original report

Autologous Transplantation, Consolidation, and Maintenance Therapy in Multiple Myeloma: Results of the BMT CTN 0702 Trial

Edward A. Stadtmauer, MD[1]; Marcelo C. Pasquini, MD, MS[2]; Beth Blackwell, ScD[3]; Parameswaran Hari, MD, MS[2]; Asad Bashey, MD, PhD[4]; Steven Devine, MD[5]; Yvonne Efebera, MD[5]; Siddharta Ganguly, MD[6]; Cristina Gasparetto, MD[7]; Nancy Geller, PhD[8]; Mary M. Horowitz, MD, MS[2]; John Koreth, MD, DPhil[9]; Kristin Knust, MS[3]; Heather Landau, MD[10]; Claudio Brunstein, MD, PhD[11]; Philip McCarthy, MD[12]; Courtney Nelson[3]; Muzaffar H. Qazilbash, MD[13]; Nina Shah, MD[14]; David H. Vesole, MD, PhD[15]; Ravi Vij, MD, MBA[16]; Dan T. Vogl, MD, MS[1]; Sergio Giralt, MD[10]; George Somlo, MD[17]; and Amrita Krishnan, MD[17]

abstract

PURPOSE Single-cycle melphalan 200 mg/m^2 and autologous hematopoietic cell transplantation (AHCT) followed by lenalidomide (len) maintenance have improved progression-free survival (PFS) and overall survival (OS) for transplantation-eligible patients with multiple myeloma (MM). We designed a prospective, randomized, phase III study to test additional interventions to improve PFS by comparing AHCT, tandem AHCT (AHCT/AHCT), and AHCT and four subsequent cycles of len, bortezomib, and dexamethasone (RVD; AHCT + RVD), all followed by len until disease progression.

PATIENTS AND METHODS Patients with symptomatic MM within 12 months from starting therapy and without progression who were age 70 years or younger were randomly assigned to AHCT/AHCT + len (n = 247), AHCT + RVD + len (n = 254), or AHCT + len (n = 257). The primary end point was 38-month PFS.

RESULTS The study population had a median age of 56 years (range, 20 to 70 years); 24% of patients had high-risk MM, 73% had a triple-drug regimen as initial therapy, and 18% were in complete response at enrollment. The 38-month PFS rate was 58.5% (95% CI, 51.7% to 64.6%) for AHCT/AHCT + len, 57.8% (95% CI, 51.4% to 63.7%) for AHCT + RVD + len, and 53.9% (95% CI, 47.4% to 60%) for AHCT + len. For AHCT/AHCT + len, AHCT + RVD + len, and AHCT + len, the OS rates were 81.8% (95% CI, 76.2% to 86.2%), 85.4% (95% CI, 80.4% to 89.3%), and 83.7% (95% CI, 78.4% to 87.8%), respectively, and the complete response rates at 1 year were 50.5% (n = 192), 58.4% (n = 209), and 47.1% (n = 208), respectively. Toxicity profiles and development of second primary malignancies were similar across treatment arms.

CONCLUSION Second AHCT or RVD consolidation as post-AHCT interventions for the up-front treatment of transplantation-eligible patients with MM did not improve PFS or OS. Single AHCT and len should remain as the standard approach for this population.

J Clin Oncol 37:589-597. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 20, 2018 and published at jco.org on January 17, 2019: DOI https://doi.org/10.1200/JCO.18.00685

Clinical trial information: NCT01109004.

INTRODUCTION

High-dose chemotherapy plus autologous hematopoietic cell transplantation (AHCT) after initial induction therapy with combinations of immunomodulatory agents, proteasome inhibitors, cytotoxic drugs (primarily alkylating agents), and corticosteroids prolongs progression-free survival (PFS) and overall survival (OS) among patients with newly diagnosed multiple myeloma (MM) compared with conventional-dose chemotherapy.[1-3] The addition of lenalidomide (len) maintenance after AHCT has further improved PFS and OS.[4-6]

Several approaches to further improve outcome after initial AHCT have been investigated such as a second AHCT or consolidation with combinations of immunomodulatory agents, proteasome inhibitors, and corticosteroids, but incremental benefit compared with maintenance therapy remains to be determined.[7-9] Comparative phase III trials have yielded conflicting results regarding the benefit of tandem transplantation, and none of the trials were conducted in the era of induction therapy with the newer antimyeloma agents. Initial myeloma reductive therapy followed by high-dose melphalan plus AHCT with long-term len is currently the standard of care for patients in the United States. Despite substantive improvements in outcomes with this approach, most patients will experience disease progression and ultimately die as a result of the disease.

This three-arm phase III clinical trial comparing tandem AHCT followed by len maintenance (AHCT/AHCT + len), AHCT plus four cycles of len, bortezomib, and dexamethasone (RVD) followed by len (AHCT + RVD + len), and AHCT and len only (AHCT + len) for patients who had received initial therapy without progression and who had active MM was conducted to assess

whether additional interventions to AHCT and len further improve outcomes.

PATIENTS AND METHODS

Study Design and Patients

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0702 trial (Clinicaltrials.gov identifier: NCT01109004) was a phase III study undertaken at 54 US transplantation centers. Patients with symptomatic MM who were 70 years old or younger and who received at least two cycles of any regimen as initial systemic therapy without disease progression and who were within 2 to 12 months of the first dose of initial therapy were eligible (Data Supplement). The study was approved by the institutional review boards of the participating centers, and all patients provided informed consent.

All patients were randomly assigned in a 1:1:1 manner at the time of enrollment, which occurred within 7 days before the first high-dose melphalan conditioning regimen. Random assignment was stratified by disease risk and transplantation center. Maintenance therapy was initially designed to be given for 3 years for all patients. An amendment in 2014 (Data Supplement), based on emerging data,[4] expanded use of len to continue until toxicity, disease progression, or withdrawal of consent. High-risk MM was defined by presence of high β_2-microglobulin (> 5.5 mg/L) or presence of cytogenetic abnormalities, including t(4;14), t(14;20), t(14;16), deletion (17p) detected by fluorescence in situ hybridization or standard cytogenetics, deletion 13 detected by standard cytogenetics only, or aneuploidy. Patients without cytogenetic analysis available and β_2-microglobulin level of 5.5 mg/L or lower or with deletion 13 detected by fluorescence in situ hybridization were classified as standard risk.

Procedures

All enrolled patients were to receive high-dose melphalan (200 mg/m^2) followed by mobilized autologous peripheral-blood stem-cell infusion (minimum 2×10^6 CD34$^+$ cells/kg). Subsequent therapy was based on random assignment at the time of enrollment. The second phase of therapy started between 60 and 120 days after the first AHCT, once patients had sufficiently recovered. Patients randomly assigned to a second transplantation (AHCT/AHCT + len) received high-dose melphalan (200 mg/m^2) followed by autologous peripheral-blood stem-cell infusion. Patients randomly assigned to RVD consolidation (AHCT + RVD + len) received four cycles of len 15 mg/d on days 1 to 14; bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of every 21-day cycle; and dexamethasone 40 mg per day on days 1, 8, and 15. After their initial interventions, all patients received len starting at 10 mg per day for 3 months and increasing to 15 mg per day.[4] Dose adjustments for toxicity were permitted (Data Supplement).

End Points and Assessments

The primary study end point was PFS at 38 months; events for this end point include disease progression, initiation of nonprotocol systemic antimyeloma therapy, or death. Secondary end points included OS, disease progression, disease response, conversion to complete response (CR) after initiation of maintenance, noncompliance with assigned study treatments, treatment-related mortality (TRM), incidence of toxicities greater than grade 3 (according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3),[10] infections, and health-related quality of life (QOL). Supplemental end points included the development of second primary malignancies (SPMs) and event-free survival (EFS), where an event is defined as progression, death, or SPM. Time-to-event end points were estimated from the time of random assignment. PFS was calculated to the event time or the censoring time of loss to follow-up, last MM evaluation before 38 months, or 38 months. OS was calculated until the date of death from any cause or censored at the minimum of 38 months or last date the patient was known to be alive. Nonadherence was measured as the proportion of patients who did not proceed to their second or, if applicable, third phase of treatment or who discontinued consolidation or maintenance at any time as a result of toxicity, noncompliance, or other reasons. All patients, regardless of adherence to the second intervention, could receive len if there were no contraindications. MM disease responses were defined according to the 2006 International Myeloma Working Group criteria with the addition of a near CR category according to Durie et al[11] and Lahuerta et al.[12] All disease assessments at study entry and responses were adjudicated by an end point review committee, which was blinded to treatment assignment. QOL was assessed using the Short Form 36 and Functional Assessment of Cancer Therapy–Bone Marrow Transplant at baseline and yearly. SPM was defined as any second malignancy excluding nonmelanoma skin cancers that developed after the time of enrollment and within 38 months after enrollment.

Statistical Analysis

The study design estimated PFS to range from 30% to 60% at 3 years after transplantation based on current literature at the time of study design.[13] At the two-sided $P = .01667$ level, a sample size of 250 participants per arm yields 81% power to compare a proportion of 0.60 in arm 1 with a proportion of 0.45 in arm 2, 84% power to compare a proportion of 0.45 in arm 2 with a proportion of 0.30 in arm 3, and nearly 100% power to compare arm 1 with arm 3 (Data Supplement). Participants were randomly assigned using permuted blocks within strata. The primary analysis of PFS included all participants according to their randomly assigned treatment, regardless of treatment received (intent-to-treat population).

Planned interim analyses for futility and efficacy for the primary outcome were conducted approximately 1 and 2 years after the last patient was randomly assigned. In addition, analysis for futility as a result of nonadherence to

the assigned treatment was conducted for each arm. The analyses for efficacy consisted of three stratified log-rank tests comparing each pair of treatment groups at the overall $P = .01667$ level in error in order to maintain studywide type 1 error at .05, further adjusted using O'Brien-Fleming boundaries.[14,15] For tests of other outcomes, tests were performed pairwise at the $P = .01667$ level to maintain type I error at $\alpha = .05$ for each outcome at each time point tested. PFS and OS were estimated using the Kaplan-Meier method, and comparisons were tested using a two-sided log-rank test stratified on risk status. In the presence of competing risks, the cumulative incidence was estimated using the method of Gooley et al,[16] and pairwise comparisons were tested using Gray's test.[17]

Cox proportional hazards models with treatment group and risk strata (with and without interactions)[18] were used to estimate hazard ratios (HRs) and 95% CIs, and effects were tested at the $P = .05$ level. None of the interactions were significant in the models (OS, $P = .53$; PFS, $P = .74$); therefore, the models without interactions are reported here. Treatment group differences in QOL were tested using pairwise t tests or Wilcoxon rank sum tests if the assumptions of the t test were not met. Treatment group differences in disease response were tested using pairwise χ^2 tests. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC). The data cutoff was August 15, 2017.

RESULTS

Patients

From June 2010 through November 2013, 758 patients were enrolled (Fig 1). Baseline demographic and disease characteristics were well balanced among groups (Table 1). Ninety-four percent of participants were observed for at least 38 months or met the PFS end point before 38 months. Before enrollment, 73% of patients initially received triple-drug antimyeloma initial therapy; RVD was used as initial therapy in 55% of patients and bortezomib, cyclophosphamide, and dexamethasone (VCD) was used in 14% of patients. The median time from initiating therapy to enrollment was 5.2 months (range, 2.1

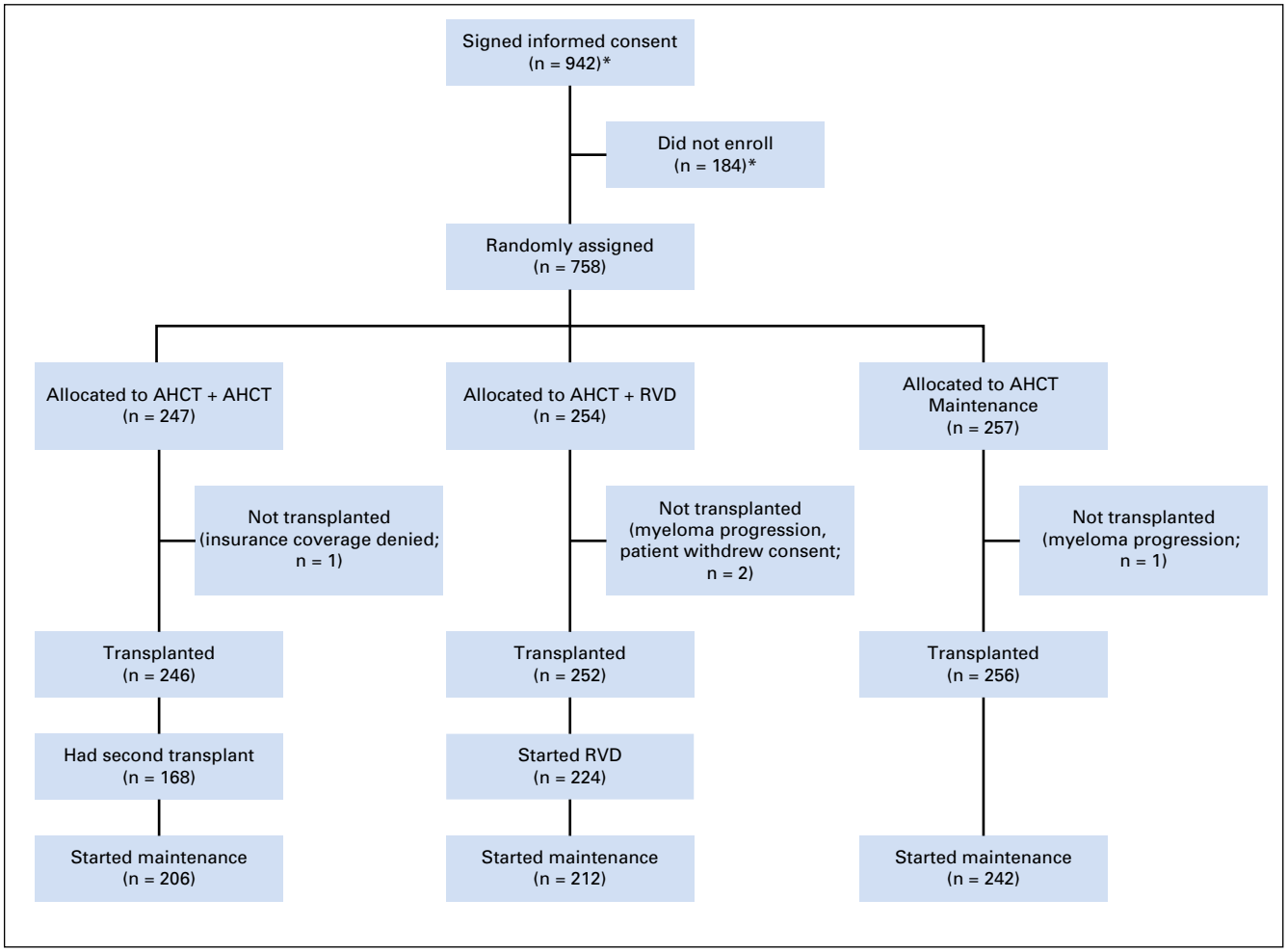

FIG 1. CONSORT diagram. (*) Sites were not required to register patients who signed informed consent but did not enroll. AHCT, autologous hematopoietic cell transplantation; RVD, lenalidomide, bortezomib, and dexamethasone.

TABLE 1. Patient Characteristics

Characteristic	No. of Patients (%)*			
	AHCT/AHCT + Len (n = 247)	AHCT + RVD + Len (n = 254)	AHCT + Len (n = 257)	Total (N = 758)
Age, years				
Median	56	57	56	56
Range	28-70	20-70	30-70	20-70
Male sex	147 (60)	146 (57)	161 (63)	454 (60)
Karnofsky performance score ≥ 90	182 (74)	169 (67)	172 (67)	523 (69)
Ethnicity				
White	178 (72)	192 (76)	201 (78)	571 (75)
African American	50 (20)	39 (15)	41 (16)	130 (17)
Multiple/other/unknown	19 (8)	23 (9)	15 (6)	57 (8)
Median serum β_2-microglobulin at registration, mg/L	2.6	3.0	2.9	2.9
Disease risk†				
Standard	175 (71)	178 (70)	182 (71)	535 (71)
High	72 (29)	76 (30)	75 (29)	223 (29)
Del(13q) by karyotype	15 (6)	21 (8)	25 (10)	61 (8)
t(4;14)	16 (6)	22 (9)	20 (8)	58 (8)
Del(17p)	16 (6)	19 (7)	21 (8)	56 (7)
Hypodiploid or aneuploid	59 (24)	60 (24)	65 (25)	184 (24)
Median time since initial therapy to registration, months (range)	5 (2-14)	5 (2-12)	5 (2-12)	5 (2-14)
Initial therapy				
RVD	141 (57)	136 (54)	143 (56)	420 (55)
Bortezomib, cyclophosphamide, and dexamethasone	33 (13)	35 (14)	40 (16)	108 (14)
Len and dexamethasone	24 (10)	28 (11)	22 (9)	74 (10)
Bortezomib and dexamethasone	29 (12)	32 (13)	32 (12)	93 (12)
Other	19 (8)	19 (7)	20 (8)	58 (8)
Unknown	1 (< 1)	4 (2)	0	5 (1)
No. of lines of therapy‡				
1	210 (85)	213 (84)	218 (85)	641 (85)
2	31(13)	36 (14)	37(14)	104 (14)
3	5 (2)	1 (< 1)	2 (1)	8 (1)
Unknown	1 (< 1)	4 (2)	0	5 (1)

(continued on following page)

to 14.4 months). At enrollment, 91% of patients had a partial response or better, 47% had a very good partial response or better, and 18% had CR (CR or stringent CR). According to cytogenetic assessment, 29% of patients were classified as having high-risk disease.

Efficacy

The estimates of 38-month PFS were 58.5% (95% CI, 51.7% to 64.6%), 57.8% (95% CI, 51.4% to 63.7%), and 53.9% (95% CI, 47.4% to 60%) for AHCT/AHCT + len, AHCT + RVD + len, and AHCT + len, respectively (Fig 2A). Corresponding estimates of 38-month OS were 81.8% (95% CI, 76.2% to 86.2%), 85.4% (95% CI, 80.4% to 89.3%), and 83.7% (95% CI, 78.4% to 87.8%), respectively (Fig 2B). The most common cause of death was MM progression, although in both the AHCT/AHCT + len (n = 3) and AHCT + RVD + len (n = 3) arms, deaths occurred as a result of SPMs (Data Supplement). Cumulative

TABLE 1. Patient Characteristics (continued)

Characteristic	No. of Patients (%)*			
	AHCT/AHCT + Len (n = 247)	AHCT + RVD + Len (n = 254)	AHCT + Len (n = 257)	Total (N = 758)
Disease status at registration				
Stringent complete response	21 (9)	26 (10)	23 (9)	70 (9)
Complete response	22 (9)	19 (7)	24 (9)	65 (9)
Near complete response	27 (11)	22 (9)	24(9)	73 (10)
Very good partial response	52 (21)	53 (21)	43 (17)	148 (20)
Partial response	106 (43)	108 (43)	123 (48)	337 (44)
Stable disease	14 (6)	21 (8)	14 (5)	49 (6)
Progression	4 (2)	2 (1)	3 (1)	9 (1)
Not evaluable	1 (< 1)	3 (1)	3 (1)	7 (1)

Abbreviations: AHCT, autologous hematopoietic cell transplantation; Len, lenalidomide; RVD, len, bortezomib, and dexamethasone.

*Values represent numbers and percentages, unless otherwise noted.

†The proportion of high-risk patients is after data review. The proportion of patients with high risk defined at enrollment and used for stratification was 24% overall and 23% to 26% across arms.

‡Lines of therapy is defined as the number of different regimens received before study entry.

incidences of disease progression at 38 months were 39.8% (95% CI, 33.4% to 46.1%), 41% (95% CI, 34.7% to 47%), and 45.6% (95% CI, 39.2% to 51.8%) for AHCT/AHCT + len, AHCT + RVD + len, and AHCT + len, respectively (Fig 2C).

Cox proportional hazards models were used to explore the association between PFS and risk strata and treatment group; similar models were used for OS. Neither the OS model nor the PFS model showed a significant effect for treatment arm (OS, $P = .52$; PFS, $P = .48$). However, patients with high-risk disease experienced higher rates of treatment failure (progression or death; HR, 1.66; 95% CI, 1.30 to 2.11) and overall mortality (HR, 1.49; 95% CI, 1.01 to 2.20) compared with patients with standard-risk disease (Fig 3). PFS and OS for patients with high-risk disease are provided in the Data Supplement.

MM response assessments at 1 year demonstrated that 79.7% (n = 192), 82.3% (n = 209), and 76% (n = 208) of evaluable patients in the AHCT/AHCT + len, AHCT + RVD + len, and AHCT + len arms, respectively, who had not experienced disease progression or died ultimately achieved very good partial response or better (AHCT/AHCT + len, $P = .37$ and AHCT + RVD + len, $P = .11$, compared with AHCT + len). Among patients not in CR before initiation of maintenance, CR conversions at 1 year after maintenance initiation were seen in 20%, 26.8%, and 19.9% of patients in the AHCT/AHCT + len, AHCT + RVD + len, and AHCT + len arms, respectively.

Safety

TRM over 38 months occurred in four patients in the AHCT/AHCT + len arm, three patients in the AHCT + RVD + len arm, and one patient in the AHCT + len arm. The percentages of patients with nonadherence with a second transplantation or RVD consolidation were 32% and 22%, respectively, which were in line with anticipated rates. The reasons for not initiating these treatments included toxicity, patient refusal, and physician decision (Data Supplement).

Among all reported nonhematologic grade 3 to 5 toxicities during the 38-month period, the majority occurred in the first year after enrollment, and the percentage of patients with at least one grade 3 to 5 toxicity by 1 year was similar across treatment arms (49%, 47%, and 48% in the AHCT/AHCT + len, AHCT + RVD + len, and AHCT + len arms, respectively; Data Supplement). The percentage of patients with probable or definite fungal infections or any bacterial or viral infections in the first year after random assignment and before progression was 46% in the AHCT/AHCT + len arm and 37% in the AHCT + RVD + len and AHCT + len arms (Data Supplement).

Forty-one SPMs developed during the study period, and leukemia was the most common diagnosis. Among 15 second hematologic malignancies, 10 were observed in the AHCT + RVD + len arm (Data Supplement). The 38-month overall cumulative incidences of first SPM were 5.6% (95% CI, 3.2% to 9.1%), 5.7% (95% CI, 3.2% to 9%), and 4.1% (95% CI, 2.1% to 7.1%) in the AHCT/AHCT + len, AHCT + RVD + len, and AHCT + len arms, respectively. EFS rates at 38 months were 54.6% (95% CI, 47.9% to 60.8%), 55.8% (95% CI, 49.4% to 61.8%), and 51.7% (95% CI, 45.3% to 57.8%), respectively; pairwise treatment group comparisons did not show a significant difference ($P = .62$, $P = .54$, and $P = .25$ for AHCT/AHCT + len compared with AHCT + RVD + len, AHCT/AHCT + len compared with AHCT + len, and AHCT + RVD + len compared with AHCT + len, respectively; Fig 4).

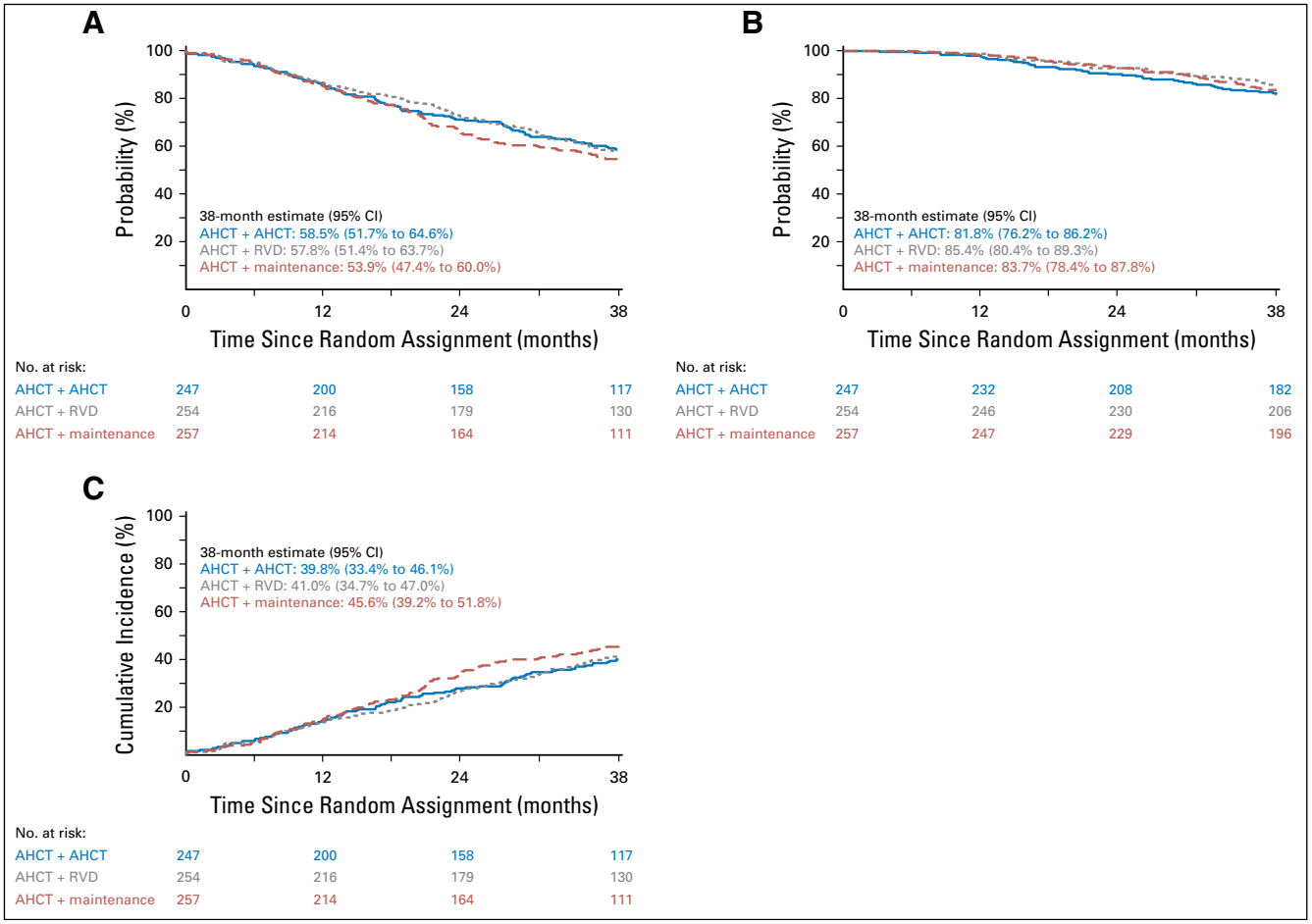

FIG 2. (A) Progression-free survival, (B) overall survival, and (C) disease progression in the tandem autologous hematopoietic cell transplantation (AHCT) + lenalidomide (len), AHCT + len, bortezomib, and dexamethasone (RVD) + len and AHCT + len arms.

QOL

Median Functional Assessment of Cancer Therapy–Bone Marrow Transplant total scores increased by 8 to 11 points on all three arms at 1 year compared with scores at baseline (change from baseline analysis: AHCT/AHCT + len, $P = .10$ and AHCT + RVD + len, $P = .55$, compared with AHCT + len) and remained stable in subsequent years. Similarly, the Short Form 36 physical and mental components did not differ significantly across the arms at the first year after enrollment (Data Supplement).

DISCUSSION

After initial induction therapy, a single consolidation with high-dose melphalan and AHCT followed by len produced similar PFS and OS rates at 38 months of follow-up as more intensive approaches. The treatment strategy of AHCT+ len was associated with 38-month PFS and OS rates from the time of random assignment of 53.9% and 83.7%, respectively.

Similar CR and OS rates were seen with the two more intensive regimens as compared with AHCT + len, and this was true for patients with high- and standard-risk disease. Although the rates of grade 3 to 5 toxicities were similar across treatment arms, there was a higher number of infections in the first year observed in the AHCT/AHCT + len arm. However, this observation did not translate into worse TRM or QOL as measured for 3 years. Rates of nonadherence to second intervention in the AHCT/AHCT + len and AHCT + RVD + len arms (32% and 22%, respectively) were determined, with rates greater than 40% defined by the protocol as a stopping rule for these arms. These rates of nonadherence were within statistically defined expectations and likely represent standard MM practice in the aftermath of transplantation, but they are nonetheless high. Nevertheless, there was no difference between groups in the intent-to-treat outcomes and an earlier ad hoc as-treated analysis (data not shown) of the PFS of the three groups, suggesting that this degree of nonadherence did not significantly dilute the effect of these interventions.

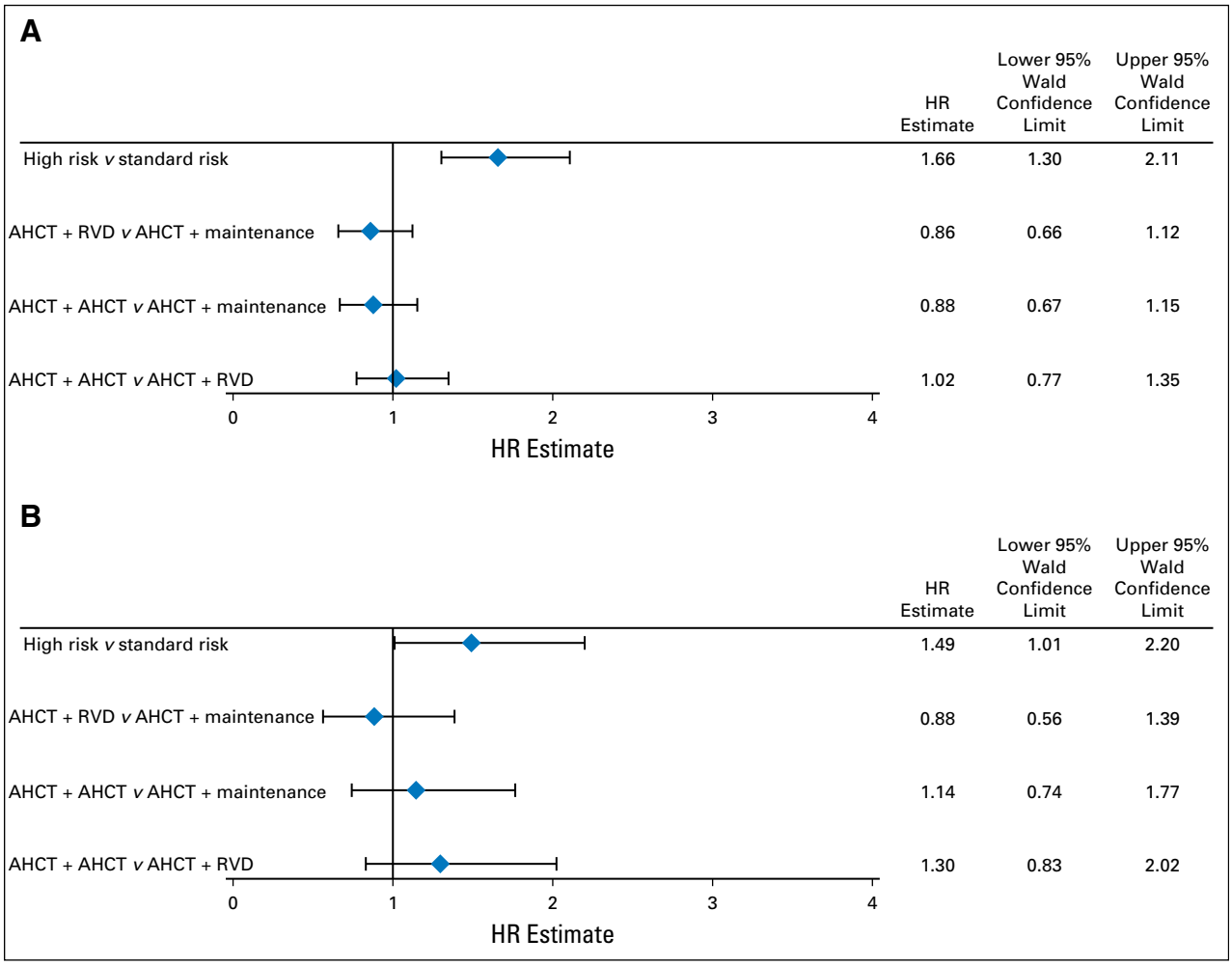

FIG 3. Hazard ratios (HR) from (A) progression-free survival and (B) overall survival analyses using separate Cox proportional hazard models that included random assignment risk strata and treatment group. AHCT, autologous hematopoietic cell transplantation; RVD, lenalidomide, bortezomib, and dexamethasone.

The role of intensive post-AHCT interventions is of interest in patients with high-risk cytogenetics. The Cancer and Leukemia Group B (CALGB) 100104 trial (Clinicaltrials.gov identifier: NCT00114101) did not specifically address the benefit of len for these patients.[4] A recent meta-analysis of three len studies showed a benefit in OS with len with the exception of patients with high-risk cytogenetics.[19] Another phase III trial, performed by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and the German Multicenter Myeloma Group (GMMG)(HOVON-65/GMMG-4) trial, did assess outcomes in patients with 17p deletion or t(4;14) and suggested a benefit of bortezomib in the maintenance phase.[20] Hence, it is notable that there was no discernible PFS or OS benefit of AHCT + RVD + len in patients with high-risk cytogenetics.

The results of this trial contrast with concurrent trials investigating post-transplantation approaches in myeloma. One such trial presented in an abstract form to date is the European Myeloma Network (EMN) 02 trial (Clinicaltrials.gov identifier: NCT01208766), which enrolled 1,510 patients younger than age 65 years at the time of initial therapy.[21,22] All patients started with four cycles of VCD, and the first random assignment was to either AHCT or four cycles of bortezomib, melphalan, and prednisone. Among transplantation recipients, there was another randomized comparison of one versus two AHCTs at centers that performed two AHCTs as standard practice. Then, patients were randomly assigned to two cycles of RVD or no consolidation followed by len. In the preliminary report of this trial, patients who received a tandem AHCT had greater 3-year PFS than patients who received a single AHCT (73% *v* 60%, respectively), and the 3-year PFS rates with and without RVD consolidation were 65% and 60%, respectively. In particular, in patients with high-risk cytogenetics, there was a benefit with tandem AHCT compared with a single AHCT (3-year PFS, 65% *v* 41%, respectively; $P = .05$). Additional analysis demonstrated that tandem AHCT was associated with improved 3-year OS compared with single AHCT (89% *v* 85%, respectively).[23]

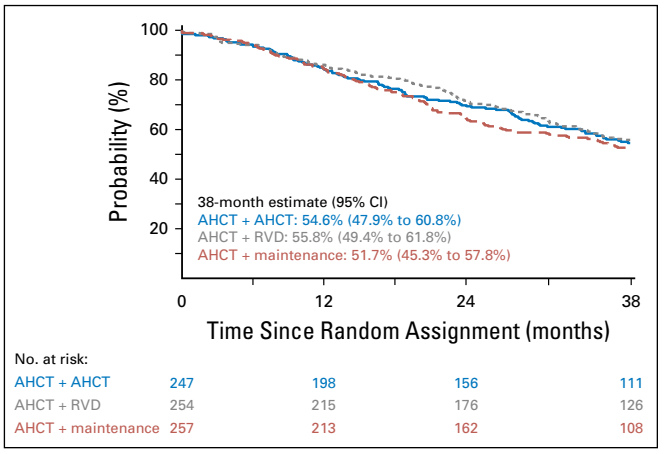

FIG 4. Event-free survival in the tandem autologous hematopoietic cell transplantation (AHCT) + lenalidomide (len), AHCT + len, bortezomib, and dexamethasone (RVD) + len, and AHCT + len arms.

The results of the EMN02 trial cannot be easily compared with the current report for several reasons. By design, in the EMN02 trial, patients were enrolled before initial therapy and had a predetermined number of induction therapy cycles, which did not include an immunomodulatory agent. By contrast, patients were enrolled to the BMT CTN 0702 trial after initial therapy, and as a group, they had lengthier induction therapy (up to 12 months). In addition, the three treatment groups were evenly balanced with respect to prior therapies; most patients received an immunomodulatory agent and most received the RVD regimen. This reflects the current practice of induction therapy in the United States with a combination that has demonstrated better outcome than VCD.[24,25] This use of up-front more effective therapy in BMT CTN 0702 may account for the failure of tandem AHCT or RVD consolidation after transplantation to improve survival in this study, whereas in other studies without initial immunomodulatory agent exposure, patients benefitted from more intensive therapy after transplantation. A prospective trial would be needed to definitively answer this question.

The current trial was modified to prolong len treatment based on the results of the CALGB 100104 trial.[4] However, this did not affect the primary results of this trial because at the time of the primary end point analysis, all patients were still within the 3 years of len treatment, as planned initially. Patients who completed 3 years of len were enrolled onto a separate follow-on protocol to continue maintenance and monitoring for long-term responses.

The risk of SPM is under scrutiny because results from two randomized clinical trials (CALGB 100104 and Intergroupe Francophone du Myelome 2005-02 [Clinicaltrials.gov identifier: NCT00430365]) investigating len demonstrated an increased risk of SPM with the combination of len and high-dose melphalan compared with the observation arms.[4,6] However, after incorporating the risk of SPM into an EFS composite end point, patients randomly assigned to len still experienced longer EFS compared with controls.[5] A meta-analysis of multiple clinical trials that included len-containing regimens reported the rate of SPM with len was 6.9%, compared with 4.8% with placebo, with a slightly higher incidence of solid tumors over hematologic malignancies.[26] Of note, the higher SPM incidence was also seen in the Intergroupe Francophone du Myelome 2005-02 trial despite the more abrogated use of len (2 years) compared with the CALGB 100104 trial (indefinitely or until disease progression).[26] It is reassuring that there was a similar incidence of SPMs in each treatment group in the current trial.

In conclusion, initial therapy followed by high-dose melphalan and AHCT and then more intensive therapy with second AHCT or four cycles of RVD followed by len did not improve PFS or OS compared with a single AHCT followed by len during the 38-month period of this clinical trial. Single AHCT followed by len remains the standard of care. Greater than 80% of patients were alive at 38 months, which highlights excellent contemporary outcomes of patients with MM when treated with a standard approach of a multidrug induction followed by AHCT consolidation and maintenance.

AFFILIATIONS

[1]University of Pennsylvania, Philadelphia, PA
[2]Medical College of Wisconsin, Milwaukee, WI
[3]The Emmes Corporation, Rockville, MD
[4]BMT Group of Georgia, Atlanta, GA
[5]The Ohio State University, Columbus, OH
[6]University of Kansas Hospital, Kansas City, KS
[7]Duke University, Durham, NC
[8]National Heart, Lung, and Blood Institute, Rockville, MD
[9]Dana-Farber Cancer Institute, Boston, MA
[10]Memorial Sloan Kettering Cancer Center, New York, NY
[11]University of Minnesota, Minneapolis, MN
[12]Roswell Park Cancer Institute, Buffalo, NY
[13]The University of Texas MD Anderson Cancer Center, Houston, TX
[14]University of California, San Francisco, San Francisco, CA
[15]Hackensack University, Hackensack, NJ
[16]Washington University, St Louis, MO
[17]City of Hope, Los Angeles, CA

CORRESPONDING AUTHOR

Edward A. Stadtmauer, MD, Perelman Center for Advanced Medicine, 12th Floor, South Pavilion, Office No. 12-171, 34th and Civic Center Blvd, Philadelphia, PA 19104; e-mail: edward.stadtmauer@uphs.upenn.edu.

EQUAL CONTRIBUTION

E.A.S. and M.C.P. contributed equally to this work as first authors. S. Giralt, G.S., and A.K. contributed equally as senior authors.

SUPPORT

Supported by Grant No. U10HL069294 to the Blood and Marrow Transplant Clinical Trials Network from the National Heart, Lung, and Blood Institute and the National Cancer Institute; by Celgene Corporation and Millennium (Takeda) Pharmaceuticals; and by The Alliance for Clinical Trials in Oncology, the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network Cancer Research Group, and SWOG.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the author and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.00685.

AUTHOR CONTRIBUTIONS

Conception and design: Edward A. Stadtmauer, Marcelo C. Pasquini, Parameswaran Hari, Nancy Geller, Mary M. Horowitz, John Koreth, Philip McCarthy, Muzaffar H. Qazilbash, David H. Vesole, Sergio Giralt, George Somlo, Amrita Krishnan

Administrative support: Mary M. Horowitz, Philip McCarthy, Courtney Nelson

Provision of study material or patients: Edward A. Stadtmauer, Parameswaran Hari, Siddharta Ganguly, Cristina Gasparetto, Heather Landau, Philip McCarthy, Muzaffar H. Qazilbash, Dan T. Vogl, George Somlo

Collection and assembly of data: Edward A. Stadtmauer, Marcelo C. Pasquini, Beth Blackwell, Parameswaran Hari, Yvonne Efebera, Siddharta Ganguly, Cristina Gasparetto, Mary M. Horowitz, John Koreth, Kristin Knust, Heather Landau, Philip McCarthy, Courtney Nelson, Nina Shah, Ravi Vij, Dan T. Vogl, Sergio Giralt, George Somlo, Amrita Krishnan

Data analysis and interpretation: Edward A. Stadtmauer, Marcelo C. Pasquini, Beth Blackwell, Parameswaran Hari, Asad Bashey, Steven Devine, Siddharta Ganguly, Cristina Gasparetto, Nancy Geller, Mary M. Horowitz, John Koreth, Kristin Knust, Heather Landau, Claudio Brunstein, Philip McCarthy, Nina Shah, David H. Vesole, Ravi Vij, Dan T. Vogl, Sergio Giralt, George Somlo, Amrita Krishnan

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

REFERENCES

1. Palumbo A, Triolo S, Argentino C, et al: Dose-intensive melphalan with stem cell support (MEL100) is superior to standard treatment in elderly myeloma patients. Blood 94:1248-1253, 1999
2. Child JA, Morgan GJ, Davies FE, et al: High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 348:1875-1883, 2003
3. Attal M, Harousseau JL, Stoppa AM, et al: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma: Intergroupe Français du Myélome. N Engl J Med 335:91-97, 1996
4. McCarthy PL, Owzar K, Hofmeister CC, et al: Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 366:1770-1781, 2012
5. 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 35:3279-3289, 2017
6. Attal M, Lauwers-Cances V, Marit G, et al: Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 366:1782-1791, 2012
7. Barlogie B, Jagannath S, Vesole DH, et al: Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. Blood 89:789-793, 1997
8. Cavo M, Pantani L, Petrucci MT, et al: Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood 120:9-19, 2012
9. Attal M, Harousseau JL, Facon T, et al: Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 349:2495-2502, 2003
10. National Cancer Institute, Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events, Version 3.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf
11. Durie BG, Harousseau JL, Miguel JS, et al: International uniform response criteria for multiple myeloma. Leukemia 20:1467-1473, 2006
12. Lahuerta JJ, Martinez-Lopez J, Serna JD, et al: Remission status defined by immunofixation vs. electrophoresis after autologous transplantation has a major impact on the outcome of multiple myeloma patients. Br J Haematol 109:438-446, 2000
13. 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 25:2434-2441, 2007
14. Gordon Lan KK, Demets DL: Discrete sequential boundaries for clinical trials. Biometrika 70:659-663, 1983
15. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35:549-556, 1979
16. Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 18:695-706, 1999
17. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988
18. Cox D: Regression models and lifetables (with discussion). J R Stat Soc B 34:187-220, 1972
19. Singh PP, Kumar S, LaPlant BR, et al: Lenalidomide maintenance therapy in multiple myeloma: A meta-analysis of randomized trials. Blood 122:407a, 2013
20. 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 30:2946-2955, 2012
21. Cavo M, Petrucci MT, Di Raimondo F, et al: Upfront single versus double autologous stem cell transplantation for newly diagnosed multiple myeloma: An intergroup, multicenter, phase III study of the European Myeloma Network (EMN02/HO95 MM trial). Blood 128:991, 2016
22. Sonneveld P, Beksac M, van der Holt B, et al: Consolidation followed by maintenance therapy versus maintenance alone in newly diagnosed, transplant eligible patients with multiple myeloma (MM): A randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM trial). Blood 128:242, 2016
23. Cavo M, Gay FM, Patriarca F, et al: Double autologous stem cell transplantation significantly prolongs progression-free survival and overall survival in comparison with single autotransplantation in newly diagnosed multiple myeloma: An analysis of phase 3 EMN02/HO95 study. Blood 130:401, 2017 (suppl 1)
24. Cavo M, Pantani L, Pezzi A, et al: Bortezomib-thalidomide-dexamethasone (VTD) is superior to bortezomib-cyclophosphamide-dexamethasone (VCD) as induction therapy prior to autologous stem cell transplantation in multiple myeloma. Leukemia 29:2429-2431, 2015
25. 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 127:2569-2574, 2016
26. Palumbo A, Bringhen S, Kumar SK, et al: Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: A meta-analysis of individual patient data. Lancet Oncol 15:333-342, 2014

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Autologous Transplantation, Consolidation, and Maintenance Therapy in Multiple Myeloma: Results of the BMT CTN 0702 Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Edward A. Stadtmauer
Consulting or Advisory Role: Celgene, Takeda, Novartis, Teva, Janssen, Amgen, Sanofi

Marcelo C. Pasquini
Honoraria: Celgene
Consulting or Advisory Role: Pfizer, Medigene (Inst)

Beth Blackwell
Research Funding: Confidential (Inst), Celgene (Inst), Takeda (Inst)

Parameswaran Hari
Honoraria: Celgene, Millennium, Sanofi, Amgen, Spectrum Pharmaceuticals, Novartis
Consulting or Advisory Role: Celgene, Sanofi, Spectrum Pharmaceuticals, Takeda, Bristol-Myers Squibb, Janssen, Amgen
Research Funding: Millennium (Inst), Celgene (Inst), Onyx (Inst), Spectrum Pharmaceuticals (Inst)

Steven Devine
Honoraria: Incyte, Bristol-Myers Squibb, Kiadis
Consulting or Advisory Role: Incyte

Yvonne Efebera
Honoraria: Takeda
Speakers' Bureau: Takeda, Janssen, Akcea

Siddharta Ganguly
Honoraria: Seattle Genetics, Amgen, Janssen, Kite Pharma, Daiichi Sankyo
Consulting or Advisory Role: Amgen, Kite Pharma
Speakers' Bureau: Seattle Genetics
Research Funding: Daiichi Sankyo (Inst), Janssen (Inst)
Travel, Accommodations, Expenses: Daiichi Sankyo, Seattle Genetics, Amgen, Kite Pharma

Cristina Gasparetto
Leadership: Celgene
Honoraria: Takeda
Consulting or Advisory Role: Celgene, Takeda, Karyopharm Therapeutics, Amgen, Janssen
Research Funding: Celgene (Inst)
Travel, Accommodations, Expenses: Celgene, Karyopharm Therapeutics

Nancy Geller
Stock and Other Ownership Interests: Danaher Corporation

Mary M. Horowitz
Consulting or Advisory Role: Magenta (Inst)
Research Funding: Biovitrum (Inst), Telomere Diagnostics, Gamida Cell, Jazz Pharmaceuticals (Inst), Magenta (Inst)

John Koreth
Consulting or Advisory Role: Amgen, Equillium, Fortress Biotech
Research Funding: Millennium, Bristol-Myers Squibb, Miltenyi Biotec, Prometheus
Patents, Royalties, Other Intellectual Property: Use patents for low-dose interleukin-2 in immune inflammation, assigned to Dana-Farber Cancer Institute (Inst)
Travel, Accommodations, Expenses: Amgen

Heather Landau
Consulting or Advisory Role: Celgene, Takeda, Caelum Biosciences, Juno Therapeutics
Research Funding: Takeda

Claudio Brunstein
Consulting or Advisory Role: Bayer (I), Elcelyx (I), Gilead Sciences (I)
Research Funding: Gamida Cell, Astex Pharmaceuticals, Amgen, Bayer (I)

Philip McCarthy
Honoraria: Celgene, Karyopharm Therapeutics, Bristol-Myers Squibb, Sanofi, Janssen, The Binding Site
Consulting or Advisory Role: Celgene, Bristol-Myers Squibb, Karyopharm Therapeutics, Sanofi, Janssen, The Binding Site, Magenta
Research Funding: Celgene (Inst)

Muzaffar H. Qazilbash
Consulting or Advisory Role: Amgen
Speakers' Bureau: Merck, Sanofi
Research Funding: Amgen, Tesaro

Nina Shah
Stock and Other Ownership Interests: Indapta Therapeutics
Consulting or Advisory Role: Takeda, Celgene, Indapta Therapeutics, TeneoBio, Bristol-Myers Squibb, Sanofi
Research Funding: Celgene, Bluebird Bio, Janssen

David H. Vesole
Stock and Other Ownership Interests: Amgen, AbbVie, Biogen, Gilead Sciences, Johnson & Johnson, Eli Lilly, Novartis
Honoraria: Amgen, Takeda
Speakers' Bureau: Amgen, Celgene, Janssen Oncology, Takeda

Ravi Vij
Consulting or Advisory Role: Bristol-Myers Squibb, Celgene, Janssen, Sanofi, Karyopharm Therapeutics, Jazz Pharmaceuticals, Amgen, Takeda, AbbVie
Research Funding: Amgen, Takeda, Celgene, Bristol-Myers Squibb
Travel, Accommodations, Expenses: Celgene, Bristol-Myers Squibb, Sanofi, Janssen, DAVA Oncology, Karyopharm Therapeutics, Amgen, Takeda, AbbVie

Dan T. Vogl
Consulting or Advisory Role: Celgene, Amgen, Karyopharm Therapeutics, Teva, Janssen
Research Funding: Millennium (Inst), Acetylon Pharmaceuticals (Inst), GlaxoSmithKline (Inst), Calithera Biosciences (Inst), Constellation Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: Amgen

Sergio Giralt
Honoraria: Celgene, Takeda, Amgen, Jazz Pharmaceuticals, Sanofi
Consulting or Advisory Role: Celgene, Takeda, Sanofi, Jazz Pharmaceuticals, Amgen, Janssen
Research Funding: Celgene (Inst), Celgene (Inst), Takeda, Miltenyi Biotec (Inst), Johnson & Johnson, Amgen
Travel, Accommodations, Expenses: Celgene, Sanofi, Amgen, Jazz Pharmaceuticals

George Somlo
Consulting or Advisory Role: AstraZeneca, AbbVie, Pfizer, Takeda, Genentech
Speakers' Bureau: Takeda
Research Funding: Celgene (Inst), Genentech (Inst), Agendia (Inst)
Other Relationship: AbbVie

Amrita Krishnan
Stock and Other Ownership Interests: Celgene (I), Kite Pharma (I)
Consulting or Advisory Role: Celgene, Onyx, Janssen Oncology, Takeda, Kite Pharma, Seattle Genetics
Speakers' Bureau: Celgene, Onyx, Janssen Oncology, Takeda
Research Funding: Celgene (Inst), Takeda (Inst)

No other potential conflicts of interest were reported.

APPENDIX

The following centers and local investigators participated in this trial: Advocate Lutheran General Hospital, Leonard Klein; Arizona Cancer Center/University of Arizona, Andrew Yeager; Augusta University, Sharad Ghamande; Baylor College of Medicine/The Methodist Hospital, George Carum; Blood and Marrow Transplant Program at Northside Hospital, Lawrence Morris; Christiana Care Health System, Frank Beardell; City of Hope National Medical Center, Amrita Krishnan; Colorado Blood Cancer Institute, Jeffrey Matous; Dana-Farber Cancer Institute, John Koreth; Massachusetts General Hospital, Yi-Ben Chen; Duke University Medical Center, Mitchel Horwitz; Florida Hospital Cancer Institute, Mori Shahram; Fred Hutchinson Cancer Research Center, Leona Holmberg; H Lee Moffitt Cancer Center, Taiga Nishihori; Hackensack University Medical Center, Scott Rowley; Jewish Hospital, Edward Randolph Brown; Karmanos Cancer Institute, Divaya Bhutani, Louisiana State University Health Sciences Center, Srinivas Devarakonda; Medical College of Wisconsin, Parameswaran Hari; Memorial Sloan Kettering Cancer Center, Heather Landau; Mount Sinai Medical Center, Luis Isola; North Shore University Hospital, Ruthee-Lu Bayer; Ohio State/Arthur G. James Cancer Hospital, Yvonne Efebera; Oregon Health and Science University, Emma Scott; Penn State College of Medicine–The Milton S. Hershey Medical Center, Giampaolo Talamo; Roswell Park Cancer Institute, Phil McCarthy; Rush University Medical Center, John Maciejewski; Sarah Cannon Blood and Marrow Transplant Program, Jesus Berdeja; St Luke's Mountain States Tumor Institute, William Kreisle; Stanford Hospital and Clinics, Wen-Kai Weng; Texas Transplant Institute, Paul Shaughnessy; Thompson Cancer Survival Center, Everett Ribakove; University of California, San Diego Medical Center, Edward Ball; University Hospitals of Cleveland/Case Western, Hillard Lazarus; University of California, San Francisco, Thomas Martin; University of Florida College of Medicine, John Wingard; University of Illinois, Damiano Rondelli; University of Kansas Hospital, Siddhartha Ganguly; University of Kentucky, Gregory Monohan; University of Miami, Denise Pereira; University of Michigan Medical Center, Gregory Yanik; University of Minnesota, Brian McClune; University of Nebraska Medical Center, Julie Vose; University of North Carolina Hospital at Chapel Hill, Thomas Shea; University of Oklahoma Medical Center, George Selby; University of Pennsylvania Abramson Cancer Center, Edward A. Stadtmauer; University of Rochester Medical Center, Jonathan Friedberg; University of Texas Southwestern Medical Center, Larry Anderson; The University of Texas MD Anderson Cancer Research Center, Muzaffar H. Qazilbash; University of Wisconsin Hospital and Clinics, Natelie Callander; Vanderbilt University Medical Center, Adetola Kassim; Wake Forest University Health Sciences, Cesar Rodriguez Valdes; Washington University/Barnes Jewish Hospital, Ravi Vij; West Virginia University Hospital, Michael Craig; Wichita Community Clinical Oncology Program, Bassam Mattar.