original reports

Minimal Residual Disease After Autologous Stem-Cell Transplant for Patients With Myeloma: Prognostic Significance and the Impact of Lenalidomide Maintenance and Molecular Risk

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abstract

PURPOSE Minimal residual disease (MRD) can predict outcomes in patients with multiple myeloma, but limited data are available on the prognostic impact of MRD when assessed at serial time points in the context of maintenance therapy after autologous stem-cell transplant (ASCT) and the interaction between MRD and molecular risk.

METHODS Data from a large phase III trial (Myeloma XI) were examined to determine the relationship between MRD status, progression-free survival (PFS), and overall survival (OS) in post-ASCT patients randomly assigned to lenalidomide maintenance or no maintenance at 3 months after ASCT. MRD status was assessed by flow cytometry (median sensitivity 0.004%) before maintenance random assignment (ASCT + 3) and 6 months later (ASCT + 9).

RESULTS At ASCT + 3, 475 of 750 (63.3%) patients were MRD-negative and 275 (36.7%) were MRD-positive. MRD-negative status was associated with improved PFS (hazard ratio [HR] = 0.47; 95% CI, 0.37 to 0.58 $P < .001$) and OS (HR = 0.59; 95% CI, 0.40 to 0.85; $P = .0046$). At ASCT + 9, 214 of 326 (65.6%) were MRD-negative and 112 (34.4%) were MRD-positive. MRD-negative status was associated with improved PFS (HR = 0.20; 95% CI, 0.13 to 0.31; $P < .0001$) and OS (HR = 0.33; 95% CI, 0.15 to 0.75; $P = .0077$). The findings were very similar when restricted to patients with complete response/near complete response. Sustained MRD negativity from ASCT + 3 to ASCT + 9 or the conversion to MRD negativity by ASCT + 9 was associated with the longest PFS/OS. Patients randomly assigned to lenalidomide maintenance were more likely to convert from being MRD-positive before maintenance random assignment to MRD-negative 6 months later (lenalidomide 30%, observation 17%). High-risk molecular features had an adverse effect on PFS and OS even for those patients achieving MRD-negative status. On multivariable analysis of MRD status, maintenance therapy and molecular risk maintained prognostic impact at both ASCT + 3 and ASCT + 9.

CONCLUSION In patients with multiple myeloma, MRD status at both ASCT + 3 and ASCT + 9 is a powerful predictor of PFS and OS.

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ASSOCIATED CONTENT

Data Supplement
Protocol

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

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INTRODUCTION

The presence of minimal residual disease (MRD) after treatment predicts poor outcomes in multiple myeloma. Numerous studies have examined the prognostic impact of MRD status, particularly when assessed after autologous stem-cell transplantation (ASCT).[1-8] A meta-analysis confirmed that MRD status is a significant predictor of progression-free survival (PFS) and overall survival (OS) in patients with myeloma,[9] and approximately 1 year of survival is gained for each log depletion in MRD.[10] As a result, the use of MRD as a surrogate end point, quicker to read out than PFS or OS, has been debated. Most studies have assessed MRD status at approximately 3 months after ASCT.[9,11] More recent studies have assessed MRD at other time points in the treatment course, such as during maintenance therapy, giving an understanding of the effect of temporal dynamics of MRD assessment on outcomes.[1,12,13]

Enrolling 2,568 transplant-eligible patients, the Myeloma XI trial is one of the largest studies conducted to

CONTEXT

Key Objective

To explore the impact of postautologous stem-cell transplant (ASCT) minimal residual disease (MRD) status on progression-free survival (PFS) and overall survival (OS) outcomes for patients with myeloma and the interaction between MRD status, molecular risk status, and the use of lenalidomide maintenance.

Knowledge Generated

MRD status at both ASCT + 3 and ASCT + 9 is a powerful predictor of PFS and OS in myeloma in the whole population and in patients achieving complete response. Sustained MRD negativity at both time points, or conversion to MRD negativity by ASCT + 9, was associated with the longest PFS and OS. Negative MRD status, standard molecular risk, and the use of lenalidomide maintenance are independently associated with improved PFS and OS.

Relevance *(S. Lentzsch)*

MRD negativity post-ASCT is associated with significantly longer PFS and OS irrespective of the molecular risk status and the use of lenalidomide maintenance therapy. Serial MRD measurements might help to identify low-risk patients requiring only a limited period of maintenance.*

*Relevance section written by *JCO* Associate Editor Suzanne Lentzsch, MD, PhD.

date in patients with multiple myeloma.[14-16] Among other key results, the trial demonstrated that lenalidomide maintenance therapy, when given after induction therapy and ASCT, improved the PFS from 30 to 57 months compared with observation in transplant-eligible patients (hazard ratio [HR] 0.48 [95% CI, 0.40 to 0.58]; $P < .0001$) and the OS at 3 years from 80.2% to 87.5% (HR 0.69 [95% CI, 0.52 to 0.93]; $P = .014$). The results from Myeloma XI added to the body of evidence that has made lenalidomide maintenance the standard of care for patients with newly diagnosed myeloma after ACST.[17] This analysis aims to assess the impact of MRD status on PFS and OS in patients receiving lenalidomide maintenance or observation in the Myeloma XI trial, the interaction with molecular risk, and the impact of sustained MRD negativity.

METHODS

Study Design

The study design of Myeloma XI has been reported;[14-16] in brief, it is a phase III, open-label, parallel-group, multiarm, adaptive design trial for patients with newly diagnosed myeloma with three random assignment stages (EudraCT 2009-010956-93, ClinicalTrials.gov identifier: NCT01554852). The study was approved by the National Research Ethics Service (London, UK), local institutional review boards, and the competent regulatory authority (MHRA, London, UK) and was undertaken according to the Declaration of Helsinki and the principles of Good Clinical Practice. All patients provided written informed consent. At around 3 months (100 days) after ASCT, patients who had achieved at least a minimal response were eligible for the maintenance random assignment between lenalidomide monotherapy, lenalidomide and vorinostat, or no further therapy. Patients were excluded from maintenance random assignment if they did not respond to Rdc induction, had no response to any prior study treatment, or relapsed after achieving a complete response. Maintenance therapy continued until progressive disease or unacceptable toxicity. The lenalidomide and vorinostat arm was added and then removed from the study following a Protocol (online only) amendment to add research questions to this adaptive design study. For this analysis, only those patients randomly assigned to lenalidomide alone or observation are included. Full details of all treatment regimens are given in the Data Supplement (online only).

MRD and Molecular Risk Assessment

Bone marrow aspirates were obtained before maintenance random assignment, which occurred at 100 days (around 3 months) after ASCT (ASCT + 3) and 6 months after maintenance random assignment (ASCT + 9). The presence of MRD was assessed using a validated flow cytometry assay (median sensitivity 0.004% of leukocytes equivalent to 4×10^{-5} [range 8×10^{-6} to 1×10^{-4}]) performed at a single central laboratory (Haematological Malignancy Diagnostic Service, Leeds Cancer Centre, Leeds, UK) as previously reported (and Data Supplement).[2]

Adverse molecular risk abnormalities, identified at trial baseline (Data Supplement), were defined as gain(1q), del(17p), t(4;14), t(14;16), or t(14;20). High risk was defined as the presence of one of these lesions, and ultra–high risk the presence of more than one.

Statistical Analyses

PFS and OS were estimated with summaries of time to event per MRD group using the Kaplan-Meier method landmarked from the date of ASCT + 3/ASCT + 9. Comparisons between the groups were made using the Cox proportional hazards model and to estimate HRs and 95% CIs. Univariate and multivariable analyses were conducted at both ASCT + 3 and ASCT + 9 for PFS and OS, considering MRD status,

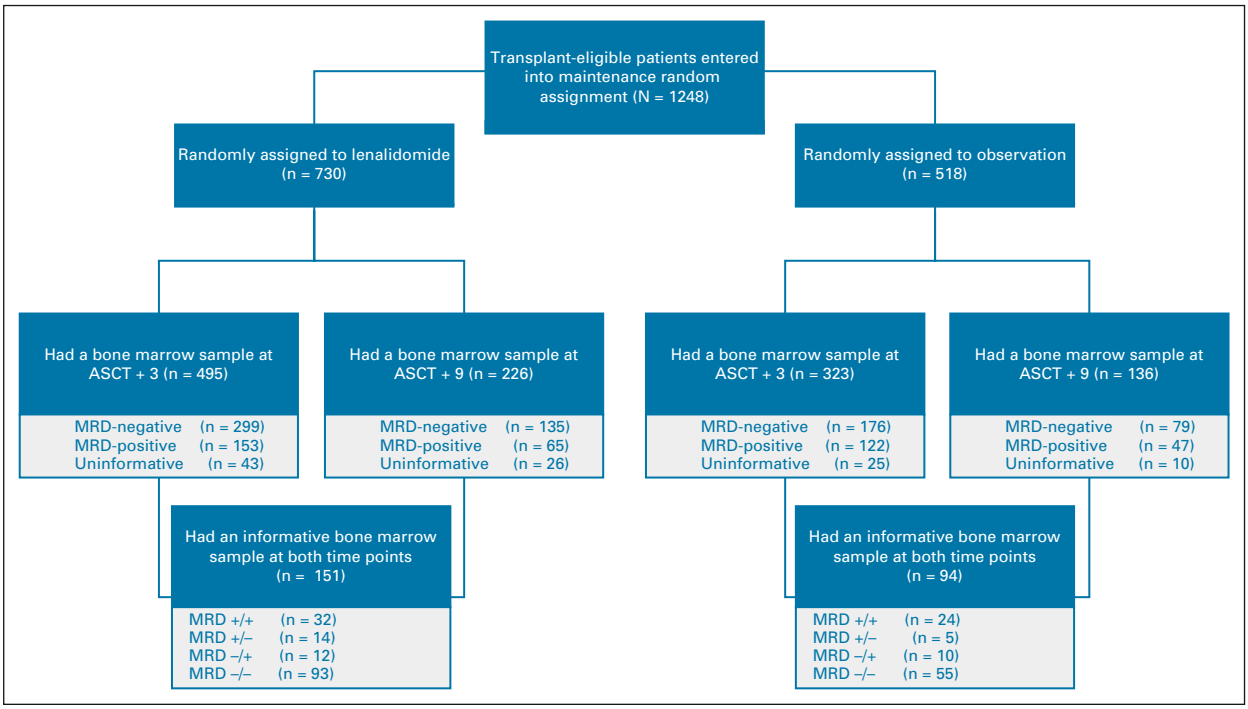

FIG 1. CONSORT diagram. Uninformative samples were mostly hemodilute samples or samples delayed in transit and with insufficient viable cells for analysis. ASCT, autologous stem-cell transplant; MRD, minimal residual disease.

maintenance treatment, response after ASCT, ISS, cytogenetic risk status, sex, age, randomized induction treatment, and randomized consolidation treatment. The impact of randomized allocation on MRD status at ASCT + 9 was estimated using logistic regression (adjusted for the minimization factors and MRD status at ASCT + 3). All reported *P* values are two-sided and considered significant at an overall significance level of 5%. Further details can be found in the Data Supplement.

RESULTS

Patients

In the Myeloma XI trial, 1,248 transplant-eligible patients were randomly assigned to lenalidomide (n = 730) or observation (n = 518) at 3 months after ASCT. A total of 818 patients had ASCT + 3 bone marrow samples sent to the central laboratory (lenalidomide, n = 495; observation, n = 323). Of the samples received, 750 (91.7%) were informative for MRD status (lenalidomide n = 452 of 495 [91.3%] and observation n = 298 of 323 [92.3%]). The distribution of patients is shown in Figure 1. A comparison of those patients with and without informative MRD data showed no significant difference in OS or baseline characteristics (Data Supplement). The baseline characteristics for the patients with informative samples at ASCT + 3 and ASCT + 9 are shown in Table 1 and the Data Supplement, respectively.

Impact of MRD Status at ASCT + 3

At a median follow-up of 32.9 months (interquartile range, 18.7-50.3 months), patients who were MRD-negative at ASCT + 3 had a significantly longer median PFS than MRD-positive patients (44 *v* 24 months; HR = 0.47, 95% CI, 0.37 to 0.58; $P < .0001$; Fig 2A). Median OS was not reached in either group at the time of the analysis, but the OS at 3 years increased from 78.7% (95% CI, 72.9 to 84.4) of MRD-positive patients to 86.5% (95% CI, 82.2 to 90.7) of MRD-negative patients. The difference between groups was statistically significant, favoring the MRD-negative group (HR = 0.59; 95% CI 0.40-0.85; $P = .0046$; Fig 2B). Regardless of MRD status, in comparison with observation, lenalidomide maintenance was associated with a significant improvement in PFS. For those patients who were MRD-negative at ASCT + 3, lenalidomide was associated with an improvement in the PFS from a median of 36 months with observation to 56 months with lenalidomide (HR = 0.62; 95% CI, 0.45 to 0.86; $P = .0042$). For those patients who were MRD-positive at ASCT + 3, lenalidomide was associated with an improvement in the PFS from a median of 18 months with observation to 33 months with lenalidomide (HR = 0.43; 95% CI, 0.32 to 0.60; $P < .0001$; Fig 2C). For those patients who were MRD-negative at ASCT + 3, lenalidomide was associated with an improvement in the OS from 83.4% at 3 years with observation to 88.9% with lenalidomide. For those patients who were MRD-positive at ASCT + 3, lenalidomide was associated with an improvement in the OS from 75.4% at 3

TABLE 1. Patient and Treatment Characteristics by ASCT + 3 MRD Status

	MRD-Positive		MRD-Negative	
Characteristic	**Lenalidomide (n = 153)**	**Observation (n = 122)**	**Lenalidomide (n = 299)**	**Observation (n = 176)**
Median age, years (range)	60 (28-73)	59.5 (29-73)	60 (30-74)	62.0 (37-71)
Male, No. (%)	103 (67.3)	90 (73.8)	195 (65.2)	108 (61.4)
Cytogenetic risk, No. (%)				
Standard	39 (25.5)	33 (27.0)	50 (16.7)	46 (26.1)
High	24 (15.7)	13 (10.7)	49 (16.4)	21 (11.9)
Ultra-high	5 (3.3)	3 (2.5)	21 (7.0)	11 (6.3)
Missing	85 (55.6)	73 (59.8)	179 (59.9)	98 (55.7)
WHO performance status, No. (%)				
0	67 (43.8)	63 (51.6)	127 (42.5)	81 (46.0)
1-2	79 (51.6)	46 (37.7)	142 (47.5)	81 (46.0)
3-4	4 (2.6)	10 (8.2)	9 (3.0)	4 (2.3)
Missing	3 (2.0)	3 (2.5)	21 (7.0)	10 (5.7)
Initial treatment, No. (%)				
Tdc	67 (43.8%)	44 (36.1)	85 (28.4)	71 (40.3)
Rdc	60 (39.2)	56 (45.9)	90 (30.1)	55 (31.3)
KRdc	26 (17.0)	22 (18.0)	124 (41.5)	50 (28.4)
Additional treatment, No. (%)				
Vdc	20 (13.1)	14 (11.5)	21 (11.0)	14 (8.0)
Response at ASCT + 3, No. (%)				
CR/nCR	64 (41.8)	64 (52.5)	229 (76.6)	125 (71.0)
Not CR/nCR	89 (58.2)	58 (47.5)	70 (23.4)	51 (29.0)

Abbreviations: ASCT, autologous stem-cell transplant; CR, complete response; KRdc, carfilzomib, lenalidomide, dexamethasone, cyclophosphamide; MRD, minimal residual disease; nCR, near complete response; Rdc, enalidomide, dexamethasone, cyclophosphamide; Tdc, thalidomide, dexamethasone, cyclophosphamide; Vdc, bortezomib, dexamethasone, cyclophosphamide.

years with observation to 81.4% with lenalidomide (Fig 2D). The analyses of PFS and OS at ASCT + 3 were very similar when restricted to those patients with complete response (CR) or near CR (nCR; Data Supplement).

Impact of MRD Status at ASCT + 9

Patients who were MRD-negative at ASCT + 9 had a significantly longer median PFS than MRD-positive patients (50 *v* 13 months; HR = 0.20; 95% CI, 0.13 to 0.31; $P < .0001$; Fig 3A). Median OS was not reached in either group at the time of the analysis, but the OS at 3 years increased from 69.5% (95% CI, 55.0 to 84.0) of MRD-positive patients to 86.9% (95% CI, 78.0 to 95.7) of MRD-negative patients. The difference between groups was statistically significant, favoring the MRD-negative group (HR = 0.33; 95% CI, 0.15 to 0.75; $P = .0077$; Fig 3B). As at ASCT + 3, at ASCT + 9, regardless of MRD status, lenalidomide maintenance was associated with a significant improvement in PFS compared with observation. For those patients who were MRD-negative at ASCT + 9, lenalidomide was associated with an improvement in the PFS, from a median of 31 months with observation to not yet observed with lenalidomide (HR = 0.32; 95% CI, 0.15 to 0.67; $P = .0025$). For those patients who were MRD-positive at ASCT + 9, lenalidomide was associated with an improvement in the PFS from a median of 9 months with observation to 47 months with lenalidomide (HR = 0.41; 95% CI, 0.25 to 0.69; $P = .0008$; Fig 3C). For those patients who were MRD-negative at ASCT + 9, lenalidomide was associated with an improvement in the OS from 75.4% at 3 years with observation to 94.5% with lenalidomide. For those patients who were MRD-positive at ASCT + 9, lenalidomide was associated with an improvement in the OS from 58% at 3 years with observation to 83.1% with lenalidomide (Fig 3D). The analyses of PFS and OS at ASCT + 9 were very similar when restricted to those patients with CR or nCR (Data Supplement).

Impact of Sustained MRD-Negative Status and Conversion to MRD-Negative Status

Data were available at both ASCT + 3 and ASCT + 9 for 245 patients (Fig 1). In a logistic regression analysis accounting for MRD status, ASCT + 3 patients in the lenalidomide group had a 47% higher odds of being MRD-negative at ASCT + 9 than those observed although

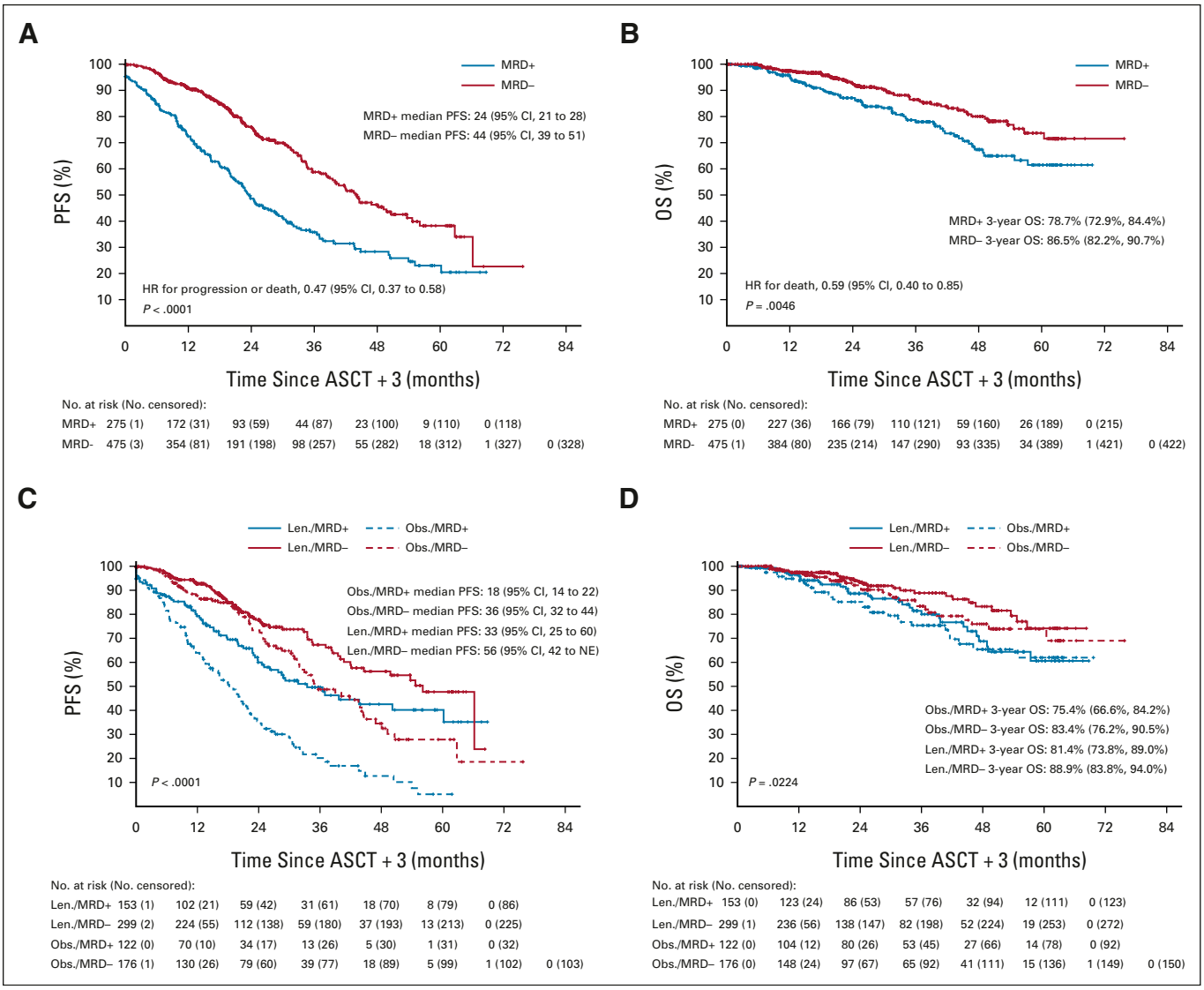

FIG. 2. Impact of MRD status at ASCT + 3 on (A) PFS, (B) OS, (C) PFS by maintenance arm, and (D) OS by maintenance arm. ASCT, autologous stem-cell transplant; HR, hazard ratio; Len., lenalidomide; MRD, minimal residual disease; NE, not estimable; Obs., observation; OS, overall survival; PFS, progression-free survival.

this did not reach statistical significance (odds ratio 1.47; 95% CI, 0.70 to 3.09; $P = .3035$).

Seventy five (30.6%) were MRD-positive and 170 (69.4%) were MRD-negative at ASCT + 3. Outcomes were most favorable in patients who were MRD-negative at both ASCT + 3 and ASCT + 9, and outcomes were least favorable in those who were MRD-positive at both time points ($P < .0001$; Fig 4). Patients with sustained MRD negativity had a PFS at 3 years (landmarked from ASCT + 9) of 63.5% and an OS of 81.5% Conversion from MRD positivity at ASCT + 3 to MRD negativity at ASCT + 9 occurred in 19 of 75 patients (25.3%) and was observed in all induction therapy subgroups and in both the standard-risk and high-risk molecular subgroups. (There were no ultra–high-risk patients who were MRD-positive at ASCT + 3 for whom ASCT + 9 MRD data were available.) Among MRD-positive patients at ASCT + 3 assigned to lenalidomide maintenance, 14 of 46 (30.4%) achieved MRD negativity at ASCT + 9. By contrast, only 5 of 29 (17.2%) MRD-positive patients at ASCT + 3 assigned to observation achieved MRD negativity at ASCT + 9. Conversion from MRD-positive at ASCT + 3 to MRD-negative at ASCT + 9 was associated with similar PFS outcomes as patients who were MRD-negative at both time points (Fig 4A). Conversion from MRD-negative at ASCT + 3 to MRD-positive at ASCT + 9 was observed in 22 of 170 patients (12.9%; lenalidomide 12 of 105, 11.4% observation 10 of 65, 15.4%). Outcomes in this subgroup were similar to outcomes in patients who were MRD-positive at both time points

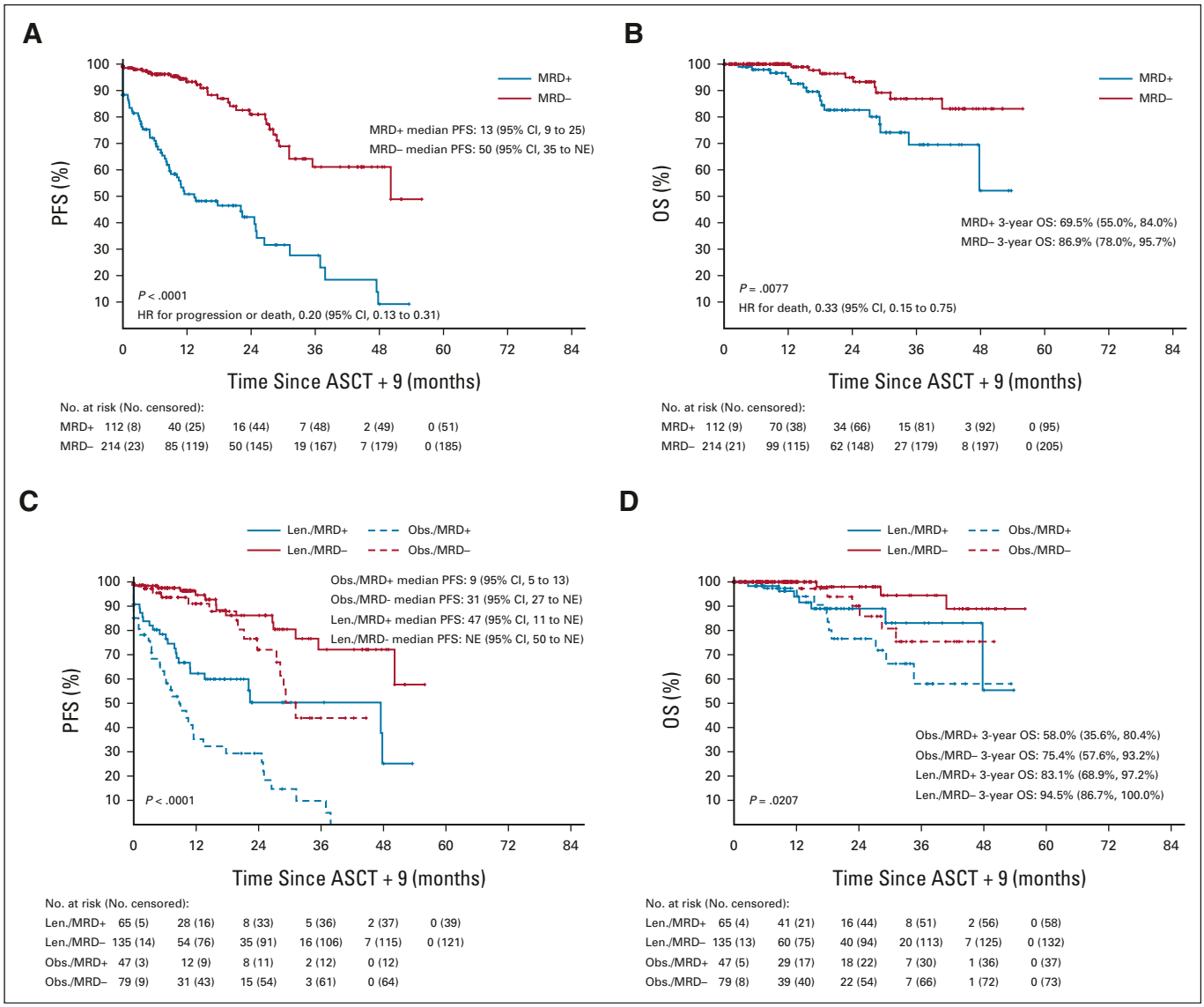

FIG 3. Impact of MRD status at ASCT + 9 on (A) PFS ,(B) OS, (C) PFS by maintenance arm, and (D) OS by maintenance arm. ASCT, autologous stem-cell transplant; HR, hazard ratio; Len., lenalidomide; MRD, minimal residual disease; NE, not estimable; Obs., observation; OS, overall survival; PFS, progression-free survival.

(Fig 4A). Similar trends were seen for OS although it should be noted that the data remain immature (Fig 4B).

Impact of MRD Status by Molecular Risk Subgroups at ASCT + 3 and ASCT + 9

At ASCT + 3, MRD negativity was predictive of improved PFS in patients with standard-risk and high- or ultra-high-risk disease (Fig 5A). MRD-negative patients with one or more high-risk lesion had a shorter median PFS compared with MRD-negative standard-risk patients (33 *v* 63 months; HR = 2.57; 95% CI, 1.55 to 4.26; $P = .0002$; Fig 5A), suggesting that achieving MRD negativity was not able to overcome the adverse PFS associated with genetic high risk. This was true for patients defined as high risk with the presence of only one adverse lesion and also those with ultra–high risk (two or more adverse lesions; Data Supplement). MRD-negative high- and/or ultra–high-risk patients also had a shorter OS compared with MRD-negative standard-risk patients (median not reached *v* 45 months; HR = 3.25; 95% CI, 1.37 to 7.75; $P = .0078$; Fig 5B and Data Supplement). A similar pattern was seen at ASCT + 9 (Figs 5C and 5D). Again, both one and more than one adverse lesions were associated with adverse PFS and OS in the MRD-negative group (Data Supplement).

Multivariable Analysis of the Effect of MRD Status of Outcomes at ASCT + 3 and ASCT + 9

Multivariable analysis at ASCT + 3 showed that MRD status, lenalidomide maintenance, and molecular risk all retained prognostic significance for both PFS and OS. At

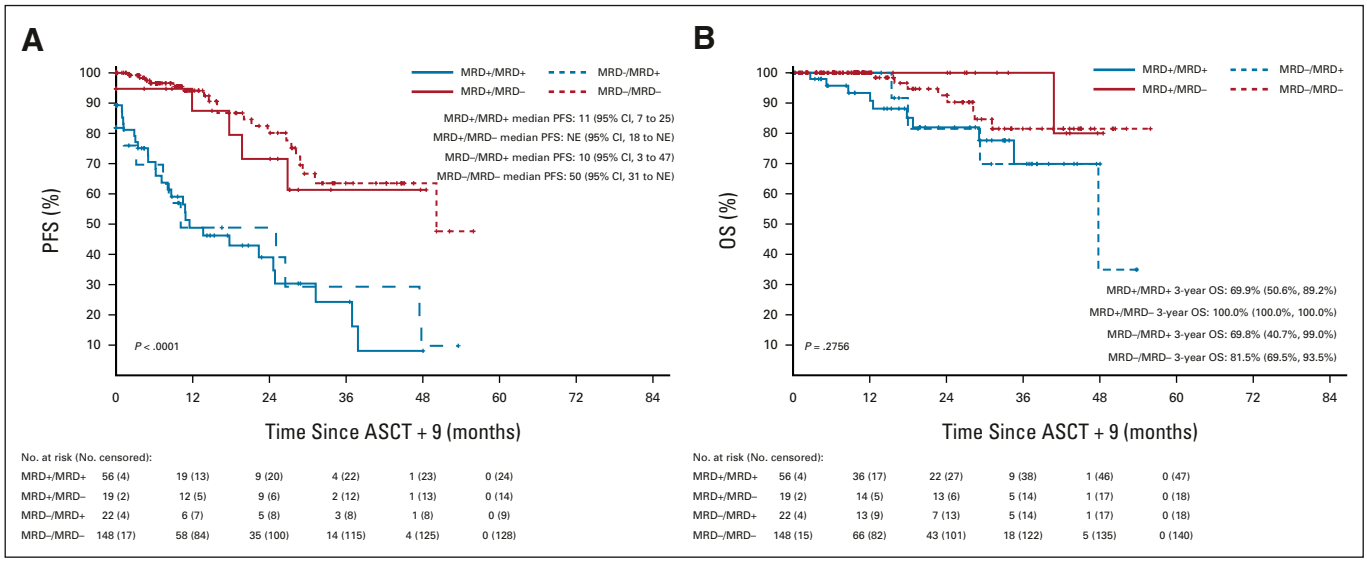

FIG 4. Impact of MRD status at ASCT + 3 and ASCT + 9 on (A) PFS and (B) OS. ASCT, autologous stem-cell transplant; HR, hazard ratio; MRD, minimal residual disease; NE, not estimable; OS, overall survival; PFS, progression-free survival.

ASCT + 9, all these variables retained significance for PFS, with only lenalidomide maintenance and molecular risk retaining a significant effect on OS (Table 2). However, it should be noted that the number of events is low in the multivariable analysis for OS for ASCT + 3 and ASCT + 9 and there is a risk of overfitting, which means that the results should be interpreted with caution. Comparing between time points for PFS while the HR for cytogenetics remained similar (2.6 at ASCT + 3 and 2.4 at ASCT + 9), the HR for MRD status improved from 0.4 at ASCT + 3 to 0.2 at ASCT + 9. A sensitivity analysis was also performed including missing data categories with no change to the results (Data Supplement).

DISCUSSION

Results of this analysis from the Myeloma XI trial show that MRD status is a particularly powerful predictor of survival outcomes when measured both 3 months after ASCT (ASCT + 3) and 6 months later (ASCT + 9). MRD negativity at ASCT + 3 was associated with a 53% reduction in the risk of PFS events (HR = 0.47) and a 41% reduction in the risk of death (HR 0.59). Achieving MRD-negative status at ASCT + 9 was associated with an 80% reduction in the risk of PFS events (HR = 0.20) and a 67% reduction in the risk of death (HR = 0.33).

The magnitude of the prognostic impact of MRD status at ASCT + 3 seen here compares favorably with results from previous studies.[9,18,19] In one large meta-analysis of published data, the absence of MRD was associated with significantly longer PFS and OS, with HRs of 0.41 and 0.57, respectively.[9] Most of the studies included in this and other meta-analyses assessed MRD status up to 3 months after ASCT; data on the impact of MRD status assessed at later time points after ASCT and in the context of lenalidomide maintenance have been increasing in recent years but remain limited.[13,20,21] Similar to previous studies, at ASCT + 9, the data presented here show an even greater magnitude of prognostic impact on outcomes than those seen at ASCT + 3 with HRs of 0.20 and 0.33 for PFS and OS, respectively. This analysis was conducted in all patients to understand the effect of maintenance therapy in the population as a whole. The analysis was, however, repeated restricted to only patients with CR or nCR with very similar results.

In the Myeloma XI study, maintenance therapy with lenalidomide was associated with superior PFS compared with observation in both the MRD-negative and MRD-positive cohorts at both ASCT + 3 and ASCT + 9, which is consistent with the overall findings from the Myeloma XI trial.[15] MRD status retained the prognostic impact on multivariable analysis at both time points. Approximately a quarter of patients who were MRD-positive at ASCT + 3 became MRD-negative by ASCT + 9, and this conversion was associated with improved PFS. Conversion from MRD-positive to MRD-negative occurred more frequently in patients receiving lenalidomide (30.4%) than in those undergoing observation (17.2%). Previous studies have also shown that the depth of response, including MRD status, may improve during maintenance therapy.[1,12,20] In the phase III EMN02/HO95 trial of transplant-eligible patients, 10 of 24 (41%) patients who were MRD-positive at ASCT + 3 and had a second evaluation of MRD status at least 1 year after starting lenalidomide maintenance (ASCT + 12) became MRD-negative and had a similar outcome to those with persistent MRD negativity.[20] This is slightly higher than that seen in the Myeloma XI data (30.4% of those on lenalidomide), which may be due to the longer time period before the second MRD assessment. In addition,

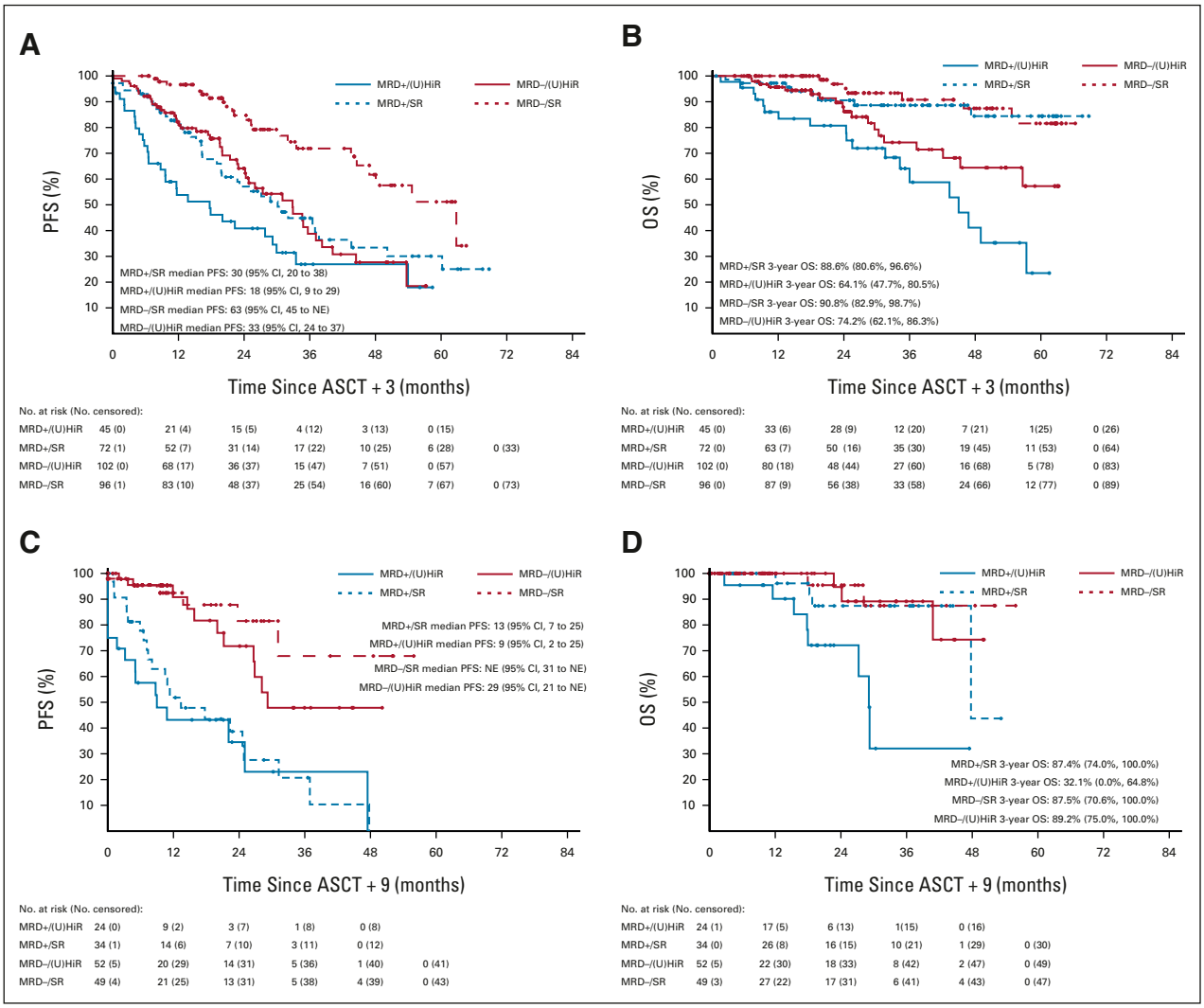

FIG 5. Impact of MRD status by molecular risk groups for (A) PFS at ASCT + 3, (B) OS at ASCT + 3, (C) PFS at ASCT + 9, and (D) OS at ASCT + 9. ASCT, autologous stem-cell transplant; MRD, minimal residual disease; NE, not estimable; OS, overall survival; PFS, progression-free survival; SR, standard risk; (U)HiR, high-risk or ultra–high-risk.

some conversions in the EMN02 trial may reflect a consolidation effect because of exposure to an agent with a different mechanism of action as there was limited patient exposure to immunomodulatory therapy in the EMN02 induction and consolidation regimens (with only half of patients having been previously randomly assigned to just two cycles of VRd). This highlights some of the challenges of comparing trials with differing approaches with consolidation and duration of maintenance.

A beneficial effect of lenalidomide maintenance was evident even in patients who remained MRD-positive, and this may be due to the fact that maintenance treatment was associated with a significantly lower level of residual disease compared with patients assigned to observation. Importantly, in patients who were MRD-negative before starting maintenance therapy, re-emergence of MRD during maintenance was associated with poor outcomes that were comparable with patients who had never achieved MRD-negative status. These results support the role of MRD monitoring when evaluating the efficacy of consolidation or maintenance strategies in clinical trials and the critical role of sustained MRD-negative status in predicting outcomes for patients. Sustained MRD negativity at ASCT + 9 was associated with the best outcomes. In the longer term, a stratified approach to treatment on the basis of sequential MRD assessments may be feasible, where maintenance therapy is intensified when MRD positivity is detected to try and sustain disease control. Several ongoing clinical trials are exploring whether the achievement of MRD negativity during maintenance therapy could be used as an indicator to stop ongoing maintenance, for example, the phase II nonrandomized MASTER trial.[22] The results from Myeloma XI do not support this strategy using an assessment at ASCT + 9 as even patients who were MRD-negative at ASCT + 9 had a significant benefit from the ongoing use of lenalidomide

TABLE 2. Univariate and Multivariable Analyses at ASCT + 3 and ASCT + 9 for PFS and OS

	Univariate Analysis			Multivariable Analysis		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
ASCT + 3 PFS						
MRD (–ve *v* +ve)	**0.465**	**0.372 to 0.583**	**< .0001**	**0.401**	**0.271 to 0.592**	**< .0001**
Treatment (len *v* obs)	**0.523**	**0.417 to 0.656**	**< .0001**	**0.388**	**0.268 to 0.561**	**< .0001**
Response at ASCT + 3 (≥ VGPR *v* < VGPR)	**0.653**	**0.485 to 0.880**	**.0050**	1.131	0.635 to 2.014	.6757
International Staging System (III *v* I)	**1.459**	**1.067 to 1.995**	**.0180**	1.563	0.969 to 2.521	.0671
International Staging System (II *v* I)	1.189	0.907 to 1.558	.2100	1.031	0.677 to 1.571	.8871
Cytogenetics (UHiR + HiR *v* SR)	**1.938**	**1.377 to 2.728**	**.0001**	**2.576**	**1.770 to 3.748**	**< .0001**
Sex (M *v* F)	**1.377**	**1.073 to 1.766**	**.0119**	1.015	0.698 to 1.477	.9378
Age (continuous)	1.007	0.992 to 1.022	.3860	1.007	0.982 to 1.032	.5714
Induction (KRdc *v* Tdc)	**0.580**	**0.398 to 0.845**	**.0045**	0.735	0.392 to 1.377	.3359
Induction (Rdc *v* Tdc)	0.963	0.757 to 1.224	.7574	0.739	0.504 to 1.084	.1217
Consolidation (not Rand. *v* Vdc)	0.895	0.612 to 1.310	.5681	1.207	0.683 to 2.131	.5173
Consolidation (Rand. No Vdc *v* Vdc)	1.253	0.751 to 2.091	.3876	0.916	0.429 to 1.953	.8195
ASCT + 3 OS						
MRD (–ve *v* +ve)	**0.586**	**0.405 to 0.848**	**.0046**	**0.457**	**0.246 to 0.849**	**.0132**
Treatment (len *v* obs)	0.764	0.528 to 1.105	.1533	**0.528**	**0.297 to 0.938**	**.0294**
Response at ASCT + 3 (≥ VGPR *v* < VGPR)	0.883	0.508 to 1.366	.4681	1.352	0.525 to 3.490	.5321
International Staging System (III *v* I)	**1.977**	**1.210 to 3.231**	**.0063**	1.049	0.476 to 2.314	.9051
International Staging System (II *v* I)	1.236	0.775 to 1.971	.3727	1.029	0.516 to 2.049	.9360
Cytogenetics (UHiR + HiR *v* SR)	**3.794**	**2.082 to 6.915**	**< .0001**	**4.286**	**2.272 to 8.086**	**< .0001**
Sex (M *v* F)	1.110	0.745 to 1.654	.6084	0.893	0.500 to 1.595	.7020
Age (continuous)	1.012	0.987 to 1.037	.3405	1.008	0.967 to 1.051	.6988
Induction (KRdc *v* Tdc)	0.840	0.434 to 1.626	.6048	0.798	0.310 to 2.053	.6395
Induction (Rdc *v* Tdc)	0.979	0.662 to 1.447	.9151	0.508	**0.267 to 0.965**	**.0386**
Consolidation (not Rand. *v* Vdc)	0.960	0.525 to 1.754	.8936	1.242	0.482 to 3.202	.6536
Consolidation (Rand. No Vdc *v* Vdc)	0.771	0.315 to 1.887	.5692	0.748	0.201 to 2.786	.6654
ASCT + 9 PFS						
MRD (–ve *v* +ve)	**0.199**	**0.128 to 0.310**	**< .0001**	**0.220**	**0.102 to 0.472**	**.0001**
Treatment (len *v* obs)	**0.397**	**0.259 to 0.608**	**< .0001**	**.218**	**0.102 to 0.463**	**< .0001**
Response at ASCT + 3 (≥ VGPR *v* < VGPR)	0.848	0.461 to 1.559	.5954	1.942	0.604 to 6.238	.2652
International Staging System (III *v* I)	1.388	0.755 to 2.551	.2912	1.325	0.529 to 3.316	.5476
International Staging System (II *v* I)	1.532	0.919 to 2.552	.1015	0.647	0.283 to 1.478	.3010
Cytogenetics (UHiR + HiR *v* SR)	1.160	0.682 to 1.973	.5846	**2.357**	**1.084 to 5.126**	**.0305**
Sex (M *v* F)	0.912	0.598 to 1.392	.6701	0.838	0.432 to 1.626	.6006
Age (continuous)	0.994	0.966 to 1.022	.6525	0.983	0.943 to 1.026	.4362
Induction (KRdc *v* Tdc)	**0.492**	**0.245 to 0.989**	**.0465**	0.536	0.138 to 2.074	.4535
Induction (Rdc *v* Tdc)	1.009	0.647 to 1.572	.9701	0.972	0.475 to 1.989	.9326
Consolidation (not Rand. *v* Vdc)	0.788	0.394 to 1.574	.4993	0.929	0.297 to 2.912	.9000
Consolidation (Rand. No Vdc *v* Vdc)	0.656	0.202 to 2.133	.4837	0.626	0.098 to 3.993	.6200
ASCT + 9 OS						
MRD (–ve *v* +ve)	**0.332**	**0.148 to 0.746**	**.0077**	0.242	0.055 to 1.073	.0619
Treatment (len *v* obs)	**0.401**	**0.181 to 0.891**	**.0248**	**0.252**	**0.070 to 0.906**	**.0347**
Response at ASCT + 3 (≥ VGPR *v* < VGPR)	1.182	0.355 to 3.941	.7850	1.260	0.143 to 11.085	.8350

(continued on following page)

TABLE 2. Univariate and Multivariable Analyses at ASCT + 3 and ASCT + 9 for PFS and OS (continued)

	Univariate Analysis			Multivariable Analysis		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
International Staging System (III *v* I)	1.305	0.395 to 4.311	.6625	0.426	0.067 to 2.703	.3656
International Staging System (II *v* I)	1.634	0.627 to 4.258	.3148	0.394	0.086 to 1.808	.2307
Cytogenetics (UHiR + HiR *v* SR)	2.614	0.962 to 7.105	.0597	**6.658**	**1.311 to 33.82**	**.0222**
Sex (M *v* F)	0.805	0.369 to 1.755	.5850	**0.184**	**0.048 to 0.700**	**.0130**
Age (continuous)	0.995	0.947 to 1.045	.8348	0.948	0.873 to 1.030	.2069
Induction (KRdc *v* Tdc)[a]	0.958	0.196 to 4.683	.9574	0.948	0.000 to NE	.9941
Induction (Rdc *v* Tdc)	1.192	0.533 to 2.667	.6887	3.531	0.833 to 14.976	.0870
Consolidation (not Rand. *v* Vdc)	0.725	0.217 to 2.424	.6015	0.383	0.062 to 2.355	.3005
Consolidation (Rand. No Vdc *v* Vdc)	0.493	0.051 to 4.763	.5407	0.459	0.020 to 10.729	.6282

NOTE. Bold indicates $P < .05$.

Abbreviations: ASCT, autologous stem-cell transplant; HiR, high risk; HR, hazard ratio; KRdc, carfilzomib, lenalidomide, dexamethasone, cyclophosphamide; Len, lenalidomide; MRD, minimal residual disease; NE, not estimable; Obs, observation; OS, overall survival; PFS, progression-free survival; Rand, randomized; Rdc, lenalidomide, dexamethasone, cyclophosphamide; SR, standard risk; Tdc, thalidomide, dexamethasone, cyclophosphamide; UHiR, ultra–high risk; Vdc, bortezomib, dexamethasone, cyclophosphamide; VGPR, very good partial response.

[a]No KRdc deaths in the multivariable complete case set.

maintenance. Whether stopping maintenance would be possible at ASCT + 12, ASCT + 24, or ASCT + 36 in patients with sustained MRD negativity is yet to be determined and would ideally be addressed by a random assignment to stop or continue maintenance at selected time points, such as that studied in the DRAMMATIC (SWOG S1803) trial.[23]

Achievement of MRD negativity was associated with improved outcomes in all risk subgroups; however, molecular risk factors retained prognostic impact in both MRD-positive and MRD-negative patients at both time points. The achievement of MRD negativity may therefore ameliorate the adverse outcomes associated with high-risk genetics and emphasizes the goal of achieving this end point in this subgroup. This was also seen in data from the EMN02 and IFM2009 trials using flow cytometry and next-generation sequencing, respectively,[20,24] and the pooled analysis of 72 patients enrolled in RV-MM-EMN-441 and RV-MM-EMN-441 where MRD was analyzed using flow cytometry and RT-PCR.[25] Interestingly, in the Myeloma XI data set, the PFS HR for cytogenetics was similar at both ASCT + 3 and ASCT + 9 while the PFS HR for MRD status improved from 0.4 at ASCT + 3 to 0.2 at ASCT + 9. However, achieving MRD negativity was not able to overcome the adverse effect of high-risk molecular lesions completely even when only one such lesion is present, at both ASCT + 3 and ASCT + 9.

The role of MRD assessment in multiple myeloma continues to evolve, and several areas of uncertainty remain. The optimal timing and frequency of MRD assessment have not been established. In this study, sustained MRD at ASCT + 9 was associated with improved outcomes, but this is also likely to be true if assessed at later time points. Various methods for MRD detection are in use with different advantages and disadvantages. The Myeloma XI trial used flow cytometry, but next-generation sequencing approaches are also available and may give different quality and depth of response. Definitions of MRD-negative are also in flux as methods of detecting MRD improve and more effective treatment options become available. Most of the available data on MRD by flow cytometry are based on the level of detection of 10^{-4} or 10^{-5}, which is achievable in most laboratories. A threshold of 10^{-5} has been recommended,[26] and methods with even higher sensitivity (10^{-6}) are being explored in clinical trials. As the MRD level is a continuous variable, stratification of the MRD level (eg, MRD4, MRD5, and MRD6) may prove to be more useful than a single threshold for MRD-negative. The term measurable rather than minimal residual disease has been suggested to acknowledge the concept that increasing advances in analytic techniques may be able to measure ever smaller minimal amounts of disease.[21,27] Other measures that capture MRD dynamics (eg, log reduction) may also help predict outcomes.[10] The Myeloma XI study had slightly lower sensitivity (4×10^{-5}) than some others since it was initiated in 2010 and the analysis of MRD data has evolved over time. This meant that the cutoff to define MRD negativity was similar in Myeloma XI to that used in the EMN02 study but higher than that used in the IFM2009 study (10^{-6}). In the PETHEMA/GEM2012MENOS65 trial, only 1% of patients achieved 10^{-6} and 88% 10^{-5} so the lower level of sensitivity is more achievable and might be better for routine practice.

The therapies used as induction before maintenance have also evolved since the Myeloma XI trial, with most patients now receiving combination immunomodulatory drug and proteasome inhibitor therapy as standard induction with anti-CD38 antibodies added where these are available and

reimbursed. Such combinations are able to achieve very high rates of MRD negativity such as those seen in the GRIFFIN study of bortezomib, lenalidomide, and dexamethasone with or without daratumumab followed by ASCT[28] and even in induction without subsequent ASCT such as in the MANHATTAN study of daratumumab, carfilzomib, lenalidomide, and dexamethasone.[29] In addition, in the Myeloma XI trial, paired imaging studies to evaluate the presence of extramedullary disease at the same time points were not mandated. The prognostic impact of imaging negativity paired with bone marrow MRD negativity has been demonstrated.[30]

In summary, data from Myeloma XI/+ suggest that MRD status at ASCT + 3 and ASCT + 9 predicts PFS and OS in transplant-eligible patients with multiple myeloma. Regardless of MRD status, lenalidomide maintenance therapy was associated with improved PFS compared with no maintenance therapy. Achievement of MRD negativity at ASCT + 9 may be considered a key treatment goal.

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DATA SHARING STATEMENT

Deidentified participant data will be made available when all trial primary and secondary end points have been met. Any requests for trial data and supporting material (data dictionary, Protocol, and statistical analysis plan) will be reviewed by the trial management group in the first instance. Only requests that have a methodologically sound proposal and whose proposed use of the data has been approved by the independent trial steering committee will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requestors will need to sign a data access agreement.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Minimal Residual Disease After Autologous Stem-Cell Transplant for Patients With Myeloma: Prognostic Significance and the Impact of Lenalidomide Maintenance and Molecular Risk

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