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# Impact of prior treatment on selinexor, bortezomib, dexamethasone outcomes in patients with relapsed/refractory multiple myeloma: Extended follow-up subgroup analysis of the BOSTON trial

Maria-Victoria Mateos[1] | Monika Engelhardt[2] | Xavier Leleu[3] | Mercedes Gironella Mesa[4] | Michele Cavo[5] | Meletios Dimopoulos[6] | Martina Bianco[7] | Giovanni Marino Merlo[7] | Charles la Porte[8] | Paul G. Richardson[9] | Philippe Moreau[10]

[1]Instituto de Investigación Biomédica de Salamanca (IBSAL), Hospital Universitario de Salamanca, Salamanca, Spain

[2]Interdisciplinary Cancer Center, University of Freiburg, Faculty of Freiburg, Freiburg, Germany

[3]University of Potiers and CHU, Poitiers, France

[4]University Hospital Vall d'Hebron, Barcelona, Spain

[5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Seràgnoli Institute of Haematology, Bologna University School of Medicine, Bologna, Italy

[6]National and Kapodistrian University of Athens School of Medicine, Athens, Greece

[7]Menarini Group, Florence, Italy

[8]Menarini Group, Machelen, Belgium

[9]Dana-Farber Cancer Institute, Boston, Massachusetts, USA

[10]University Hospital Hotel-Dieu, Nantes, France

**Correspondence**
Maria-Victoria Mateos, Instituto de Investigación Biomédica de Salamanca (IBSAL), Hospital Universitario de Salamanca, Paseo de San Vicente, 58-182, 37007 Salamanca, Spain.
Email: mvmateos@usal.es

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## Abstract

**Objectives:** To analyze the impact of prior therapies on outcomes with selinexor, bortezomib, and dexamethasone (SVd) versus bortezomib and dexamethasone (Vd) in 402 patients with relapsed/refractory multiple myeloma (RRMM) in the phase 3 BOSTON trial.

**Methods:** Post hoc analysis of progression-free survival (PFS), overall survival (OS), and safety for lenalidomide-refractory, proteasome inhibitor (PI)-naïve, bortezomib-naïve, and one prior line of therapy (1LOT) patient subgroups.

**Results:** At a median follow-up of over 28 months, clinically meaningful improvements in PFS were noted across all groups with SVd. The median SVd PFS was longer in all subgroups (lenalidomide-refractory: 10.2 vs. 7.1 months, PI-naïve: 29.5 vs. 9.7; bortezomib-naïve: 29.5 vs. 9.7; 1LOT: 21.0 vs. 10.7; $p < .05$). The lenalidomide-refractory subgroup had longer OS with SVd (26.7 vs. 18.6 months; HR 0.53; $p = .015$). In all subgroups, overall response and ≥very good partial response rates were higher with SVd. The manageable safety profile of SVd was similar to the overall patient population.

**Conclusions:** With over 2 years of follow-up, these clinically meaningful outcomes further support the use of SVd in patients who are lenalidomide-refractory, PI-naïve, bortezomib-naïve, or who received 1LOT (including a monoclonal antibody) and underscore the observed synergy between selinexor and bortezomib.

KEYWORDS
bortezomib, follow-up studies, lenalidomide, multiple myeloma, proteasome inhibitor, selinexor

## 1 | INTRODUCTION

Despite the significant progress made in the treatment of multiple myeloma (MM) with the introduction of new therapy options, MM remains a largely incurable and fatal disease.[1,2] The majority of patients experience subsequent relapses or develop refractory disease.[1–4] Following the regulatory approval and increasing use of daratumumab, lenalidomide, and dexamethasone (DRd) in first-line MM in patients not eligible for stem cell transplantation (SCT), at first relapse many patients are already refractory to an immunomodulatory agent (IMiD) and an anti-CD38 monoclonal antibody. Guidelines and experts recommend that patients with relapsed/refractory MM (RRMM) should be treated with more than one drug and/or drug class switch to which they had no previous exposure.[5,6] Switching to a different drug class is an important tactic that becomes more difficult to enact after subsequent relapses when remaining options become severely limited. Therefore, treatments with new mechanisms of action (MOAs) are required for subsequent lines of therapy. To improve short- and long-term outcomes for patients with MM, there is an ongoing need for more effective and tolerable novel treatments with different MOAs and less burdensome modes of administration.

Selinexor is a first-in-class, orally available inhibitor of exportin 1 (XPO1), a nuclear export protein overexpressed in numerous types of cancers, including MM.[7,8] XPO1 orchestrates the nuclear export and subsequent functional inactivation of a vast array of tumor suppressor proteins, while simultaneously promoting the translation of specific oncoproteins.[9] When dysregulated, XPO1 contributes to uncontrolled tumor growth and the survival of cancerous cells.[7] The overexpression of XPO1 has been associated with poorer patient outcomes and patients are less likely to respond to bortezomib.[1,7,10,11] By inhibiting XPO1, selinexor offers a unique MOA that results in the nuclear retention and functional activation of tumor suppressor proteins, ultimately reducing cellular proliferation and tumor growth rates.[7,12,13]

Nonclinical studies of MM and other cancers have shown that selinexor strongly synergizes with proteasome inhibitors (PIs), such as bortezomib,[7,14–16] leading to inhibition of cell proliferation and induction of MM cell death. The mechanisms uncovered for this synergy include marked increases in thrombospondin levels in the nucleus due to a blockade of proteasome-mediated degradation by PIs and nuclear entrapment by selinexor, nuclear retention of high levels of inhibitor of nuclear factor-κB and inhibition of nuclear factor-κB transcription, overcoming resistance to PIs, and induction of autophagy.[11,15,17–20]

Selinexor is approved by the US Food and Drug Administration and the European Medicines Agency in combination with bortezomib and dexamethasone (SVd) for adults with RRMM who have received ≥1 prior therapy, and in combination with dexamethasone (Sd) for adults with RRMM who have received ≥4 prior therapies and whose disease is refractory to ≥2 PIs, ≥2 IMiD agents, and an anti-CD38 monoclonal antibody.[21–23]

The BOSTON (NCT03110562) randomized, open-label, phase 3 study evaluated the efficacy and safety of SVd compared with bortezomib and dexamethasone (Vd) in adults with RRMM who had received one to three prior lines of therapy (LOT).[24] After a median follow-up of 13.2 months for SVd and 16.5 months for Vd, treatment with SVd was associated with a statistically significant increase in progression-free survival (PFS) versus Vd (PFS; 13.9 months vs. 9.5 months; $p = .0075$; hazard ratio [HR] 0.70), a higher overall response rate (ORR; 76.4% vs. 62.3%; $p = .0012$) and a higher proportion of patients achieving a very good partial response (VGPR) or better (44.6% vs. 32.4%).[24] The 30% reduction in the risk of disease progression or death and the higher ORR associated with SVd demonstrated the efficacy of the regimen in patients with RRMM. A post hoc analysis of data from the STOMP and BOSTON trials found selinexor combination therapy to be tolerated and efficacious in patients exposed to or refractory to daratumumab or isatuximab, with median PFS ranging from 8.7 to 15.0 months depending on the combination.[25]

In light of the positive efficacy and safety results from the BOSTON trial and the new MOA provided by selinexor, the 2021 European Hematology Association (EHA)-European Society for Medical Oncology (ESMO) MM guidelines recommend SVd as a second-line option for patients with lenalidomide-refractory, lenalidomide-sensitive, or bortezomib-sensitive disease and for patients previously treated with daratumumab (regardless of lenalidomide sensitivity).[1] Among the EHA-ESMO MM guideline-recommended[1] options post-DRd in patients with lenalidomide-refractory disease, SVd, carfilzomib plus dexamethasone (Kd), and pomalidomide plus Vd (PVd) are the only ones with regulatory approval in Europe. Other approved regimens in clinical practice include isatuximab plus carfilzomib and dexamethasone (IKd) and, after two prior lines, isatuximab plus pomalidomide and dexamethasone (IPd).

As patients who are refractory to lenalidomide represent a high unmet need, in the current analysis we evaluated the impact of SVd in patients who were lenalidomide-refractory in the BOSTON trial. Moreover, since patients relapsing on first-line DRd have no prior exposure to a PI, we also assessed the efficacy of SVd in patients who were PI-naïve, bortezomib-naïve, and/or who had received only one prior LOT. Thus, the present report updates and expands upon a preliminary BOSTON subgroup analysis[26] with longer follow-up, more extensive analyses, and the addition of a bortezomib-naïve subgroup.

## 2 | METHODS

### 2.1 | Study design

This post hoc subgroup analysis uses extended follow-up data from BOSTON, for which the methodology and primary/secondary analyses have been published.[24] BOSTON included patients ≥18 years with measurable myeloma, documented evidence of progressive disease (PD), and one to three previous treatments for MM, and excluded patients with systemic light-chain amyloidosis, central nervous system involvement, or grade 2 painful or grade ≥2 peripheral neuropathy.

Patients were randomized 1:1 to SVd or Vd treatment.[24] During each 5-week cycle, patients in the SVd arm received oral selinexor 100 mg (Days 1, 8, 15, 22, 29), bortezomib 1.3 mg/m$^2$ subcutaneously (SC) once per week (Days 1, 8, 15, 22), and oral dexamethasone 20 mg (Days 1, 2, 8, 9, 15, 16, 22, 23, 29, 30). In the Vd arm, patients received bortezomib 1.3 mg/m$^2$ SC (Days 1, 4, 8, 11) and oral dexamethasone 20 mg (Days 1, 2, 4, 5, 8, 9, 11, 12) during eight 3-week cycles; starting at cycle 9, each cycle lasted 5 weeks with bortezomib given on Days 1, 8, 15, and 22 and dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30. Dose modifications were allowed to help manage tolerability.[24]

## 2.2 | Study endpoints

Prespecified clinical endpoints included PFS, overall survival (OS), ORR, ≥VGPR rate, time to next treatment (TTNT), and adverse events (AEs) using Common Terminology Criteria for Adverse Events (version 4.03).

The PI-naïve and one prior LOT subgroups in the present analysis were prespecified subgroups in BOSTON,[24] whereas the lenalidomide-refractory and bortezomib-naïve subgroups were not prespecified. Patients were classified as being PI-naïve if they had never received a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) and as bortezomib-naïve if they had never received bortezomib. Lenalidomide-refractory status was defined as PD within 60 days of lenalidomide treatment or best response of stable disease or PD.

## 2.3 | Statistical analysis

As previously published,[24] Kaplan–Meier analysis was used to estimate PFS and OS, and reverse Kaplan–Meier OS analysis to estimate median follow-up time. We compared PFS and OS between treatment arms using a stratified log-rank test, estimated HRs and corresponding 95% CIs using a stratified Cox proportional hazards model, and analyzed ORR odds ratios using the Cochran–Mantel–Haenszel test. One-sided $p$ values are presented for efficacy endpoints. All reported $p$ values are nominal. There were no multiplicity adjustments for alpha. Because the BOSTON clinical trial allowed crossover from the Vd arm to the SVd arm after progression, we estimated OS with crossover adjustment using a two-stage estimation method.[27,28] Covariates used in stage one of this analysis included mean age at enrollment, number of ongoing medical history, number of AEs of special interest, Revised International Staging System stage, time of progression, physician experience with SVd, Eastern Cooperative Oncology Group (ECOG) performance status score, lymphocyte scores, prior exposure, sensory component of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Chemotherapy Induced Peripheral Neuropathy 20-item scale (QLQ-CIPN20), and number of prior anti-MM regimens. Only the ECOG, sensory component of EORTC QLQ-CIPN20, and lymphocyte scores were available at the secondary baseline, which was defined as progression for this analysis. Efficacy and safety analyses used the February 2021 BOSTON trial final data cut off.

# 3 | RESULTS

## 3.1 | Demographics and baseline characteristics

All 402 patients randomized in the BOSTON study were included in this post hoc analysis. The baseline characteristics of the SVd and VD treatment arms have been previously reported.[24] We classified 106 patients as lenalidomide-refractory, 95 patients as PI-naïve, 123 patients as bortezomib-naïve, and 198 patients as having had one prior LOT (Table 1). The patient characteristics in these subgroups were generally well balanced and consistent with the previously reported overall patient population.[24] However, in all four subgroups, high-risk cytogenetics in the SVd arm were higher than in the Vd arm. In the PI-naïve subgroup, patients in the SVd arm tended to have longer median time since diagnosis than the Vd arm (4.7 vs. 3.4 years, respectively). In the one prior LOT subgroup, a higher percentage of patients in the SVd arm had prior stem cell transplantation (SCT) than in the Vd arm (39% vs. 23%).

## 3.2 | Efficacy

Median follow-up for the overall population was 28.7 months for the SVd arm and 28.6 months for the Vd arm. At the time of this analysis, 21 (11%) patients in the SVd arm and 16 (8%) of patients in the Vd arm remained on treatment. The primary reason for discontinuation was disease progression in both arms. The median PFS for the overall population was 13.2 months (95% CI, 11.7–23.4) in the SVd arm compared with 9.5 months (95% CI, 8.1–10.8) in the Vd arm (HR 0.71 [95% CI, 0.54–0.93]; $p = .006$). The median crossover-adjusted OS was 36.7 months (95% CI, 30.2–not evaluable [NE]) with SVd and 32.8 months (95% CI, 25.1–NE) with Vd (HR 0.84 [95% CI, 0.60–1.17]; $p = .147$).

In the lenalidomide-refractory subgroup, two patients in the SVd arm and three patients in the Vd arm remained on treatment. The primary reason for treatment discontinuation was disease progression in this and all subgroups in this analysis. The median follow-up was 28.2 months for the SVd arm and 27.1 months for the Vd arm. In this subgroup, the median PFS was longer in the SVd arm compared with the Vd arm (10.2 vs. 7.1 months; HR 0.52 [95% CI, 0.31–0.88]; $p = .006$) (Figure 1A). The crossover-adjusted median OS was longer with SVd compared with Vd (26.7 vs. 18.6 months; HR 0.53 [95% CI, 0.30–0.95]; $p = .015$; Figure 2A). Lenalidomide-refractory patients in the SVd arm had a higher ORR (67.9% vs. 47.2%; odds ratio [OR] 2.59 [95% CI, 1.17–5.77]; $p = .009$) and a higher VGPR or better rate (35.8% vs. 24.5%, OR 1.74 [95% CI, 0.72–4.21]; $p = .109$) compared with the Vd arm (Figure 3A). The median TTNT was 13.0 months with SVd and 7.6 months with Vd ($p = .006$; Table 2).

**TABLE 1** Baseline demographics by subgroup.

| | Lenalidomide-refractory | | PI-naïve | | Bortezomib-naïve | | One prior LOT | |
|---|---|---|---|---|---|---|---|---|
| | SVd ($n = 53$) | Vd ($n = 53$) | SVd ($n = 47$) | Vd ($n = 48$) | SVd ($n = 61$) | Vd ($n = 62$) | SVd ($n = 99$) | Vd ($n = 99$) |
| Age, years median (range) | 65 (40–87) | 66 (45–85) | 68 (45–87) | 68 (44–84) | 68 (45–87) | 68 (44–84) | 67 (45–87) | 69 (44–90) |
| Sex, *n* (%) | | | | | | | | |
| Male | 37 (70) | 29 (55) | 26 (55) | 27 (56) | 36 (59) | 32 (52) | 55 (56) | 53 (54) |
| Female | 16 (30) | 24 (45) | 21 (45) | 21 (44) | 25 (41) | 30 (48) | 44 (44) | 46 (46) |
| ECOG performance status, *n* (%) | | | | | | | | |
| 0 | 23 (43) | 20 (38) | 15 (32) | 17 (35) | 19 (31) | 25 (40) | 39 (39) | 38 (38) |
| 1 | 26 (49) | 29 (55) | 26 (55) | 23 (48) | 34 (56) | 18 (29) | 52 (53) | 55 (56) |
| 2 | 4 (8) | 4 (8) | 6 (13) | 8 (17) | 8 (13) | 9 (15) | 8 (8) | 6 (6) |
| High-risk cytogenetic abnormalities,[a] *n* (%) | 29 (55) | 23 (43) | 20 (43) | 19 (40) | 28 (46) | 26 (42) | 50 (51) | 48 (48) |
| R-ISS stage, *n* (%) | | | | | | | | |
| I | 15 (28) | 11 (21) | 15 (32) | 14 (29) | 17 (28) | 18 (29) | 33 (33) | 23 (23) |
| II | 30 (57) | 32 (60) | 30 (64) | 25 (52) | 41 (67) | 33 (53) | 52 (53) | 62 (63) |
| III | 4 (8) | 7 (13) | 1 (2) | 4 (8) | 1 (2) | 4 (6) | 9 (9) | 6 (6) |
| Unknown | 4 (8) | 3 (6) | 1 (2) | 5 (10) | 2 (3) | 7 (11) | 5 (5) | 8 (8) |
| Time since diagnosis, years median (range) | 3.7 (0.9–12.0) | 3.5 (0.4–13.4) | 4.7 (0.4–23.0) | 3.4 (0.4–17.8) | 4.4 (0.4–23.0) | 4.2 (0.4–17.8) | 2.9 (0.4–23.0) | 2.8 (0.4–18.4) |
| Prior line of treatments, *n* (%) | | | | | | | | |
| 1 | 16 (30) | 14 (26) | 20 (43) | 25 (52) | 35 (57) | 34 (55) | 99 (100) | 99 (100) |
| 2 | 21 (40) | 20 (38) | 15 (32) | 14 (29) | 20 (33) | 18 (29) | | |
| 3 | 16 (30) | 19 (36) | 3 (6) | 9 (19) | 6 (10) | 10 (16) | | |
| Prior SCT, *n* (%) | 23 (43) | 20 (38) | 13 (28) | 10 (21) | 17 (28) | 14 (23) | 39 (39) | 23 (23) |
| Creatinine clearance at baseline, *n* (%) | | | | | | | | |
| <30 mL/min | 1 (2) | 4 (8) | 0 | 3 (6) | 0 | 4 (6) | 2 (2) | 4 (4) |
| 30–60 mL/min | 13 (25) | 15 (28) | 15 (32) | 15 (31) | 18 (30) | 18 (29) | 27 (27) | 31 (31) |
| >60 mL/min | 39 (74) | 34 (64) | 32 (68) | 30 (62) | 43 (70) | 40 (65) | 70 (71) | 64 (65) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; LOT, line of therapy; PI, proteasome inhibitor; R-ISS, Revised International Staging System; SCT, stem cell transplantation; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.

[a]High-risk cytogenetic abnormalities include any of the following: del(17p), t(4;14), t(14;16), amp 1q21.

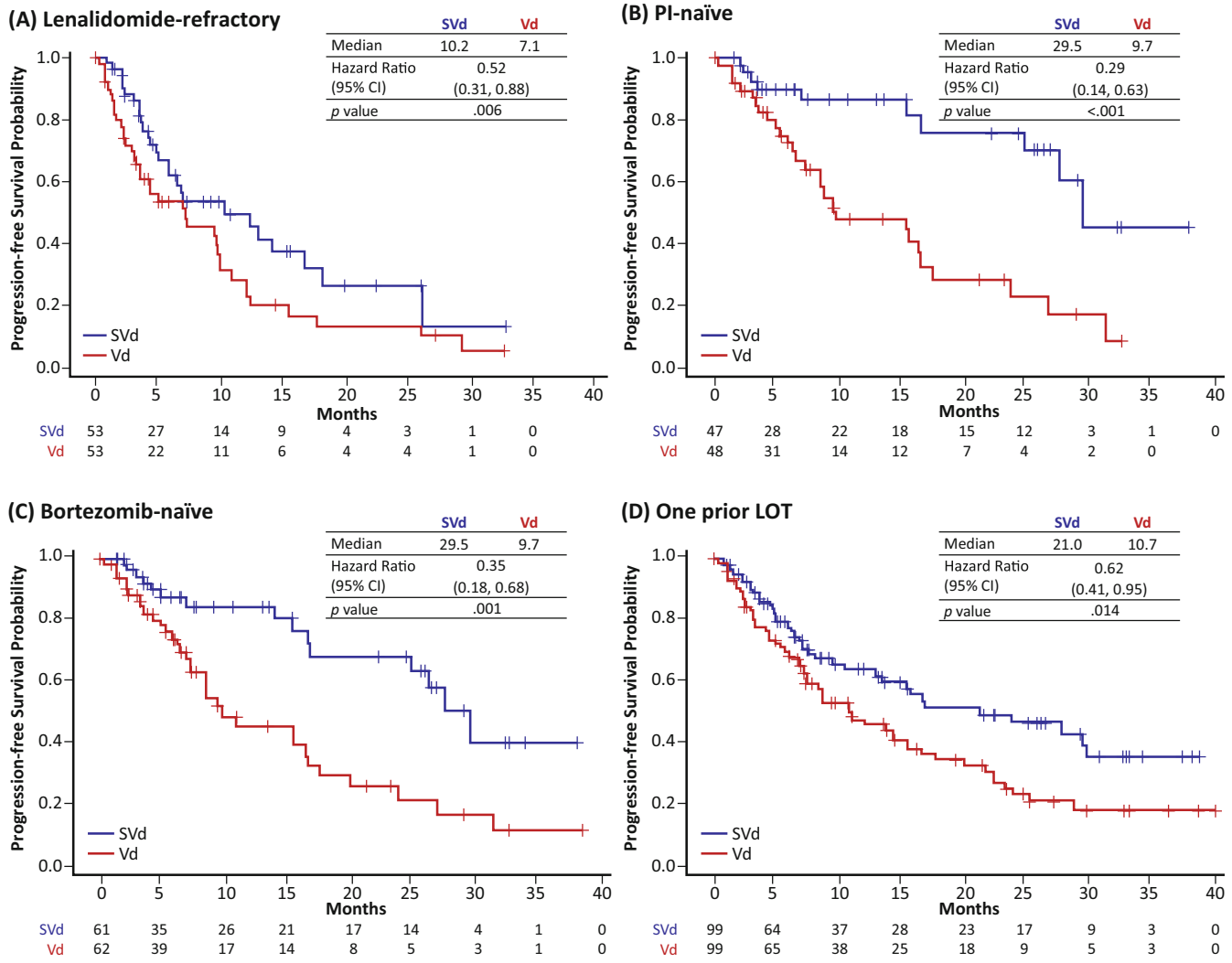


**FIGURE 1** Progression-free survival with (A) lenalidomide-refractory, (B) PI-naïve, (C) bortezomib-naïve, and (D) one prior LOT subgroups. CI, confidence interval; LOT, line of therapy; PI, proteasome inhibitor; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone. *p* values are 1-sided.

In the PI-naïve subgroup, eight patients in the SVd arm and three patients in the Vd arm remained on treatment. The median follow-up was 27.8 months for the SVd arm and 29.7 months for the Vd arm. The median PFS was 29.5 months with SVd compared with 9.7 months with Vd (HR 0.29 [95% CI, 0.14–0.63]; $p < .001$) (Figure 1B). The crossover-adjusted median OS was not reached (NR) in both treatment arms (Figure 2B). PI-naïve patients in the SVd arm had a numerically higher ORR (76.6% vs. 70.8%; OR 1.30 [95% CI, 0.51–3.33]; $p = .290$) and VGPR or better rate (53.2% vs. 41.7%, OR 1.54 [95% CI, 0.68–3.48]; $p = .154$) compared with the Vd arm (Figure 3B). The PI-naïve subgroup had a median TTNT of 30.2 months with SVd and 10.8 months with Vd ($p = .002$; Table 2).

In the bortezomib-naïve subgroup, nine patients in the SVd arm and four patients in the Vd arm remained on treatment. The median follow-up was 27.8 months for the SVd arm and 29.7 months for the Vd arm. The median PFS was 29.5 months with SVd compared with 9.7 months with Vd (HR 0.35 [95% CI, 0.18–0.68]; $p = .001$) (Figure 1C). The crossover-adjusted median OS was NR in both treatment arms (Figure 2C). The bortezomib-naïve subgroup had a numerically higher ORR (75.4% vs. 69.4%; OR 1.57 [95% CI, 0.68–3.64]; $p = .148$) and VGPR or better rate (49.2% vs. 41.9%, OR 1.51 [95% CI, 0.73–3.14]; $p = .138$) with SVd compared with Vd (Figure 3C). The bortezomib-naïve subgroup had a median TTNT of 29.8 months with SVd and 12.9 months with Vd ($p = .003$; Table 2).

In the one prior LOT subgroup, 12 patients in the SVd arm and seven patients in the Vd arm remained on treatment. The median follow-up was 29.0 months for the SVd arm and 28.7 months for the Vd arm. The median PFS was 21.0 months for the SVd arm compared with 10.7 months for the Vd arm (HR 0.62 [95% CI, 0.41–0.95]; $p = .014$) (Figure 1D). The crossover-adjusted median OS was NR in the SVd arm and 32.8 months in the Vd arm (Figure 2D). Patients with one prior LOT in the SVd arm had higher ORR (80.8% vs. 66.7%; OR 2.40 [95% CI, 1.22–4.70]; $p = .005$) and VGPR or better rate (52.5% vs. 29.3%, OR 2.65 [95% CI, 1.46–4.78]; $p < .001$) compared with the

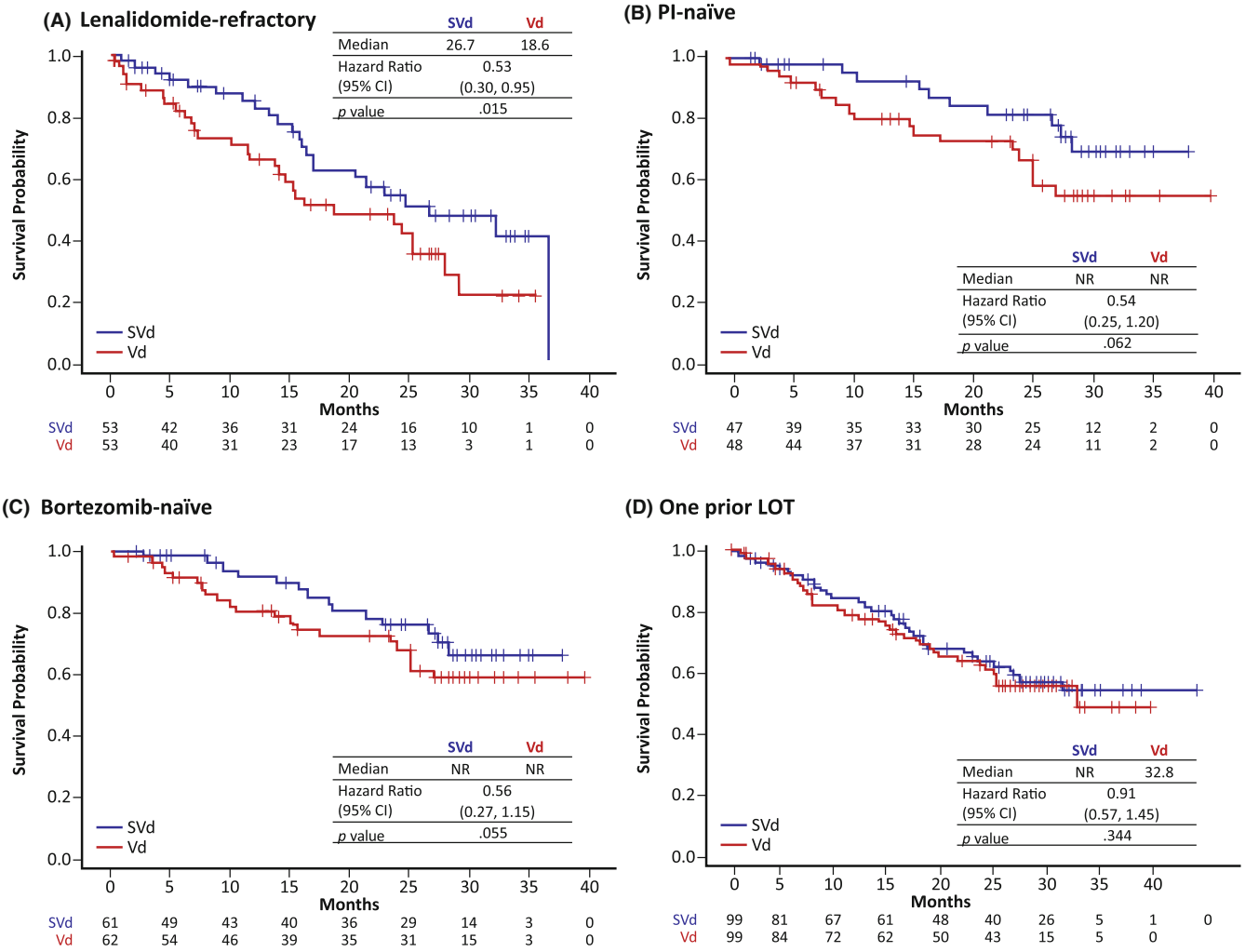


**FIGURE 2** Overall survival of (A) lenalidomide-refractory, (B) PI-naïve, (C) bortezomib-naïve, and (D) one-prior LOT subgroups. CI, confidence interval; LOT, line of therapy; NR, not reached; PFS, progression-free survival; PI, proteasome inhibitor; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone. *p* values are 1-sided.

Vd arm (Figure 3D). The one prior LOT subgroup had a median TTNT of 19.0 months with SVd and 12.9 months with Vd ($p = .028$; Table 2).

With the increased use of daratumumab-based regimens in earlier LOT, an exploratory analysis was performed in a small subgroup of patients with prior anti-CD38 monoclonal antibody exposure. In the BOSTON dataset, 11 patients in the SVd arm and six patients in the Vd arm had prior daratumumab. These patients had a median PFS of 12.2 months (95% CI, 2.86–NE) and 5.6 months (95% CI, 0.69–NE), respectively, for a HR of 0.93 (95% CI, 0.18–4.83).

### 3.3 | Safety

The median time to discontinuation for the respective SVd and Vd arms was 6.1 and 4.7 months for the LEN-refractory subgroup, 7.9 and 7.5 for the PI-naïve subgroup, 6.9 and 7.4 for bortezomib-naïve subgroup, and 7.4 and 8.3 for the 1 prior LOT subgroup. Treatment-emergent AEs across all grades were consistent with the previously reported BOSTON primary analysis (data not shown).[24] Grade 1–2 (Table S1) and grade 3–4 (Table 3) treatment-related AEs were generally consistent within and between subgroups.

## 4 | DISCUSSION

The results of this BOSTON post hoc study, which has a follow-up over twice as long as previously reported,[24,25] show efficacy benefits of treatment with SVd over Vd in all analyzed subgroups of patients with RRMM. The median PFS was longer with SVd compared with Vd in all subgroups, with the bortezomib-naïve and PI-naïve subgroups having the largest clinically meaningful improvements in PFS. In addition, the lenalidomide-refractory subgroup had longer OS with SVd. The TTNT for the SVd arm compared with the Vd arm was also extended in the lenalidomide-refractory ($p = .006$), PI-naïve ($p = .002$), and bortezomib-naïve ($p = .003$) subgroups.

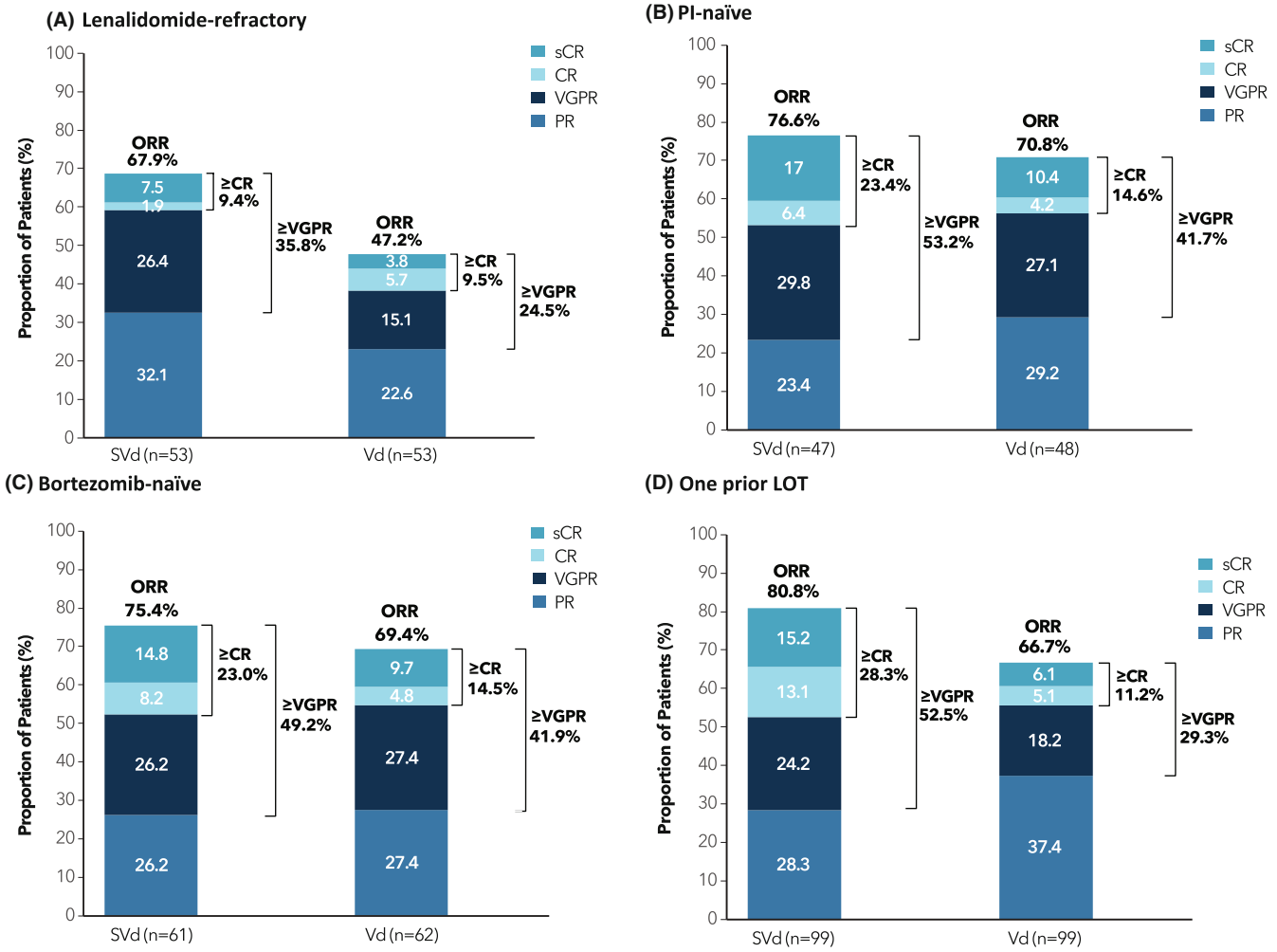


**FIGURE 3** Response rates of patients in (A) lenalidomide-refractory, (B) PI-naïve, (C) bortezomib-naïve, and (D) one prior LOT subgroups. CR, complete response; LOT, line of therapy; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; sCR, stringent complete response; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone; VGPR, very good partial response.

Specifically, BOSTON patients in the PI-naïve and bortezomib-naïve subgroups had a clinically meaningful 20-month improvement in median PFS with SVd compared with Vd (PI-naive: 29.5 vs. 9.7 months; HR 0.29; $p < .0001$; bortezomib-naïve: 29.5 vs. 9.7 months; HR 0.35; $p = .001$). PI-naïve patients randomized to SVd also had higher ORR (76.6% vs. 70.8%) and were more likely to achieve VGPR or better (53.2% vs. 41.7%) compared with patients randomized to Vd. The bortezomib-naïve subgroup randomized to SVd had a numerically higher ORR (75.4% vs. 69.4%). More patients in the SVd arm achieved a VGPR or better (49.2% vs. 41.9%). These findings are clinically relevant given that more patients are likely to be PI-naïve at first-relapse because of the previously noted increased use of DRd as first-line therapy for SCT-ineligible patients. The ENDEAVOR trial, which compared Kd with Vd, and the OPTIMISMM trial, which compared PVd with Vd, included similar RRMM subgroup analyses. Among 427 (45% of the total study population) patients with no prior bortezomib exposure in ENDEAVOR, the median PFS was not estimable in the Kd subgroup compared with 11.2 months with Vd (HR 0.48 [95% CI, 0.35–0.66]).[29] Patients with no prior bortezomib at first relapse ($n = 92$, 16% of the total study population) in OPTIMISMM had a median PFS of 20.7 months (95% CI, 8.3–NE) with PVd and 9.5 months (95% CI, 6.3–16.2) with Vd (HR 0.62 [95% CI, 0.35–1.11]; $p = .1055$).[30] The PFS seen with SVd versus Vd in the PI-naïve and bortezomib-naïve subgroups in the present BOSTON subgroup analysis appear to compare favorably with those reported with once per week SVd relative to PVd and Kd in the ENDEAVOR and OPTIMISMM trials.

The BOSTON lenalidomide-refractory subgroup treated with SVd had a clinically meaningful 8-month improvement in median OS (HR 0.53; $p = .015$), 3-month improvement in PFS (HR 0.52; $p = .006$), improvement in ORR (OR 2.59; $p = .009$), and an improvement in VGPR or better response (OR 1.74; $p = .109$) compared with the subgroup treated with Vd. With over 2 years of follow-up, the median crossover adjusted OS among patients with lenalidomide-refractory disease was 26.7 months with SVd compared with 18.6 months with Vd. In the ENDEAVOR trial, there were no statistically significant differences in PFS (median 8.6 vs. 6.6 months; HR 0.80 [95% CI, 0.57–1.11]) and OS (median OS 29.2 vs. 21.4 months;

**TABLE 2** Time to next treatment by subgroup.[a]

| Subgroup | SVd | Vd |
|---|---|---|
| **Lenalidomide-refractory** | **(*n* = 53)** | **(*n* = 53)** |
| Patients with events, *n* (%) | 34 (64) | 41 (77) |
| Patients censored, *n* (%) | 19 (36) | 12 (23) |
| Median TTNT (95% CI) | 13.0 (6.9–22.6) | 7.6 (4.7–11.7) |
| Hazard ratio (95% CI) | 0.55 (0.34–0.89) | |
| *p* Value | .006 | |
| **Subgroup** | **SVd** | **Vd** |
| **PI-naïve** | **(*n* = 47)** | **(*n* = 48)** |
| Patients with events, *n* (%) | 17 (36) | 34 (71) |
| Patients censored, *n* (%) | 30 (64) | 14 (29) |
| Median TTNT (95% CI) | 30.2 (26.7–NE) | 10.8 (10.2–21.2) |
| Hazard ratio (95% CI) | 0.42 (0.23–0.78) | |
| *p* Value | .002 | |
| **Subgroup** | **SVd** | **Vd** |
| **Bortezomib-naïve** | **(*n* = 61)** | **(*n* = 62)** |
| Patients with events, *n* (%) | 25 (41) | 41 (66) |
| Patients censored, *n* (%) | 36 (59) | 21 (34) |
| Median TTNT (95% CI) | 29.8 (22.9–NE) | 12.9 (10.4–21.2) |
| Hazard ratio (95% CI) | 0.47 (0.28–0.81) | |
| *p* Value | .003 | |
| **Subgroup** | **SVd** | **Vd** |
| **One prior LOT** | **(*n* = 99)** | **(*n* = 99)** |
| Patients with events, *n* (%) | 55 (56) | 70 (71) |
| Patients censored, *n* (%) | 44 (44) | 29 (29) |
| Median TTNT (95% CI) | 19.0 (15.3–27.4) | 12.9 (9.8–16.2) |
| Hazard ratio (95% CI) | 0.70 (0.49–1.01) | |
| *p* Value | .028 | |

Abbreviations: CI, confidence interval; HR, hazard ratio; LEN, lenalidomide; LOT, line of therapy; NE, not evaluable; PI, proteasome inhibitor; SVd, selinexor + bortezomib + dexamethasone; TTNT, time to next treatment; Vd, bortezomib + dexamethasone.
[a]*p* Values are 1-sided.

HR 0.86 [95% CI, 0.62–1.18]) with Kd compared with Vd, respectively, in 235 patients with lenalidomide-refractory disease, comprising 25% of the total study population.[29,31,32] In the OPTIMISMM trial, patients who were lenalidomide-refractory ($n = 391$, 70% of the total study population) had a median PFS of 9.5 months (95% CI, 8.0–11.3) with PVd and 5.6 months (95% CI, 4.4–7.0) with Vd (HR 0.65 [95% CI, 0.50–0.84]; $p = .0008$).[33] The OPTIMISMM trial recently reported OS data with no significant differences in the ITT population (HR 0.94, [95% CI, 0.77–1.15]; $p = .57$).[34] As such, the clinically meaningful benefits of SVd (prolonging PFS to 10.2 months coupled with the OS improvement) observed in this BOSTON subgroup analysis support another treatment option for a RRMM population with a critical unmet need, patients with lenalidomide-refractory disease.

Patients in the one prior LOT subgroup in BOSTON had clinically meaningful greater improvements in PFS (21.0 vs. 10.7 months; HR 0.62; $p = .014$), ORR (80.8% vs. 66.7%; OR 2.40; $p = .005$), and VGPR or better (52.5% vs. 29.3%; OR 2.65; $p < .001$) with SVd than with Vd. Patients with one prior LOT in the ENDEAVOR trial had improvements with Kd compared with Vd in median PFS (22.2 vs. 10.1 months; HR 0.45 [95% CI, 0.33–0.61]; $p < .0001$) and ORR (81.9% vs. 65.5%).[29] Patients with only one prior LOT in the OPTIMISMM trial had improved PFS with PVd compared with Vd (20.7 vs. 11.6 months; HR 0.54 [95% CI, 0.36–0.82]; $p = .0027$).[33] The results of our BOSTON one prior LOT subgroup analysis are similar to these other studies.

The safety profile for the overall patient population in this extended follow-up analysis was similar to that observed in the primary analysis of the BOSTON trial.[24] The safety profile for all subgroups was consistent both among themselves as well as with that observed for the overall patient population. Overall, AEs were mild and generally manageable.

A limitation of our analysis is that while the PI-naïve and one prior LOT subgroups were BOSTON prespecified subgroups,[24] the lenalidomide-refractory and bortezomib naïve subgroups were not prespecified. In addition, because of the timing of anti-CD38 treatment regulatory approvals and market availability, only a small number of patients received these therapies prior to entering the BOSTON trial.

The results of our post hoc analysis support the role for SVd as a treatment option upon first relapse, including for patients with lenalidomide-refractory disease. Our findings corroborate European clinical practice guidelines that include SVd (among other contemporary triplet combinations) as a second-line treatment option after VRd or DRd across a range of RRMM subpopulations, regardless of lenalidomide sensitivity, and at second or subsequent relapse in lenalidomide-refractory and PI-sensitive disease.[1] For younger patients who relapse after receiving SCT and lenalidomide maintenance, an anti-CD38 monoclonal antibody-based combination may be the preferred choice. For older patients, who are not eligible for SCT and are candidates for VRd or DRd, other options include IKd, PVd, and Kd; IPd could be considered an option after a minimum of 2 prior lines of treatment. However, these options may be limited. Carfilzomib carries a risk of new or worsening cardiac disorders especially in patients ≥75 years[35] which might preclude Kd eligibility. Also, while PVd is an effective option, guidelines[1] recommend switching drug class. Second-line treatment with SVd in patients with lenalidomide-refractory or daratumumab-refractory disease has the advantage of applying a double switch in the MOA. While efficacy findings for SVd in the latter setting are limited, our exploratory data from the small subgroup of BOSTON patients with prior daratumumab suggest that the benefit of SVd over Vd was sustained. It is likely that in the future, novel immunotherapies such as chimeric antigen receptor T-cell therapy and bispecific monoclonal antibodies will transition to treat early relapses. Viable options are needed in the interim before and in addition to these modalities as they receive regulatory approval and become more widely available.

**TABLE 3** Grade 3–4 treatment-related adverse events occurring in >5% of patients in any subgroup.

| | Lenalidomide-refractory | | PI-naïve | | Bortezomib-naïve | | One prior LOT | |
|---|---|---|---|---|---|---|---|---|
| | SVd | Vd | SVd | Vd | SVd | Vd | SVd | Vd |
| **Preferred term, *n* (%)** | **(*n* = 53)** | **(*n* = 52)** | **(*n* = 47)** | **(*n* = 48)** | **(*n* = 61)** | **(*n* = 62)** | **(*n* = 99)** | **(*n* = 99)** |
| Hematological | | | | | | | | |
| Thrombocytopenia | 24 (45) | 16 (31) | 16 (34) | 6 (12) | 20 (33) | 8 (13) | 37 (37) | 16 (16) |
| Anemia | 4 (8) | 2 (4) | 5 (11) | 1 (2) | 5 (8) | 1 (2) | 5 (5) | 2 (2) |
| Neutropenia | 2 (4) | 1 (2) | 2 (4) | 0 | 3 (5) | 0 | 9 (9) | 2 (2) |
| Non-hematological | | | | | | | | |
| Fatigue | 5 (9) | 0 | 7 (15) | 1 (2) | 10 (16) | 1 (2) | 12 (12) | 0 |
| Nausea | 5 (9) | 0 | 4 (9) | 0 | 5 (8) | 0 | 8 (8) | 0 |
| Diarrhea | 6 (11) | 0 | 3 (6) | 1 (2) | 3 (5) | 1 (2) | 3 (3) | 0 |
| Neuropathy peripheral | 2 (4) | 4 (8) | 2 (4) | 5 (10) | 2 (3) | 7 (11) | 6 (6) | 9 (9) |
| Asthenia | 1 (2) | 1 (2) | 2 (4) | 1 (2) | 2 (3) | 1 (2) | 9 (9) | 2 (2) |
| Cataract | 7 (13) | 1 (2) | 5 (11) | 1 (2) | 8 (13) | 1 (2) | 8 (8) | 0 |
| Vomiting | 4 (8) | 0 | 4 (9) | 0 | 4 (7) | 0 | 5 (5) | 0 |

Abbreviations: LOT, line of therapy; PI, proteasome inhibitor; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + dexamethasone.

In conclusion, this post hoc subgroup analysis presents clinically meaningful outcomes with SVd over Vd in RRMM populations that include patients with lenalidomide-refractory disease, no prior PI or bortezomib exposure, and treatment with only one prior LOT. These findings stand favorably with existing alternatives and may be particularly relevant for lenalidomide-refractory patients, a group which has the fewest viable treatment options. The safety profile was similar to that observed in the BOSTON trial, which in turn suggests that meaningfully translating these findings to real world practice is likely.[36] These clinically-relevant outcomes emphasize the importance of a double mode of action switch for patients with RRMM and further support the use of SVd in patients who are lenalidomide-refractory, PI-naïve, or who had relapsed after first-line treatment and also underscores the synergy between selinexor and bortezomib.[7,14–16]

## AUTHOR CONTRIBUTIONS

MVM, ME, XL, MGM, MC, MD, and PM collected the data; MB, CLP, and GMM designed the analysis; GMM performed the statistical analyses; and all authors were involved in the interpretation of data, contributed to the manuscript review and revisions, and approved the final version for submission.

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## CONFLICT OF INTEREST STATEMENT

MVM received research funding from Janssen, Amgen, Celgene/Brystol Myers Squibb (BMS), Pfizer, and GSK, honoraria from Janssen, Amgen, Celgene/BMS, Pfizer, GSK, Sanofi, Menarini Group, and AbbVie, and participated in consulting/advisory roles for Janssen, Amgen, BMS-Celgene, Pfizer, GSK, Sanofi, Menarini Group, and Roche. ME received research funding from Amgen, BMS, and Janssen, honoraria from Amgen, BMS, Janssen, GSK, Sanofi, Takeda, and Pfizer, and participated in consulting/advisory roles for Amgen, BMS, Janssen, GSK, Sanofi, Takeda, and Pfizer. MGM received honoraria from Janssen, Sanofi, and GSK, and participated in consulting/advisory roles for Menarini Group, Janssen, and Sanofi. MD received honoraria from and participated in consulting/advisory roles for Amgen, Beigene, Janssen, Sanofi, Regeneron, Takeda, Menarini Group, GSK, and BMS. PGR received research funding from Oncopeptides, Celgene/BMS, Karyopharm, and Takeda, and participated in consulting/advisory roles for Oncopeptides, Celgene/BMS, Karyopharm, Sanofi, and GSK. PM received honoraria and participated in consulting/advisory roles from Janssen, Celgene/BMS, Amgen, Takeda, AbbVie, Sanofi, and Pfizer. CLP, MB, and GMM are employed by the Menarini Group. The other authors (XL, MGM) have no conflicts of interest to disclose.

## DATA AVAILABILITY STATEMENT

The data that support the results of this study may be requested for products and the relevant indications that have been authorized by the regulatory authorities in Europe/the United States (or, if not, 2 years have elapsed since the study completion). The Menarini Group, will review requests individually to determine whether (1) the requests are legitimate and relevant and meet sound scientific research principles, (2) the requests are within the scope of the participants' informed consent, and (3) the request is compliant with any

applicable law and regulation and with any contractual relationship that Menarini Group and its affiliates and partners have in place with respect to the study and/or the relevant product. Prior to making data available, requestors will be required to agree in writing to certain obligations, including without limitation, compliance with applicable privacy and other laws and regulations. Proposals should be directed to medicalinfo@menarini-stemline.com.

## ORCID

*Monika Engelhardt* https://orcid.org/0000-0003-0405-1676
*Meletios Dimopoulos* https://orcid.org/0000-0001-8990-3254
*Paul G. Richardson* https://orcid.org/0000-0002-7426-8865
*Philippe Moreau* https://orcid.org/0000-0003-1780-8746

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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