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Reviews

Augmenting Autologous Stem Cell Transplantation to Improve Outcomes in Myeloma

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A B S T R A C T

Consolidation with high-dose chemotherapy and autologous stem cell transplantation (ASCT) is the standard of care for transplantation-eligible patients with multiple myeloma, based on randomized trials showing improved progression-free survival with autologous transplantation after combination chemotherapy induction. These trials were performed before novel agents were introduced; subsequently, combinations of immunomodulatory drugs and proteasome inhibitors as induction therapy have significantly improved rates and depth of response. Ongoing randomized trials are testing whether conventional autologous transplantation continues to improve responses after novel agent induction. Although these results are awaited, it is important to review strategies for improving outcomes after ASCT. Conditioning before ASCT with higher doses of melphalan and combinations of melphalan with other agents, including radiopharmaceuticals, has been explored. Tandem ASCT, consolidation, and maintenance therapy after ASCT have been investigated in phase III trials. Experimental cellular therapies using ex vivo–primed dendritic cells, ex vivo–expanded autologous lymphocytes, Killer Immunoglobulin Receptor (KIR)-mismatched allogeneic natural killer cells, and genetically modified T cells to augment ASCT are also in phase I trials. This review summarizes these strategies and highlights the importance of exploring strategies to augment ASCT, even in the era of novel agent induction.

INTRODUCTION

Myeloma represents just over 1% of all cancers and despite a recent increase in available therapeutics, the disease remains incurable with an estimated 5-year survival just over 50% [1]. Randomized controlled trial (RCT) evidence from France and the United Kingdom demonstrated improved disease response and overall survival (OS) after autologous hematopoietic stem cell transplantation (ASCT) compared with after conventional chemotherapy [2,3]. However, subsequent trials from France, the United States, and Spain did not show an OS benefit, although Fermand et al. [4] did show an improvement in progression-free survival (PFS) [4-6]. The differences in outcomes between groups may be accounted for by prolonged use of conventional chemotherapy in the study by Fermand et al. and a high rate of ASCT salvage therapy at relapse in the study by Barlogie et al. [6]. A Dutch trial demonstrated that after treatment with intermediate-dose melphalan, further treatment with ASCT did not improve outcomes [7]. These trials support the use of high-dose alkylating agents in myeloma treatment. For patients who are fit for high-dose therapy (approximately one-third of newly diagnosed patients), treatment with chemotherapy conditioning followed by ASCT has been the standard of care, and the standard conditioning regimen has been a single dose of intravenous melphalan at 200 mg/m^2 [8]. There has been much interest in augmenting conditioning but no single regimen has been shown to improve outcomes in a randomized trial. Adjunctive strategies have also been explored: second tandem ASCT; consolidation and maintenance chemotherapy; attempts to augment immune responses after transplantation; and new drugs, particularly monoclonal antibodies. This review will evaluate the strategies employed and make recommendations for further research in this area.

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METHODS

We searched Pubmed using the terms myeloma, autograft, ASCT, autologous, transplant, graft, transplantation, conditioning, preparative regimen, treatment, RCT, randomized, trial, and induction in various permutations, yielding 1393 results and abstracts from the American Society of Haematology and American Society of Clinical Oncology annual meetings. Reference lists from these search results were used to identify other relevant publications. In the tables, overall response rate (ORR) is the proportion of patients achieving a partial response (>50% reduction in paraprotein) or better.

NOVEL AGENT INDUCTION

Induction for transplantation-eligible patients with immunomodulatory drugs (IMiD) (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib) has improved response rates before ASCT. The HOVON50 trial demonstrated that substituting thalidomide for vincristine in the vincristine, doxorubicin, and dexamethasone (VAD) regimen could increase pre-ASCT ORR from 54% to 72% [9]. The benefit conferred by thalidomide combinations in induction was confirmed by the Myeloma IX and Total Therapy 2 trials [10,11]. The Intergroupe Francophone Myélome (IFM) 2005-01 trial demonstrated that bortezomib and dexamethasone was also superior to VAD, increasing the pre-ASCT response rate to 79% from 63% [12], and a similar improvement with bortezomib-based induction was observed in the HOVON65/GMMGHD4 trial [13]. Cavo et al. tested the addition of bortezomib to thalidomide plus dexamethasone (VTD), and this combination of both IMiD and proteasome inhibitor significantly improved both pre-ASCT ORR (93% versus 79%) and PFS [14]. This combination, VTD, is also superior to bortezomib, cyclophosphamide, and dexamethasone, producing pre-ASCT ORR of 92% versus 83% in a phase III trial [15]. Combining lenalidomide with bortezomib plus dexamethasone (VRD) produced an ORR of 94% in a phase II IFM study [16]. An ongoing phase II study of carfilzomib, lenalidomide, and dexamethasone for both induction and maintenance obtained an ORR pre-ASCT of 98% and demonstrated no unexpected toxicity [17].

The improvement in responses seen with newer induction programs has prompted further trials after induction comparing upfront ASCT with a nontransplantation option of novel agent consolidation followed by maintenance. Recently published phase III trials comparing ASCT with lenalidomide-containing regimens found ASCT confers superior PFS, although at a median follow up of 52 months, no differences in OS were observed [18,19]. An ongoing French/American RCT (the IFM/DFCI 2009 study) compares ASCT plus 2 cycles of VRD with 5 cycles of VRD alone, and results from the French cohort show superior complete response (CR) rate (58% versus 46%) and 3-year PFS (61% versus 48%) in the ASCT arm [20]. EMN02/HO95 is a European 2×2 factorial RCT, currently recruiting patients to compare ASCT versus bortezomib, melphalan and prednisolone (VMP) intensification and then consolidation with VRD versus no consolidation [21]. The possible merits of a delayed transplantation strategy are being evaluated in the PADIMAC phase II study for patients achieving very good partial response (VGPR) or CR after bortezomib, doxorubicin, and dexamethasone: up to 20% of patients had negative minimal residual disease (MRD) after induction, and survival outcomes are awaited [22].

CONDITIONING FOR ASCT

High-dose melphalan 200 mg/m^2 (mel200) delivered as a single dose for conditioning has been shown in a randomized trial to be less toxic and at least as effective as melphalan 140 mg/m^2 (mel140) plus 8 Gy total body irradiation (TBI) [8], and mel200 has since remained the gold standard for single ASCT in patients with normal renal function. Escalating the dose of melphalan above 200 mg/m^2 is prohibitively toxic to the gastrointestinal tract. Minimizing oral mucositis with protective agents amifostine [23] and palifermin, a keratinocyte growth factor, may facilitate dose increases to 280 mg/m^2 for a proportion of patients [24]. However, wide variability in melphalan exposure due to pharmacokinetic differences has been reported. In a pharmacokinetic study of high-dose melphalan in 100 patients, higher mucositis rates and improved disease response were seen in patients with higher exposure to melphalan, as measured by increased area under the curve of both total and unbound melphalan [25].

Melphalan and Chemotherapeutic Agent Combinations

A number of chemotherapeutic agents and combinations with mel200 have been tested in clinical studies, but the majority of these studies enrolled fewer than 100 patients and were nonrandomized studies, so it is difficult to draw significant conclusions (Table 1).

Regarding alkylating agents in combination with melphalan, oral busulfan is demonstrably too toxic, as 8% of patients in a Spanish study developed veno-occlusive disease, with a case fatality rate of 25% [26]. The intravenous busulfan formulation introduced in 2003 reduces hepatic exposure via the portal circulation, and a nonrandomized study (n = 153) comparing mel140 plus busulfan 9.6 mg/kg i.v. with mel200 suggested a small benefit in terms of PFS but increased treatment-related mortality, with neither difference reaching statistical significance [27]. Adding cyclophosphamide 120 mg/kg to mel200 worsens outcomes [28], and further addition of idarubicin progressively increases treatment-related mortality to 20% [29]. An RCT of cyclophosphamide, oral busulfan, and total marrow irradiation versus 2 consecutive ASCT with mel200 found the chemoradiotherapy regimen to be more toxic with no significant improvement in efficacy [30]. Reports from MD Anderson Cancer Centre using mel140 plus topotecan and cyclophosphamide in combination show outcomes comparable to mel200 but a controlled comparison is required [31,32]. The addition of carmustine to mel200 was found to be safe in single-arm studies, with comparable PFS and OS to previously published mel200 studies [33,34]. More recently, bendamustine, which has shown single agent activity in relapsed myeloma, was combined with mel200 at escalated doses reaching 225 mg/m^2 with only 1 dose-limiting toxicity in the first 100 days after transplantation [35].

Melflufen is a dipeptide prodrug of melphalan, which by virtue of increased intracellular hydrolysis is concentrated in myeloma cells. Melflufen induces apoptosis in melphalan-resistant cells and is highly effective in mouse models [36]. A phase I/II trial of melflufen and dexamethasone in relapsed-refractory myeloma is ongoing, but initial results are encouraging with an ORR of 60% [37]. Based on these encouraging results, melflufen as a conditioning regimen before ASCT should be explored in future trials.

Topoisomerase inhibitors (doxorubicin, idarubicin, mitoxantrone, topotecan) have been tested in combination with melphalan as conditioning, although in vitro data on the combination are limited. The addition of cyclophosphamide and idarubicin to mel200 was shown in an RCT to markedly increase treatment-related mortality [29], but adding cyclophosphamide and topotecan to mel140 produced promising outcomes in an uncontrolled series [32]. Two small phase II studies of mitoxantrone combined with

Table 1
Trials of ASCT Conditioning Regimens Since Mel200 Was Established as the Standard of Care

Study	Treatment Regimen	n	TRM, %	ORR, %	Median PFS, mo	Median OS, mo
Alkylating agents						
GEM2000	Oral busulfan 12 mg/kg plus mel140	225	8.4*	91	41*	79
Lahuerta et al. (2010) [26]	Mel200	542	3.5	91	31	71
2 sequential single arms						
Blanes et al. (2013) [27]	Busulfan 9.6 mg/kg plus mel140	51	4	90	33	65.5
Matched control study	Mel200	102	2	91	24	63
Desikan et al. (2000) [28]	Cyclophosphamide 120 mg/kg plus mel200	19	0		27	39
Three-way matched control study (conditioning	TBI 1125cGy plus mel140	24	8		15	25
for the second of 2 tandem ASCTs)	Mel200	43	0		61*	76*
Fenk et al. (2005) [29]	Idarubicin 42 mg/m^2, mel200, and	26	20*	85	20	46
RCT	cyclophosphamide 120 mg/kg					
	Mel200	30	0	83	16	66
Knop et al. (2007) [30]	Total marrow irradiation 9 Gy, oral busulfan	100			38	
RCT	12 mg/kg, and cyclophosphamide 120 mg/kg					
	Mel200 (×2 ASCTs)	98			35	
Donato et al. (2004) [31]	Cyclophosphamide 3 g/m^2, mel140, and	18	0	89		
Uncontrolled phase I; mixed patient population	topotecan 17.5 mg/m^2					
Kazmi et al. (2011) [32]	Cyclophosphamide 3 g/m^2, mel140, and	60	0	85	18.5	4 yr 66%
Uncontrolled phase II; mixed patient population	topotecan 17.5 mg/m^2					
Comenzo et al. (2006) [33]	Carmustine 300 mg/m^2 plus mel200	49	2	88	28	56
Uncontrolled phase I/II						
Chen et al. (2012) [34]	Carmustine 15 mg/kg plus mel200	118	0	96	34	61
Mark et al. (2013) [35]	Mel200 plus bendamustine escalating up	25	0	100		
	to 225 mg/m^2					
Proteasome inhibitors						
Roussel et al. (2010) [43]	Bortezomib 4 mg/m^2 plus mel200	54	0	94		
Uncontrolled; matched comparison	Mel200	115		97		
Huang et al. (2012) [44]	Bortezomib 4 mg/m^2 plus mel200	10	0	100	20	
2 arms stratified by tolerance of bortezomib	Mel200	11	0	100	22	
Miyamoto et al. (2013) [45]	Bortezomib 1.3 or 2.6 mg/m^2 plus mel200	17	0	100		
Uncontrolled; matched comparison	Mel200	17	0	100		
Nishihori et al. (2012) [47]	Tandem ASCTs with mel200 plus bortezomib	25	0	84	15	40
Uncontrolled study in primary refractory population	.7-1.3 mg/m^2					
Topoisomerase inhibitors						
Kazmi et al. (2011) [32]	Topotecan 17.5 mg/m^2, mel140, and	60	0	85	18.5	
Uncontrolled study (upfront and refractory)	cyclophosphamide 3 g/m^2					
Ballestrero et al. (2002) [38]	Mitoxantrone 60 mg/m^2 plus mel180	20	0	90	26	45
Uncontrolled study						
Beaven et al. (2011) [39]	Mitoxantrone 60 mg/m^2 plus mel180	35	3		22	68
Uncontrolled study (upfront and refractory)						
Other agents						
Qazilbash et al. (2008) [40]	Mel200, ascorbic acid 1 g, plus arsenic trioxide	15	0	86	25 (combined)	
Phase II RCT	1.75 mg/kg					
	Mel200, ascorbic acid 1 g plus arsenic trioxide	17	0	70		
	1.05 mg/kg					
	Mel200 plus ascorbic acid 1 g	16	0	87		

TRM indicates treatment-related mortality; Mel180, melphalan 180 mg/m^2.
* Denote a statistically significant difference between arms ($P < .05$).

melphalan (combined n = 55) suggest outcomes comparable to mel200 [38,39].

Arsenic trioxide with ascorbic acid has been explored in a randomized trial recruiting 48 patients, combined with mel200. There was no difference in response rate or survival, but no additional toxicity was noted [40].

Melphalan with Proteasome Inhibitors and IMiDs

Synergistic myeloma cell kill in vitro has been noted with the combination of melphalan and bortezomib [41,42]. Bortezomib, by inhibiting the proteasome, interferes with DNA repair pathways and inhibitors of apoptosis, thus sensitizing cells to DNA-damaging agents such as melphalan. There are currently no randomized data for the addition of bortezomib to ASCT conditioning. A French nonrandomized phase II study found that adding 1 mg/m^2 bortezomib to mel200 improved CR rates from 11% to 35% [43]; however, in contrast, 2 other small studies (combined n = 27) using nonrandomized control patients observed no difference in response rate. Reassuringly, no increase in toxicity was observed [44,45]. A phase I study suggests that bortezomib is more effective when given after melphalan dosing, rather than before, with an increase in CR rates from 11% to 30% [46]. In an uncontrolled series, 36% of patients with primary refractory myeloma obtained a CR after tandem ASCT with bortezomib given after melphalan [47]. Lenalidomide at

higher-than-licensed doses has been combined with mel200 in a phase I study of relapsed/refractory myeloma and no lenalidomide-related dose-limiting toxicities were observed, with 8 of 21 patients (38%) achieving ≥ CR [48]. Carfilzomib is a recently licensed irreversible proteasome inhibitor, which has been studied in phase III trials in relapsed/refractory myeloma [49]; a phase I/II trial is currently underway in combination with melphalan as a conditioning regimen (CARAMEL trial, NCT01842308).

Augmentation with Radiotherapy/Radiopharmaceuticals

TBI displays excessive toxicity in trials, but targeted radiotherapy shows promising early results. Phase I/II trials of radiophosphonates (containing ^{153}Sm or ^{166}Ho, respectively) added to mel200 conditioning showed no change in outcomes with little toxicity, though renal failure due to thrombotic microangiopathy was seen with doses > 30 Gy of the ^{166}Holmium conjugate [50,51]. The combination of bortezomib with the ^{153}Samarium conjugate demonstrated promising synergy in mice and merits further clinical investigation [52]. CD66 is expressed on myeloma cells as well as the myeloid lineage: an anti-CD66 radioconjugate monoclonal antibody is selective for bone marrow and appears to be safe in a phase I trial [53], with results from the phase II trial awaited. Radio-conjugated CD20 antibodies show additional toxicity in phase I when added to mel200 for conditioning (^{90}Y-ibritumomab) [54] and limited efficacy when used as a single agent (^{131}I-tositumomab), which may relate to low CD20 expression on myeloma cells, with higher response rates correlating with expression of CD20 [55]. Radio-conjugate antibodies against CD38 and CD138 have been studied in animal models, but clinical trials are awaited [56,57]. Tomotherapy (radiotherapy delivered from many emitters arranged radially to focus treatment, analogous to computed tomography [CT] scans) has hitherto only been studied in leukemias and lymphomas [58], but studies in myeloma are underway. This would require a head-to-head comparison with molecularly targeted radiotherapy in future.

TANDEM TRANSPLANTATION

Two consecutive cycles of high-dose chemotherapy, with each cycle followed by hematopoietic stem cell transplantation/rescue (tandem ASCT), has been extensively investigated by both European and US cooperative groups in an attempt to improve responses (Table 2). The Arkansas group have undertaken a series of Total Therapy Trials using intensive treatment including tandem ASCT, which have achieved impressive results, with a 41% CR rate and median OS of 68 months in Total Therapy 1 [59,60]. However, these studies were uncontrolled and patient selection was wholly at the discretion of the investigators. A fuller retrospective dataset from the same center, which included patients treated off study protocols, demonstrated inferior results, but on multivariate analysis, a second transplantation was still associated with prolonged PFS and OS [61].

Most randomized trials comparing single with tandem ASCT have shown no benefit in OS from tandem stem cell transplantation [7,62-65] (reviewed by Kumar et al. [66]). Many of these trials utilized nonstandard conditioning regimens (eg, oral busulfan or TBI), which have since been shown to be inferior to standard mel200 [7,62,63,65]. However the GMMG-HD2 trial, which used tandem standard mel200 ASCT, showed no difference in survival [64]. The only trial to show a significant benefit for both PFS and OS was the IFM-94 study, but the outcomes (in both groups) were poor compared with those from more recent trials using newer agents as part of

Table 2
Trials of Tandem ASCT after Induction

Study	Treatment Regimen	n	TRM, %	Response	Median PFS, mo	Median OS, mo
TT1 Barlogie et al. (2006) [59]	3 × VAD, cyclophosphamide 6 g/m^2, EDAP, 2 × ASCT with mel200 (or mel140 + 8.5 Gy TBI), interferon maintenance	231	5	40% ≥ VGPR	31	68
TT3 Barlogie et al. (2007) [60]	2 × VTD-PACE, 2 × ASCT with mel200, 2 × VTD-PACE, VTD for 1 yr then TD for 2 yr	303	5	56% ≥ VGPR	65% 5 yr	74% 5 yr
IFM-94 Attal et al. (2003) [62]	3-4 × VAD, 1 × ASCT with mel140, 1 × ASCT with mel140 + 8 Gy TBI, interferon maintenance	200	6	50% ≥ VGPR	36*	58*
RCT	3-4 × VAD, 1 × ASCT with mel140 + 8 Gy TBI, interferon maintenance	199	4	42% ≥ VGPR	29	48
MAG95 Fermand et al. (2005) [65]	High-dose steroid and cyclophosphamide, 1 × ASCT with mel140, 1 × ASCT with high-dose chemotherapy + TBI 12 Gy	114	7	38% ≥ VGPR	34	75
RCT	High-dose steroid and cyclophosphamide, 3-4× VAD, 1 × ASCT with high-dose chemotherapy + TBI 12 Gy	113	12	37% ≥ VGPR	31	57
Bologna 96 Cavo et al. (2007) [63]	4× VAD, cyclophosphamide 7 g/m^2, 1 × ASCT with mel200, 1 × ASCT mel120 + busulfan 12 mg/kg, interferon maintenance	158	6	47% ≥ nCR	42*	71
RCT	4× VAD, cyclophosphamide 7 g/m^2, 1 × ASCT mel200, interferon maintenance	163	6	33% ≥ nCR	24	65
GMMG-HD2 Mai et al. (2016) [64]	Up to 6× VAD or VID, cyclophosphamide 4 g/m^2, 2 × ASCT with mel200, interferon maintenance	181	5	19% CR*	29	75
RCT	Up to 6× VAD or VID, cyclophosphamide 4 g/m^2, 1 × ASCT with mel200, interferon maintenance	177	2	16% CR	25	73
HOVON 24 Sonneveld et al. (2007) [7]	3-4× VAD, cyclophosphamide 4 g/m^2, 2 × mel70 (*without* ASCT), ASCT with cyclophosphamide 120 mg/kg + TBI 9 Gy, interferon maintenance	155	10	32% CR*	27*	50
RCT	3-4× VAD, cyclophosphamide 4 g/m^2, 2 × mel70 (*without* ASCT), interferon maintenance	148	4	13% CR	24	55

EDAP indicates etoposide/dexamethasone/cytarabine/cisplatin; VTD-PACE, bortezomib/thalidomide/dexamethasone with cisplatin/doxorubicin/cyclophosphamide/etoposide; TD, thalidomide/dexamethasone; VID, vincristine, idarubicin, dexamethasone; nCR, near-complete response (paraprotein only detectable with immunofixation).

* Denotes a statistically significant difference between arms ($P < .05$).

the treatment protocol [62]. In a nonrandomized comparison between the Dutch protocol (single transplantation) and the German protocol (tandem ASCT), the latter was superior for OS, but regional variations in demographics and treatment could account for this difference [67]. Subgroup analyses suggest there may be a survival advantage from a second ASCT in those patients who fail to achieve a deep response to the first ASCT [62,63]. In the majority of trials, treatment-related mortality is higher in the tandem ASCT arm, and in addition to this acute risk, there may be an increased risk of long-term complications, such as second malignancies and myelodysplastic syndrome, although it is not clear that ASCT increases that risk over high-dose conventional chemotherapy [68]. The deep responses achieved with proteasome inhibitors and IMiD-based conditioning regimens, and wider use of consolidation and maintenance therapies, have both limited the use of tandem stem cell transplantation.

CONSOLIDATION

Relapse remains inevitable after ASCT and consolidation therapy after transplantation has been investigated as a way of prolonging PFS by deepening post-transplantation response. Several phase II and phase III studies of post-ASCT consolidation have been performed over the last 5 years (Table 3), but there is a lack of randomized data to support its efficacy. Only 1 phase III trial is placebo controlled [69] and uncontrolled studies are not instructive because responses improve over months after ASCT regardless of further treatment. In a phase II comparison with historical controls, patients receiving cyclophosphamide, thalidomide, and dexamethasone consolidation achieved better responses at 12 months (72% ≥ VGPR versus 51%) [70]. In a phase III RCT, bortezomib as a single agent improved response and PFS but with no improvement in OS [69]. In a phase III trial of adding bortezomib to thalidomide and dexamethasone (ie, VTD versus thalidomide and dexamethasone for both induction and consolidation, there was no OS benefit, but 3-year PFS increased from 56% to 68%, commensurate with deepening response [14]. The consistent finding of deeper responses with delayed progression but no effect on OS likely reflects more effective salvage treatment at relapse for the control group.

There are no randomized data on lenalidomide-based consolidation, but in an RCT of lenalidomide maintenance, all patients from both arms first received 2 months of lenalidomide consolidation and over this period, the rate of ≥ VGPR increased from 58% to 69% [71]. A phase II study of lenalidomide, bortezomib, and dexamethasone in both induction and consolidation demonstrated good responses and impressive survival data, with an estimated 77% 3-year PFS [16]. Results from a phase II study of carfilzomib, lenalidomide, and dexamethasone for induction, consolidation and maintenance (with lower doses of carfilzomib) showed that 88% of patients were MRD-negative after 4 cycles of consolidation, which will hopefully be reflected in future improved survival data [17]. Survival benefits from consolidation strategies after ASCT have yet to be confirmed in randomized studies.

MAINTENANCE

Relapse after ASCT is primarily due to residual myeloma cells that continue to survive and proliferate, and maintenance therapy aims to control this process, by giving continuous low-dose therapy until relapse (Table 4). However, a concern is that although progression is delayed on maintenance, at relapse the disease could be refractory to further treatment and so benefits in OS would be limited. Such benefits must be balanced against toxicity, quality of life, and cost effectiveness, given the long duration of maintenance approaches. Earlier maintenance studies did not include any consolidation,

Table 3
Consolidation Trials after ASCT in Myeloma

Study	Treatment Regimen	n	Proportion with Adverse Events of Grade 3/4, %	Proportion Attaining ≥ VGPR (%)	Median PFS, mo	Median OS, mo
Rabin et al. (2012) [70] Phase II after ASCT	3-6 cycles of CTD consolidation	45	40	72*	26 (from consolidation)	NR
	No consolidation	40		51	21	71 mo
Mellqvist et al. (2013) [69] RCT after ASCT	Bortezomib 1.3 mg/m^2 (20 doses)	187	11*	71*	27 (from consolidation)*	79% 3 yr
	No consolidation	183	2	57	20	82% 3 yr
Cavo et al. (2010) [14] RCT	3 × VTD induction, tandem ASCT then 2 × VTD consolidation	236	56*	89*	68% 3 yr (from induction)*	86% 3 yr
	3 × TD induction, tandem ASCT then 2 × TD consolidation	238	33	74	56% 3 yr	84% 3 yr
Ladetto et al. (2010) [123] Phase II Recruiting ≥ VGPR after ASCT	4 × VTD consolidation	39	54	100% (at recruitment)	60 (from induction)	89% 3 yr
Leleu et al. (2013) [124] Retrospective cohort study	3 × VTD, ASCT, then 2 × VTD consolidation	121		83	62% 4 yr*	91% 4 yr (estimated)
	3 × VTD, ASCT, no consolidation	96		64	29% 4 yr	84% 4 yr (estimated)
Attal et al. (2012) [71] (Premaintenance analysis)	After ASCT, 2 × lenalidomide consolidation (thereafter randomized to maintenance or nil)	577		69% (after consolidation)	32% 4 yr (from consolidation)	74% 4 yr
Roussel et al. (2014) [16] Phase II	3 × RVD induction, ASCT with mel200, then 2 × RVD consolidation, then 1 yr lenalidomide maintenance	31	74	84	77% 3 yr (from induction)	100% 3 yr

CTD indicates cyclophosphamide/thalidomide/dexamethasone; RVD, lenalidomide/bortezomib/dexamethasone.
* Denotes a statistically significant difference between arms ($P < .05$).

Table 4
Maintenance Therapy Trials after ASCT

Study	Treatment Regimen	No. of Patients	Adverse Events of Grade 3/4 (% of Patients, or Absolute Number)	Proportion Attaining ≥ VGPR, %	Median PFS, mo	Median OS, mo
S9321 Barlogie et al. (2006) [6] RCT	After ASCT or conventional therapy, interferon maintenance	121			23	69
	After ASCT or conventional therapy, no maintenance	121			18	62
Attal et al. (2006) [75] RCT	After ASCT, pamidronate 90 mg plus thalidomide 400 mg maintenance	201	177 events	67	51% 3 yr*	87% 4 yr*
	After ASCT, pamidronate maintenance	196	65 events	57	39% 3 yr	74% 4 yr
	After ASCT, no maintenance	200	40 events	55	38% 3 yr	77% 4 yr
Stewart et al. (2013) [78] RCT	After ASCT, thalidomide 200 mg and prednisolone maintenance	165	140 events*		28*	68% 4 yr
	After ASCT, no maintenance	163	39 events		17	60% 4 yr
Spencer et al. (2009) [76] RCT after ASCT	Thalidomide 100-200 mg for 1 yr and indefinite prednisolone maintenance	114	51 events	65*	31 (from maintenance)*	86% 3 yr (from maintenance)*
	Indefinite prednisolone maintenance	129	32 events	44	18	75% 3 yr
Maiolino et al. (2012) [77] RCT	After ASCT, dexamethasone plus thalidomide 200 mg maintenance for 1 yr	56	20 events	50	36*	85% 2 yr
	After ASCT, dexamethasone maintenance for 1 yr	52	4 events	48	19	70% 2 yr
Sonneveld et al. (2012) [13] RCT	PAD induction, ASCT, bortezomib 1.3 mg/m^2 maintenance for 2 yr	413	48%	76*	35*	61% 5 yr
	VAD induction, ASCT, thalidomide 50 mg maintenance for 2 yr	414	46%	56	28	55% 5 yr
Attal et al. (2012) [71] RCT	After ASCT, 2 cycles lenalidomide consolidation (25 mg), then lenalidomide 10-15 mg until relapse	307	74%*	84*	41*	73% 4 yr
	After ASCT, 2 cycles lenalidomide consolidation (25 mg), then no maintenance	307	43%	76	23	75% 4 yr
McCarthy et al. (2012) [80] RCT	After ASCT, lenalidomide 10-15 mg maintenance	231	60%*		46*	88% 3 yr*
	After ASCT, placebo	229	30%		27	80% 3 yr
Palumbo et al. (2014) [18] 2 × 2 RCT	After ASCT or MPR, lenalidomide 10 mg maintenance	126	53 events*		42*	88% 3 yr
	After ASCT or MPR, no maintenance	125	7 events		22	80% 3 yr
Gay et al. (2015) [19] 2 × 2 RCT	After ASCT or CRD, lenalidomide 10 mg plus prednisolone maintenance	194	20%		38 (from maintenance)	83% 3 yr
	After ASCT or CRD, lenalidomide 10 mg maintenance	198	20%		29	88% 3 yr
Nair et al. (2010) [82] Comparison between TT3 and TT6 cohorts	After 2 × ASCT, 3 yr of VRD	177		61% CR	80% 2 yr	85% 2 yr
	After 2 × ASCT, 1 yr of bortezomib and 3 yr of thalidomide plus dexamethasone	303		59% CR	83% 2 yr	87% 2 yr
Nooka et al. (2014) [81] Phase II study in high risk disease	After ASCT, 3 yr of RVD	45		96	32	93% 3 yr

PAD, bortezomib, doxorubicin and dexamethasone; MPR, melphalan, prednisolone, and lenalidomide; CRD, cyclophosphamide/lenalidomide/dexamethasone.
* Denotes a statistically significant difference between arms ($P < .05$).

and the survival plots often diverge early, which suggests that most benefit is gained early after transplantation. It is unclear if there are advantages to commencing maintenance after an effective course of consolidation treatment.

Interferon alpha had been used as a maintenance agent for many years, but it is uniformly poorly tolerated. Used as maintenance therapy after conventional chemotherapy, interferon alpha modestly prolonged PFS with no effect on OS [72] but the US Intergroup S9321 trial found that it made no difference on progression or survival after ASCT [6]. A therapeutic dose of prednisolone conferred a survival benefit when used after VAD-based conventional chemotherapy [73], but glucocorticoids as monotherapy in the post-ASCT
population are redundant now, given the improved clinical activity and tolerability observed with IMiDs and proteasome inhibitors. In a phase III comparison between dexamethasone and interferon maintenance, the dexamethasone group responded very badly to melphalan/dexamethasone at relapse, presumably because of selection of resistant clones [74].

Thalidomide maintenance has been subjected to a number of phase III trials, conferring a 10% increase in the 4-year survival rate compared with no maintenance [75], and in an RCT comparing thalidomide plus prednisolone versus prednisolone alone, OS was increased by 10% at 3 years [76]. A smaller RCT of similar design found a nonsignificant trend towards increased survival in the thalidomide arm [77]. However, an RCT of thalidomide plus prednisolone versus no maintenance found no OS difference and highlighted worse quality-of-life scores in the maintenance group [78]. In all of these trials, adverse events of grade 3 or 4 were much more common in the thalidomide arm; this is reflected in a thalidomide discontinuation rate of 30% within 1 year in the study by Spencer et al. [76].

In a joint German/Dutch trial comparing induction and maintenance with bortezomib versus vincristine-based induction and thalidomide maintenance, there were improved response rates and PFS, but the OS difference barely reached statistical significance ($P = .049$) on a multivariate analysis [13]. There was no difference in response during the maintenance

phase, between the 2 arms. In a post-hoc analysis, patients with renal impairment gained a significant benefit from the bortezomib arm [79].

Two large RCTs of lenalidomide maintenance against placebo showed an early benefit in PFS, which in the Cancer and Leukemia Group B (CALGB) study prompted early termination [80]. The CALGB trial (n = 460) subsequently showed a small OS benefit, but no OS difference was seen in the IFM study (n = 614). This study gave both arms 2 cycles of lenalidomide consolidation at a higher dose before randomization [71] and the Kaplan-Meier OS plot of the CALBG study diverges early and is parallel thereafter, which suggested that any benefit in OS is derived from the first few months on lenalidomide. Both studies agreed that there are considerable toxicities from lenalidomide, with increased hematological adverse events and secondary cancers seen in the lenalidomide groups.

Combining bortezomib with lenalidomide in maintenance confers a high side effect burden, but in a phase II study demonstrated good results in patients with high risk myeloma or plasma cell leukemia, with 93% OS at 3 years, and no patients stopped maintenance due to toxicity [81]. A nonrandomized comparison between sequential cohorts receiving bortezomib and dexamethasone with either lenalidomide or thalidomide, as maintenance for low-risk myeloma found no difference in survival or relapse rates [82]. Maintenance with VRD is yet to be studied in a phase III randomized trial.

NEW AGENTS

Histone deacetylase inhibitors (vorinostat and panobinostat) have been explored in phase III trials of relapsed/refractory myeloma in combination with bortezomib. Vorinostat demonstrated limited activity [83] but panobinostat in combination with bortezomib and dexamethasone increased PFS with OS data yet to show a significant difference [84]. Vorinostat has been combined with lenalidomide for maintenance after ASCT in a phase I study, with 14 of the 16 subjects having grade 3 or 4 adverse events during maintenance [85], which compares unfavorably with lenalidomide-monotherapy maintenance trials [71,80].

Several new monoclonal antibodies, antibody-drug conjugates, and small molecules are in phase II and III trials for both newly diagnosed and relapsed/refractory myeloma. Adding elotuzumab (targeting SLAMF7, Signaling Lymphocyte Activation Molecule Family member 7) to lenalidomide and dexamethasone increased the response rate from 66% to 79% in relapsed or refractory patients and PFS from 14.9 months to 19.4 months in a phase III trial [86]. A phase I trial of elotuzumab in combination with bortezomib induced responses in 48% of patients with relapsed/refractory myeloma [87]. The anti-CD38 daratumumab looks promising in phase I/II trials [88-90], and 3 phase III trials of daratumumab plus various chemotherapy regimens are currently recruiting in newly diagnosed and relapsed populations. The antibody-drug conjugates lorvotuzumab mertansine (with lenalidomide/dexamethasone, ORR 59%) [91] and indatuximab ravanstine (with lenalidomide/dexamethasone, ORR 78%) [92] and the AKT inhibitor afuresertib (with bortezomib/dexamethasone, ORR 49%) [93] demonstrate activity in phase I trials in relapsed/refractory patients. Phase I trials of anti-PD1 monoclonal antibodies in combination with IMiDs [94,95], the anti-CD74 conjugate milatuzumab-doxorubicin, and an anti-CD200 antibody are currently ongoing in relapsed myeloma.

None of these new agents are currently being investigated as part of an ASCT treatment protocol. Monoclonal antibodies are not particularly myelosuppressive: elotuzumab has lower neutropenia rates than the control group [86] and although a minority of patients receiving daratumumab developed low cell counts, this was not dose dependent [90]. Given this low toxicity, they are attractive targeted therapies for use in consolidation and maintenance phases to suppress residual myeloma clones.

IMMUNOTHERAPY AND CELLULAR THERAPY

The reconstitution of the immune system after ASCT is an opportunity to augment the immune response against myeloma. Natural killer (NK) cells, components of the innate immune system with the potential to kill cancer cells, reconstitute quickly after ASCT, and the number of NK cells at day 30 correlates with PFS after ASCT [96]. Lymphocyte populations recover gradually over 1 year or more, and the early populations are abnormal, with an excess of $CD8^+$ T cells and few $CD4^+$ T cells, which have a narrow T cell–receptor repertoire. The lymphodepletion brought on by high-dose therapy causes levels of cytokines IL-5 and IL-17 to rise, which in turn drive extrathymic proliferation of $CD4^+$ T cells. This expansion of T cells in the absence of regulatory T cell expansion may facilitate an effective antimyeloma adaptive immune response.

Maintenance therapy with interferon alpha was the earliest IMiD therapy, augmenting the cellular antimyeloma response and, although modestly effective as maintenance after ASCT, it was not adopted because of poor tolerability [6]. Another approach used cyclosporin in a small population of mixed hematological malignancies for 1 month after ASCT, leading to a reaction akin to acute graft-versus-host disease, which was associated with improved disease-free survival but no OS difference [97].

Vaccine strategies include myeloma dendritic cell (DC) fusion, autologous serum-loaded DCs, myeloma-peptide–stimulated T cells, and idiotypic DNA vaccination (Figure 1). A phase I trial of autologous DC-myeloma cell fusion cells injected into myeloma patients found these induced expansion of myeloma-specific T cells in vivo and stabilized disease progression in 11 of 16 patients [98]. A small trial from the Mayo clinic of ex vivo–stimulated DCs accompanying ASCT found improved survival compared with matched historical controls [99], and a small Czech study looking at ex vivo stimulated DCs as monotherapy in pretreated patients found a modest improvement in outcomes [100]. Two small trials of myeloma peptide vaccines followed by ex vivo T cell expansion and reinfusion showed these to be safe and effective at inducing lymphocyte responses [101,102], but no effect on clinical outcomes could be discerned from these small groups, with only the former including a control arm. DNA vaccines (variable regions of paraprotein heavy and light chains, fused to tetanus toxin, in an expression vector) appear to be safe in phase I trials, though they only elicited an anti-idiotype immune response in 4 of 14 subjects [103]. These vaccine strategies merit further investigation in clinical trials.

Engineered T cells with chimeric antigen receptors (CAR), which combine the antigen-binding fragment of antibodies with the signaling domains of the T cell receptor, have been used with some success against advanced leukemias and lymphomas [104,105]. CAR T cells targeting CD19 have been used as part of ASCT in 10 myeloma patients who were heavily pretreated; 4 have responded to date, with 1 patient achieving

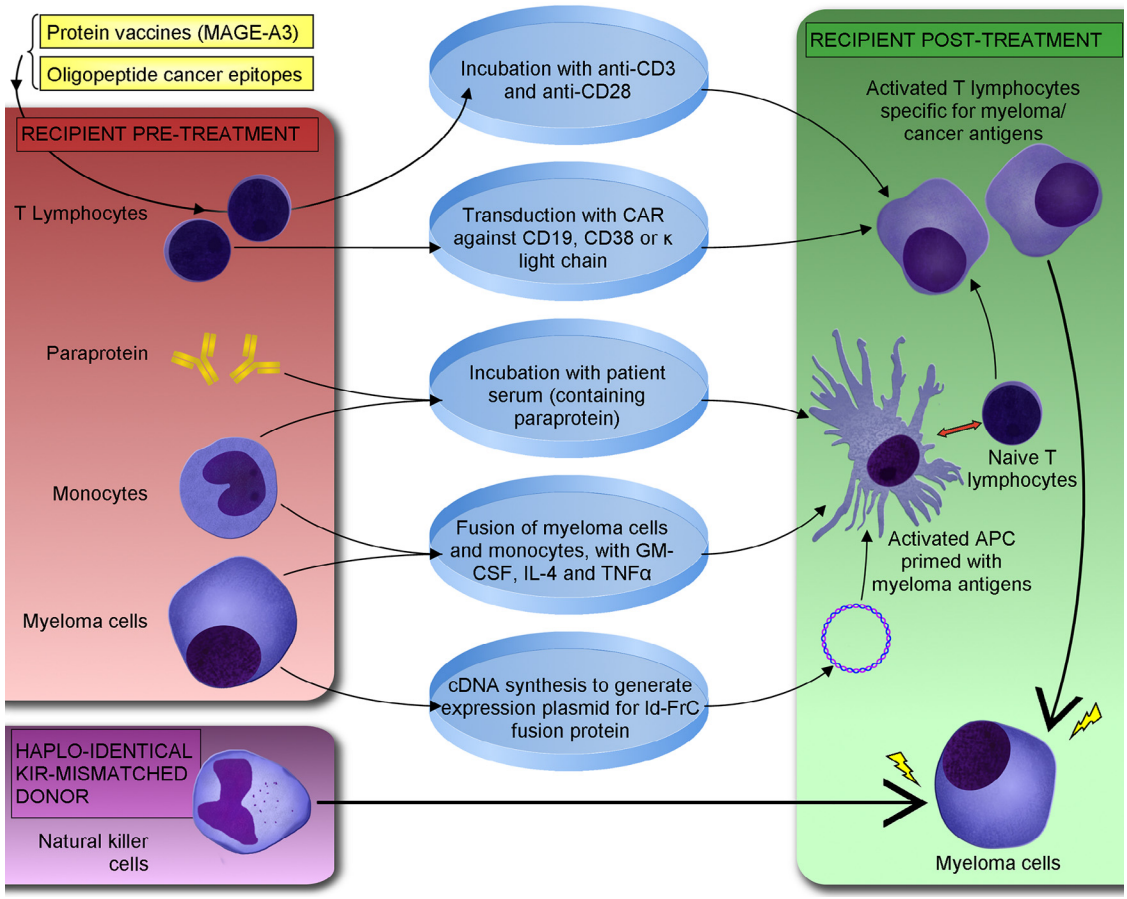

Figure 1. Experimental immunomodulatory and cellular therapies to augment immune system responses against myeloma ([98-103,106,107,109]).

a stringent CR that has lasted over 12 months [106]. CAR T cells against CD38 can effectively kill myeloma cells in vitro [107], and phase I trials are ongoing for these (NCT01886976), and chimeric anti-kappa light chain T cells (NCT00881920). Toxicities from CAR T cell therapies include an infusional cytokine release syndrome and potential off target effects. In mouse studies, ex vivo–expanded NK cells can inhibit growth of myeloma tumors [108]. This concept is explored in phase I studies of autologous expanded NK cells (with chemotherapy but without transplantation) in relapsed myeloma patients (NCT01313897 and NCT01884688). Haploidentical but KIR-mismatched allogeneic NK cells are also being investigated as an adjunct to ASCT [109].

TRIAL ENDPOINTS

Overall survival remains the gold standard endpoint for trials in myeloma, but survival rates have improved, with over one-third of newly diagnosed patients living longer than 10 years in the United Kingdom [110], so OS is a late endpoint for trials to report. The CR rate has historically correlated poorly with OS [111-113] and clearly does not take account of quality of life aspects, which are affected by increasingly prolonged myeloma therapy regimens. In early trials, time to progression did correlate with OS, but with consolidation treatment, this association is no longer seen [13,71,74,77,78]. PFS2, the time from first treatment to second relapse, takes account of tumor resistance induced by the first line of treatment, and to date studies have shown it is prolonged in association with PFS [114,115], but it has not yet been validated as a surrogate for OS, and still takes years of follow-up to report mature data. In contrast, recent ASCT trials have shown an association between the depth of response and OS [116,117], and this is particularly the case for prolonged (> 3 years) CR [118]. However, the CR rate still remains a relatively insensitive surrogate for OS, and as median survival continues to improve, particularly for transplantation-eligible populations, we have to adopt earlier endpoints to study the gamut of new agents entering the field. Measuring MRD by multiparameter flow cytometry accurately predicts OS in patients who have achieved a CR [119,120] and represents an opportunity to vastly shorten the time required for trials of aggressive treatment to report. ^{18}F-flurodeoxyglucose positron emission tomography (PET) CT scanning is also a predictor of PFS and OS, both after induction [121] and after ASCT [122]. Its predictive power is independent of CR status, but further studies are needed combining MRD measurement and PET CT to determine whether both independently provide prognostic information. These trials will still need long-term follow-up to identify late adverse events, the impact on quality of life, and hopefully confirm the predictive power of these new endpoints.

OUTSTANDING QUESTIONS AND FUTURE TRIAL DESIGNS

We await with interest the final results of several studies testing ASCT against a block of novel agent consolidation therapy. Both PFS and OS remain crucial endpoints, as the latter depends on the ability to salvage patients after relapse. Future trials should be randomized and stratified by genetic

risk to provide clear guidance for treatment decisions. Trials should consider using new endpoints, such as MRD negativity (by high-throughput flow cytometry or genetic sequencing) and sustained CR rates in addition to PFS and OS. A number of key questions should be addressed in the debate over ASCT as standard practice after induction therapy:

1. Is there a more effective conditioning regimen than mel200?
2. Does a block of consolidation therapy between ASCT and maintenance therapy improve clinical outcomes versus maintenance alone?
3. Does the addition of a proteasome inhibitor to IMiD-based maintenance improve outcomes?
4. What role should new monoclonal antibodies and kinase inhibitors play to improve post-ASCT response?
5. Are MRD negativity, sustained CR, and PET CT–negativity valid surrogate endpoints for OS?

CONCLUSION

ASCT remains the standard of care for eligible newly diagnosed myeloma patients, despite improvements in induction chemotherapy with IMiDs and proteasome inhibitors. Early trials of ASCT achieved complete remission lasting >10 years in a small minority of patients [59], and with advances in induction protocols, it is likely that with ASCT consolidation, this proportion will continue to increase. The most promising strategies for improving conditioning therapy, on the basis of phase II studies, are the addition of proteasome inhibitors or topoisomerase inhibitors, but these require confirmation in randomized trials. Melflufen and radio-conjugate drugs have yet to be assessed as part of conditioning, but they hold theoretical promise. Tandem ASCT upfront may improve responses in patients not achieving CR after their first transplantation, but it does not offer an OS benefit over delayed second ASCT at relapse for most patients. We await with interest long-term OS data to see if there is a benefit from lenalidomide maintenance. Treatment after ASCT, with both an IMiD and a proteasome inhibitor in combination, has achieved impressive results in phase II studies, but this has not yet been systematically tested in a phase III study. Several monoclonal antibodies and kinase inhibitors are promising in early clinical trials and, although these targeted drugs are unlikely to replace ASCT, they may find a role in post-ASCT consolidation. Experimental therapies to augment cellular immune responses to myeloma have demonstrated biological activity in patients refractory to other lines of treatment, and despite high potential for toxicity, they merit investigation in the post-ASCT period, when patients are lymphocyte depleted and the burden of disease is low. These new therapeutic strategies could substantially increase the proportion of patients achieving long-term disease control after ASCT. At the same time, clinical trials need to report more rapidly and hopefully, if MRD negativity continues to robustly translate into survival in reported studies, then the adoption in clinical trials of MRD detection as a key endpoint will greatly facilitate this.

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REFERENCES

1. Pulte D, Jansen L, Castro FA, et al. Trends in survival of multiple myeloma patients in Germany and the United States in the first decade of the 21st century. *Br J Haematol*. 2015;171:189-196.
2. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med*. 1996;335:91-97.
3. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003;348:1875-1883.
4. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myélome-Autogreffe. *J Clin Oncol*. 2005;23:9227-9233.
5. Bladé J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood*. 2005;106:3755-3759.
6. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol*. 2006;24:929-936.
7. Sonneveld P, van der Holt B, Segeren CM, et al. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. *Haematologica*. 2007;92:928-935.
8. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood*. 2002;99:731-735.
9. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, et al. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. *Haematologica*. 2008;93:124-127.
10. Morgan GJ, Davies FE, Gregory WM, et al. Effects of induction and maintenance plus long-term bisphosphonates on bone disease in patients with multiple myeloma: the Medical Research Council Myeloma IX Trial. *Blood*. 2012;119:5374-5383.
11. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354:1021-1030.
12. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol*. 2010;28:4621-4629.
13. Sonneveld P, Schmidt-Wolf IG, van der Holt B, 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.
14. Cavo M, Tacchetti P, Patriarca F, 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.
15. Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. *Blood*. 2016;127:2569-2574.
16. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myélome. *J Clin Oncol*. 2014;32:2712-2717.
17. Zimmerman TM, Griffith KA, Jasielec J, et al. Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM). *J Clin Oncol*. 2015;33:8510. ASCO meeting abstracts.
18. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371:895-905.
19. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple

myeloma: a randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16:1617-1629.
20. Attal M, Lauwers-Cances V, Hulin C, et al. Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone Du Myélome (IFM/DFCI 2009 Trial). *Blood*. 2015;126:391.
21. Sonneveld P, Cavo M, Einsele H, Mellqvist U. A randomized phase III study to compare bortezomib, melphalan, prednisone (VMP) with high dose melphalan followed by bortezomib, lenalidomide, dexamethasone (VRD) consolidation and lenalidomide maintenance in patients with newly diagnosed multiple myeloma. Study Protocol version 6. 2014. Available at: http://hovon.nl/studies/studies-per-ziektebeeld/mm.html?getfile=1&studie=75&studieveld=26. Accessed October 10, 2015.
22. Popat R, Cavenagh JD, Owen RG, et al. Subcutaneous PAD as induction therapy for patients with newly diagnosed myeloma: a phase 2 trial assessing the impact of Minimal Residual Disease (MRD) in patients with deferred autologous stem cell transplantation (PADIMAC). *Blood*. 2014;124:4745.
23. Spencer A, Horvath N, Gibson J, et al. Prospective randomised trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. *Bone Marrow Transplant*. 2005;35:971-977.
24. Abidi MH, Agarwal R, Tageja N, et al. A phase I dose-escalation trial of high-dose melphalan with palifermin for cytoprotection followed by autologous stem cell transplantation for patients with multiple myeloma with normal renal function. *Biol Blood Marrow Transplant*. 2013;19:56-61.
25. Nath CE, Shaw PJ, Trotman J, et al. Population pharmacokinetics of melphalan in patients with multiple myeloma undergoing high dose therapy. *Br J Clin Pharmacol*. 2010;69:484-497.
26. Lahuerta JJ, Mateos MV, Martinez-Lopez J, et al. Busulfan 12 mg/kg plus melphalan 140 mg/m^2 versus melphalan 200 mg/m^2 as conditioning regimens for autologous transplantation in newly diagnosed multiple myeloma patients included in the PETHEMA/GEM2000 study. *Haematologica*. 2010;95:1913-1920.
27. Blanes M, Lahuerta JJ, González JD, et al. Intravenous busulfan and melphalan as a conditioning regimen for autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: a matched comparison to a melphalan-only approach. *Biol Blood Marrow Transplant*. 2013;19:69-74.
28. Desikan KR, Tricot G, Dhodapkar M, et al. Melphalan plus total body irradiation (MEL-TBI) or cyclophosphamide (MEL-CY) as a conditioning regimen with second autotransplant in responding patients with myeloma is inferior compared to historical controls receiving tandem transplants with melphalan alone. *Bone Marrow Transplant*. 2000;25:483-487.
29. Fenk R, Schneider P, Kropff M, et al. High-dose idarubicin, cyclophosphamide and melphalan as conditioning for autologous stem cell transplantation increases treatment-related mortality in patients with multiple myeloma: results of a randomised study. *Br J Haematol*. 2005;130:588-594.
30. Knop S, Bauer K, Hebart H, et al. A randomized comparison of total-marrow irradiation, busulfan and cyclophosphamide with tandem high-dose melphalan in patients with multiple myeloma. *Blood*. 2007;110:728.
31. Donato ML, Aleman A, Champlin RE, et al. High-dose topotecan, melphalan and cyclophosphamide (TMC) with stem cell support: a new regimen for the treatment of multiple myeloma. *Leuk Lymphoma*. 2004;45:755-759.
32. Kazmi SM, Saliba RM, Donato M, et al. Phase II trial of high-dose topotecan, melphalan and CY with autologous stem cell support for multiple myeloma. *Bone Marrow Transplant*. 2011;46:510-515.
33. Comenzo RL, Hassoun H, Kewalramani T, et al. Results of a phase I/II trial adding carmustine (300 mg/m^2) to melphalan (200 mg/m^2) in multiple myeloma patients undergoing autologous stem cell transplantation. *Leukemia*. 2006;20:345-349.
34. Chen AI, Negrin RS, McMillan A, et al. Tandem chemo-mobilization followed by high-dose melphalan and carmustine with single autologous hematopoietic cell transplantation for multiple myeloma. *Bone Marrow Transplant*. 2012;47:516-521.
35. Mark TM, Reid W, Niesvizky R, et al. A phase 1 study of bendamustine and melphalan conditioning for autologous stem cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:831-837.
36. Chauhan D, Ray A, Viktorsson K, et al. In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells. *Clin Cancer Res*. 2013;19:3019-3031.
37. Magarotto V, Sonneveld P, Paba-Prada C, et al. Encouraging preliminary data in ongoing open-label phase 1/2 study of safety and efficacy of melflufen and dexamethasone for patients with relapsed and relapsed-refractory multiple myeloma. *Haematologica*. 2015;100:89.
38. Ballestrero A, Ferrando F, Miglino M, et al. Three-step high-dose sequential chemotherapy in patients with newly diagnosed multiple myeloma. *Eur J Haematol*. 2002;68:101-106.
39. Beaven AW, Moore DT, Sharf A, Serody JS, Shea TC, Gabriel DA. Infusional mitoxantrone plus bolus melphalan as a stem cell transplant conditioning regimen for multiple myeloma. *Cancer Invest*. 2011;29:214-219.
40. Qazilbash MH, Saliba RM, Nieto Y, et al. Arsenic trioxide with ascorbic acid and high-dose melphalan: results of a phase II randomized trial. *Biol Blood Marrow Transplant*. 2008;14:1401-1407.
41. Ma MH, Yang HH, Parker K, 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.
42. Mitsiades N, Mitsiades CS, Richardson PG, et al. The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. *Blood*. 2003;101:2377-2380.
43. Roussel M, Moreau P, Huynh A, et al. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone du Myélome (IFM). *Blood*. 2010;115:32-37.
44. Huang W, Li J, Li H, et al. High-dose melphalan with bortezomib as conditioning regimen for autologous stem cell transplant in patients with newly diagnosed multiple myeloma who exhibited at least very good partial response to bortezomib-based induction therapy. *Leuk Lymphoma*. 2012;53:2507-2510.
45. Miyamoto T, Yoshimoto G, Kamimura T, et al. Combination of high-dose melphalan and bortezomib as conditioning regimen for autologous peripheral blood stem cell transplantation in multiple myeloma. *Int J Hematol*. 2013;98:337-345.
46. Lonial S, Kaufman J, Tighiouart M, et al. A phase I/II trial combining high-dose melphalan and autologous transplant with bortezomib for multiple myeloma: a dose- and schedule-finding study. *Clin Cancer Res*. 2010;16:5079-5086.
47. Nishihori T, Alekshun TJ, Shain K, et al. Bortezomib salvage followed by a phase I/II study of bortezomib plus high-dose melphalan and tandem autologous transplantation for patients with primary resistant myeloma. *Br J Haematol*. 2012;157:553-563.
48. Forsberg P, Guarneri D, Rossi A, et al. A phase I study of the addition of high-dose lenalidomide to melphalan conditioning for autologous stem-cell transplant in relapsed or refractory multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2015;15:e291-e292.
49. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372:142-152.
50. Giralt S, Bensinger W, Goodman M, et al. ^{166}Ho-DOTMP plus melphalan followed by peripheral blood stem cell transplantation in patients with multiple myeloma: results of two phase 1/2 trials. *Blood*. 2003;102:2684-2691.
51. Dispenzieri A, Wiseman GA, Lacy MQ, et al. A phase II study of ^{153}Sm-EDTMP and high-dose melphalan as a peripheral blood stem cell conditioning regimen in patients with multiple myeloma. *Am J Hematol*. 2010;85:409-413.
52. Goel A, Dispenzieri A, Geyer SM, Greiner S, Peng KW, Russell SJ. Synergistic activity of the proteasome inhibitor PS-341 with non-myeloablative 153-Sm-EDTMP skeletally targeted radiotherapy in an orthotopic model of multiple myeloma. *Blood*. 2006;107:4063-4070.
53. Orchard K, Cooper M, Lewington V, et al. Targeted radiotherapy in the conditioning prior to haematopoietic stem cell transplantation: results of a phase I radiation dose escalation study using Yttrium-90-labelled anti-CD66 monoclonal antibody demonstrating high BM uptake of radiation. *Blood*. 2005;106:2189.
54. Dispenzieri A, Gertz MA, Lacy MQ, et al. A Phase I Trial of zevalin radioimmunotherapy with high-dose melphalan (HDM) and autologous stem cell transplant (ASCT) for multiple myeloma (MM). *Blood*. 2011;118:3095.
55. Lebovic D, Kaminski MS, Anderson TB, et al. A phase II study of consolidation treatment with iodione-131 tositumomab (Bexxar™) in multiple myeloma (MM). *Blood*. 2012;120:1854.
56. Green DJ, Jones JC, Hylarides MD, et al. Anti-CD38 pretargeted radioimmunotherapy eradicates multiple myeloma xenografts in a murine model. *Blood*. 2013;122:882.
57. Chérel M, Gouard S, Gaschet J, et al. ^{213}Bi radioimmunotherapy with an anti-mCD138 monoclonal antibody in a murine model of multiple myeloma. *J Nucl Med*. 2013;54:1597-1604.
58. Pica G, Vagge S, Beltrami G, et al. A Phase I study of hypofractionated tailored total marrow or total lymphoid irradiation with helical tomotherapy plus chemotherapy as a conditioning regimen for autologous stem cell transplantation. *Blood*. 2011;118:4523.
59. Barlogie B, Tricot GJ, van Rhee F, et al. Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. *Br J Haematol*. 2006;135:158-164.
60. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. *Br J Haematol*. 2007;138:176-185.

61. Pineda-Roman M, Barlogie B, Anaissie E, et al. High-dose melphalan-based autotransplants for multiple myeloma: the Arkansas experience since 1989 in 3077 patients. *Cancer*. 2008;112:1754-1764.
62. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349:2495-2502.
63. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol*. 2007;25:2434-2441.
64. Mai EK, Benner A, Bertsch U, et al. Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD2 trial. *Br J Haematol*. 2016;173:731-741.
65. Fermand J. High dose therapy supported with autologous blood stem cell transplantation in multiple myeloma: long term follow-up of the prospective studies of the MAG group. Xth International Myeloma Foundation Workshop, Sydney. 2005. Available at: http://myeloma.org/pdfs/Sydney2005_Fermand_P8.pdf. Accessed June 20, 2015.
66. Kumar A, Kharfan-Dabaja MA, Glasmacher A, Djulbegovic B. Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2009;101:100-106.
67. Sonneveld P, Scheid C, van der Holt B, et al. Bortezomib induction and maintenance treatment improves survival in patients with newly diagnosed multiple myeloma: extended follow-up of the HOVON-65/GMMG-HD4 Trial. *Blood*. 2013;122:404.
68. Govindarajan R, Jagannath S, Flick JT, et al. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. *Br J Haematol*. 1996;95:349-353.
69. Mellqvist UH, Gimsing P, Hjertner O, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. *Blood*. 2013;121:4647-4654.
70. Rabin N, Percy L, Khan I, Quinn J, D'Sa S, Yong KL. Improved response with post-ASCT consolidation by low dose thalidomide, cyclophosphamide and dexamethasone as first line treatment for multiple myeloma. *Br J Haematol*. 2012;158:499-505.
71. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1782-1791.
72. Drayson MT, Chapman CE, Dunn JA, Olujohungbe AB, Maclennan IC. MRC trial of alpha2b-interferon maintenance therapy in first plateau phase of multiple myeloma. MRC Working Party on Leukaemia in Adults. *Br J Haematol*. 1998;101:195-202.
73. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood*. 2002;99:3163-3168.
74. Alexanian R, Weber D, Dimopoulos M, Delasalle K, Smith TL. Randomized trial of alpha-interferon or dexamethasone as maintenance treatment for multiple myeloma. *Am J Hematol*. 2000;65:204-209.
75. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood*. 2006;108:3289-3294.
76. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol*. 2009;27:1788-1793.
77. Maiolino A, Hungria VT, Garnica M, et al. Thalidomide plus dexamethasone as a maintenance therapy after autologous hematopoietic stem cell transplantation improves progression-free survival in multiple myeloma. *Am J Hematol*. 2012;87:948-952.
78. Stewart AK, Trudel S, Bahlis NJ, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinical Trials Group Myeloma 10 Trial. *Blood*. 2013;121:1517-1523.
79. Scheid C, Sonneveld P, Schmidt-Wolf IG, et al. Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial. *Haematologica*. 2014;99:148-154.
80. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770-1781.
81. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. *Leukemia*. 2014;28:690-693.
82. Nair B, van Rhee F, Shaughnessy JD Jr, 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.
83. Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. *Lancet Oncol*. 2013;14:1129-1140.
84. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol*. 2014;15:1195-1206.
85. Sborov DW, Benson DM, Williams N, et al. Lenalidomide and vorinostat maintenance after autologous transplant in multiple myeloma. *Br J Haematol*. 2015;171:74-83.
86. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373:621-631.
87. Jakubowiak AJ, Benson DM, Bensinger W, et al. Phase I trial of anti-CS1 monoclonal antibody elotuzumab in combination with bortezomib in the treatment of relapsed/refractory multiple myeloma. *J Clin Oncol*. 2012;30:1960-1965.
88. Plesner T, Arkenau H, Lokhorst HM, et al. Safety and efficacy of daratumumab with lenalidomide and dexamethasone in relapsed or relapsed, refractory multiple myeloma. *Blood*. 2014;124:84.
89. Moreau P, Mateos M, Bladé J, et al. An open-label, multicenter, phase 1b study of daratumumab in combination with backbone regimens in patients with multiple myeloma. *Blood*. 2014;124:176.
90. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;373:1207-1219.
91. Berdeja JG, Hernandez-Ilizaliturri F, Chanan-Khan A, et al. Phase I study of lorvotuzumab mertansine (LM, IMGN901) in combination with lenalidomide (Len) and dexamethasone (Dex) in patients with CD56-positive relapsed or relapsed/refractory multiple myeloma (MM). *Blood*. 2012;120:728.
92. Kelly KR, Chanan-Khan A, Heffner LT, et al. Indatuximab ravtansine (BT062) in combination with lenalidomide and low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma: clinical activity in patients already exposed to lenalidomide and bortezomib. *Blood*. 2014;124:4736.
93. Voorhees PM, Spencer A, Sutherland HJ, et al. Novel AKT inhibitor afuresertib in combination with bortezomib and dexamethasone demonstrates favorable safety profile and significant clinical activity in patients with relapsed/refractory multiple myeloma. *Blood*. 2013;122:283.
94. San Miguel J, Mateos M, Shah JJ, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): keynote-023. *Blood*. 2015;126:505.
95. Badros AZ, Kocoglu MH, Ma N, et al. A phase II study of anti PD-1 antibody pembrolizumab, pomalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). *Blood*. 2015;126:506.
96. Rueff J, Medinger M, Heim D, Passweg J, Stern M. Lymphocyte subset recovery and outcome after autologous hematopoietic stem cell transplantation for plasma cell myeloma. *Biol Blood Marrow Transplant*. 2014;20:896-899.
97. Marin GH, Menna ME, Bergna MI, et al. Induction of anti-tumor activity following autologous stem cell transplantation: immunotherapeutic implications. *Transplant Proc*. 2001;33:2004-2007.
98. Rosenblatt J, Vasir B, Uhl L, et al. Vaccination with dendritic cell/tumor fusion cells results in cellular and humoral antitumor immune responses in patients with multiple myeloma. *Blood*. 2011;117:393-402.
99. Lacy MQ, Mandrekar S, Dispenzieri A, et al. Idiotype-pulsed antigen-presenting cells following autologous transplantation for multiple myeloma may be associated with prolonged survival. *Am J Hematol*. 2009;84:799-802.
100. Zahradova L, Mollova K, Ocadlikova D, et al. Efficacy and safety of Id-protein-loaded dendritic cell vaccine in patients with multiple myeloma—phase II study results. *Neoplasma*. 2012;59:440-449.
101. Rapoport AP, Aqui NA, Stadtmauer EA, et al. Combination immunotherapy using adoptive T-cell transfer and tumor antigen vaccination on the basis of hTERT and survivin after ASCT for myeloma. *Blood*. 2011;117:788-797.
102. Rapoport AP, Aqui NA, Stadtmauer EA, et al. Combination immunotherapy after ASCT for multiple myeloma using MAGE-A3/Poly-ICLC immunizations followed by adoptive transfer of vaccine-primed and costimulated autologous T cells. *Clin Cancer Res*. 2014;20:1355-1365.
103. McCann KJ, Godeseth R, Chudley L, et al. Idiotypic DNA vaccination for the treatment of multiple myeloma: safety and immunogenicity in a phase I clinical study. *Cancer Immunol Immunother*. 2015;64:1021-1032.
104. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014;371:1507-1517.
105. Kochenderfer JM, Dudley ME, Kassim SH, et al. Effective treatment of chemotherapy-refractory diffuse large B-cell lymphoma with autologous T cells genetically-engineered to express an anti-CD19 chimeric antigen receptor. *Blood*. 2013;122:168.

106. Garfall AL, Maus MV, Hwang WT, et al. Chimeric antigen receptor T cells against CD19 for multiple myeloma. *N Engl J Med*. 2015;373:1040-1047.
107. Mihara K, Bhattacharyya J, Kitanaka A, et al. T-cell immunotherapy with a chimeric receptor against CD38 is effective in eliminating myeloma cells. *Blood*. 2011;118:885.
108. Garg TK, Szmania SM, Khan JA, et al. Highly activated and expanded natural killer cells for multiple myeloma immunotherapy. *Haematologica*. 2012;97:1348-1356.
109. Shi J, Tricot G, Szmania S, et al. Infusion of haplo-identical killer immunoglobulin-like receptor ligand mismatched NK cells for relapsed myeloma in the setting of autologous stem cell transplantation. *Br J Haematol*. 2008;143:641-653.
110. Cancer Research UK. Myeloma survival statistics. 2014. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma. Accessed April 23, 2016.
111. Baldini L, Radaelli F, Chiorboli O, et al. No correlation between response and survival in patients with multiple myeloma treated with vincristine, melphalan, cyclophosphamide, and prednisone. *Cancer*. 1991;68:62-67.
112. Riccardi A, Mora O, Tinelli C, 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.
113. 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.
114. Palumbo A, Gay F, Musto P, et al. Continuous treatment (CT) versus fixed duration of therapy (FDT) in newly diagnosed myeloma patients: PFS1, PFS2, OS endpoints. *J Clin Oncol*. 2014;32:8515. ASCO meeting abstracts.
115. Tacchetti P, Pantani L, De Stefano V, et al. Superior PFS2 with VTD vs TD for newly diagnosed, transplant eligible, multiple myeloma (MM) patients: updated analysis of gimema MMY-3006 study. *Blood*. 2014;124:196.
116. Lahuerta JJ, Mateos MV, Martinez-Lopez 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.
117. Harousseau JL, Avet-Loiseau H, Attal M, 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.
118. Barlogie B, Anaissie E, Haessler J, 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.
119. Paiva B, Gutierrez NC, Rosinol L, 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.
120. Rawstron AC, Gregory WM, de Tute RM, et al. Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction. *Blood*. 2015;125:1932-1935.
121. Bartel TB, Haessler J, Brown TL, et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. *Blood*. 2009;114:2068-2076.
122. Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma. *Clin Cancer Res*. 2015;21:4384-4390.
123. Ladetto M, Pagliano G, Ferrero S, 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.
124. Leleu X, Fouquet G, Hebraud B, et al. Consolidation with VTd significantly improves the complete remission rate and time to progression following VTd induction and single autologous stem cell transplantation in multiple myeloma. *Leukemia*. 2013;27:2242-2244.