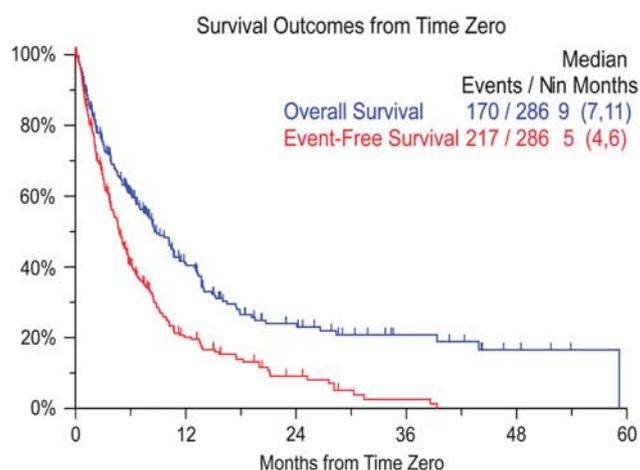


Figure 2 Figure shows the Kaplan–Meier curves for event-free survival (red curve, median 5 months) and overall survival (blue curve, median 9 months) from T_0 for all patients ($n = 286$) enrolled on the study.

9 months (95% CI; 7, 11) from T_0 (Figure 2). The overall survival from diagnosis for the entire cohort was 56 months (95% CI; 44, 72). The median OS for the 213 patients who received at least one regimen after T_0 was 12 months (95% CI; 10, 14), and for the remaining patients it was 3 months (95% CI; 2, 3). We also examined the OS 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, similar 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 OS 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 OS 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. We further examined the outcome based on whether the patients received the alternate IMiD. The median OS for lenalidomide refractory patients receiving thalidomide for salvage was 8 months and for thalidomide refractory patients receiving lenalidomide was 12 months from the start of the second IMiD, with the analysis landmarked at the start of the alternate IMiD. The median OS from the time they were refractory to any

Table 4 Univariate analysis of prognostic factors for OS and EFS from T₀

Variable	n/N (%)	OS from time zero		EFS from time zero	
		HR (95% CI)	P-value	HR (95% CI)	P-value
<i>At Diagnosis</i>					
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/μl	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
<i>At Time zero</i>					
Age ≥ 65 year	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)	<0.001	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)	<0.001	1.47 (1.12, 1.93)	0.006
B2M ≥ 3.5 mg/l	108/173 (62)	2.36 (1.55, 3.60)	<0.001	1.71 (1.20, 2.44)	0.003
B2M > 5.5 mg/l	59/173 (34)	2.20 (1.50, 3.25)	<0.001	1.55 (1.09, 2.21)	0.015
ISS Stage 3	59/172 (34)	2.24 (1.52, 3.31)	<0.001	1.57 (1.10, 2.24)	0.013
Creatinine > ULN	64/185 (35)	2.19 (1.48, 3.25)	<0.001	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)	<0.001
At least 1 transplant before time zero	178/286 (62)	1.17 (0.85, 1.61)	0.331	1.29 (0.98, 1.71)	0.072

Abbreviations: CI, confidence interval; EFS, event-free survival; FISH, fluorescence *in situ* hybridization; HR, hazard ratio; OS, overall survival. P-value from Wald Chi-square test in cox regression.

one of the novel agent (bortezomib or IMiD) was 10 months (95% CI: 7,14).

The per regimen outcome of patients on this study is detailed in Supplementary Table 6, which provides patient disposition data in terms of treatment status and survival at various time points from T₀. The numbers 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.

Prognostic factors

We performed additional analyses to identify prognostic factors predicting event-free survival and OS following T₀. Factors impacting the OS and event-free survival from T₀ identified in a univariate analysis are shown in Table 4. In a multivariate model using stepwise selection that included most of these variables only B2M > 5.5 mg/l at T₀ (HR: 3.58; P = 0.047) and albumin < 3.5 mg/dl at T₀ (HR: 5.62; P = 0.009) were independently significant for OS. 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 T₀. As shown in Figure 3, the ISS stage was prognostic for overall survival following T₀, 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.

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 7, demonstrated significant differences between the two groups in terms of lower B2M and fewer patients with ISS stage 3 both at diagnosis and at T₀, normal creatinine at T₀, and at least a partial response or better before T₀ among the group with longer survival.

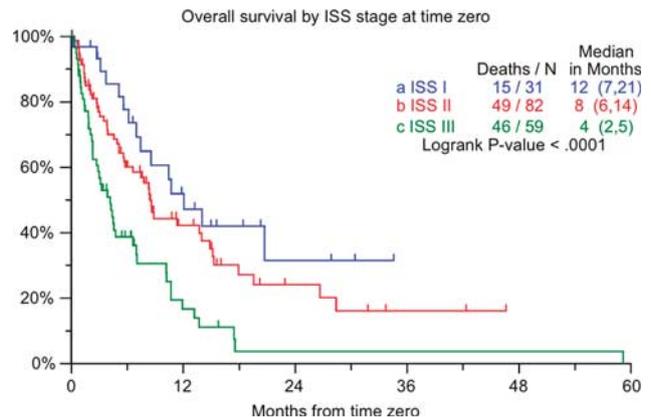


Figure 3 Figure shows the overall survival from T₀ by ISS stage at T₀.

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 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. The median survival of patients who had three previous therapies in the initial trials of bortezomib for similar patients was 12 months compared with the 5 months seen in that 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 these data are no longer 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 can 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 point at which 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} which does limit the generalizability of the results to the myeloma patient population as a whole; but at the same time allows better comparison with the current clinical trials. We also only required 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.^{19,20}

One of the most striking findings in our study has been the response rates seen in this patient population with the first regimen used 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 used for treatment of patients once they stopped responding to the newer drugs in the current study. In addition, transplant is increasingly being used later in the disease course, as is second transplants as salvage therapy. In fact in the current study nearly 20% of patients received a transplant after T₀, 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 degrees of responses.²² Bortezomib has activity with retreatment²²⁻²⁵ 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 in phase 3 trials utilizing standard of care for the 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 with 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 event-free survival 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 the poor outcome of patients refractory to IMiDs even in the context of stem cell transplantation.²⁷ Another important finding from the study was the continued value of conventional prognostic factors in this patient group. Interestingly, the ISS staging parameters B2M and serum albumin at T₀ best predicted survival outcome in this group of patients and should be taken into account when comparing results between different trials. They could in fact be incorporated as stratification factors in clinical trials of new drugs.²⁸ Unfortunately, limited data were available with respect to cytogenetic and fluorescence *in situ* hybridization 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 OS compared with the other patients.²⁹⁻³¹ As has been seen in previous studies in the context of newly diagnosed disease, the presence of renal insufficiency predicted 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 novel therapies. Clearly there are some disadvantages with the current study, such as the inclusion of only 'trial eligible' patients and the lack of uniform availability of modern prognostic factors such as cytogenetic and fluorescence *in situ* hybridization 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.

Conflicts of interest

JJL is on the Scientific advisory boards of Celgene and Janssen-Cilag. PGR and JSM are Advisory board participants for Celgene, Millenium, Johnson and Johnson. DS is on the Speakers Bureau

and BD is an Advisory board participant for Celgene and Millenium. AP is an Advisory Board participant for Celgene, Johnson and Johnson. JB has received Honoraria for lectures and advisory boards from Celgene, Jansen Cilag and Grant support from Celgene and Jansen-Cilag. The remaining authors declare no conflict of interest.

Author's 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.

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