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REVIEW

Association of response endpoints with survival outcomes in multiple myeloma

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Since the introduction of the proteasome inhibitor bortezomib and the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, more patients with multiple myeloma are achieving deep, durable responses and disease control, and are living longer. These improvements have afforded more robust analyses of the relationship between response and survival. Generally, these studies have demonstrated that improvements in the quality of response across all stages of treatment are associated with better disease control and longer survival. Thus, achievement of maximal response should be strongly considered, particularly in the frontline setting, but must also be balanced with tolerability, quality of life and patient preferences. In select patients, achievement of a lesser response may be adequate to prolong survival, and attempts to treat these patients to a deeper response may place them at unnecessary risk without significant benefit. Maintenance therapy has been shown to improve the quality of response and disease control and, in some studies, survival. Studies support maintenance therapy for high-risk patients as a standard of care, and there are emerging data supporting maintenance therapy in standard-risk patients to improve progression-free and possibly overall survival. Multidrug regimens combining a proteasome inhibitor and an IMiD have shown exceptional response outcomes with acceptable increases in toxicity in both the frontline and salvage settings, and are becoming a standard treatment approach. Moving forward, the use of immunophenotypic and molecular response criteria will be essential in better understanding the impact of highly active and continuous treatment regimens across myeloma patient populations. Future translational studies will help to develop antimyeloma agents to their fullest potential. The introduction of novel targeted therapies, including the IMiD pomalidomide and the proteasome inhibitors carfilzomib and ixazomib (MLN9708), will provide greater options to individualize treatment and help patients achieve a clinically meaningful response.

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INTRODUCTION

Over the past decade, the introduction of targeted therapy with the proteasome inhibitor (PI) bortezomib (approved by the US Food and Drug Association in 2003) and immunomodulatory drugs (IMiDs) lenalidomide and thalidomide (both approved in 2006) have vastly improved the outcomes for patients with multiple myeloma (MM).[1–3] When used alone or as part of combination regimens, these therapies have been shown to provide deep and durable, quality responses, which have translated into advances in disease control and survival. During the early years of their use from 2003 to 2006, the 5-year survival estimate in MM increased to 40.3% compared with 32.8% between 1998 and 2002.[2] Unfortunately, most patients still face the challenges of disease progression and eventually succumb to the disease.

The treatment paradigm for MM is evolving, but the general goals continue to include rapid disease control to reverse complications, extending disease control and survival, and maintaining quality of life.[4–6] In recent years, a growing body of evidence indicates a relationship between the quality of response to treatment (depth and durability) and clinical outcomes. Before the introduction of targeted therapies, most patients were unable to achieve quality responses without undergoing high-dose therapy with autologous stem cell transplant (HD-ASCT). Given that HD-ASCT was initially limited to patients under 65 years of age and MM has a median onset of 70 years,[5] many patients were ineligible for transplantation and instead received a less-intensive treatment. As a consequence, achievement of a deep and durable response was rare and thus, it was challenging to relate response and survival.[7–10] Furthermore, these studies generally excluded high-risk patients for whom the benefit of achieving and maintaining a complete response (CR) is more evident.[11]

The rapid adoption of targeted therapies has afforded a greater focus on depth and duration of response and their impact on outcomes.[12–17] Both transplant-eligible and -ineligible patients now achieve quality responses, including CRs, across all phases of treatment (induction, consolidation, maintenance and salvage).[18] The development of triplet combinations that combine a PI with an IMiD and a corticosteroid or chemotherapy has provided unprecedented levels of response in the frontline and relapsed settings in high-risk patients.[19–25] Generally, studies with targeted therapies support an aggressive treatment paradigm to maximize the quality of response and minimize the burden of the malignant clone, particularly in the early treatment phase.[26–32] Even at the time of presentation multiple clones can be present. Theoretically, an aggressive upfront treatment strategy may improve the depth and durability of response and inhibit clonal evolution, but clinical studies are needed to support this premise.[33–35]

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However, there are important considerations.[6,36,37] Quality of response alone is not a validated surrogate marker of overall survival (OS).[38] There are currently no definitive data to validate the association between quality of response and survival outcomes. Moreover, the association of depth of response with outcomes is not universal across studies. Biologically, MM is a spectrum of diseases and its course and response to therapy can be highly variable. Some patients achieve very good initial responses that are short-lived, whereas others achieve only minimal responses (MRs) that are durable and clinically relevant.[39–41] Furthermore, aggressive treatment can be associated with greater toxicity than conventional approaches, and thus, the risk-to-benefit must be compared with alternative approaches that favor 'disease control' with less-intensive sequential regimens.[6,37] Both strategies have merit but in the context of specific patient populations and disease characteristics. Risk-adapted strategies favor aggressive treatment in high-risk patients and more conventional approaches in standard-risk patients.[5] However, risk stratification is not sufficiently accurate to predict the quality of a treatment response for individual patients. Undertreatment could result in failure to achieve a potential cure in standard-risk patients or rapid loss of disease control in high-risk patients. For these reasons, it may be preferable to maximize the response of all patients at diagnosis and use personalized treatment in the consolidation and maintenance phases.

In view of the evolving treatment strategies in MM, it is important to consider the impact depth of response has on clinical outcomes collectively and within the various treatment phases and disease settings. Although current data do not address all gaps in our knowledge, they do help to better inform treatment decisions. Here, we provide an overview of studies that have explored the impact of quality of response on outcomes by transplant status and stage of treatment, and consider our knowledge gaps. We review recent studies of triplet combinations and highlight the need for more sensitive response criteria that will better inform short- and long-term treatment decisions.

DEPTH OF RESPONSE AND CLINICAL OUTCOMES

A number of caveats to the data reviewed here should be acknowledged upfront. It is important to keep in mind that before 1998 multiple response criteria were in use with variable definitions for CR or no definition at all.[9,10,42,43] In 1998, the European Group for Bone Marrow and Blood Transplantation developed the first uniform response criteria for MM based on: monoclonal paraprotein serum and urine levels with electrophoresis and immunofixation; the proportion of plasma cells in the bone marrow aspirates/biopsies with histologic and cytologic studies; bone lesions and soft tissue plasmacytomas, with radiographic imaging and clinical evaluations.[44] Response categories included CR, partial response (PR), MR, stable disease and progressive disease. Then, in 2006, the International Myeloma Working Group developed response criteria similar to that of European Group for Bone Marrow and Blood Transplantation but with some differences, including the addition of stringent CR and very good partial response (VGPR) response categories.[45] Studies also sometimes use near CR (nCR) as an additional response category.[46]

We also acknowledge that many of the studies discussed here are retrospective, observational or exploratory analyses with limited number of patients. Patient populations and treatments were more homogeneous and well controlled in some studies than in others. Also, survival data may be confounded by the impact of subsequent or salvage therapies at the time of progression,[1,3,47–49] which may vary based on the depth and duration of the initial response and access to treatments. Analysis of outcomes by the level of response may introduce selection bias, with standard-risk patients being more likely to achieve a quality response than high-risk patients. It is not surprising that studies have reported no association between depth of response and outcomes, but generally these studies were conducted before the advent of the targeted therapy era.[9,42,50–53]

In the targeted therapy era, more patients across the myeloma spectrum are achieving quality responses with improved survival outcomes. In a meta-analysis of phase 3 bortezomib trials that included 2086 transplant-eligible patients,[54] the use of bortezomib during induction significantly improved overall response rate (ORR), $\geqslant$VGPR and CR compared with non-bortezomib regimens, which corresponded to improvements in progression-free survival (PFS) and OS. Despite the lack of definitive data, the body of evidence linking quality of response to outcomes is growing and has become more compelling.

Newly diagnosed MM

Several studies have assessed the impact of response levels on outcomes in patients with newly diagnosed MM (NDMM) receiving HD-ASCT (Table 1). In general, studies show that a quality response at each treatment stage—induction, HD-ASCT, and consolidation—is associated with improved outcomes.[19,26,55,56] Lahuerta *et al.*[26] evaluated response in 632 patients with NDMM treated with the GEM2000 protocol, which used a chemotherapy induction regimen followed by HD-ASCT. Post transplantation, there was a significant association between response level and outcomes with a 5-year OS rate of 74% in patients achieving a CR compared with 63% for nCR ($P=0.01$), 50% for PR ($P<0.0001$) and 57% for stable disease ($P=0.01$). Post induction, there were trends of improved survival by level of response, but the association was less robust. There was no difference in OS for achievement of CR post induction versus post transplantation. Outcomes were worse for patients with persistent nCR (before and after transplantation) compared with patients whose response improved to nCR post transplantation with a 5-year OS rate of 45% versus 72% ($P=0.001$). In a separate phase 3 IFM 2005-01 study, which randomized 482 patients to induction with bortezomib and dexamethasone or vincristine, doxorubicin and dexamethasone (VAD), PFS was significantly longer for patients achieving a VGPR post induction compared with post transplantation (median 41.2 versus 31.1 months; $P=0.01$).[27] In multivariate analysis, a response $\leqslant$VGPR overall and post induction were both retained as negative prognostic factors. Taken together, data from these and other studies[26,27,55,56] suggest that it is important to attain a quality response early with induction therapy and drive the response further in the subsequent treatment stages.

Studies have also demonstrated the prognostic implications of response durability.[51,57] Barlogie *et al.*[57] conducted a retrospective analysis of OS by response at a 36-month landmark in patients enrolled in a total therapy (TT)2 study (double HD-ASCT supported by induction, consolidation and maintenance with thalidomide; $n=668$). Response categories included CR sustained for $\geqslant$36 months ($n=256$), CR lost before 36 months ($n=39$) and non-CR ($n=211$). Median OS was significantly longer in the sustained CR group (not reached) versus the non-CR group (5.6 years, $P<0.0001$) and the lost-CR group (1.6 years, $P<0.0001$), as well as for the comparison of non-CR to lost-CR ($P<0.0001$). These survival trends were also observed in patients enrolled in a TT1 study as well as a cohort receiving other transplant protocols. Similarly, a pooled analysis of GEM2000 and GEM2005 studies showed that median survival was significantly shorter for patients with unsustained CR at 100 days ($n=29$) compared with those with a lesser response sustained for at least 100 days ($n=667$), and those with a sustained CR ($n=241$)—39 months, 76 months and not reached, respectively ($P<0.001$).[41]

As mentioned earlier, a number of caveats of these studies should be considered. Survival outcomes can be confounded by

Table 1. Prognostic impact of response level in patients with newly diagnosed multiple myeloma: transplant studies

Reference *Response criteria* *Study type*	*Treatment*	*Response*		n	*PFS/TTP/EFS (median, mo[a]/rate, %)*			*OS (median, mo[a]/rate, %)*		
					mEFS	5 yr	*P*-value	mOS	5 yr	*P*-value
Lahuerta *et al.*[26] mEBMT Prospective	GEM2000→HD-SCT→ IFN + prednisone (maint)	Post induction	CR	101	56	53	0.05 CR versus PR	NR	78	0.02 CR versus SD
			nCR	96	47	49		NR	65	
			PR	346	43	34		NR	63	
			SD	63	41	33		NR	56	
			PD	26	20	12		25	25	
		Post transplant	CR	278	61	52	<0.01 CR versus nCR,	NR	74	⩽0.01 CR versus nCR, PR, and SD;
			nCR	124	40	27	PR and SD	NR	63	0.04 nCR versus PR
			PR	175	34	23		61	50	
			SD	30	44	27		NR	57	
			PD	25	13	4		15	24	
					PFS	4 yr	*P*-value	OS	4 yr	*P*-value
Dytfeld *et al.*[114] mEBMT Phase 2	VDD ± SCT	Post induction	⩾VGPR	25	—	67.2	0.08	—	86.5	0.04
			<VGPR	15		46.3			58.2	
	VDD + SCT (subgroup)	Post induction	⩾VGPR	16	—	77.8	0.036	—	92.9	0.027
			<VGPR	14		53.8			64.3	
					mPFS		*P*-value	mOS		*P*-value
Gertz *et al.*[115] Retrospective	T or R regimen→SCT	Post induction	PR	232	22.1		<0.001	73.5	—	<0.001
			<PR	54	13.1			30.4		
Moreau *et al.*[27] mEBMT Ph 3 *post hoc*	VD or VAD ± DCEP→SCT	Post induction	⩾VGPR	125	41.2		<0.0001	—	—	—
			<VGPR	357	29.0					
					mEFS	5 yr	*P*-value	OS	5 yr	*P*-value
Harousseau *et al.*[28] EBMT Pooled analysis (2 prospective studies)	VAD→double SCT→no treatment, Pam or Pam + T	Post transplant	⩾VGPR	445	42	34	0.005	—	74	0.0017
			<VGPR	288	32	26			61	
								mOS[b]	4 yr[c]	*P*-value
Kapoor *et al.*[116] IMWG Retrospective	SCT	Post transplant	sCR	115	—	—	—	NR	86	0.007
			CR	28				59	60	
			nCR	46				53	—	
								mOS	4 yr	*P*-value
Barlogie *et al.*[57] EBMT Retrospective	TT2	36-mo landmark	Sust-CR	256	—	—	—	NR	83	<0.0001 Sust-CR versus non-CR
			Non-CR	211				67.2	59	and <0.0001 versus lost-CR;
			Lost-CR	39				19.2	19	<0.0001 non-CR versus lost-CR
	TT1	36-mo landmark	Sust-CR	44				127.2	—	0.06 Sust-CR versus non-CR
			Non-CR	88				72	—	and 0.001 versus lost-CR; 0.04
			Lost-CR	33				34.8	—	
	Tandem SCT	36-mo landmark	Sust-CR	197				76.8	—	<0.0001 Sust-CR versus non-
			Non-CR	252				46.8	—	CR/lost-CR; 0.0002 non-
			Lost-CR	60				21.6	—	CR versus lost-CR
					mPFS		*P*-value	mOS		*P*-value
Alegre *et al.*[117] Observational	HD-ASCT ± IFN-α maint	Post induction	CR	56	35	—	0.001 CR/PR versus	39	—	0.001 CR/PR versus SD/PD
			PR	153	28		SD/PD	36		
			SD	25	20			24		
			PD	25	8			12		
					EFS	5 yr	*P*-value	OS	5 yr	*P*-value
Galli *et al.* [29] mEBMT Observational	TT1	Post induction	CR	17	—	65	0.025 CR versus <CR	—	63	0.31 CR versus <CR
			⩾VGPR	29		54	0.006 ⩾VGPR versus		63	
			PR/SD	81		24	PR/SD		47	
			SD	18		27			56	
		Post ASCT1	CR	43		32			50	
			<VGPR	53		30			58	
		Post ASCT2	CR	51		33			59	
			<VGPR	28		34			63	

Abbreviations: DCEP, dexamethasone, cyclophosphamide, etoposide, and cisplatin; GEM2000, induction therapy with six alternating 5-week cycles of vincristine, carmustine, cyclophosphamide, melphalan and prednisone/vincristine, carmustine, doxorubicin and dexamethasone→HD-SCT; HD-ASCT, high-dose therapy with autologous stem cell transplant; IFN, interferon; IMWG, International Myeloma Working Group; maint, maintenance therapy; mEBMT, modified European Group for Blood and Marrow Transplantation; mEFS, median event-free survival; mOS, median overall survival; mPFS, median progression-free survival; nCR, near complete response; NR, not reached; Pam, pamidronate; PD, progressive disease; R, lenalidomide; sCR, stringent complete response; SCT, stem cell transplant; SD, stable disease; Sust, sustained; T, thalidomide; TT; total therapy; VAD, vincristine, doxorubicin, dexamethasone; VD, bortezomib, dexamethasone; VDD, bortezomib, pegylated liposomal doxorubicin, dexamethasone; VGPR, very good partial response; yr, years. [a]Conversion to months for studies reporting other time increments. [b]From diagnosis $P = 0.0004$. [c]From SCT.

the use of subsequent treatments, including maintenance and salvage therapies with targeted therapies. In the IFM 2005-01 study, patients who achieved at least a PR could enroll onto the IFM 2005-02 study of maintenance therapy with lenalidomide.[27] Also, the relationship between quality of response and outcomes may be confounded by tumor biology.[53] In the pooled analysis of GEM2000 and GEM2005 studies, high-risk cytogenetics was an independent predictor of unsustained CR.[41] On the other hand, subgroup analyses of the IFM 2005-01 study demonstrated that a quality response improved outcomes in high-risk patients. The median PFS was significantly longer in patients with International Staging System (ISS) 2/3 disease who achieved a post-induction VGPR versus those who did not (not reached versus 23 months; $P<0.0001$), as well as in patients with high-risk cytogenetics (37 versus 24 months, respectively, $P=0.0036$).

Without a trial specifically designed to assess the quality of response, tumor biology remains a confounding factor. However, more patients, including patients with high-risk MM, are achieving quality responses with targeted therapy regimens compared with conventional chemotherapy, and there is compelling evidence that achieving a quality response can at least partially overcome the impact of negative prognostic factors, including cytogenetic abnormalities. This is particularly evident in the more recent non-transplant studies where HD-ASCT is not an option, and aggressive treatment with targeted therapies has been shown to improve the quality of response and outcomes in high-risk patients. These studies have generally demonstrated important associations between the quality of response and outcomes (Table 2),[9,31,43,58–63] and pooled analyses have allowed for more robust subgroup analyses to better examine the potential impact of selection bias.[30,31]

Gay *et al.*[31] conducted a pooled analysis of three phase 3 studies that treated 1175 patients with MP with or without thalidomide (GISMM-2001[17] and HOVON 49[64] studies) and/or bortezomib (GIMEMA-MM-03-05[65]). The highest CR rate was observed in patients receiving VMPT plus VT maintenance (49%) with the lowest rate in patients receiving MP (5%), with a robust association between depth of response and outcomes. The 3-year OS rate was 91% for CR compared with 70% for VGPR ($P<0.001$), and 67% for PR ($P<0.001$). These relationships were maintained in subgroups older and younger than 75 years of age, and after adjustment for other prognostic factors with multivariate analysis. The time to achieve a CR did not have a significant impact on the outcomes.

More recently, Gay *et al.*[30] conducted a separate pooled analysis of 771 patients enrolled in the GIMEMA-MM-03-05[65] and GEM05MAS65[21] studies, which assessed the combinations of bortezomib with an IMiD for induction and the use of bortezomib regimens for maintenance therapy. In response-evaluable patients ($n=751$), 36% achieved a CR, 19% a VGPR and 32% a PR. Baseline age, ISS stage and cytogenetics—t(4;14), t(14;16) and del17p—were similar across these response subgroups. In a landmark analysis using a 12-month time point, the OS rate at 3 years was 75% overall and 94% in the CR subgroup versus 86% in the VGPR subgroup (hazard ratio (HR) 0.30, 95% confidence interval (CI) 0.16–0.52, $P<0.001$). The 3-year OS rate was superior for standard-risk versus high-risk cytogenetics overall (76 versus 65%; HR 0.65, 95% CI 0.47–0.91, $P=0.01$), but in patients with a CR, the rates did not differ (94% versus 90%, respectively; HR 0.66, 95% CI

Table 2. Prognostic impact of response level in patients with newly diagnosed multiple myeloma: non-transplant studies

Reference *Response criteria* *Study type*	*Treatment*	*Response*	n	*PFS/TTP/EFS (median, mo[a]/rate, %)*			*OS (median, mo[a]/rate, %)*		
							mOS		*P*-value
Kyle *et al.*[43] ECOG Ph 3 *post hoc*	VBMCP ± IFN or HD-Cyc	CR PR	85 335	—	—	—	61.2[b,] 39.6[b]	—	<0.0001
				EFS	3 yr	*P*-value	OS	3 yr	*P*-value
Offidani *et al.*[59] EBMT Ph 2	ThaDD	⩾VGPR <VGPR	28 22	—	78[c,] 37[c]	0.021	—	84 61	0.053
				EFS	1 yr				
Palumbo *et al.*[61] EBMT Ph 1/2	MPR	CR/VGPR PR/MR	20 33	—	100 88	0.034	—	—	—
				mTTP			mOS		
Harousseau *et al.*[60] EBMT Ph 3 *post hoc*	VMP arm only	CR PR	102 136	NR 21.7	—	0.004[d]	46.2 NR	—	0.54[d]
				PFS	3 yr	*P*-value		3 yr	*P*-value
Gay *et al.*[31] IMWG Pooled analysis of three Ph 3 studies	MP, MPT, VMP or VMPT→VT	CR VGPR PR	195 212 397	—	67 27 27	<0.001 CR versus VGPR and versus PR	—	91 70 67	<0.001 CR versus VGPR and versus PR
							mOS		
Oivanen *et al.*[9] CLMTF Pooled analysis of four prospective studies	MP or combination chemotherapy	Age ⩽70 yr CR 75% Response PR MR SD PD Age >70 yr CR 75% Response PR MR SD PD	 21 95 101 42 16 49 8 26 37 10 6 20	—	—	—	 63 58 59 49 57 10 44 44 40 32 22 4	—	 <0.0001 for any category versus PD ⩽0.003 for any category versus PD

Abbreviations: CLMTF, Chronic Leukemia-Myeloma Task Force; EBMT, European Group for Blood and Marrow Transplantation; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HD, high dose; mOS, median overall survival; MP, melphalan, prednisone; mPFS, median progression-free survival; MPT, melphalan, prednisone, thalidomide; mTTP, median time to progression; MPR, melphalan, prednisone, and lenalidomide; NR, not reached; ThaDD, thalidomide, dexamethasone and pegylated liposomal doxorubicin; VBMCP, vincristine, carmustine (BCNU), melphalan, cyclophosphamide and prednisone; VGPR, very good partial response; VMP, bortezomib, melphalan, prednisone; VT, bortezomib, thalidomide; yr, years. [a]Conversion to months for studies reporting other time increments. [b]From time of response, converted from years to months. [c]Landmark analysis after 4 months of treatment. [d]Multivariate analysis.

0.29–1.50, $P = 0.32$). A similar trend was seen in a subgroup analysis by ISS stage—significant differences between the ISS stages when considering all evaluable patients, but no difference for patients with a CR. The prognostic significance of CR versus VGPR was maintained following multivariate analysis (HR 0.24, 95% CI 0.10–0.55, $P < 0.001$). Thus, quality of response was a more robust predictor of survival than cytogenetics or ISS stage. Nonetheless, the potential confounding impact of salvage therapies cannot be ruled out, although in maintenance therapy trials variations in treatment after induction can be better controlled because of long-term treatment protocols. Improvement in OS in the context of maintenance trials represents the highest level of evidence achievable in clinical practice.

Relapsed and/or refractory

In the relapsed or refractory setting, studies have also shown associations between depth of response and outcomes, although data are limited (Table 3).[32,58,66–71] In the phase 3 APEX study, bortezomib was superior to high-dose dexamethasone for patients with relapsed MM with respect to response results, time to progression and OS.[14] An exploratory analysis of the bortezomib arm ($n = 315$) showed no statistical difference in median TTP among patients who achieved a CR (9.7 months) compared with a VGPR (10.8 months) or a PR (8.5 months), whereas CR was associated with significant improvements in the median treatment-free interval (24.1 months) compared with VGPR (6.9 months, $P = 0.007$) and PR (6.4 months, $P = 0.002$).[66] This was likely due in part to the design of the study—once patients achieved a CR, they continued treatment for only two additional cycles. Finally, patients who achieved an MR had a significantly longer TTP compared with non-responders (4.9 versus 2.8 months, $P = 0.016$) and there was a trend of improved OS (24.9 versus 18.7 months).

Other studies have also demonstrated the benefit of achieving an MR in the relapsed/refractory setting. A pooled analysis of two phase 2 studies using thalidomide-containing regimens in patients with relapsed MM showed an association between the level of response and OS with a median OS of >70 months for achievement of ⩾VGPR, 35 months for PR and 11.7 months for MR or non-response ($P < 0.001$).[69] MR was favored over non-response for PFS (6.1 versus 3.8 months) but not for OS (11 versus 14 months). In a phase 2 study of carfilzomib in patients with relapsed and refractory MM ($n = 266$), median PFS was 10.6 months for patients achieving ⩾VGPR ($n = 14$), 8.3 months for PR ($n = 47$) and 9.6 months for MR ($n = 34$), whereas the median for the response-evaluable population overall ($n = 257$) was 3.7 months.[72]

IMPROVING THE QUALITY OF RESPONSE AND OUTCOMES

Despite positive trends in treatment outcomes over the past decade, it has become apparent that treatment strategies need to be further developed to improve the depth and durability of response for the individual patient with MM, particularly those with high-risk disease, where the risk of increased toxicity with prolonged or more aggressive treatment is outweighed by the potential survival benefit.[73] Patients with high-risk cytogenetic abnormalities generally have a shorter duration of response, PFS and OS than standard-risk patients, but the benefit of a CR can be more pronounced.[11,74] Given that 25–30% of the NDMM patients present with high-risk disease,[75] efforts have been made to improve the quality of response and outcomes in these patients, including maintenance therapy and combinations of targeted therapies.

Maintenance therapy

A number of studies have investigated the efficacy and safety of maintenance treatment with targeted therapies.[76–82] Studies have consistently demonstrated that thalidomide maintenance after HD-ASCT improves the quality of response and PFS, and some

Table 3. Prognostic impact of response level in patients with relapsed or refractory multiple myeloma

Reference *Response criteria* *Study type* *Patients*	*Treatment*	*Response*	n	*PFS/TTP/EFS (median, mo[a]/rate, %)*			*OS (median, mo[a]/rate, %)*		
				mTTP		*P*-value	mOS		*P*-value
Niesvizky *et al.*[66]	BTZ arm	CR	27	9.7	—		NR	—	—
mEBMT		VGPR	31	10.8			NR		
Ph 3 *post hoc*		PR	77	8.5		0.016 MR versus	NR		
Relapsed		MR	21	4.9		non-response	24.9		
		non-response	159	2.8			18.7		
				EFS	1 yr	*P*-value	OS	1 yr	*P*-value
Palumbo *et al.*[67]	VD + Dox	⩾VGPR	16	—	83	0.02	—	90	0.06
IMWG	or PLD	PR	27		16			63	
Observational									
Relapsed or refractory									
							OS	1 yr	*P*-value
Pineda-Roman *et al.*[68]	VT ± D	⩾MR	62	—	—	—	—	73	<0.0001
Ph 1/2		<MR	20					20	
Relapsed or refractory									
				mPFS		*P*-value	mOS		*P*-value
Quach *et al.*[69]	T + IFN or	⩾VGPR	9	69	—		>70	—	
EMBT	T + celecoxib	PR	47	14		<0.001 PR versus	35		<0.001 PR versus
Pooled analysis of two Ph 2 studies		MR or non-response	48	4		MR or non-response	11.7		MR or nonR
Relapsed or refractory		MR	18	6.1			11		
		non-response	30	3.8			14		
				mTTP		*P*-value	mOS	2 yr	*P*-value
Harousseau et al[32]	RD arm	CR/VGPR	114	27.7		<0.001	NR	59.6	0.021
mEBMT		PR	100	12.0			44.2	42.0	
Retro of two Ph 3 trial									
Relapsed or refractory									

Abbreviations: BTZ, bortezomib; EFS, event-free survival; IFN, interferon; IMWG, International Myeloma Working Group; mEBMT, modified European Group for Blood and Marrow Transplantation; mo, months; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; NR, not reached; nonR, non-response; RD, lenalidomide and dexamethasone; T, thalidomide; VD, bortezomib, dexamethasone; VGPR, very good partial response; yr, years. [a]Conversion to months for studies reporting other time increments.

studies have also shown an OS benefit.[83] However, there is concern about cumulative neurotoxicity with thalidomide.

Lenalidomide maintenance has been assessed in three randomized controlled trials.[76–78] In one phase 3 trial, 460 patients who had achieved at least stable disease with HD-ASCT were randomized to maintenance with lenalidomide or placebo.[77] Lenalidomide maintenance was associated with significantly improved TTP compared with placebo (46 versus 27 months; $P<0.001$) and OS with a 3-year rate of 88% versus 80% ($P=0.03$). This benefit was notable in patients who had not achieved CR with HD-ASCT. In patients who achieved CR with HD-ASCT, the median TTP was not reached in the lenalidomide maintenance arm versus 36 months in the placebo arm (natural log HR 0.53, 95% CI −0.001–1.1), with corresponding values of 43 versus 23 months in the non-CR subgroup (natural log HR 0.86, 95% CI 0.53–1.2; P for interaction = 0.38). Lenalidomide maintenance was also associated with improved OS in both subgroups, and again the benefit was more pronounced in the non-CR subgroup (natural log HR 0.53, 95% CI 0.05–1.0; P for interaction = 0.64.) than in the CR group (natural log HR 0.25, 95% CI −0.67–1.2). Lenalidomide maintenance was associated with increased toxicity, including grade 3/4 hematologic events (48% versus 17%, respectively, $P<0.001$) and secondary primary malignancies (8% versus 3%, respectively; $P=0.008$). In the other two studies, lenalidomide maintenance improved PFS, particularly among transplant-eligible patients who achieved <VGPR with HD-ASCT[78] and transplant-ineligible patients <75 years of age.[76] There was no improvement in OS in either of these studies, but the investigators from both studies noted the need for longer follow-up.

Bortezomib may also be beneficial as a maintenance therapy.[80–82,84] Sonneveld *et al.*[81] recently reported results of a phase 3 study in 827 patients with NDMM who were randomized to induction with VAD or bortezomib, doxorubicin and dexamethasone, followed by HD-ASCT and maintenance with thalidomide for VAD and bortezomib for bortezomib, doxorubicin and dexamethasone. The CR rate overall was 24% for the VAD arm versus 36% for the bortezomib, doxorubicin and dexamethasone arm ($P<0.001$), the rate of improved response during maintenance treatment was 24% and 23% ($P=0.64$), respectively. Median PFS was 28 versus 35 months, respectively ($P=0.002$), and median OS had not been reached in either arm. Subgroup analysis of patients with the 17p13 deletion showed a ⩾nCR rate of 20% in the VAD arm versus 52% in the bortezomib, doxorubicin and dexamethasone arm ($P=0.008$), which corresponded to median OS of 24 versus >54 months (HR 0.36, 95% CI 0.18–0.74; $P=0.003$). In the subgroup without the 17p13 deletion, there was no difference in OS (HR 0.96, 95% CI 0.69–1.34; $P=0.81$).

As data for maintenance therapy accumulate, it will be important to assess the impact quality of response has on outcomes in different risk groups. Although there is compelling evidence that driving response deeper with maintenance therapy in standard-risk patients improves PFS and possibly OS,[26,55] PFS is not a suitable surrogate for OS in this patient population.[15,78,85,86] Without prolonged follow-up and OS data, it is unclear if those achieving CR after HD-ASCT should receive maintenance treatment or wait until relapse. In high-risk patients where CR has been shown to be an important predictor of outcome, PFS is a suitable primary endpoint as it usually correlates with OS.[11,30,87] For high-risk patients, it is not so much a question of maintenance therapy but rather if a multidrug combination is appropriate.[80,83,84,87]

Multidrug treatment strategies—combining PIs and immunomodulatory drugs

Pairing PIs with IMiDs or cytotoxic agents, usually in triplet combinations with a corticosteroid, is changing the treatment landscape in MM as factors associated with poor outcomes appear to have far less impact.[88] The rationale for using these combinations is supported by the preclinical data demonstrating that IMiDs potentiate the activity of PIs and dexamethasone[89–92] and of synergistic activity between PIs and cytotoxic agents.[93–95] Many of the toxicities associated with these drug classes are non-overlapping. So far, triplet combinations with a PI, IMiD and corticosteroid have demonstrated exceptional responses in both the frontline and salvage settings, and in patients with high-risk disease (Table 4).[19–24,96–99] Generally, these combinations have been well tolerated, as high anti-MM activity has allowed the development of regimens with reduced doses or different dosing schedules of the individual agents.[20,22,24,98] Nonetheless, there are increases in some toxicities, and there may be limits to the combinations currently available. In the phase 2 EVOLUTION study, for example, a quadruplet combination of bortezomib, dexamethasone, cyclophosphamide and lenalidomide was highly active in NDMM but did not provide a clinical benefit over bortezomib-based triplet combinations and was associated with greater toxicity.[100] Other than the pooled analysis of the GIMEMA-MM-03-05 and GEM05MAS65 studies discussed earlier,[30] the impact of quality of response on outcomes has not been well studied with these combination regimens.[19,30]

REDEFINING CR—IMMUNOPHENOTYPIC AND MOLECULAR CRS

As the rates of CR and stringent CR continue to advance, it is of interest to further stratify the CR category. Assessment of minimal residual disease (MRD) in bone marrow plasma cells with sensitive assays that define immunophenotypic and molecular responses is becoming a useful measure of response with potential prognostic implications.[21,56,101–105] Immunophenotypic response is assessed by multiparametric flow cytometry, which uses immunofluorescence with monoclonal antibodies to plasma cell proteins (for example, CD38, CD19 and CD117) to identify, quantify and characterize bone marrow plasma cell composition.[101–103] Molecular response is assessed with allele-specific oligonucleotide PCR. Tumor-specific primers are constructed for individual patients from the rearranged variable region of immunoglobulin heavy-chain genes through reverse transcription of RNA (extracted from bone marrow plasma cells) and generation of the immunoglobulin heavy-chain genes complementary DNA.[56,106]

In a prospective analysis of 295 patients with NDMM uniformly treated with the GEM2000 protocol, the immunophenotypic response was assessed by the multiparametric flow cytometry method (sensitivity 10^{-4}) at 100 days post transplantation.[103] At day 100, 147 patients had achieved a CR, with 58% being MRD positive and 42% MRD negative. In the MRD-positive group, the proportion of abnormal plasma cells corresponded to depth of response, with a mean of 0.10% for CR, 0.21% for nCR and 0.76% for PR ($P=0.001$). PFS was significantly longer for MRD-negative versus MRD-positive patients (median, 71 versus 37 months, $P<0.001$), as was OS (5-year rate of 82 versus 60%, $P=0.002$), with the benefit independent of immunofixation status. For the immunofixation-negative subgroup (that is, CR), the 5-year PFS rate was 62% in MRD-negative versus 30% in MRD-positive patients ($P<0.001$) and the 5-year OS rate was 87% versus 59%, respectively ($P=0.009$).

Ladetto *et al.*[56] assessed MRD by the nested-PCR method (sensitivity 10^{-6}) in 39 patients with NDMM who achieved a ⩾VGPR with HD-ASCT received consolidation therapy with bortezomib, thalidomide, dexamethasone. At study entry, 33 patients (85%) had a VGPR following HD-ASCT, 6 had a CR (15%) with 1 (3%) a molecular CR. All patients received one course of bortezomib, thalidomide, dexamethasone and 31 completed four courses. After consolidation, the CR rate improved to 49% and molecular CR improved to 18%. After a median follow-up of 42

Table 4. Clinical studies in patients with multiple myeloma receiving combination regimens that include a proteasome inhibitor and an IMiD

Reference *Response criteria* *Study type*	*Treatment arm*	n	*Maximal response (%)*	*PFS/TTP (median, mo[a]/rate, %)*	*OS (median, mo[a]/rate, %)*	
Frontline transplant eligible						
			CR induction	Overall	3-yr PFS	3 yr
Cavo *et al.*[19]	VTD induction/consolidation	241	19	58	68	86
mEBMT	TD induction/consolidation	239	5	41	56	84
Ph 3			$P<0.0001$	$P=0.0001$	$P=0.0057$	$P=0.3$
			CR induction	Transplant	mPFS	—
Moreau *et al.*[20]	vtD induction		13	29	26	
IMWG	VD induction		12	31	30	
Ph 3			$P=0.74$	$P=0.77$	$P=0.22$	
Transplant ineligible						
			CR induction	mPFS	3-yr PFS	3 yr
Palumbo *et al.*[65]	VMPT induction →VT maint	254	38	NR	56	89
IMWG	VMP induction	257	24	27.3	41	87
Ph 3			$P<0.001$		$P=0.008$	$P=0.77$
			CR induction	mPFS	3 yr	
Mateos *et al.*[21]	VTP induction→VT or VP maint	130	28	25	65	
mEBMT	VMP induction→VT or VP maint	130	20	34	74	
Ph 3			$P=0.2$	$P=0.1$	$P=0.3$	
Transplant eligible/ineligible						
			CR overall	18-mo PFS	18 mo	
Richardson *et al.*[22]	VRD induction→VRD maint or HD-ASCT	66	29	75	97	
mIMWG						
Ph 1/2						
			sCR overall	2-yr PFS		
Jakubowiak *et al.*[24]	CRd induction→CRd maint or HD-ASCT	53	42	92	—	
mIMWG						
Ph 1/2						
				CR overall		
Kumar *et al.*[25]	IRd→ixazomib maint	65		18	—	—
mIMWG						
Ph 1/2						
Relapsed						
			CR overall	mTTP	24 mo	
Garderet *et al.*[23]	VTD	135	25	19.5	71	
mEBMT	TD	134	14	13.8	65	
Ph 3			$P=0.024$	$P=0.001$	$P=0.093$	

Abbreviations: CRd, carfilzomib, lenalidomide, low-dose dexamethasone; HD-ASCT, high-dose therapy with autologous stem cell transplant; IRd, ixazomib (MLN9708), lenalidomide, low-dose dexamethasone; maint, maintenance therapy; mEBMT, modified European Group for Blood and Marrow Transplantation; mIMWG, modified International Myeloma Working Group; mo, months; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; TD, thalidomide, dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, prednisone; vtD, low-dose bortezomib, thalidomide with dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; VTP, bortezomib, thalidomide, prednisone; yr, years. [a]Conversion to months for studies reporting other time increments.

months, all patients who achieved a molecular response were relapse-free, whereas 11 patients who were MRD-positive had relapsed.

These new assays will be critical in determining the benefit of aggressive and prolonged therapies, and are potential surrogate markers for OS. In 2011, the International Myeloma Working Group updated the response criteria to include immunophenotypic CR, defined as a stringent CR with evidence of MRD-negative disease by multiparametric flow cytometry (absence of phenotypically aberrant clonal plasma cells in $\geqslant 1$ million analyzed cells), and molecular CR, a CR with evidence of MRD-negative disease by the PCR method (sensitivity 10^{-5}).[107] Although a number of studies are now using MRD as a study endpoint,[21,24,100,108] these assays are complex, not applicable to all patients and allele-specific oligonucleotide PCR can be expensive and time consuming, so their wider adoption may take time.

FUTURE CONSIDERATIONS

The development of targeted therapies for MM has not only resulted in clinically significant improvements in outcomes but has also advanced our understanding of this complex disease. Collectively, the results from studies of targeted therapies support maximizing response at all treatment stages and in most patient subgroups. However, these are not definitive data and there remain important gaps in our knowledge. We need to more accurately predict the individual response level that is durable and will extend disease control and survival without significant risk of treatment-related morbidity. Some patients can achieve long-term survival with a lesser response, but this may or may not require continuous treatment, and the potential benefit of treating a patient to a deeper response with more aggressive treatment of shorter duration should also be weighed. Treatment decisions—initiating a new treatment or intensifying the current treatment—need to be better informed across the levels of reponse.[10] This will require a greater understanding of the molecular evolution of MM over the course of the disease and treatment, to identify and differentiate high- to low-risk subclones and their sensitivity to the selective pressures of specific treatments at initial diagnosis and disease progression.[33–35] This could lead to strategies that primarily target the highly proliferative and genetically dynamic subclones with aggressive multi-agent treatment, and secondarily target indolent and genetically stable subclones with more selective regimens but this will require further study in the clinical setting. Finally, the cost of targeted therapies—particularly, prolonged treatment (for example, maintenance or salvage therapy)—is an important barrier that should be acknowledged, as some healthcare systems may not provide support for their use in certain settings without definitive data.

In the transplant setting, the development of triplet combinations pairing PIs and IMiDs has improved the depth of response with induction therapy. Triplet combinations allow for more rapid and high-level responses, and may overwhelm the potential resistance through synergistic and complementary antimyeloma activity.[88] The quality of response with some triplet combinations has reached a level where it might be better to defer HD-ASCT until relapse or use it strategically to improve response.[109]

Ongoing studies should help to address these issues (ClinicalTrials.gov NCT01191060 and NCT01208766).

Although tolerability with multidrug regimens is always a concern, various treatment strategies (for example, attenuated dosing[5]) are available to address these in specific patients and will help to broaden the spectrum of patients considered for multidrug regimens. Furthermore, novel PIs (for example, carfilzomib and ixazomib [MLN9708]) and IMiDs (for example, pomalidomide) have demonstrated good clinical activity and are well tolerated,[24,25,72,98,99,110,111] and other classes of targeted therapy (for example, histone deacetylase inhibitors and monoclonal antibodies) have shown encouraging activity.[112,113] With more options, treatment regimens can be better tailored to the individual patient.

The development of laboratory and animal models of myeloma and the bone marrow microenvironment in the 1990s proved instrumental in rapidly bringing the targeted therapies from the bench to the bedside and in the development of combination regimens.[18] Moving forward, preclinical models will help us to better understand the mechanisms underlying the quality of responses, to develop biomarkers that predict treatment response and outcomes, and to maximize the potential of targeted therapies. It is equally important to continue to develop response assays that can further differentiate the impact of high-level response and are accessible to a range of institutions.

CONCLUSIONS

In the era of targeted therapies, quality of response is associated with disease control and survival in patients with MM, including patients with high-risk disease, but until clinical trials are specifically designed to assess this relationship, it will remain only an association. Achievement of maximal response should be considered upfront and at all stages of treatment, bearing in mind tolerability, quality of life and treatment barriers including cost and the lack of definitive data. In select patients, achievement of a lesser response may be adequate to prolong survival and attempts to treat these patients to a better response may place them at unnecessary risk without a significant benefit. Multidrug regimens combining PIs with IMiDs have improved depth of response, have acceptable tolerability and are becoming a standard treatment approach. The development of novel targeted therapies should further advance these goals as clinical data in conjunction with laboratory findings should help to facilitate the use of antimyeloma agents to their fullest potential. Treatment should be tailored to the disease characteristics and needs and goals of the individual patient.

CONFLICT OF INTEREST

Dr Lonial has received compensation as a consultant for Millennium, Celgene, Novartis, Bristol-Myers Squibb, Onyx Pharmaceuticals and Merck. Dr Anderson has received compensation as a member of the scientific advisory boards of Celgene, Onyx, Gilead, and Sanofi-Aventis. He is also a scientific founder of Acetylon and Oncopep.

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REFERENCES

1 Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK *et al.* Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008; **111**: 2516–2520.
2 Pulte D, Gondos A, Brenner H. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER data. *Oncologist* 2011; **16**: 1600–1603.
3 Brenner H, Gondos A, Pulte D. Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010. *Haematologica* 2009; **94**: 270–275.
4 Kumar S. Treatment of newly diagnosed multiple myeloma in transplant-eligible patients. *Curr Hematol Malig Rep* 2011; **6**: 104–112.
5 Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med* 2011; **364**: 1046–1060.
6 Kumar S. Multiple myeloma—current issues and controversies. *Cancer Treat Rev* 2010; **36**(Suppl 2): S3–S11.
7 Davies FE, Forsyth PD, Rawstron AC, Owen RG, Pratt G, Evans PA *et al.* The impact of attaining a minimal disease state after high-dose melphalan and autologous transplantation for multiple myeloma. *Br J Haematol* 2001; **112**: 814–819.
8 Blade J, Lopez-Guillermo A, Bosch F, Cervantes F, Reverter JC, Montserrat E *et al.* Impact of response to treatment on survival in multiple myeloma: results in a series of 243 patients. *Br J Haematol* 1994; **88**: 117–121.
9 Oivanen TM, Kellokumpu-Lehtinen P, Koivisto AM, Koivunen E, Palva I. Response level and survival after conventional chemotherapy for multiple myeloma: a Finnish Leukaemia Group study. *Eur J Haematol* 1999; **62**: 109–116.
10 Chanan-Khan AA, Giralt S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. *J Clin Oncol* 2010; **28**: 2612–2624.
11 Haessler J, Shaughnessy Jr. JD, Zhan F, Crowley J, Epstein J, van Rhee F *et al.* Benefit of complete response in multiple myeloma limited to high-risk subgroup identified by gene expression profiling. *Clin Cancer Res* 2007; **13**: 7073–7079.
12 Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A *et al.* Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007; **357**: 2123–2132.
13 Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA *et al.* Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007; **357**: 2133–2142.
14 Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005; **352**: 2487–2498.
15 Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F *et al.* Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006; **354**: 1021–1030.
16 San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M *et al.* Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008; **359**: 906–917.
17 Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V *et al.* Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet* 2006; **367**: 825–831.
18 Anderson KC. The 39th David A. Karnofsky Lecture: bench-to-bedside translation of targeted therapies in multiple myeloma. *J Clin Oncol* 2012; **30**: 445–452.
19 Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M *et al.* Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 2010; **376**: 2075–2085.
20 Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C *et al.* Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. *Blood* 2011; **118**: 5752–5758.
21 Mateos MV, Oriol A, Martinez-Lopez J, Gutierrez N, Teruel AI, de Paz R *et al.* Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol* 2010; **11**: 934–941.
22 Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS *et al.* Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood* 2010; **116**: 679–686.
23 Garderet L, Iacobelli S, Moreau P, Dib M, Lafon I, Niederwieser D *et al.* Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005-04 Randomized Phase III Trial From the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol* 2012; **30**: 2475–2482.

24 Jakubowiak AJ, Dytfeld D, Griffith KA, Lebovic D, Vesole DH, Jagannath S *et al.* A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood* 2012; **120**: 1801–1809.

25 Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Hamadani M, Stewart AK *et al.* A phase 1/2 study of weekly MLN9708, an investigational oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma (MM). *ASH Annual Meeting Abstracts* 2012; **120**: 332.

26 Lahuerta JJ, Mateos MV, Martinez-Lopez J, Rosinol L, Sureda A, de la Rubia J *et al.* Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. *J Clin Oncol* 2008; **26**: 5775–5782.

27 Moreau P, Attal M, Pegourie B, Planche L, Hulin C, Facon T *et al.* Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. *Blood* 2011; **117**: 3041–3044.

28 Harousseau JL, Avet-Loiseau H, Attal M, Charbonnel C, Garban F, Hulin C *et al.* Achievement of at least very good partial response is a simple and robust prognostic factor in patients with multiple myeloma treated with high-dose therapy: long-term analysis of the IFM 99-02 and 99-04 Trials. *J Clin Oncol* 2009; **27**: 5720–5726.

29 Galli M, Nicolucci A, Valentini M, Belfiglio M, Delaini F, Crippa C *et al.* Feasibility and outcome of tandem stem cell autotransplants in multiple myeloma. *Haematologica* 2005; **90**: 1643–1649.

30 Gay F, Larocca A, Mateos M, Oliva S, Offidani M, Ria R *et al.* Complete response is a stronger predictor of survival than cytogenetic profile and International Staging System stage in elderly myeloma patients treated with bortezomib: analysis of 771 patients. *EHA 2012 Haematologica* **97**(supp 1); abstract O0591.

31 Gay F, Larocca A, Wijermans P, Cavallo F, Rossi D, Schaafsma R *et al.* Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. *Blood* 2011; **117**: 3025–3031.

32 Harousseau JL, Dimopoulos MA, Wang M, Corso A, Chen C, Attal M *et al.* Better quality of response to lenalidomide plus dexamethasone is associated with improved clinical outcomes in patients with relapsed or refractory multiple myeloma. *Haematologica* 2010; **95**: 1738–1744.

33 Egan JB, Shi CX, Tembe W, Christoforides A, Kurdoglu A, Sinari S *et al.* Whole genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution and clonal tides. *Blood* 2012; **120**: 1060–1066.

34 Keats JJ, Chesi M, Egan JB, Garbitt VM, Palmer SE, Braggio E *et al.* Clonal competition with alternating dominance in multiple myeloma. *Blood* 2012; **120**: 1067–1076.

35 Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer* 2012; **12**: 335–348.

36 Harousseau JL, Attal M, Avet-Loiseau H. The role of complete response in multiple myeloma. *Blood* 2009; **114**: 3139–3146.

37 Rajkumar SV, Gahrton G, Bergsagel PL. Approach to the treatment of multiple myeloma: a clash of philosophies. *Blood* 2011; **118**: 3205–3211.

38 Anderson KC, Kyle RA, Rajkumar SV, Stewart AK, Weber D, Richardson P. Clinically relevant end points and new drug approvals for myeloma. *Leukemia* 2008; **22**: 231–239.

39 Pineda-Roman M, Bolejack V, Arzoumanian V, Anaissie E, van Rhee F, Zangari M *et al.* Complete response in myeloma extends survival without, but not with history of prior monoclonal gammopathy of undetermined significance or smouldering disease. *Br J Haematol* 2007; **136**: 393–399.

40 Zhan F, Barlogie B, Arzoumanian V, Huang Y, Williams DR, Hollmig K *et al.* Gene-expression signature of benign monoclonal gammopathy evident in multiple myeloma is linked to good prognosis. *Blood* 2007; **109**: 1692–1700.

41 Paiva B, Gutierrez NC, Rosinol L, Vidriales MB, Montalban MA, Martinez-Lopez J *et al.* High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. *Blood* 2012; **119**: 687–691.

42 Riccardi A, Mora O, Tinelli C, Porta C, Danova M, Brugnatelli S *et al.* Response to first-line chemotherapy and long-term survival in patients with multiple myeloma: results of the MM87 prospective randomised protocol. *Eur J Cancer* 2003; **39**: 31–37.

43 Kyle RA, Leong T, Li S, Oken MM, Kay NE, Van Ness B *et al.* Complete response in multiple myeloma: clinical trial E9486, an Eastern Cooperative Oncology Group study not involving stem cell transplantation. *Cancer* 2006; **106**: 1958–1966.

44 Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G *et al.* Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol* 1998; **102**: 1115–1123.

45 Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K *et al.* International uniform response criteria for multiple myeloma. *Leukemia* 2006; **20**: 1467–1473.

46 Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D *et al.* A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med* 2003; **348**: 2609–2617.

47 Krejci M, Scudla V, Tothova E, Schutzova M, Koza V, Adam Z *et al.* Long-term outcomes of autologous transplantation in multiple myeloma: significant survival benefit of novel drugs in post-transplantation relapse. *Clin Lymphoma Myeloma* 2009; **9**: 436–442.

48 Venner CP, Connors JM, Sutherland HJ, Shepherd JD, Hamata L, Mourad YA *et al.* Novel agents improve survival of transplant patients with multiple myeloma including those with high-risk disease defined by early relapse (<12 months). *Leuk Lymphoma* 2011; **52**: 34–41.

49 Pazdur R. Endpoints for assessing drug activity in clinical trials. *Oncologist* 2008; **13**(Suppl 2): 19–21.

50 Lenhoff S, Hjorth M, Turesson I, Westin J, Gimsing P, Wisloff F *et al.* Intensive therapy for multiple myeloma in patients younger than 60 years. Long-term results focusing on the effect of the degree of response on survival and relapse pattern after transplantation. *Haematologica* 2006; **91**: 1228–1233.

51 Durie BG, Jacobson J, Barlogie B, Crowley J. Magnitude of response with myeloma frontline therapy does not predict outcome: importance of time to progression in southwest oncology group chemotherapy trials. *J Clin Oncol* 2004; **22**: 1857–1863.

52 Singhal S, Powles R, Sirohi B, Treleaven J, Kulkarni S, Mehta J. Response to induction chemotherapy is not essential to obtain survival benefit from high-dose melphalan and autotransplantation in myeloma. *Bone Marrow Transplant* 2002; **30**: 673–679.

53 Rajkumar SV, Fonseca R, Dispenzieri A, Lacy MQ, Witzig TE, Lust JA *et al.* Effect of complete response on outcome following autologous stem cell transplantation for myeloma. *Bone Marrow Transplant* 2000; **26**: 979–983.

54 Nooka AK, Kaufman JL, Behera M, Gleason C, Langston A, Steuer CE *et al.* The improved efficacy of bortezomib containing induction regimens (BCIR) versus non-bortezomib containing induction regimens (NBCIR) in transplant-eligible patients with multiple myeloma (MM): meta-analysis of phase III randomized controlled trials (RCTs). *Blood* 2011; **118**: (abstract 3994).

55 Wang M, Delasalle K, Feng L, Thomas S, Giralt S, Qazilbash M *et al.* CR represents an early index of potential long survival in multiple myeloma. *Bone Marrow Transplant* 2010; **45**: 498–504.

56 Ladetto M, Pagliano G, Ferrero S, Cavallo F, Drandi D, Santo L *et al.* Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *J Clin Oncol* 2010; **28**: 2077–2084.

57 Barlogie B, Anaissie E, Haessler J, van Rhee F, Pineda-Roman M, Hollmig K *et al.* Complete remission sustained 3 years from treatment initiation is a powerful surrogate for extended survival in multiple myeloma. *Cancer* 2008; **113**: 355–359.

58 Hussein MA, Baz R, Srkalovic G, Agrawal N, Suppiah R, Hsi E *et al.* Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed-refractory multiple myeloma. *Mayo Clin Proc* 2006; **81**: 889–895.

59 Offidani M, Corvatta L, Piersantelli MN, Visani G, Alesiani F, Brunori M *et al.* Thalidomide, dexamethasone, and pegylated liposomal doxorubicin (ThaDD) for patients older than 65 years with newly diagnosed multiple myeloma. *Blood* 2006; **108**: 2159–2164.

60 Harousseau JL, Palumbo A, Richardson PG, Schlag R, Dimopoulos MA, Shpilberg O *et al.* Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. *Blood* 2010; **116**: 3743–3750.

61 Palumbo A, Falco P, Corradini P, Falcone A, Di Raimondo F, Giuliani N *et al.* Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA--Italian Multiple Myeloma Network. *J Clin Oncol* 2007; **25**: 4459–4465.

62 Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ *et al.* Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. *Blood* 2011; **118**: 1231–1238.

63 Schaar CG, Kluin-Nelemans JC, le Cessie S, Franck PF, te Marvelde MC, Wijermans PW. Early response to therapy and survival in multiple myeloma. *Br J Haematol* 2004; **125**: 162–166.
64 Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H *et al.* Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. *J Clin Oncol* 2010; **28**: 3160–3166.
65 Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R *et al.* Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol* 2010; **28**: 5101–5109.
66 Niesvizky R, Richardson PG, Rajkumar SV, Coleman M, Rosinol L, Sonneveld P *et al.* The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma. *Br J Haematol* 2008; **143**: 46–53.
67 Palumbo A, Gay F, Bringhen S, Falcone A, Pescosta N, Callea V *et al.* Bortezomib, doxorubicin and dexamethasone in advanced multiple myeloma. *Ann Oncol* 2008; **19**: 1160–1165.
68 Pineda-Roman M, Zangari M, van Rhee F, Anaissie E, Szymonifka J, Hoering A *et al.* VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma. *Leukemia* 2008; **22**: 1419–1427.
69 Quach H, Mileshkin L, Seymour JF, Milner A, Ritchie D, Harrison S *et al.* Predicting durable remissions following thalidomide therapy for relapsed myeloma. *Leuk Lymphoma* 2009; **50**: 223–229.
70 Alegre A, Aguado B, Giraldo P, Rios E, Canovas A, Ibanez A *et al.* Lenalidomide is effective as salvage therapy in refractory or relapsed multiple myeloma: analysis of the Spanish Compassionate Use Registry in advanced patients. *Int J Hematol* 2011; **93**: 351–360.
71 Richardson PG, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T *et al.* Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* 2007; **110**: 3557–3560.
72 Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S *et al.* A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* 2012; **120**: 2817–2825.
73 Avet-Loiseau H. Ultra high-risk myeloma. *Hematology Am Soc Hematol Educ Program* 2010; **2010**: 489–493.
74 Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2012; **87**: 78–88.
75 Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia* 2009; **23**: 3–9.
76 Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J *et al.* Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med* 2012; **366**: 1759–1769.
77 McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG *et al.* Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; **366**: 1770–1781.
78 Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T *et al.* Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012; **366**: 1782–1791.
79 Nooka AK, Behera M, Boise LH, Watson M, Kaufman JL, Lonial S. Thalidomide as maintenance therapy in multiple myeloma (MM) improves progression free survival (PFS) and overall survival (OS): a meta-analysis. *Blood* 2011; **118**: (abstract 1855).
80 Mateos MV, Oriol A, Martinez-Lopez J, Gutierrez N, Teruel AI, Lopez de la Guia A *et al.* Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. *Blood* 2012; **120**: 2581–2588.
81 Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H *et al.* Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol* 2012; **30**: 2946–2955.
82 Niesvizky R, Flinn IW, Rifkin RM, Gabrail NY, Charu V, Clowney B *et al.* Phase 3b UPFRONT study: safety and efficacy of weekly bortezomib maintenance therapy after bortezomib-based induction regimens in elderly, newly diagnosed multiple myeloma patients. *Blood* 2010; **116**: (abstract 619).
83 Ludwig H, Durie BG, McCarthy P, Palumbo A, San Miguel J, Barlogie B *et al.* IMWG consensus on maintenance therapy in multiple myeloma. *Blood* 2012; **119**: 3003–3015.
84 Nair B, van Rhee F, Shaughnessy Jr. JD, Anaissie E, Szymonifka J, Hoering A *et al.* Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. *Blood* 2010; **115**: 4168–4173.
85 Ludwig H, Adam Z, Tothova E, Hajek R, Labar B, Egyed M *et al.* Thalidomide maintenance treatment increases progression-free but not overall survival in elderly patients with myeloma. *Haematologica* 2010; **95**: 1548–1554.
86 Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L *et al.* Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; **108**: 3289–3294.
87 Kaufman JL, Nooka AK, Muppidi S, Heffner LT, Gleason C, Boise L *et al.* Survival outcomes of early autologous stem cell transplant (ASCT) followed by lenalidomide, bortezomib, and dexamethasone (RVD) maintenance in patients with high-risk multiple myeloma (MM). *J Clin Oncol* 2012; **30**: (abstract 8100).
88 Lonial S, Kaufman JL. The era of combination therapy in myeloma. *J Clin Oncol* 2012; **30**: 2434–2436.
89 Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Richardson PG, Hideshima T *et al.* Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. *Blood* 2002; **99**: 4525–4530.
90 Hideshima T, Chauhan D, Shima Y, Raje N, Davies FE, Tai YT *et al.* Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood* 2000; **96**: 2943–2950.
91 Chauhan D, Tian Z, Zhou B, Kuhn D, Orlowski R, Raje N *et al.* *In vitro* and *in vivo* selective antitumor activity of a novel orally bioavailable proteasome inhibitor MLN9708 against multiple myeloma cells. *Clin Cancer Res* 2011; **17**: 5311–5321.
92 Chauhan D, Singh AV, Ciccarelli B, Richardson PG, Palladino MA, Anderson KC. Combination of novel proteasome inhibitor NPI-0052 and lenalidomide trigger *in vitro* and *in vivo* synergistic cytotoxicity in multiple myeloma. *Blood* 2010; **115**: 834–845.
93 Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D *et al.* The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. *Blood* 2003; **101**: 2377–2380.
94 Ma MH, Yang HH, Parker K, Manyak S, Friedman JM, Altamirano C *et al.* The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. *Clin Cancer Res* 2003; **9**: 1136–1144.
95 Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J *et al.* The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res* 2001; **61**: 3071–3076.
96 Dimopoulos MA, Kastritis E, Christoulas D, Migkou M, Gavriatopoulou M, Gkotzamanidou M *et al.* Treatment of patients with relapsed/refractory multiple myeloma with lenalidomide and dexamethasone with or without bortezomib: prospective evaluation of the impact of cytogenetic abnormalities and of previous therapies. *Leukemia* 2010; **24**: 1769–1778.
97 Richardson PG, Jagannath S, Jakubowiak AJ, Lonial S, Raje N, Alsina M *et al.* Phase II trial of lenalidomide, bortezomib, and dexamethasone in patients (pts) with relapsed and relapsed/refractory multiple myeloma (MM): updated efficacy and safety data after >2 years of follow-up. *ASH Annual Meeting Abstracts* 2010; **116**: 3049.
98 Niesvizky R, Martin 3rd TG, Bensinger WI, Alsina M, Siegel DS, Kunkel LA *et al.* Phase Ib dose-escalation study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. *Clin Cancer Res* 2013; **19**: 2248–2256.
99 Richardson PGG, Berdeja JG, Niesvizky R, Lonial S, Roy V, Hari P *et al.* Oral weekly MLN9708, an investigational proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma (MM): A phase I/II study. *J Clin Oncol* 2012; **30**: (abstract 8033).
100 Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ *et al.* Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood* 2012; **119**: 4375–4382.
101 Paiva B, Almeida J, Perez-Andres M, Mateo G, Lopez A, Rasillo A *et al.* Utility of flow cytometry immunophenotyping in multiple myeloma and other clonal plasma cell-related disorders. *Cytometry B Clin Cytom* 2010; **78**: 239–252.
102 Paiva B, Martinez-Lopez J, Vidriales MB, Mateos MV, Montalban MA, Fernandez-Redondo E *et al.* Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. *J Clin Oncol* 2011; **29**: 1627–1633.
103 Paiva B, Vidriales MB, Cervero J, Mateo G, Perez JJ, Montalban MA *et al.* Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood* 2008; **112**: 4017–4023.
104 Putkonen M, Kairisto V, Juvonen V, Pelliniemi TT, Rauhala A, Itala-Remes M *et al.* Depth of response assessed by quantitative ASO-PCR predicts the outcome

after stem cell transplantation in multiple myeloma. *Eur J Haematol* 2010; **85**: 416–423.
105 Martinez-Sanchez P, Montejano L, Sarasquete ME, Garcia-Sanz R, Fernandez-Redondo E, Ayala R *et al.* Evaluation of minimal residual disease in multiple myeloma patients by fluorescent-polymerase chain reaction: the prognostic impact of achieving molecular response. *Br J Haematol* 2008; **142**: 766–774.
106 Corradini P, Voena C, Tarella C, Astolfi M, Ladetto M, Palumbo A *et al.* Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. *J Clin Oncol* 1999; **17**: 208–215.
107 Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R *et al.* Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; **117**: 4691–4695.
108 Terragna C, Zamagni E, Petrucci MT, Durante S, Patriarca F, Narni F *et al.* Molecular remission after bortezomib-thalidomide-dexamethasone compared with thalidomide-dexamethasone as consolidation therapy following double autologous transplantation for multiple myeloma: results of a qualitative and quantitative analysis. *Blood* 2010; **116**: (abstract 861).
109 Bensinger W. Stem-cell transplantation for multiple myeloma in the era of novel drugs. *J Clin Oncol* 2008; **26**: 480–492.
110 Lacy MQ, Hayman SR, Gertz MA, Dispenzieri A, Buadi F, Kumar S *et al.* Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *J Clin Oncol* 2009; **27**: 5008–5014.
111 Vij R, Wang M, Kaufman JL, Lonial S, Jakubowiak AJ, Stewart AK *et al.* An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naïve patients with relapsed and/or refractory multiple myeloma. *Blood* 2012; **119**: 5661–5670.
112 Wolf JL, Siegel D, Goldschmidt H, Hazell K, Bourquelot PM, Bengoudifa BR *et al.* Phase II trial of the pan-deacetylase inhibitor panobinostat as a single agent in advanced relapsed/refractory multiple myeloma. *Leuk Lymphoma* 2012; **53**: 1820–1823.
113 Lonial S, Vij R, Harousseau JL, Facon T, Moreau P, Mazumder A *et al.* Elotuzumab in combination with lenalidomide and low-dose dexamethasone in relapsed or refractory multiple myeloma. *J Clin Oncol* 2012; **30**: 1953–1959.
114 Dytfeld D, Griffith KA, Friedman J, Lebovic D, Harvey C, Kaminski MS *et al.* Superior overall survival of patients with myeloma achieving very good partial response or better to initial treatment with bortezomib, pegylated liposomal doxorubicin, and dexamethasone, predicted after two cycles by a free light chain- and M-protein-based model: extended follow-up of a phase II trial. *Leuk Lymphoma* 2011; **52**: 1271–1280.
115 Gertz MA, Kumar S, Lacy MQ, Dispenzieri A, Dingli D, Hayman SR *et al.* Stem cell transplantation in multiple myeloma: impact of response failure with thalidomide or lenalidomide induction. *Blood* 2010; **115**: 2348–2353.
116 Kapoor P, Kumar S, Dispenzieri A, Lacy M, Dingli D, Hayman SR *et al.* Survival outcomes of patients with multiple myeloma (MM) achieving stringent complete response (sCR) following upfront autologous stem cell transplantation (SCT). *J Clin Oncol* 2011; **29**: (abstract 8069).
117 Alegre A, Diaz-Mediavilla J, San-Miguel J, Martinez R, Garcia Larana J, Sureda A *et al.* Autologous peripheral blood stem cell transplantation for multiple myeloma: a report of 259 cases from the Spanish Registry. Spanish Registry for Transplant in MM (Grupo Espanol de Trasplante Hematopoyetico-GETH) and PETHEMA. *Bone Marrow Transplant* 1998; **21**: 133–140.