Consolidation and Maintenance in Newly Diagnosed Multiple Myeloma

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Abstract

Purpose

To address the role of consolidation treatment for newly diagnosed, transplant eligible patients with multiple myeloma in a controlled clinical trial.

Patients and Methods

The EMN02/HOVON95 trial compared consolidation treatment with two cycles of bortezomib, lenalidomide, and dexamethasone (VRD) or no consolidation after induction and intensification therapy, followed by continuous lenalidomide maintenance. Primary study end point was progression-free survival (PFS).

Results

Eight hundred seventy-eight eligible patients were randomly assigned to receive VRD consolidation (451 patients) or no consolidation (427 patients). At a median follow-up of 74.8 months, median PFS with adjustment for pretreatment was prolonged in patients randomly assigned to VRD consolidation (59.3 v 42.9 months, hazard ratio [HR] = 0.81; 95% CI, 0.68 to 0.96; P = .016). The PFS benefit was observed across most predefined subgroups, including revised International Staging System (ISS) stage, cytogenetics, and prior treatment. Revised ISS3 stage (HR, 2.00; 95% CI, 1.41 to 2.86) and ampl1q (HR, 1.67; 95% CI, 1.37 to 2.04) were significant adverse prognostic factors. The median duration of maintenance was 33 months (interquartile range 13-86 months). Response ≥ complete response (CR) after consolidation versus no consolidation before start of maintenance was 34% versus 18%, respectively (P < .001). Response ≥ CR on protocol including maintenance was 59% with consolidation and 46% without (P < .001). Minimal residual disease analysis by flow cytometry in a subgroup of 226 patients with CR or stringent complete response or very good partial response before start of maintenance demonstrated a 74% minimal residual disease–negativity rate in VRD-treated patients. Toxicity from VRD was acceptable and manageable.

Conclusion

Consolidation treatment with VRD followed by lenalidomide maintenance improves PFS and depth of response in newly diagnosed patients with multiple myeloma as compared to maintenance alone.

Background and Motivation

The role of consolidation treatment for newly diagnosed, transplant-eligible patients with multiple myeloma (TE-NDMM) needs prospective evaluation.

Introduction

The treatment outcome of patients with multiple myeloma (MM) significantly improved by the introduction of proteasome inhibitors and immunomodulatory agents, resulting in higher response rates, as well as longer progression-free survival (PFS) and overall survival (OS).

High-dose melphalan followed by autologous stem-cell transplantation (HDM/ASCT) remains a backbone.1 Maintenance with lenalidomide is now a standard treatment.2 We reported the results of the EMN02/HO95 trial, which demonstrates the superiority for PFS of HDM/ASCT over chemotherapy.3 Few trials prospectively addressed the effect of consolidation treatment in NDMM.4 Superior complete response (CR) or near-complete response rates and PFS were demonstrated with bortezomib, thalidomide, and dexamethasone (VTD) versus thalidomide-dexamethasone as consolidation after double ASCT for NDMM.5 The BMT CTN0702 (STaMINA) trial compared a second ASCT with consolidation plus maintenance or maintenance alone.6 At a follow-up of 38 months, no difference was observed. A later analysis demonstrated a PFS advantage of double ASCT in high-risk disease.7 One retrospective analysis demonstrated an advantage for VTD consolidation.8 Recent prospective trials usually included standard consolidation.9-11 In the EMN02/HO95 trial, patients were randomly assigned to consolidation treatment with two cycles of bortezomib, lenalidomide, and dexamethasone (VRD) versus no consolidation, followed by lenalidomide maintenance until progressive disease or toxicity.

Context

Key Objective

The role of consolidation treatment in multiple myeloma (MM) has not been conclusively established. In the EMN02/HOVON95 trial, the relevance of consolidation therapy using bortezomib, lenalidomide, and dexamethasone (VRD) followed by lenalidomide maintenance compared with maintenance alone in transplant-eligible newly diagnosed patients with MM was prospectively evaluated.

Knowledge Generated

The results show that consolidation plus maintenance after either bortezomib, melphalan, and prednisone or high-dose melphalan, autologous stem-cell transplantation deepens the response and significantly improves the progression-free survival (PFS) in comparison with maintenance alone. In patients achieving minimal residual disease negativity, the PFS was superior to those not achieving such state.

Relevance (S. Lentzsch)

Consolidation with VRD followed by lenalidomide maintenance improves PFS and overall response rate in transplant-eligible and lenalidomide-naïve newly diagnosed patients with MM compared with maintenance alone. By contrast, in the STaMINA trial (BMT CTN 0702), VRD consolidation did not improve PFS. The data suggest a significant benefit of lenalidomide, bortezomib, and dexamethasone consolidation in lenalidomide-naïve patients.*

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

Patients and Methods

Study Design

This randomized, open-label, phase III study was performed by the European Myeloma Network (EMN).3 Previously untreated patients age 18-65 years with symptomatic MM stage 1-3 according to the International Staging System (ISS), measurable disease defined by the presence of serum M-protein > 10 g/L or urine M-protein > 200 mg/24 hours or abnormal free light-chain ratio with involved free light-chain > 100 mg/L or proven plasmacytoma by biopsy, and a WHO performance status grade 0-2 or 3 when because of myeloma were included (Appendix Table A1, online only). Exclusion criteria were listed in the recent publication of Part 1 and in the Protocol (online only). All patients provided written informed consent. The study was approved by independent ethics committees or the institutional review board of participating sites and performed according to the International Conference on Harmonization Guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki. The Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) sponsored and designed this study.

Treatment and Procedures

After registration patients received induction with 3-4 cycles of vincristine, cyclophosphamide, and dexamethasone and mobilization of stem cells was performed.3 Next, patients were randomly assigned (R1) to receive four cycles of bortezomib, melphalan, and prednisone (VMP) or HDM/ASCT once or twice as described.3 Within 2 months after ASCT or last VMP, a second random assignment (R2) assigned eligible patients to two 28-day cycles of VRD consolidation VRD (bortezomib [1.3 mg/m2

either intravenous or subcutaneously once daily on days 1, 4, 8, and 11] combined with lenalidomide [25 mg orally once daily, days 1-21] and dexamethasone [20 mg orally once daily, on days 1, 2, 4, 5, 8, 9, 11, and 12]) or no consolidation. No masking or stratification was done. Patients started lenalidomide maintenance (10 mg orally once daily on days 1-21 of a 28-day cycle) 1-2 months after ASCT or consolidation until disease progression (PD) or toxicity.

Outcomes

The primary end point PFS was defined as time from R2 to disease progression or death. Secondary end points were partial response or higher defined by the International Uniform Response Criteria for Multiple Myeloma12 (Appendix Table A3, online only), OS from R2 until death from any cause, and toxicity. Predefined high-risk prognostic subgroups for PFS included cytogenetic abnormalities defined by fluorescent in situ hybridization: deletion (17p) in ≥ 20% of enriched plasma cells; t(4;14) in ≥ 10% of enriched plasma cells; t(14;16) in ≥ 10% of enriched plasma cells; and amplification 1q. Standard clinical variables such as hemoglobin content, serum creatinine, and serum lactate dehydrogenase were included.13

Disease assessment was performed before and after consolidation and every 2 months until progression according to standard criteria (Appendix Table A3). Minimal residual disease (MRD) assessment was performed by multicolor flow cytometry in bone marrow with a detection of 10−4 to 10−5 in central laboratories of the EMN Network using a standard protocol.14,15 Here, we report the final analysis, which was performed in November 2020 at a median follow-up of 74.8 months from R2.

Statistical Analysis

The sample size was estimated based on the primary end point PFS from R2. Assuming a median PFS of 25 months without consolidation and 32 months with consolidation, we estimated that with uniform accrual for 30 months and additional follow-up of 24 months after the last patient was randomly assigned, 848 patients were required to be randomly assigned 1:1 and 514 events of PD or death would be needed to provide 80% power to detect a 22% reduced risk of PD or death (hazard ratio [HR] 0.78) in the consolidation group compared with no consolidation, using Cox regression analysis, with an overall two-sided significance level of 0.05. Two prespecified interim analyses were performed in 2016 and 2018 after 33% and 66% of events had occurred; therefore, the P value for the primary end point at the final analysis was set at .045. These interim analyses showed PFS was longer with consolidation than without consolidation. An independent data monitoring committee reviewed the results of interim analyses. Efficacy was analyzed in the intention-to-treat population, which includes all eligible patients in R2 who also were in R1. PFS and OS were estimated by Kaplan-Meier method from the date of R2. Cox regression analysis including only the R2 arm and the stratification factor R1 group (VMP v HDM) was used for the primary comparison of PFS between treatment groups and to estimate HRs and 95% CIs. The consistency of effects of consolidation versus no consolidation within predefined subgroups was evaluated using interaction-p terms between each of the covariates included in the Cox model. Forest plots were generated to illustrate PFS from R2 within subgroups.

As a post hoc analysis, we also performed a multivariable Cox regression analysis with R2 arm together with the variables that were statistically significant in the multivariable analysis for PFS in the VMP versus HDM random assignment.3 To include all patients in this analysis, the method of multiple imputation by chained equations was used to cope with possible missing data on these covariates. Responses were compared between treatments using the chi-squared test. Safety was assessed in all patients who received at least one dose of study drugs. Toxicities were tabulated as adverse events (CTCAE version 4) and second primary malignancies (SPMs). Cumulative incidence curves of SPMs were generated by treatment group. MRD was evaluated in patients with at least one evaluable MRD sample. The prognostic impact of MRD on PFS from R2 was assessed by comparing PFS from R2 in

MRD-negative versus MRD-positive patients. Patients with the last sample during or after intensification with VMP or HDM/ASCT but before start of VRD or start of maintenance, whichever first, were considered MRD-negative if the last sample was MRD-negative. All other patients, including those without an evaluable MRD sample, were considered as MRD-positive at R2. Similarly, the prognostic impact of MRD on PFS from start of maintenance was assessed. In that analysis, patients were considered MRD-negative if the last sample during or after intensification, VRD consolidation, or within 4 months after start maintenance was MRD-negative. All analyses were performed using Stata (version 15.1). Data were monitored by an external contract organization and verified for accuracy by a supporting research team at the EMN data center. This trial is registered with the EU Clinical Trials Register (EudraCT 2009-017903-28) and ClinicalTrials.gov identifier: NCT01208766.

Role of Funding Sources

Funding for this study was provided by the Dutch National Cancer Society and by Janssen and Celgene. The study was performed as an independent, investigator-sponsored study. All patients provided written informed consent and the study was approved by the independent ethics committee or institutional review board of each participating hospital. Funders had no role in study design, data collection, data analysis, data interpretation, or manuscript writing. The corresponding author had full access to the data and carried the final responsibility for the submission of the manuscript.

Results

Consolidation

From February 2011 to April 2014, a total of 1,503 patients age ≤ 65 years with MM were enrolled in 172 EMN centers, of whom 1,500 were eligible. 1,197 patients were randomly assigned (stratified by ISS stage) to VMP (495 patients) or HDM (one or two ASCT; 702 patients). The results were recently published and an update on OS was presented.3,16 For the second random assignment, 878 patients were eligible and 24 patients were ineligible (Appendix Table A1). Patients were randomly assigned to consolidation (arm B, 451 patients) or no consolidation (arm A, 427 patients; Appendix Fig A1, online only). Median follow-up from R2 of 630 patients still alive was 74.8 months (interquartile range [IQR] 64.4-82.3 months). Response status at R2 was equal in both arms, ie, ≥ CR (18%, 22%), ≥ very good partial response (67%, 67%), and ≥ PR (91%, 93%) according to uniform criteria (ST3). At the time of analysis, 519 events for PFS after R2 had been reported. The median PFS from R2 was 59.3 (95% CI, 49.8 to 66.9) versus 42.9 (95% CI, 39.3 to 50.5) months, respectively (HR 0.81 in favor of consolidation, 95% CI, 0.68 to 0.96; P = .016; Fig 1). Five-year PFS from R2 was 50% (95% CI, 45 to 54) with consolidation and 41% (95% CI, 37 to 46) without consolidation. The primary comparison of PFS from R2 between treatment groups also included the R1 group (VMP v HDM), and showed that prior treatment with HDM/ASCT (HR, 0.77; 95% CI, 0.64 to 0.92; P = .003) was statistically significant. There was no significant interaction between the first random assignment (R1) and the arms of the R2 random assignment, indicating that the benefit of consolidation is not different between VMP and HDM (Fig 2).

Consolidation reduced the risk of progression or death in most predefined subgroups, including revised ISS stage I-III, standard-risk cytogenetics, and prior treatment arms (Fig 3). However, the interaction term for del(17p) was significant (P = .04), indicating that VRD consolidation was beneficial in patients without del(17p), HR = 0.77 (95% CI, 0.64 to 0.94), but not in del(17p), HR = 1.50 (95% CI, 0.84 to 2.67).

Univariate Cox regression analysis of all patients randomly assigned in R2 showed that revised ISS stage 3 (HR, 2.00; 95% CI, 1.41 to 2.86), B2M > 5.5, ISS stage 3, t(4;14), revised ISS 2 versus 1, high-risk cytogenetics (HR, 1.49; 95% CI, 1.20 to 1.85), and addition of chromosome 1q by fluorescent in situ hybridization (HR, 1.67; 95% CI, 1.37 to 2.04) at diagnosis were adverse prognostic factors for PFS from R2.

The multiple imputation by chained equation method was used to cope with missing data in the multivariable analysis because platelet count was missing in 2%, revised ISS in 15%, and cytogenetics in 20% of patients. The post hoc multivariable Cox regression analysis with R2 arm together with the variables that were statistically significant in the multivariable analysis for PFS in the R1 (VMP v HDM) random assignment revealed that all covariates were statistically significant, except for standard-risk cytogenetics (P = .08). The significant covariates as displayed in Table 1 also show that the HRs for VRD consolidation (R2; 0.81 v 0.81) and HDM (R1; 0.79 v 0.77) are almost identical to those in the primary analysis of PFS2.16

Before R2, response ≥ CR was 22% (95% CI, 18 to 26) versus 18% (95% CI, 15 to 22) of patients. Response ≥ CR before start of maintenance was 34% (95% CI, 29 to 38) versus 18% (95% CI, 15 to 22) after consolidation or no consolidation, respectively ($P < .001$). Response ≥ CR on protocol was 59% (95% CI, 54 to 63) with consolidation and 46% (95% CI, 41 to 51) without ($P < .001$; Table 2).

Maintenance

Maintenance with lenalidomide 10 mg was initiated in 847 patients, 428 (95%) with and 419 (98%) without consolidation. The median duration of maintenance was not different at 35.7 months (IQR 13-78 months) and 31.8 months (IQR 14-88 months), respectively (P = .24; Appendix Fig A2, online only). At 5 years after random assignment, 35% (consolidation) and 30% (no consolidation) of patients were still receiving maintenance treatment. Maintenance was discontinued in 288 of 428 (67%) versus 302 of 419 (72%) patients, of whom 186 of 288 (65%) versus 189 of 302 (63%) because of progressive disease after consolidation or no consolidation, respectively.

At a median follow-up of 73.4 months, median PFS from start of maintenance was 57.5 months in the consolidation arm and 42.3 months without consolidation (HR = 0.83; 95% CI, 0.70 to 0.99; P = .04).

At 4 years after R2, OS was 81%-82% in both arms, whereas at 6 years, OS was 76% (95% CI, 71 to 79) with consolidation and 69% (95% CI, 64 to 73) without consolidation, indicating that longer follow-up is required to evaluate OS (Appendix Fig A3, online only).

Toxicity

Ninety-six percent of patients randomly assigned to consolidation completed two cycles of VRD. Toxicity was acceptable and manageable with 28% CTCAE grade 3 or 4, mainly neutropenia (13%), thrombocytopenia (12%), and infections (5%; Appendix Table A2, online only). The cumulative incidence of SPM excluding superficial skin cancer at 6 years was 5% and 6%, respectively.

MRD

Minimal residual disease studies were initiated only when a standard assessment protocol became available. MRD was performed by 8-color flow cytometry on bone marrow aspirates of patients in CR or stringent complete response or very good partial response at R2 and at the start of maintenance. Of 878 randomly assigned patients in the consolidation ITT analysis, 103 patients had an MRD sample after the last treatment before R2. Thirty-five of 49 (71%) patients without consolidation were MRD-negative, versus 44 of 54 (81%) with consolidation. Similarly, 226 patients had at least one MRD

sample before or within 4 months after start maintenance, which were considered as MRD sample at the start of maintenance. Sixty-two of 89 (70%) of evaluable patients without consolidation were MRD-negative, versus 101 of 137 (74%) with consolidation. Figure 4 shows the Kaplan-Meier curves of PFS from R2 random assignment according to R2 arm and MRD status at R2 and PFS from start maintenance according to R2 arm and MRD status at start maintenance. Both figures indicate that PFS is improved in MRD-negative patients. Median PFS from start of maintenance in patients randomly assigned to no consolidation was 85.3 months in MRD-negative patients and 39.3 months in MRD-positive patients (HR = 0.49; 95% CI, 0.32 to 0.73; P < .001), and in patients randomly assigned to consolidation, it was median 70.1 months in MRD-negative patients and 50.6 months in MRD-positive patients (HR = 0.65; 95% CI, 0.47 to 0.89; P = .008). The detailed analysis of MRD for the EMN02/HO95 trial including R1 is described elsewhere.14

Discussion

This randomized trial evaluated the efficacy of consolidation after intensification with VMP or HDM/ASCT in TE-NDMM. Standard treatment for TE-NDMM consists of 3-6 cycles of induction therapy followed by melphalan 200 mg/m2 and ASCT.17 Lenalidomide maintenance is now used for continuous or fixed duration (1-2 years). Consolidation therapy is given to improve the response after ASCT and to prevent early relapse.18 However, there are few published randomized consolidation studies.

The use of consolidation therapy with VTD compared with thalidomide-dexamethasone was associated with a significant upgrade of overall response and CR rate, resulting in enhanced PFS.5,19 The phase III PETHEMA/GEM2012 study demonstrated that consolidation with VRD in all patients after ASCT improves CR and MRD-negativity.20 Other trials used VRD as consolidation.10,21 In the STaMINA trial, four cycles of VRD consolidation did not improve PFS when compared with a second HDM/ASCT or no consolidation.6 Double HDM/ASCT was superior in the high-risk group at the longer follow-up.7 Possible explanations for the different outcome of consolidation are the heterogeneous induction regimens and 5%-32% noncompliance rate in STaMINA, whereas in EMN02, all patients were lenalidomide-naïve and randomly assigned after prior ASCT or VMP just before consolidation. Together, these trials may be informative for OS after additional follow-up.

Several trials in TE-NDMM used standard consolidation.1,22 It was part of the Cassiopeia trial comparing daratumumab-VTD versus VTD and in the Griffin trial using daratumumab-lenalidomide, bortezomib, and dexamethasone versus lenalidomide, bortezomib, and dexamethasone.9,11 It is unknown to what extent consolidation has contributed to the outcome of these trials. A superior PFS after consolidation was only demonstrated in the current EMN02/HO95 trial. The impact on OS requires still longer follow-up. This uncertainty illustrates the need for exploratory predictive end points such as MRD assessment after induction, after transplant, and during subsequent treatment.12,23-25 We observed a deepening of response after consolidation including ≥ CR rate from 22% to 34% and sCR from 6% to 12%, resulting in a ≥ CR rate on protocol of 59% compared with 46% without consolidation. The MRD-negativity rate did not significantly differ between patients with or without consolidation. The imbalance in MRD-negativity at R2 prevents any formal conclusion about MRD response achieved with consolidation before start of maintenance. The relevance of this finding pertains to the observation that MRD-negative patients had a significantly longer PFS. Overall, consolidation resulted in a consistent improvement of median PFS after R2 from 43 to 59 months.

These data indicate that consolidation improves PFS across subgroups, except in the small subgroup of high-risk (del17p) patients. The results also show that continuous maintenance with lenalidomide is feasible. Like in previous trials and in a meta-analysis, a significant PFS benefit was observed.2,26-28

A higher probability of achieving CR or sCR after start of maintenance was observed, especially after consolidation. This benefit was also observed in recent trials in transplant-eligible patients where CD38 antibody therapy was followed by maintenance.2,9,11,29 The Spanish group observed an upgrade of MRD-negativity by 17% during prolonged maintenance with lenalidomide and ixazomib.24 Hence, the question remains: Which duration of maintenance is optimal.30

In the current trial, there is a trend that consolidation improves OS. However, while the OS curves separate after 5-6 years, median OS was not reached at 84 months in both arms. Consequently, longer follow-up is needed to evaluate the full-scale impact of consolidation followed by continuous maintenance. Future trials will evaluate to what extent consolidation treatment will improve treatment outcome when quadruplet induction therapy with a CD38 antibody may become standard.

In conclusion, consolidation treatment with VRD followed by continuous lenalidomide maintenance improves PFS and quality of response in NDMM as compared to maintenance alone. The rate of toxicity and SPMs is acceptable.

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Participating physicians are listed in Appendix 1.

Study Protocol

The following protocol information is provided solely to describe how the authors conducted the research underlying this article. The information provided may not reflect the complete protocol or any previous amendments or modifications. As described in the Information for Contributors, JCO requests only specific elements of the most recent version of the protocol. The protocol information is not intended to replace good clinical judgment in selecting appropriate therapy and in determining drug doses, schedules, and dose modifications. The treating physician or other health care provider is responsible for determining the best treatment for the patient. ASCO and JCO assume no responsibility for any injury or damage to persons or property arising out of the use of this protocol material or due to any errors or omissions. Readers seeking additional information about the protocol are encouraged to consult the corresponding author directly.

Please click the protocol link below to access the information.

Protocol

Prior Presentation

Presented in part at the European Hematology Association 24th Annual Meeting, Amsterdam, the Netherlands, June 14-17, 2018; the virtual American Society of Hematology 62nd Annual Meeting and Exposition, December 5-8, 2020, San Diego, CA.

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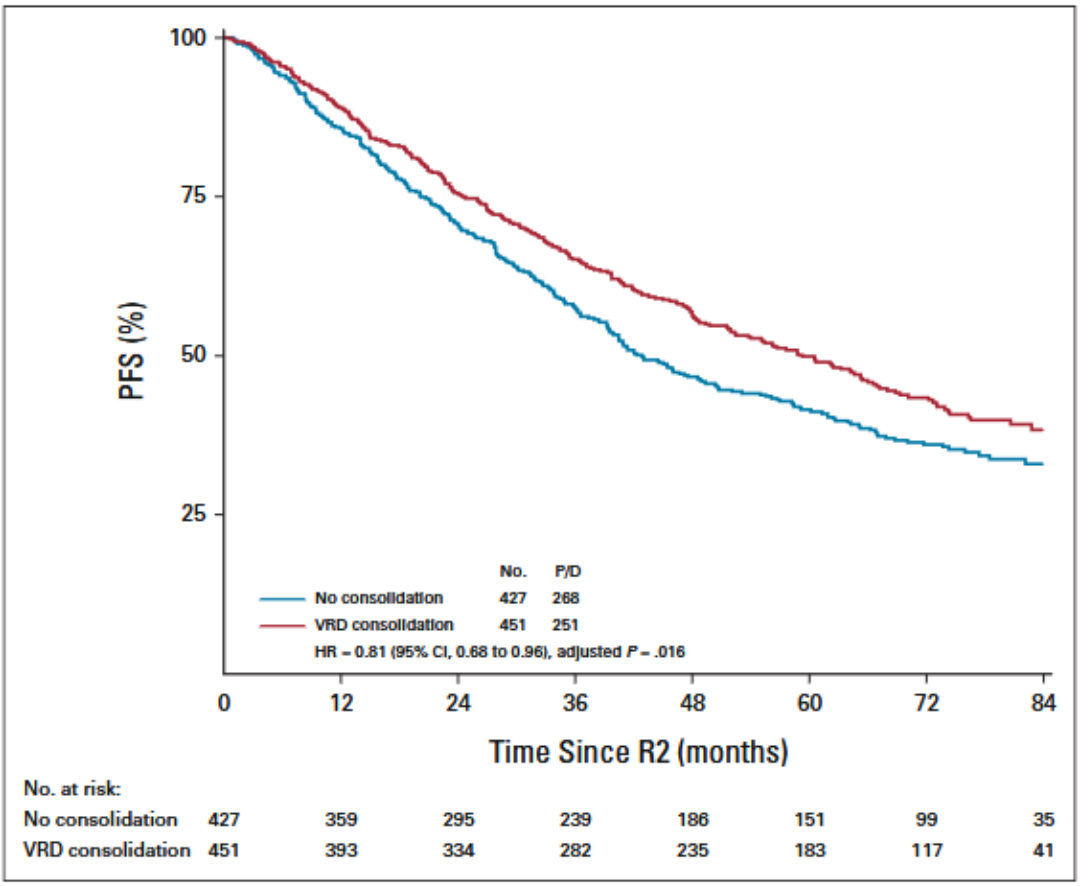


FIG 1. PFS from R2 with consolidation plus maintenance versus maintenance alone. HR, hazard ratio; P/D, progression or death; PFS, progression-free survival; VRD, bortezomib, lenalidomide, and dexamethasone.

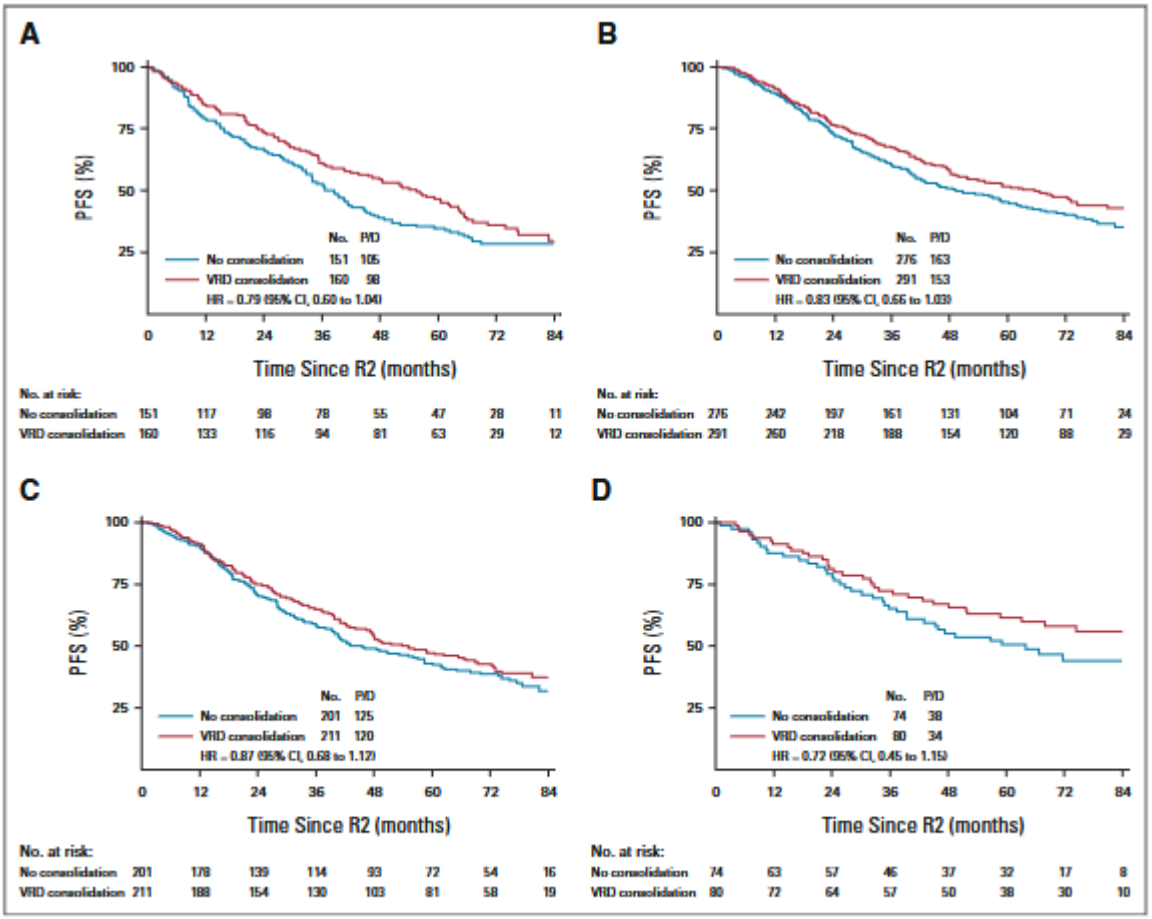


FIG 2. Effect of consolidation treatment on PFS from R2 in patients who were randomly assigned in (A) R1 according to VMP, (B) single or double ASCT, (C) single ASCT, or (D) double ASCT. ASCT, autologous stem-cell transplantation; HR, hazard ratio; P/D, progression or death; PFS, progression-free survival; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

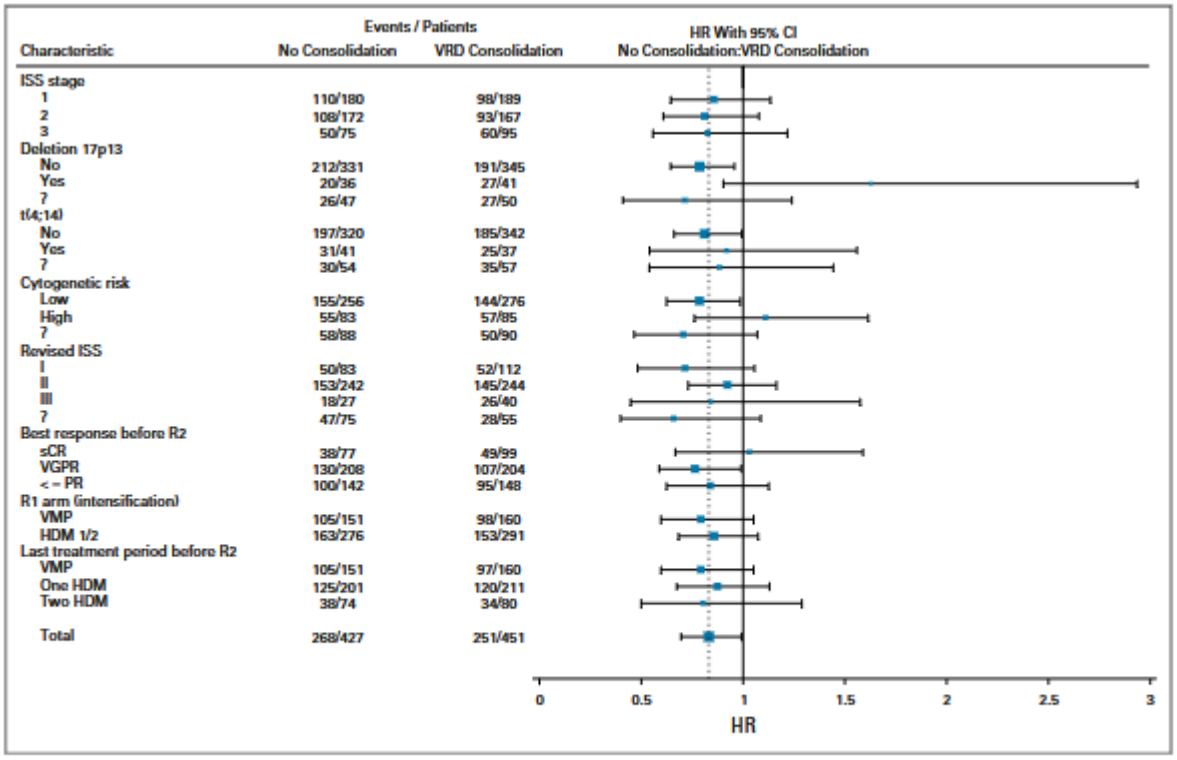


FIG 3. Forest plot for PFS from R2 of predefined subgroups. HDM, high-dose melphalan; HR, hazard ratio; ISS, International Staging System; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

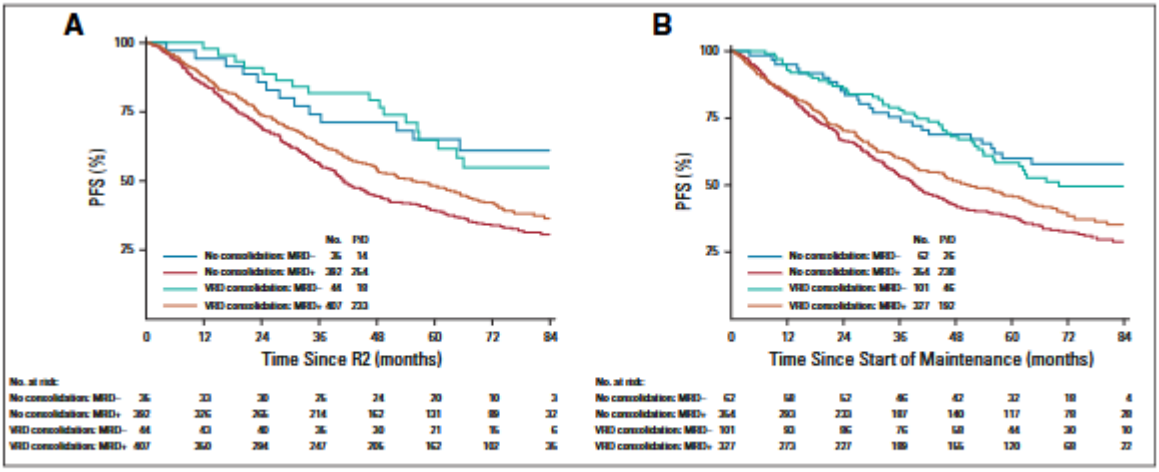


FIG 4. (A) PFS from R2 by R2-arm and MRD status and (B) PFS from start of maintenance by R2-arm and MRD status before start maintenance. MRD, minimal residual disease; P/D, progression or death; PFS, progression-free survival; VRD, bortezomib, lenalidomide, and dexamethasone.

TABLE 1. Multivariate Analysis for Progression-Free Survival

Covariates	HR	95% CI	*P*
R2: VRD consolidation *v* none	0.81	0.68 to 0.96	.015
R1: HDM *v* VMP	0.79	0.66 to 0.94	.009
≥ VGPR at the time of R2 random assignment	0.70	0.59 to 0.84	< .001
R-ISS I *v* II[a]	0.77	0.63 to 0.95	.015
R-ISS I *v* III[a]	0.52	0.37 to 0.73	< .001
Platelet count ≥ 150 × 10^9/L[a]	0.60	0.47 to 0.77	< .001

Abbreviations: HDM, high-dose melphalan; HR, hazard ratio; ISS, International Staging System; R-ISS, revised International Staging System; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

[a]R-ISS and platelet count measured at entry in the trial.

TABLE 2. Response Status

Time	Response % of Patients	Consolidation No	Consolidation Yes	*P*
Before R2	≥ CR	18	22	.15
	≥ VGPR	67	67	.94
	ORR	91	93	.38
Before maintenance	≥ CR	18	34	< .001
	≥ VGPR	67	78	< .001
Best on protocol	≥ CR	46	59	< .001
	≥ VGPR	87	89	.26

Abbreviations: CR, complete response; ORR, overall response rate; VGPR, very good partial response.

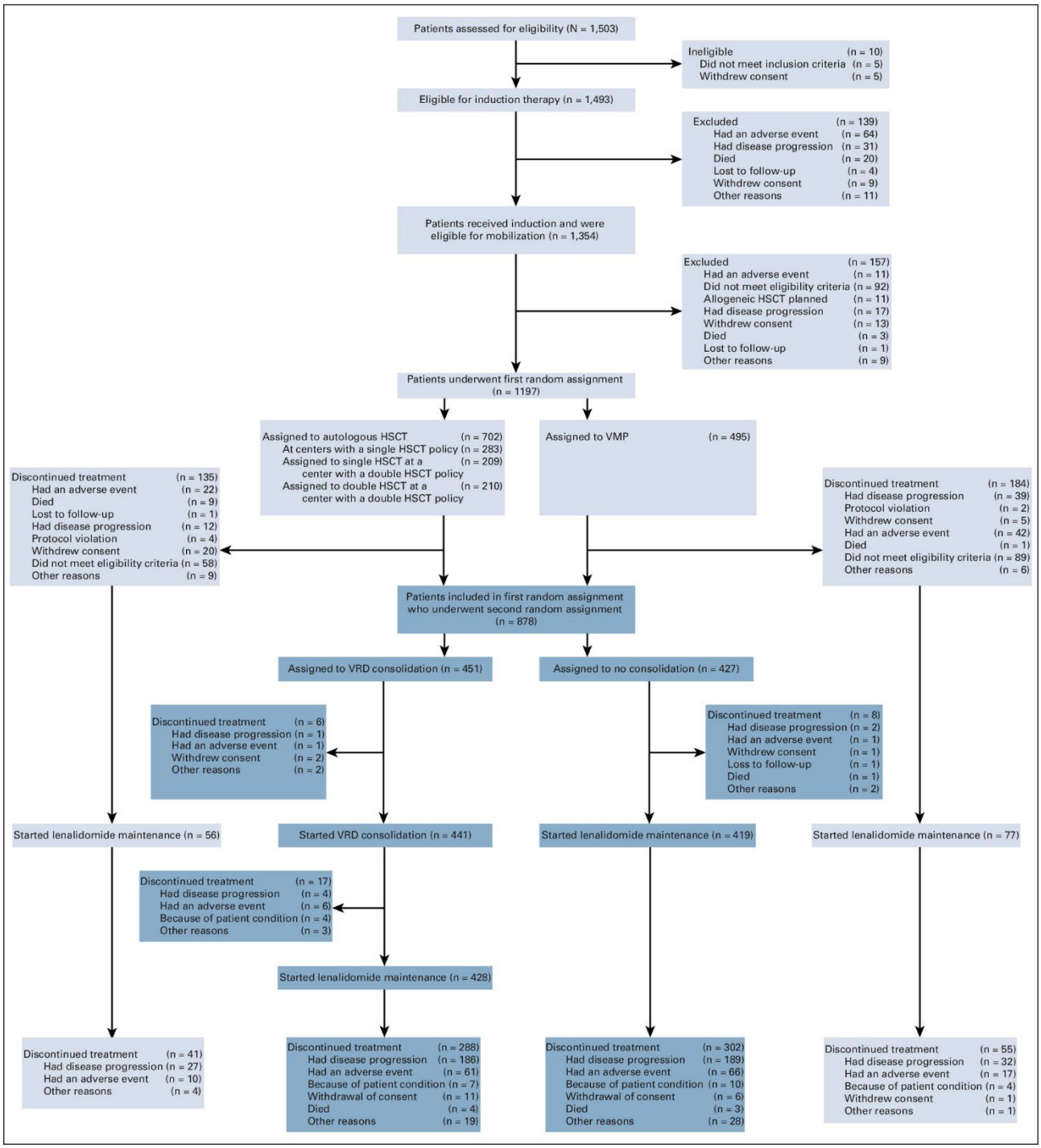
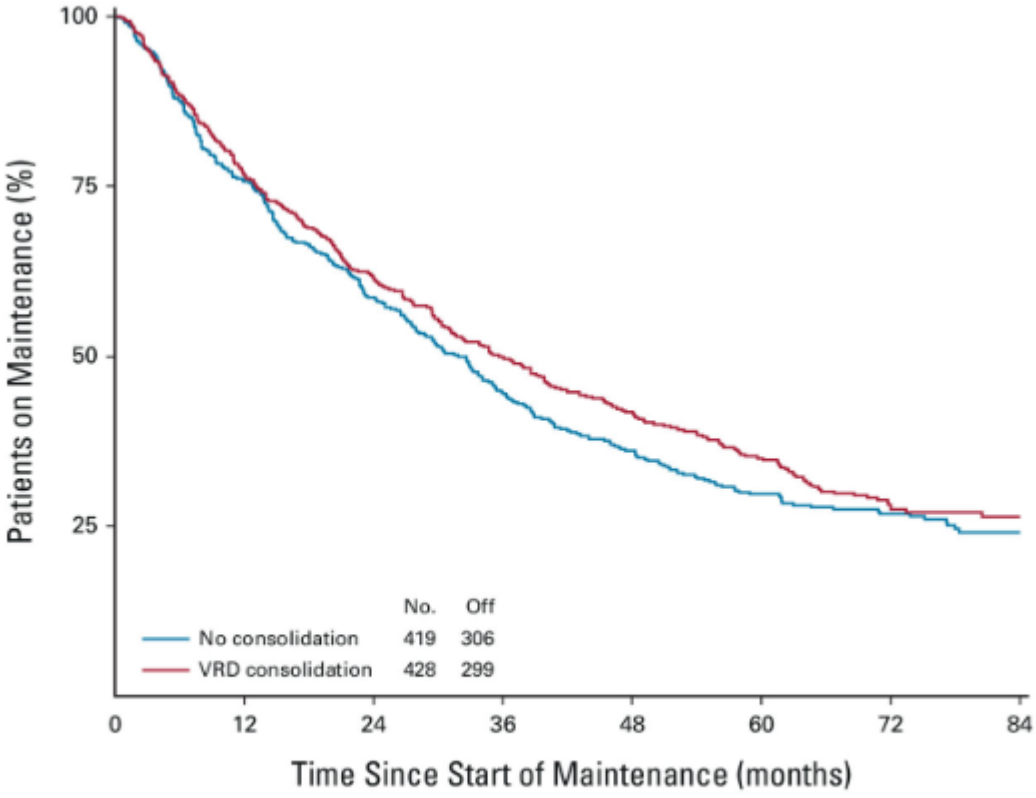


Fig A1. CONSORT diagram of trial patients. The part related to the R2 random assignment has been marked with blue. HSCT, hematopoietic stem-cell transplantation; VMP, bortezomib/melphalan/prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.



No. at risk:								
No consolidation	419	313	241	181	145	111	76	28
VRD consolidation	428	325	259	204	163	131	79	29

Fig A2. Duration of Maintenance. VRD, bortezomib, lenalidomide, and dexamethasone

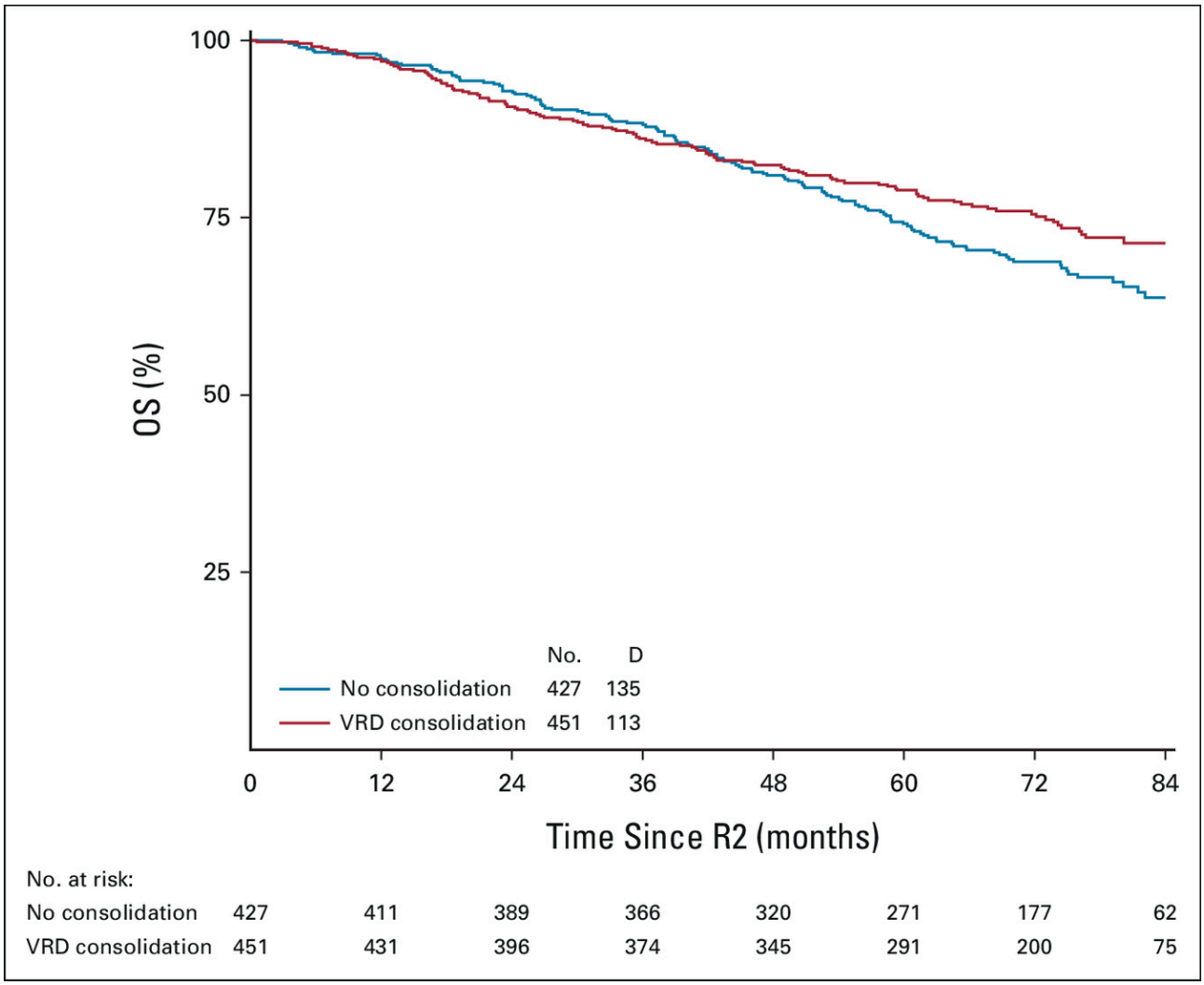


Fig A3. OS from R2. D, death; OS, overall survival; VRD, bortezomib, lenalidomide, and dexamethasone.

TABLE A1. Baseline Characteristics at Entry

Characteristic	No Consolidation	Consolidation
Patients, No.	427	451
Age, years, median (IQR)	58 (52-62)	57 (52-6
Sex, No. (%)		
Male	242 (57)	260 (58)
Female	185 (43)	191 (42)
WHO PS 2 plus 3, No. (%)	56 (13)	62 (14)
ISS stage, No. (%)		
1	180 (42)	189 (42)
2	172 (40)	167 (37)
3	75 (18)	95 (21)
FISH available, No. (%)	379 (89)	402 (89)
del(17p), No. (%)	36/367 (10)	41/386 (11)
t(4;14), No. (%)	41/361 (11)	37/379 (10)
t(14;16), No. (%)	15/335 (4)	12/370 (3)
1qampl, No. (%)	130/329 (34)	120/356 (30)
Genetic risk available, No. (%)	339 (79)	361 (80)
Standard	256 (76)	276 (76)
High	83 (24)	85 (24)
Revised ISS, No. (%)		
I	83 (19)	112 (25)
II	242 (57)	244 (54)
III	27 (6)	40 (9)
Unknown	75 (18)	55 (12)

Abbreviations: FISH, fluorescent in situ hybridization; IQR, interquartile range; ISS, International Staging System; PS,

Table A1. Baseline Characteristics at Entry

TABLE A2. AEs of CTCAE Grade 3 and 4 During Bortezomib, Lenalidomide, and Dexamethasone

AE	Grade 3, No. (%)	Grade No. (%
Any	101 (23)	21 (5)
Neutropenia	47 (11)	10 (2)
Thrombocytopenia	43 (10)	9 (2)
General disorders	10 (2)	1 (<
Infections and febrile neutropenia	17 (4)	2 (<
Nervous system disorders	4 (1)	—
Anemia	6 (1)	—
GI and hepatic disorders	3 (1)	—
Metabolic	10 (2)	—
Skin and subcutaneous disorders	1 (< 1)	2 (<
Respiratory, thoracic, and mediastinal disorders	4 (1)	1 (<
Vascular	3 (1)	—
Cardiac	1 (< 1)	—

Table A2. AEs of CTCAE Grade 3 and 4 During Bortezomib, Lenalidomide, and Dexamethasone

TABLE A3. International Uniform Response Criteria Consensus Recommendations[11]

Response	Definition
sCR	CR as defined below, plus Normal free light-chain ratio, and Absence of clonal plasma cells by immunohistochemistry, immunofluorescence[a], or two-color to fou color flow cytometry
CR[b]	Negative immunofixation of serum and urine, and Disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow
VGPR[c]	Serum and urine M-component detectable by immunofixation but not on electrophoresis, or ≥ 90% reduction in serum M-protein plus urine M-protein < 100 mg/24 hours
PR	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 2(mg/24 hours If the serum and urine M-protein are not measurable, a decrease of ≥ 50% in the difference betwee involved and uninvolved free light-chain levels is required in place of the M-protein criteria If serum and urine M-protein are not measureable and serum free light-chain assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provid baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD	Increase of 25% from lowest response value in any one of the following: Serum M-component (absolute increase must be ≥ 0.5 g/dL) Urine M-component (absolute increase must be ≥ 200 mg/24 hours) Only in patients without measureable serum and urine M-protein levels: the difference between involv and uninvolved free light-chain levels (absolute increase must be > 10 mg/dL) Only in patients without measureable serum and urine M-protein levels and without measureable disease by free light-chain levels: bone marrow plasma cell percentage (absolute percentage must be > 10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely the plasma cell proliferative disorder

NOTE. All response categories (sCR, CR, VGPR, PR, and PD) require two consecutive assessments made at any time before the institutio any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiograp studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need be confirmed. For PD, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

Abbreviations: CR, complete response; IMWG, International Myeloma Working Group; PD, disease progression; PR, partial response; s stringent complete response; SD, stable disease; VGPR, very good partial response.

[a]Presence or absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistr immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone kappa/lambda ratio of > 4:1 or < 1:2.

[b]Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum free light-chain lev CR in such subjects indicates a normal free light-chain ratio of 0.26-1.65 in addition to the CR criteria listed above. VGPR in such subje requires a > 90% decrease in the difference between involved and uninvolved free light-chain levels.

[c]Clarifications to IMWG criteria for coding PD: bone marrow criteria for PD are to be used only in subjects without measurable disease by protein and by free light-chain levels; 25% increase refers to M-protein, free light-chain, and bone marrow results, and does not refer to b

Table A3. International Uniform Response Criteria Consensus Recommendations