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Review

The Role of Salvage Second Autologous Hematopoietic Cell Transplantation in Relapsed Multiple Myeloma

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A B S T R A C T

Multiple myeloma (MM), a malignant disorder of plasma cells affecting primarily elderly patients, is the second most commonly diagnosed hematologic neoplasm. With the recent influx of effective new agents available, including proteasome inhibitors, immunomodulators, targeted monoclonal antibodies, and now chimeric antigen receptor T cell (CAR-T) therapy, the treatment landscape is evolving rapidly. Although the role of consolidative autologous stem cell transplantation (ASCT) in first remission is well established, in the relapsed setting after upfront ASCT, the role of a second ASCT (SAT) following reinduction is less clear and understudied. Practice patterns vary significantly across institutions, and most of the literature available to guide clinical decisions consists of single-institution experiences, with only 1 randomized study evaluating the role of SAT compared with a non-transplantation approach. SAT is likely underused, because it has not been included in clinical trials examining novel regimens for relapsed disease. Furthermore, outcomes likely can be improved with approaches to intensify the preparative regimen and the use of standard post-transplantation maintenance. In this review, we examine the role of SAT in the current MM treatment landscape in the context of recent data on the efficacy of CAR-T therapy in this disease. We caution the abandonment of SAT, given that CAR-T therapy is in its infancy in MM treatment, and that real-world data in the relapsed setting are consistently inferior to clinical trial outcomes.

INTRODUCTION

Multiple myeloma (MM) is a malignant disorder of plasma cells affecting primarily elderly patients, with a median age at diagnosis in the late 60s to early 70s [1]. It is the second most commonly diagnosed hematologic neoplasm, with an estimated incidence of 30,280 cases in 2017 and a prevalence of 118,539 in 2014 [2]. With the effective new agents now available, including proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies, significant advances have been made in the treatment of MM. The median progression-free survival (PFS) in up front autologous stem cell transplantation (ASCT)-eligible patients now exceeds 4 years [3]. Outcomes also have improved in the relapsed setting, with triplet combinations achieving a median PFS exceeding 2 years in some studies [4].

The role of a second autologous transplantation (SAT) in patients with relapsed MM remains controversial. According to the most recent consensus from the American Society of Blood and Marrow Transplantation, the European Society for Blood and Marrow Transplantation, and the International Myeloma Working Group (IMWG), SAT should be considered in all patients with an initial duration of remission of >18 months following up front ASCT; however, patterns of its use in practice vary significantly among transplantation centers [5]. In this review, we examine the role of SAT in the current MM treatment landscape in the context of recent data on the efficacy of CAR-T therapy in this disease. We caution the abandonment of this tried and proven therapy, given that CAR-T therapy for MM is in its infancy and that real-world data in the relapsed setting consistently show inferior outcomes compared with clinical trial data.

EXPERIENCE WITH SAT IN MM

ASCT is the standard consolidative approach following induction therapy in patients with newly diagnosed MM who are eligible for transplantation. Several international randomized trials comparing upfront ASCT and non-ASCT therapy, including the EMN02/H095 [6], EMN-411 [7], RV-MM-2019 [8], and IFM/DFCI 2009 [3] trials, have shown consistent improvement in median PFS in the 1- to 2-year range, with some studies showing improved overall survival (OS) [7,8]. This advantage in the upfront setting is seen in those treated with modern induction therapy and those heading into transplantation in deep remission [9]. Unfortunately, in the relapsed setting, randomized data and comparative studies evaluating

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SAT are lacking, and available long-term survival data evaluating its efficacy involve the treatment of patients before the incorporation of novel agents in up-front therapy. To examine the role of SAT in the current treatment landscape, we focus on trial data from the last decade. The Food and Drug Administration approved bortezomib in 2003, and SWOG 0777 showed a PFS and ultimately, as of 2017, an OS advantage in triplet (Revlimid [lenalidomide], bortezomib, and dexamethasone [RVD]) versus doublet (Revlimid and dexamethasone) induction therapy, leading to the adoption of RVD induction as standard of care in fit patients [10].

Single-Center and Retrospective Experience with SAT in MM

Despite advances in the management of relapsed myeloma, SAT continues to be frequently performed in the United States, with 600 to 700 procedures performed annually between 2012 and 2017 (Center for International Blood and Marrow Transplant Research [CIBMTR], unpublished data). Despite this large number, there remains no recent large-scale randomized trial data; thus, our interpretation concerning the effectiveness of SAT is based on single-center experiences with cohorts as small as 30 patients and as large as 200 patients. Table 1 reports single-center experiences with SAT reported in the literature over the last decade. In summary, these studies are heterogeneous, with various conditioning regimens, various intervals between first ASCT and SAT, and inconsistent use of maintenance therapy post-transplantation, and consequently have varying outcomes. Patients are heavily pretreated, often with multiple lines of therapy between first ASCT and SAT. Despite this, outcomes generally appear quite promising, with median PFS exceeding 1 year and a median OS of approximately 31 months. With improved reinduction therapies for relapsed patients, optimization of conditioning regimens, and consistent use of maintenance therapy post-SAT, this can be further improved.

The first large multi-institutional comprehensive retrospective review of SAT outcomes by Michaelis et al [11], published in 2013, examined CIBMTR data and provided the rationale for ongoing studies. A total of 187 patients undergoing SAT from 55 centers in North America were identified. Although published recently, this analysis did include patients from as early as 1995. Patients underwent SAT at a median of 32 months after their first ASCT. Most of these patients received melphalan-based conditioning (84%), and transplantation- related mortality (TRM) was very low, at 2%. The 1-, 3-, and 5-year PFS and OS after SAT were 47% and 83%, 13% and 46%, and 5% and 29%, respectively. On multivariate analysis, both PFS (P = .019) and OS (P = .026) following SAT were improved in those patients who underwent SAT after at least a 36-month PFS after first ASCT. The only other predictive measure for survival following SAT was SAT performed after 2004, likely reflecting the improved supportive care and therapeutic options for patients relapsing after SAT.

Comparative Retrospective and Randomized Data

Several retrospective and 1 prospective randomized trials evaluating SAT compared with a non-SAT approach (Table 2), including single-center, multi-institution, and registry data (eg, British Society for Blood and Marrow Transplantation [BSBMT], Korean Myeloma Registry) studies, have shown both a PFS [12-14] and OS advantage [12-16] of SAT compared with standard MM therapy after relapse. With the exception of the study by Gössi et al [12], these studies are representative of current practice, with a median time from first ASCT to relapse consistently exceeding 18 months and no differences in the interval from first ASCT to relapse between those undergoing SAT and those receiving standard MM therapy. In the study by Gössi et al [12], those who received standard MM therapy instead of SAT were a high-risk cohort relapsing at just a median of 14.3 months after first ASCT, likely reflecting their inferior outcomes. In contrast, the SAT recipients did remarkably well, with a median PFS of 30.2 months exceeding reported outcomes in the relapsed setting. This likely reflects the use of modern transplantation supportive care and maintenance approaches, with a TRM of 0% and one-half of these patients receiving maintenance lenalidomide following SAT. Importantly, the advantage of SAT over a nontransplantation approach holds true even when therapy at relapse consists solely of proteasome inhibitors and immunomodulatory drugs [13,14] and even in patients receiving maintenance therapy following upfront ASCT [17].

The BSBMT/UKMF Myeloma X study is the only randomized trial comparing a nontransplantation approach to SAT. In this multicenter, randomized, open-label Phase III trial, patients relapsing following at least a 12-month PFS after up front ASCT were reinduced with VAD (bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; i.v. doxorubicin 9 mg/m^2 on days 1 to 4; and oral dexamethasone 40 mg on days 1 to 4, 8 to 11, and 15 to 18) and then randomized to consolidation with either SAT or weekly oral cyclophosphamide at 400 mg/m^2 per week for 12 weeks [18]. This trial was stopped early at a planned interim analysis as it reached its efficacy endpoint. These 2 groups were evenly matched with the exception of more revised International Staging System stage III [19] in the SAT group. The median time from first ASCT to relapse was >2.5 years in both groups.

Although no OS advantage was seen, the SAT group had a significant advantage in PFS of 19 months versus 11 months (hazard ratio, .45; 95% confidence interval, .32 to .64; $P < .0001$) as well as in time to second objective disease progression (PFS2) of 67 months versus 35 months (hazard ratio, .37; 95% confidence interval , .24-.57; $P < .0001$). Stressing the importance of adequate stem cell collection at the time of first ASCT, investigators in the Myeloma X study encountered difficulty with remobilization at the time of relapse; 110 of the 174 patients randomized were remobilized, and 41 of 123 (33%) registered patients failed mobilization and did not proceed to randomization. This likely would be more problematic today, considering that none of the patients on that trial had received lenalidomide before SAT, which reinforces the need to collect sufficient stem cells for 2 and potentially even 3 ASCTs [20] at the time of initial mobilization.

OPTIMIZING OUTCOMES FOLLOWING SAT

Which Patients Are Appropriate for SAT? Importance of Remission Duration following First ASCT and Predictors of Outcomes following SAT

The specific patient population appropriate for SAT remains controversial. There is a clearly consistent relationship with duration of remission following first ASCT that is predictive of a PFS and often an OS advantage of SAT compared with a nontransplantation approach. The optimal PFS following first ASCT for consideration for SAT varies in the literature from as short as 12 months [15,21] to as long as 36 months [11] to be predictive of a PFS advantage following SAT and from as short as 9 months [16] to as long as 36 months [11] to be predictive of an OS advantage (Table 1). Other studies have shown a linear relationship between increasing PFS following first ASCT and PFS and OS advantages following SAT [15,21,22]. The only exception to this trend was a recent study by Tremblay et al [23], in which PFS after first ASCT was not found to be predictive of PFS or OS following SAT. However, that was a small study with an unusually short PFS after SAT of only 6.1 months. Most

Table 1
Single-Center Retrospective Studies

Reference	Number of Patients	High-Dose Therapy	Interval ASCT 1→2, mo	Lines of Therapy between First ASCT and SAT, median (range)	Maintenance Therapy, %	TRM after SAT, %	ORR after SAT, %	≥VGPR, %	Median PFS after SAT, mo	Median OS after SAT, mo	PFS after First ASCT Predictive of PFS and OS Advantage after SAT
Tremblay et al, 2017 [23]	74	Mel ≥100	53	NR	24	4	68	38	6.1	19.3	None
Singh Abbi et al, 2015 [21]	75	Mel ≥100	37.7	1 (1-4)	51	5	77	48	10.1	22.7	Linear for PFS cutoff unclear*, none for OS
Auner et al, 2013 [24]	83	Mel ≥100	35.4	NR	NR	7	NR	NR	15.5	31.5	21.5 mo for PFS, none for OS
Gonsalves et al, 2013 [15]	98	Mel ≥100, other	46	3 (1-11)	20	4	86	84	10.3	33	Linear for PFS and OS, cutoff unclear†
Lemieux et al, 2013 [26]	81	Mel ≥140, Bu/Mel, other	47	NR	37	0	93	67	18	48	24 mo for PFS; 24 mo for OS
Sellner et al, 2013 [25]	200	NR	NR	NR	57	3	80.4	22	15.2	42.3	18 mo for PFS; 18 mo for OS
Chow et al, 2012 [83]	30	Mel ≥100, Mel/Vel, Bu/Mel	NR	2 (1-≥3)	37	3	80	27	22	45	18 mo for PFS; 18 mo for OS‡
Shaw et al, 2012 [22]	44	NR	30	2 (0-5)	41	2	90	11	12.3	31.7	NR for PFS; lineal for OS§
Blimark et al, 2011 [45]	66	Mel 100	22.2	1 (0-1)	12	0	62	23	8.5	24	13 mo for PFS‖; NR for OS
Fenk et al, 2011 [84]	55	Mel ≥100, Mel/Vel, Bu/Mel	NR	2	38	5	85	18	14	52	12 mo for PFS; 12 mo for OS
Jimenez Zepeda et al, 2011 [27]	81	Mel ≥100, other	NR	1	33.3	2.6	97.4	47.4	18	NR¶	24 mo for PFS; 24 mo for OS
Burzynski et al, 2009 [85]	25	Mel ≥140	39	2 (1-6)	NR	8	64	NR	12	19	NR
Olin et al, 2009 [86]	41	Mel ≥100, other	37	NR		7	55	15	8.5	20.7	None for PFS; 12 mo for OS

TRM, transplant related mortality; indicates transplantation-related myeloma at 100 days; ORR, overall response rate; NR, not reported; Mel, melphalan; Bu, busulfan; Vel, Velcade (bortezomib).

* When time to relapse after the first ASCT was evaluated as a continuous variable, it was significantly associated with both PFS ($P = .002$) and OS ($P = .013$). However, there was no significant difference in PFS and OS when comparing patients who underwent SAT within 18 months of the first ASCT with those who had a longer interval between transplantation.

† In the multivariable analysis that included only those factors highly significant in the univariable analysis ($P = .01$), shorter time to progression (TTP) after first ASCT, more lines of therapy before SAT, not achieving a CR after SAT, and a higher plasma cell labeling index (PCLI) at SAT were predictive of a shorter PFS (Table 4). Moreover, only shorter duration of response or TTP after first ASCT was predictive of a shorter OS after SAT.

‡ Using progression free interval (PFI) cutoffs of <18 months, 18-36 months, and >36 months, the median PFS following SAT was 4.2, 13.8, and 49.1 months, respectively ($P < .0001$; Figure 1A), and the median OS was 10.7, 30.9, and 86.1 months, respectively ($P < .0001$; Figure 1B). Single PFI cutoffs of 18, 24, and 36 months also demonstrated statistically significant differences in PFS after SAT.

§ Fitted Bayesian multivariate regression model for OS showed that shorter TTP after first ASCT was predictive of worse OS.

‖ Patients with TTP after ASCT shorter than the 25th quartile (13 months) had a PFS after Mel 100 of 5.3 months (95% confidence interval [CI], 3.5-7.9), whereas patients with TTP after ASCT longer than the 75th quartile (34 months) had a PFS after Mel 100 of 12.5 months (95% CI, 8.8-21.4 months).

¶ 3-year OS of 60%.

Table 2
Comparative and Randomized Data

Reference	Number of Patients	Methodology	Time from First ASCT to Relapse	High-Dose Therapy for SAT	MT at Relapse	Maintenance Therapy, %	TRM SAT, %	ORR, %, SAT versus MT	≥VGPR, %, SAT versus MT	Median PFS, SAT versus MT	OS, SAT versus MT	Factors Impacting OS on Multivariate Analysis
Cook et al, 2011 [16]	SAT, 106; MT, 106	BSBMT case-matched control analysis	SAT, 19 mo; MT, 18 mo	NR	NR	NR	8%	CR, 26 vs 27; PR, 37 vs 37	NR	NR	4-yr: 32% vs 22%; $P < .0001$	• Age <65 yr • Remission >24 mo after first ASCT
Gonsalves et al, 2013 [15]	SAT, 98; MT, NR	Single-institution case-matched*	NR	Mel≥100	NR	SAT, 20; MT, NR	4%	NR	NR	NR	Median, 57 mo vs 46 mo; $P = .01$	• Number of previous lines of therapy • CR after SAT
Gössi et al, 2018 [12]	SAT, 61; MT, 25	Single-institution case-matched†	SAT, 28.9 mo; MT, 14.3 mo	Mel200	NR	SAT, 46; MT, NR	0%	46 vs 32	31 vs 12	30.2 mo vs 13 mo; $P = .0262$	Median, 129.6 mo vs 33.5 mo; $P = .0003$	• Undergoing SAT • Lenalidomide maintenance • At least VGPR before SAT
Grövdal et al, 2015 [13]	SAT, 111; MT, 362	Multi-institution (Denmark, Finland, Norway, Sweden); case-matched control analysis	SAT, 2.4 yr; MT, 2.3 yr	NR	Bor-based, 44%; Thal-based, 36%; Len-based, 15%; PI + IMID, 5%	NR	NR	92 vs 62	46 vs 22	2.4 yr vs 1.2 yr; $P = .004$	Median, 4.0 yr vs 3.3 yr; $P = .013$	• Undergoing SAT • Higher hemoglobin value
Yhim et al, 2013 [14]	SAT, 48; MT, 144	Korean Myeloma Registry; case-matched control analysis	NR‡	Mel200	Bor-based, 52%; Thal- based, 26%; PI + IMID, 3%	SAT, 29	2%	NR	NR	18 mo vs 9.1 mo; $P = .017$	Median, 55.5 mo vs 25.4 mo; $P = .035$	• <18 mo TTP after first ASCT • ISS III • Second-line MT alone
Cook et al, 2016 [18]	SAT, 89; MT, 85	Randomized open-label phase 3, UK; 51 centers	SAT, 2.7 yr; MT, 2.5 yr	Mel200	Oral Cy 400 mg/m^2 per wk for 12 wk§	NR	2.5%	83 vs 75	60 vs 47; $P = .0036$	19 mo vs 11 mo; $P < .0001$	3 yr: 80.3% vs 62.9%; $P = .19$	NR

MT indicates myeloma therapy (includes any nontransplantation therapy at relapse for those who did not undergo SAT); Bor, bortezomib; Thal, thalidomide; Len, lenalidomide; PI, proteosome inhibitor; IMID, immunomodulatory drug; Cy, cyclophosphamide;TRM, transplant related mortality.

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‡ Median TTP not reported in the 2 groups; median TTP for the entire cohort, 12.0 months, with no difference between groups reported.

§ Patients in both arms received identical induction at relapse consisting of PAD (proteasome inhibitor [bortezomib], anthracycline antibiotic [doxorubicin], and dexamethasone) for 4 cycles, followed by either SAT or weekly oral cyclophosphamide.

institutions use current cooperative group and society guidelines, considering any patient with at least an 18-month PFS after first ASCT a potential candidate for SAT.

Other factors have been found to be predictive of PFS and OS advantages for SAT in multivariate analyses (Table 3). Consistent with recent randomized data evaluating the role of ASCT in the upfront setting, the depth of response seems to be predictive. Achievement of at least a PR before SAT is predictive of PFS [24,25] and OS [24] advantages, whereas Gössi et al [12] showed that achieving at least a very good PR (VGPR) before SAT was predictive of OS only. Several studies have shown that response after SAT is predictive of PFS (Lemieux et al [26], achieving at least a VGPR; Gonsalves et al [15], achieving at least a complete response [CR]) and OS (Jimenez Zepeda et al [27]; achieving at least a VGPR). As is common practice in upfront ASCT, only patients responding to reinduction should undergo SAT, deferring patients who are actively progressing on therapy. Other factors influencing PFS and OS following SAT include disease risk (eg, International Staging System stage, cytogenetics, β2 microglobulin), previous treatment history, and transplantation approach (eg, melphalan dose, use of post-transplantation maintenance therapy) (Table 3).

One concern in patients undergoing SAT is the potential for increased transplantation-related morbidity and TRM. Experienced centers now achieve 1-year TRM for upfront ASCT in the ~1% range. Although treatment-related toxicity at relapse is expected to be higher with any therapy including SAT, a TRM much above this baseline would be prohibitive. The literature supports that SAT can be done safely, with most centers reporting TRM in the 0 to 8% range and the largest studies showing promising rates of 0 to 3% [11,25]. Indeed, our recent review of our institution showed a 1-year TRM for SAT of 3% (unpublished data).

Table 3
Studies Reporting Multivariate Predictors of PFS and OS

Variable	Predictors of PFS	Predictors of OS
Time between first ASCT and relapse	Cook et al, 2011 [16] (>24 mo) Yhim et al, 2013 [14] (>18 mo)	Cook et al, 2011 [16] (>24 mo) Yhim et al, 2013 [14] (>18 mo)
Melphalan dose at SAT	Tremblay et al, 2017 [23]	Tremblay et al, 2017 [23]
Use of maintenance therapy post-SAT	Lemieux et al, 2013 [26] Gössi et al, 2018 [12]	Gössi et al, 2018 [12]
Response before SAT:		
Less than PR	Auner et al, 2013 [24] Sellner et al, 2013 [25]	Auner et al, 2013 [24]
VGPR or better		Gössi et al, 2018 [12]
Response after SAT		
Less than VGPR	Lemieux et al, 2013 [26]	Jimenez Zepeda et al, 2011 [27]
Achieving CR	Gonsalves et al, 2013 [15]	
Number of previous lines of therapy	Gonsalves et al, 2013 [15] Olin et al, 2009 [86]	Shaw et al, 2012 [22] Olin et al, 2009 [86]
High-risk cytogenetics	Yhim et al, 2013 [14]	
ISS stage		Yhim et al, 2013 [14] (ISS III)
β2 microglobulin		Cook et al, 2011 [16]
Paraprotein type		
IgG	Sellner et al, 2013 [25]	Shaw et al, 2012 [22]
Light chain	Sellner et al, 2013 [25]	
Hemoglobin level		Grövdal et al, 2015 [13]
Thrombocytopenia	Tremblay et al, 2017 [23]	Fenk et al, 2011 [84]
Age	Cook et al, 2011 [16] (age <65 yr) Lemieux et al, 2013 [26] Grövdal et al, 2015 [13]	Cook et al, 2011 [16] (age <65 yr)

Another potential risk of SAT is secondary malignancies, particularly in patients receiving maintenance therapy. There are no data to support this, however, with the BSBMT/UKMF Myeloma X study showing a rate of 3% in the SAT arm versus 2% in the weekly cyclophosphamide arm [18], and the CIBMTR review by Michaelis et al [11] showing a rate of only 1%. Modern studies in which post-SAT maintenance therapy was used more routinely did not report secondary malignancy rates [12,14].

The most recent guidelines regarding the role of SAT for MM were published in 2015 by the American Society of Blood and Marrow Transplantation, European Society for Blood and Marrow Transplantation, Blood and Marrow Transplantation Clinical Trials Network (BMT CTN), and the IMWG following a consensus conference [5]. While acknowledging a lack of extensive high-quality research, this consensus conference aimed to identify knowledge gaps, propose future research, and develop a collaborative initiative to move research forward. Specifically regarding SAT, several important consensus guidelines were proposed, including the following:

1. High-dose chemotherapy and ASCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes ASCT with an initial duration of remission of >18 months.
2. The role of post-SAT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, immunomodulating agents, and oral proteasome inhibitors.
3. ASCT consolidation should be explored as a strategy for developing novel conditioning regimens or post-ASCT strategies in patients with short (<18-month) remission after primary therapy.
4. Prospective randomized trials are needed to define the role of SAT in patients with MM who relapse after primary therapy, comparing it with "best non-ASCT" therapy.

These guidelines are supported by the literature and are consistent with clinical practice in most institutions. There is an appropriate focus on designing high-quality randomized clinical trials to further evaluate the role of SAT incorporating novel approaches in the conditioning regimen and post-transplantation therapy to maximize outcomes in comparison with the best nontransplantation therapy options.

*Improving Outcomes: Conditioning Regimens, Post-Transplant*ation Maintenance, and Clinical Trial Endpoints

In contrast to the accelerated development of effective new drugs for induction and relapse, single-agent melphalan at a dose of 200 mg/m^2 (Mel200) remains the international standard for conditioning before ASCT for MM [28] in both the upfront and relapsed settings since it was first evaluated by Jagganath et al in 1992 [29]. MM is the only hematologic malignancy in which the preparative regimen for ASCT is a single agent; thus, there is likely significant room for improvement. Even though the first BMT CTN state- of-the-science symposium had intensifying and improving the preparative regimen for MM as one of its priorities, little progress had been made until recently. In the upfront setting, several recently explored approaches appear promising. Our group compared a novel conditioning regimen incorporating busulfan, melphalan, and bortezomib versus standard Mel200 in newly diagnosed patients undergoing ASCT and found an encouraging 1-year PFS of 90% in comparison with 77% in Mel200 historical control subjects from a matched cohort

obtained from the CIBMTR [30]. The superiority of busulfan and melphalan over standard Mel200 was also demonstrated by Qazilbash et al [31] in their randomized Phase III study, which showed a superior median PFS of 64.7 months versus 34.4 months in the experimental arm. Costa et al [32] recently showed in a Phase I-II trial that the combination of carfilzomib on days -3 and -2 with Mel200 on day -2 is also very active in high-risk patients with relapsed MM receiving SAT, with a 1-year PFS of 67% and a 1-year OS of 88%. Other regimens have evaluated various combinations of cytotoxic agents [33-36] (NCT03687125), immunomodulatory agents [37], proteasome inhibitors [38], and total marrow irradiation [39] with varying success [40]. Despite the promise of an intensified approach in the upfront setting, this is still not routinely used in the relapsed or upfront setting. These data suggest that intensification of the preparative regimen optimally should be considered in the SAT setting, and if a more effective regimen than single-agent melphalan can be identified in this setting, then upfront studies should be performed.

Maintenance therapy post-ASCT has become the standard of care in the upfront setting. Several randomized trials have shown a significant improvement in PFS, in the 18-month range [8,41,42]. Although an OS advantage has not been consistently shown, recent real-world data [43], as well as a large meta-analysis by McCarthy et al [44], show a survival advantage. Those patients appropriately selected for SAT also could benefit from maintenance therapy following transplantation. Notably, the few comparative studies that have reported the use of maintenance therapy post-SAT have shown improvement of OS in of 9 to 30 months [14,15] compared with standard therapy for MM at relapse. In clinical practice, the use of maintenance therapies varies across institutions, from as low as 12% [45] to as high as 57% [25]. Moving forward, clinical trials evaluating the role of SAT at relapse must incorporate maintenance therapy as either a standard or a separate randomized intervention.

With the promise of an intensified approach and the use of post-transplantation therapy, well-designed clinical trials with validated and accepted endpoints are needed to accurately measure efficacy, given the high response rates and depth of remission expected. More sensitive methods of measuring low disease burden are now predictive of outcome and are being increasingly used as potential end points. In 2016, the IMWG defined a new response category of minimal residual disease (MRD) negativity (with or without imaging), to allow for uniform reporting both within clinical trials and in nonresearch settings [46]. Furthermore, on September 28, 2018, the US Food and Drug Administration approved the marketing of the ClonoSEQ assay, a next-generation sequencing-based test for MRD in MM. This soon-to-be commercially available polymerase chain reaction-based assay can measure MRD down to <1 per 10^{-6} cells. In the relapsed setting, clinical trial endpoints will need to include PFS, OS, and disease burden by MRD level detection.

CHOOSING THERAPY IN THE RELAPSED SETTING: A CROWDED SPACE

The treatment of MM is a success story in modern hematology. As recently as the early 1990s, the 5-year survival rate for a patient at the median age of diagnosis was only 29% [47], whereas today, the median OS for standard-risk patients approaches 7 years [19]. In the relapsed setting, triplet combinations are increasingly used, and quad regimens are gaining traction, appearing to be safe and promising with deep responses (ClinicalTrials.gov NCT01965353, NCT02718833, and NCT03590652). More convenient dosing, such as weekly carfilzomib [48], oral proteasome inhibitors [49], and all oral regimens [50], have the potential to improve quality of life for relapsed patients. Monoclonal antibodies with various targets, such as CD38, SLAM7, and B cell maturation antigen (BCMA), are becoming standard of care in the relapsed setting [51-54]. Recent data show that although heterogeneity exists in treatment patterns, the use of novel agents in the nonclinical trial and real-world settings has coincided with such clinical milestones as regulatory approvals and clinical trial results [55].

Several recent large meta-analyses have compared newer regimens in the relapsed refractory setting. The combination of daratumumab, lenalidomide, and dexamethasone has consistently been shown to be the superior regimen in terms of risk of progression or death as well as depth of response [56-58]. Of note, the role of SAT was not assessed in any of these analyses, nor was it clear which patients went on to undergo SAT within individual treatment groups. In the POLLUX trial, a randomized Phase III trial comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone, the median number of previous treatment lines per patient was only 1 (range, 1 to 8 versus 1 to 11 respectively), with nearly two-thirds of patients having undergone previous ASCT and a median time from diagnoses to treatment of approximately 3.5 years [51]. It is likely that in many of these patients, there was an interval of at least 18 months between upfront ASCT and progression, and based on standard industry-sponsored inclusion and exclusion criteria, such as cytopenia, organ function, and performance status, most of these patients likely would have been candidates for SAT. In fact, patients with early relapse following upfront ASCT and those undergoing reinduction with the intent to proceed to SAT were excluded, thereby eliminating SAT as a potentially beneficial treatment option. There are no reported data from this or any other trial regarding the number of patients who came off the study and subsequently underwent SAT.

Compared with the outcomes achieved in clinical trials, the inferior outcomes recently reported for real-world patients are concerning. The Registry of Monoclonal Gammopathies, one of the largest long-term observational cohorts of its kinds examining real-world outcomes in MM, is currently ongoing in the Czech Republic. With enrollment starting in May 2007 and more than 4700 patients followed, the median PFS and OS following second- line therapy for MM are 27.2 months and 10.5 months, respectively [59]. Connect MM is the largest multisite, prospective, observational cohort study in the United States, with 3011 patients with newly diagnosed MM enrolled between September 2009 and April 2016. The median OS from initiation of second- line therapy was found to be just 29.0 months in those receiving only novel therapies, with PFS yet to be reported [43]. Consistently inferior outcomes in the real-world setting for relapsed disease have been reported, with a median PFS for second-line therapies as low as 6.8 months and 12 months in some studies [60,61]. In the real-world setting, there appears to be a contradiction between the implementation of novel therapies and outcomes compared with clinical trial data.

Finally, chimeric antigen receptor T cell (CAR-T) therapy is now making headway in MM, and its future potential is generating much interest. BCMA has been identified as a promising immunotherapeutic target, and others potential targets , such as CD229, SLAM7, and APRIL (a proliferation-inducing ligand), are currently being explored [62-64]. A member of the tumor necrosis factor receptor superfamily, BCMA is expressed only in lymphoid tissue of healthy individuals and on mature B cells or plasma cells and enhances the survival of long-lived plasma cells in patients with MM [65,66]. Phase I data reported to date

show varying results with different T cell constructs, doses, and lymphodepletion methodologies, with work being done primarily at the University of Pennsylvania, at the National Institutes of Health, and in China [67-70]. A Chinese group reported a response rate as high 100% in heavily pretreated patients, with 18 of 19 patients achieving a CR [71]. Although extremely promising, these therapies are early in development, and no long-term follow-up data are available. Based on challenges in other hematologic malignancies, such as antigen escape [72] and late relapses despite deep remission, caution must be maintained. MM has proven to be chronic in nature, with relapse the rule and not the exception, short of a small percentage of patients undergoing ASCT [73,74].

ADDITIONAL CONSIDERATIONS: COST OF CARE AND QUALITY OF LIFE

There is an increasing focus on the cost of care of MM, with many patients unable to afford treatment. Costs are likely to increase with improved clinical outcomes and sequential novel treatment combinations. ASCT remains a cost-effective option for treating relapsed MM. Rizzo et al [75] recently showed that the majority of the cost of MM treatment actually stems from complications of progressive disease, with metastatic bone disease accounting for 17% of total MM treatment costs and overall costs directly correlating with progressive disease itself, with incurred costs more than 3-fold higher in patients with disease progression compared with those without disease progression. Thus, the ideal cost-effective treatment for relapsed MM following upfront ASCT should focus on PFS and thus may be SAT. Furthermore, Niphadkar et al [76] evaluated the cost-effectiveness of ASCT for MM and showed that in a novel treatment approach incorporating lenalidomide followed by ASCT and lenalidomide maintenance, the cost of induction and transplantation accounts for only 22% of the overall costs, with a substantial portion of this cost associated with the lenalidomide maintenance portion. With the patent running out on lenalidomide and other viable, less costly maintenance approaches, such as bortezomib, under investigation, the proportional cost of an approach incorporating ASCT may very well decrease in the near future. In the study by Niphadkar et al [76], the estimated cost of ASCT was $109,856 ± $5749.83, whereas just 1 month of novel doublet or triplet therapy ranged from as low as $9903 (bortezomib and dexamethasone) to as high as $27,422 (carfilzomib, lenalidomide, and dexamethasone). To further reduce costs and improve patients' quality of life, some centers are increasingly shifting ASCT to the outpatient setting. There are ample data showing that outpatient ASCT for MM is both safe and cost-effective, saving nearly $20,000 per patient compared with

Table 4
Current Clinical Trials in Recruitment

Trial	Study Design	Treatment	Leading and Participating Sites	Recruitment Status
NCT03562169 Myeloma XII (ACCoRD) Trial	Randomized Phase III Evaluating SAT conditioning regimen Patients: relapsed at least 12 mo after first ASCT	Induction (all patients): • 4 cycles of ITD (ixazomib, thalidomide, and dexamethasone) First randomization: • Mel200 and ASCT • Mel100 on days -3 and -2 plus ixazomib 4 mg on days -4 to -1 Consolidation (all patients): 2 cycles of ITD Second randomization: • Ixazomib maintenance until PD • Observation	University of Leeds United Kingdom multi-institutional study	Recruiting Planned accrual: 406 Accrual start date: March 20, 2017 Estimated primary completion date: March 2026
NCT01745588 (CC-40407)	Randomized Phase III Evaluating SAT versus MM therapy	Induction (all patients): • 4 cycles of CRD (clarithromycin, pomalidomide, and dexamethasone)	Memorial Sloan Kettering Cancer Center	Active, nonrecruiting Planned accrual: unclear
	Patients: Relapsed at least 12 mo after initial ASCT	Randomization: • Mel200 and ASCT • 9 additional cycles of CRD Maintenance (all patients): Pomalidomide until PD	US multi-institutional study	Accrual start date: December 2012 Estimated primary completion date: December 2018
NCT03556332	Phase II Evaluating novel therapy and SAT Patients: Per institutional guidelines	Induction: 4 cycles of Dara-KRD (daratumumab, carfilzomib, lenalidomide, and dexamethasone) SAT: Mel200 Consolidation: 4 cycles of Dara-KRD Maintenance: none per protocol	Memorial Sloan Kettering Cancer Center and affiliated sites	Recruiting Planned accrual: 46 Accrual start date: July 2018 Estimated primary completion: June 2021
NCT03030261	Phase II Evaluating novel therapy and SAT Patients: Per institutional guidelines	Induction: 4 cycles of EPD (elotuzumab, pomalidomide, and dexamethasone) SAT: Mel200 Consolidation and maintenance: EPD dose reduced until progressive disease	Washington University School of Medicine	Recruiting Planned accrual: 40 Accrual start date: November 2017 Estimated primary completion: May 2021
NCT03687125	Phase I/II Evaluating tinostamustine conditioning for SAT Patients: Relapsed at least 6 mo (Phase I) or 18 mo (Phase II) after first ASCT	Induction: Any achieving at least a minimal response before SAT SAT: Phase I 3+3 dose escalation design Consolidation and maintenance: none per protocol	Froedtert & Medical College of Wisconsin Cancer Network, Froedtert Hospital International multi-institutional study	Recruiting: Planned accrual: 71 Accrual start date: September 2018 Estimated primary completion: June 2022

PD indicates progressive disease.

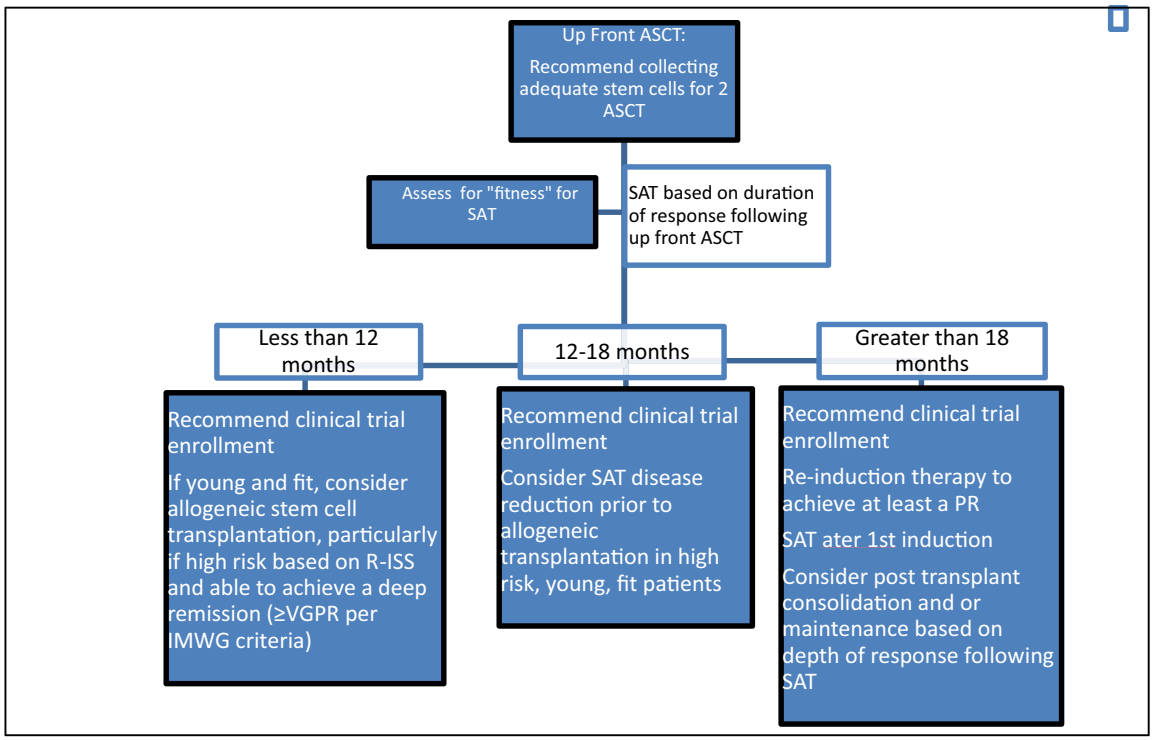
inpatient approaches, with no differences in toxicity, PFS, and OS [77-79]. This represents an opportunity to reduce the economic burden of SAT on patients with relapsed MM as well as the healthcare system.

Because MM is a chronic disease, quality of life should be an important consideration in treatment decisions and a measurement parameter of impact in clinical trial designs. Improvement in quality of life after transplantation can change clinical practice, as was reported in BMT CTN 0201, in which although no difference in OS was seen between peripheral blood and bone marrow stem cell matched unrelated donor grafts in ASCT recipients, bone marrow stem cell grafts were associated with less chronic GVHD and improved quality of life, which in turn has increased the use of bone marrow stem cells in this population [80]. Although MM is the most common indication for ASCT worldwide [81], the data on quality of life following ASCT are limited. Chakraborty et al [82] recently published a systemic review of 12 studies examining quality of life, of which only 1 had quality of life as a prespecified secondary endpoint. They found that although baseline quality of life worsens following ASCT for MM, it is quickly regained as early as 2 months post-transplantation, and long-term improvement in quality of life was noted in some studies. This is consistent with what is seen in clinical practice at our transplantation center.

CONCLUSION: CURRENT ONGOING CLINICAL TRIALS AND A SUGGESTED TREATMENT ALGORITHM FOR INCORPORATING SAT

Well-designed randomized clinical trials are needed to determine the precise role of SAT moving forward. According to a recent review of trials registered at ClinicalTrials.gov, very few such studies are currently in development or actively recruiting (Table 4). Three interventional trials examining the role of SAT in MM are currently underway, 1 of which (NCT01745588) is randomizing patients to either SAT or ongoing modern MM therapy. In addition, several Phase II trials are examining induction, mobilization, high-dose chemotherapy, post-transplantation consolidation, and post-transplantation maintenance approaches. A randomized Phase II preparative regimen study with uniform maintenance with defined early (MRD) and late (PFS) endpoints is currently in development in a US cooperative group setting. This should clarify the optimal approach to SAT and should be followed by comparisons with optimal nontransplantation therapies, likely CAR-T, in future cooperative group studies. The results of these trials will offer valuable information on novel induction and maintenance/consolidation approaches.

Based on current data and available therapies, Figure 1 depicts our recommended treatment approach regarding the role of SAT in the treatment of relapsed MM. The first step in determining whether a patient is an appropriate candidate depends primarily on the time from initial ASCT to relapse, with an ideal interval of at least 18 months. Critical to this assessment is not delaying SAT until after failure of multiple lines of therapy for relapse after upfront ASCT. Furthermore, the patient's ability to safely undergo SAT according to institutional guidelines and the transplantation clinician's judgment must be assessed early at the time of relapse. An additional consideration for SAT not directly discussed in this review is disease reduction for high-risk younger patients planning to undergo allogeneic transplantation. Currently, allogeneic transplantation for MM is not approved by Medicare/Medicaid



ASCT: Autologous Stem Cell Transplantation
SAT: Second Autologous Transplantation
R-ISS: Revised International Staging System
VGPR: Very Good Partial Remission
IMWG: International Myeloma Working Group
PR: Partial Remission

Figure 1. Treatment algorithm for patients with relapsed MM. R-ISS, Revised International Staging System.

outside of a clinical trial, and with the recent closing of BMT CTN Protocol 1302 (NCT02440464), its role in patients age >65 years remains unclear moving forward.

In conclusion, despite significant advances in therapy for relapsed MM, outcomes remain suboptimal for most patients. When used appropriately, SAT remains an excellent treatment option leading to potentially significant PFS and OS advantages in the relapsed MM setting. Further development of novel MM salvage therapies, including CAR-T therapy, will continue to refine reatment approaches in the relapsed setting and will need to be directly compared with SAT in future studies.

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REFERENCES

1. Seigel RL, Miller KD, Jemal A. Cancer Statistics, 2016. *CA Cancer J Clin*. 2016;66:7–30.
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2013. National Cancer Institute. Available at: https://seer.cancer.gov/archive/csr/1975_2013/. Accessed 16 February 2018.
3. Atttal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376:1311–1320.
4. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372:142–152.
5. Giralt S, Garderet L, Durie B, et al. American Society of Blood and Marrow Transplantation, European Society for Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma. *Biol Blood Marrow Transplant*. 2015;21:2039–2051.
6. Cavo M, Hájek R, Pantani L, et al. Autologous stem cell transplantation versus bortezomib-melphalan-prednisone for newly diagnosed multiple myeloma: second interim analysis of the phase 3 EMN02/HO95 study. *Blood*. 2017;130:397.
7. 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.
8. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371:895–905.
9. Mina R, Petrucci MT, Corradini P, et al. Treatment intensification with autologous stem-cell transplantation and lenalidomide maintenance improves survival outcomes of patients with newly diagnosed multiple myeloma in complete response. *Clin Lymphoma Myeloma Leuk*. 2018;18:533–540.
10. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389:519–527.
11. Michaelis LC, Saad A, Zhong X, et al. Salvage second hematopoietivc cell transplantation in myeloma. *Biol Blood Marrow Transplant*. 2013;19:760–766.
12. Gössi U, Jeker B, Mansouri Taleghani B, et al. Prolonged survival after second autologous transplantation and lenalidomide maintenance for salvage treatment of myeloma patients at first relapse after prior autograft. *Haematol Oncol*. 2018;36:436–444.
13. Grövdal M, Nahi H, Gahrton G, et al. Autologous stem cell transplantation versus novel drugs or conventional chemotherapy for patients with relapsed multiple myeloma after previous ASCT. *Bone Marrow Transplant*. 2015;50:808–812.
14. Yhim HY, Kim K, Kim JS, et al. Matched-pair analysis to compare the outcomes of a second salvage auto-SCT to systemic chemotherapy alone in patients with multiple myeloma who relapsed after front-line auto-SCT. *Bone Marrow Transplant*. 2013;48:425–432.
15. Gonsalves WI, Gertz MA, Lacy MQ, et al. Second auto-SCT for treatment of relapsed multiple myeloma. *Bone Marrow Transplant*. 2013;48:568–573.
16. Cook G, Liakopoulou E, Pearce R, et al. Factors influencing the outcome of a second autologous stem cell transplant (ASCT) in relapsed multiple myeloma: a study from the British Society of Blood and Marrow Transplantation Registry. *Biol Blood Marrow Transplant*. 2011;17:1638–1645.
17. Manjappa S, Fiala M, King J, Kohnen DA, Vij R. The efficacy of salvage autologous stem cell transplant among patients with multiple myeloma who received maintenance therapy post initial transplant. *Bone Marrow Transplant*. 2018;53:1483–1486.
18. Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2016;3:e340–e351.
19. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33:2863–2869.
20. Garderet L, Iacobelli S, Koster L, et al. Outcome of a salvage third autologous stem cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2018;24:1372–1378.
21. Singh Abbi K, Zheng J, Devlin SM, Giralt S, Landau H. Second autologous stem cell transplant: an effective therapy for relapsed multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21:468–472.
22. Shah N, Ahmed F, Bashir Q, et al. Durable remission with salvage second auto transplants in patients with multiple myeloma. *Cancer*. 2012;118:3549–3555.
23. Tremblay D, Lancman G, Moshier E, Bar N, Jagannath S, Chari A. Outcomes of salvage autologous stem cell transplantation for multiple myeloma with cytopenias and exposure to novel agents. *Bone Marrow Transplant*. 2017;52:1468–1470.
24. Auner HW, Szydlo R, Rone A, et al. *Leuk Lymphoma*. 2013;54:2200–2204.
25. Sellner L, Heiss C, Benner A, et al. Autologous retransplantation for patients with recurrent multiple myeloma: a single center experience with 200 patients. *Cancer*. 2013;119:2438–2446.
26. Lemieux E, Hulin C, Caillot D, et al. Autologous stem cell transplantation: an effective salvage therapy in multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:445–449.
27. Jimenez-Zepeda V, Mikhael J, Winter A, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. *Biol Blood Marrow Transplant*. 2012;18:773–779.
28. Costa LJ, Zhang MJ, Zhong X, et al. Trends in utilization and outcomes of autologous transplantation as early therapy for multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:1615–1624.
29. Jagannath S, Vesole DH, Glenn L, Crowley J, Barlogie B. Low-risk intensive therapy for multiple myeloma with combined autologous bone marrow and blood stem cell support. *Blood*. 1992;80:1666–1672.
30. Rodriguez TE, Hari P, Stiff PJ, Smith SE, Sterrenberg D, Vesole DH. Busulfan, melphalan, and bortezomib versus high-dose melphalan as a conditioning regimen for autologous hematopoietic stem cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2016;22:1391–1396.
31. Qazilbash MH, Thall PF, Fox PS, et al. Randomized phase III trial of busulfan + melphalan vs melphalan alone for multiple myeloma. *J Clin Oncol*. 2017;731:399.
32. Costa LJ, Landau HJ, Chhabra S, et al. Phase 1/2 trial of carflizomib plus high dose melphalan preparative regimen for salvage autologous hematopoietic cell transplantation followed by maintenance carfilzomib in patients with relapsed/refractory multiple myeloma. *Biol Blood Marrow Transplant*. 2018;24:1379–1385.
33. Carreras E, Rosiñol L, Terol M, et al. Veno-occlusive disease of the liver after high-dose cytoreductive therapy with busulfan and melphalan for autologous blood stem cell transplantation in multiple myeloma patients. *Biol Blood Marrow Transplant*. 2007;13:1448–1454.
34. Rosiñol L, Oriol A, Rios R, et al. Bortezomib, lenalidomide and dexamethasone (VRD-GEM) as induction therapy prior to autologous stem cell transplantation (ASCT) in multiple myeloma (MM): results of a prospective phase III Pethema/GEM Trial. *Blood*. 2017;130:2017.
35. Sivaraj D, Bacon W, Long GD, et al. High-dose BCNU/melphalan conditioning regimen before autologous stem cell transplantation in newly diagnosed multiple myeloma. *Bone Marrow Transplant*. 2018;53:34–38.
36. Veeraputhiran M, Jain T, Deol A, et al. BEAM conditioning regimen has higher toxicity compared with high-dose melphalan for salvage autologous hematopoietic stem cell transplantation in multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2015;15:531–535.
37. Suvannasankha A, Farag S, Silbermann R, et al. Phase I/II study of lenalidomide and high dose melphalan as preparative regimen in autologous transplant in myeloma: report of phase II efficacy and safety data. *Blood*. 2015;126:3193.
38. Roussell M, Hebraud B, Lauwers-Cances V, et al. Bortezomib and high-dose melphalan vs. high-dose melphalan as conditioning regimen before autologous stem cell transplantation in de novo multiple myeloma patients: a phase 3 study of the Intergroupe Francophone Du Myelome (IFM 2014-02). *Blood*. 2017;130:398.
39. Patel P, Oh AL, Koshy M, et al. A phase 1 trial of autologous stem cell transplantation conditioned with melphalan 200mg/m^2 and total marrow irradiation (TMI) in patients with relapsed/refractory multiple myeloma. *Leuk Lymphoma*. 2018;59:1666–1671.
40. Lahuerta JJ, Grande C, Blade J, et al. Myeloablative treatments for multiple myeloma: update of a comparative study of different regimens used in patients from the Spanish Registry for Transplantation in Multiple Myeloma. *Leuk Lymphoma*. 2002;43:67–75.

41. 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.
42. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770–1781.
43. Jagannath S, Abonour R, Durie BGM, et al. Impact of post-ASCT maintenance therapy on outcomes in patients with newly diagnosed multiple myeloma in Connect MM. *Blood Adv*. 2018;2:1608–1615.
44. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. *J Clin Oncol*. 2017;29:3279–3289.
45. Blimark C, Veskovski L, Westin J, et al. Melphalan 100 mg/m^2 with stem cell support as first relapse treatment is safe and effective for myeloma patients with long remission after autologous stem cell transplantation. *Eur J Hematol*. 2011;87:117–122.
46. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17:e328–e346.
47. Costa LJ, Brill IK, Omel J, et al. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. *Blood Adv*. 2017;1:282–287.
48. Moreau P, Mateos MV, Berenson JR, et al. Once-weekly versus twice-weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (ARROW): interim analysis results of a randomised, phase 3 study. *Lancet Oncol*. 2018;19:953–964.
49. Kumar SK, LaPlant BR, Reeder CB, et al. Randomized phase 2 trial of ixazomib and dexamethasone in relapsed multiple myeloma not refractory to bortezomib. *Blood*. 2016;128:2415–2422.
50. Krishnan A, Kapoor P, Palmer J, et al. Phase I/II trial of the oral regimen ixazomib, pomalidomide, and dexamethasone in relapsed/refractory multiple myeloma. *Leukemia*. 2018;32:1567–1574.
51. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:1319–1331.
52. Palumbo A, Channan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375:754–766.
53. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373:621–631.
54. Tai YT, Mayes PA, Acharya C, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood*. 2014;123:3128–3138.
55. Jagannath S, Abonour R, Durie BGM, et al. Heterogeneity of second-line treatment for patients with multiple myeloma in the Connect MM Registry (2010-2016). *Clin Lymphoma Myeloma Leuk*. 2018;18. 480-485.e3.
56. Maiese E, Le Moine JG, Ainsworth C, Ahdesmäki O, Howe E. Comparative efficacy of multiple myeloma therapies for treatment of first relapse: a systematic literature review and network meta-analysis. *J Clin Oncol*. 2017;35:8042.
57. Beurden-Tan C, Franken M, Blommestein H, Uyl-de Groot C, Sonneveld P. Systematic literature review and network meta-analysis of treatment outcomes in relapsed and/or refractory multiple myeloma. *J Clin Oncol*. 2017;35:1312–1319.
58. Botta C, Ciliberto D, Rossi M, et al. Network meta-analysis of randomized trials in multiple myeloma: efficacy and safety in relapsed/refractory patients. *Blood Adv*. 2017;1:455–466.
59. Hájek R, Jarkovsky J, Maisnar V, et al. Real-world outcomes of multiple myeloma: retrospective analysis of the Czech Registry of Monoclonal Gammopathies. *Clin Lymphoma Myeloma Leuk*. 2018;18:e219–e240.
60. Wilson J, Bruno A, Opalinska J, et al. Current real-world treatment patterns and outcomes in patients with relapsed/refractory multiple myeloma. *J Clin Oncol*. 2018;36:e20038.
61. Terpos E, Katodritou E, de la Rubia J, et al. Bortezomib-based therapy for relapsed/refractory multiple myeloma in real-world medical practice. *Eur J Haematol*. 2018;101:556–565.
62. Radhakrishnan SV, Luetkens T, Yousef S, et al. Chimeric antigen receptor (CAR) T cells specific for CD229: a potentially curative approach for multiple myeloma. *Blood*. 2017;130:3142.
63. Gogishvili T, Danhof S, Prommersberger S, et al. SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7+ normal lymphocytes. *Blood*. 2017;130:2838–2847.
64. Lee L, Draper B, Chaplin N, et al. An APRIL-based chimeric antigen receptor for dual targeting of BCMA and TACI in multiple myeloma. *Blood*. 2018;131:746–758.
65. O'Connor BP, Raman VS, Erickson LD, et al. BCMA is essential for the survival of long lived bone marrow plasma cells. *J Exp Med*. 2004;199:91–98.
66. Cho SF, Anderson KC, Tai YT. Targeting B cell maturation antigen (BCMA) in multiple myeloma: potential uses of BCMA-based immunotherapy. *Front Immunol*. 2018;9:1821.
67. Ali SA, Shi V, Maric I, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. *Blood*. 2016;128:1688–1700.
68. Brudno JN, Maric I, Hartman SD, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. *J Clin Oncol*. 2018;36:2267–2280.
69. Cohen AD, Garfall AL, Stadtmauer EA, et al. Safety and efficacy of B-cell maturation antigen (BCMA)-specific chimeric antigen receptor T cells (CART-BCMA) with cyclophosphamide conditioning for refractory multiple myeloma (MM). *Blood*. 2017;130:505.
70. Raje NS, Berdeja JG, Lin Y, et al. bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: updated results from a multicenter phase I study. *J Clin Oncol*. 2018;36:8007.
71. Fan F, Zhao W, Liu J, et al. Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma. *J Clin Oncol*. 2017;35. LBA3001.
72. Jackson HJ, Brentjens RJ. Overcoming antigen escape with CAR T-cell therapy. *Cancer Discov*. 2015;5:1238–1240.
73. Libura J, Hoffmann T, Passweg J, et al. Graft-versus-myeloma after withdrawal of immunosuppression following allogeneic peripheral stem cell transplantation. *Bone Marrow Transplant*. 1999;24:925–927.
74. Lokhorst H, Einsele H, Vesole D, et al. International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. *J Clin Oncol*. 2010;28:4521–4530.
75. Rizzo M, Xu Y, Panjabi S, Iheanacho I. A systematic literature review of the economic burden in multiple myeloma. *Value Health*. 2014;17:A628.
76. Niphadkar S, Varadarajan I, Pompa T, et al. Autologous stem cell transplant: a cost effective and efficacious treatment for newly diagnosed multiple myeloma. *Blood*. 2016;128:2358.
77. Holbro A, Ahmad I, Cohen S, et al. Safety and cost-effectiveness of outpatient autologous stem cell transplantation in patients with multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19:547–551.
78. Graff TM, Singavi AK, Schmidt W, et al. Safety of outpatient autologous hematopoietic cell transplantation for multiple myeloma and lymphoma. *Bone Marrow Transplant*. 2015;50:947–953.
79. Gertz MA, Dingli D. How we manage autologous stem cell transplantation for patients with multiple myeloma. *Blood*. 2014;124:882–890.
80. Lee SJ, Logan B, Westervelt P, et al. Bone marrow is associated with better patient-reported outcomes than peripheral blood in survivors 5 years after unrelated donor transplantation. *JAMA Oncol*. 2016;2:1583–1589.
81. D'Souza A, Fretham C. Current uses and outcomes of hematopoietic cell transplantation (HCT): CIBMTR summary slides; 2017. Available at: http://www.cibmtr.org. Accessed XXX.
82. Chakraborty R, Hamilton BK, Hashmi SK, Kumar SK, Majhail NS. Health-related quality of life after autologous stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2018;24:1546–1553.
83. Chow AW, Lee CH, Hiwase DK, To LB, Horvath N. Relapsed multiple myeloma: who benefits from salvage autografts? *Int Med J*. 2012;43:156–161.
84. Fenk R, Liese V, Neubauer F, et al. Predictive factors for successful salvage high-dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation. *Leuk Lymphoma*. 2011;52:1455–1462.
85. Burzynski JA, Toro JJ, Patel RC, et al. Toxicity of a second autologous peripheral blood stem cell transplant in patients with relapsed or recurrent multiple myeloma. *Leuk Lymphona*. 2009;50:1442–1447.
86. Olin RL, Vogl DT, Porter DL, et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. *Bone Marrow Transplant*. 2009;43:417–422.