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RESEARCH ARTICLE

Effect of age and frailty on the efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma

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Abstract

Elderly and frail patients with multiple myeloma (MM) are more vulnerable to the toxicity of combination therapies, often resulting in treatment modifications and suboptimal outcomes. The phase 3 BOSTON study showed that once-weekly selinexor and bortezomib with low-dose dexamethasone (XVd) improved PFS and ORR compared with standard twice-weekly bortezomib and moderate-dose dexamethasone (Vd) in patients with previously treated MM. This is a retrospective subgroup analysis of the multicenter, prospective, randomized BOSTON trial. Post hoc analyses were performed to compare XVd versus Vd safety and efficacy according to age and frailty status (<65 and ≥65 years, nonfrail and frail). Patients ≥65 years with XVd had higher ORR (OR 1.77, p = .024), ≥VGPR (OR, 1.68, p = .027), PFS (HR 0.55, p = .002), and improved OS (HR 0.63, p = .030), compared with Vd. In frail patients, XVd was associated with a trend towards better PFS (HR 0.69, p = .08) and OS (HR 0.62, p = .062). Significant improvements were also observed in patients <65 (ORR and TTNT) and nonfrail patients (PFS, ORR, ≥VGPR, and TTNT). Patients treated with XVd had a lower incidence of grade ≥ 2 peripheral neuropathy in ≥65 year-old (22% vs. 37%; p = .0060) and frail patients (15% vs. 44%; p = .0002). Grade ≥3 TEAEs were not observed more often in older compared to younger patients, nor in frail compared to nonfrail patients. XVd is safe and effective in patients <65 and ≥65 and in nonfrail and frail patients with previously treated MM.

1 | INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm of clonal B cells originating in the bone marrow (BM).[1-4] Novel therapeutic approaches and drug combinations are increasingly used to achieve deeper and more durable responses and to potentially overcome mechanisms of resistance. Commonly used multi-drug combinations include immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies (mAbs), alkylating agents and corticosteroids.[5-7] The median age of MM patients at diagnosis is just under 70 years, and MM-related deaths primarily occur in patients ages 65 to 84 years.[8,9] Although there has been an increase in survival for MM patients overall, older patients have not benefitted from novel therapies to the same extent as younger patients.[10] This is highlighted by the stagnant 10-year survival rate reported for patients 75 and older of <10%, while an improvement from approximately 10% to 35% was observed in patients younger than 65.[11] While chronological age is an important factor in determining outcomes, the health status, or fitness, of a patient also plays a key role in the success of a treatment.[12] Higher chronological age is often associated with reduced organ function, such as cardiac, renal, and gastrointestinal impairment, and these comorbidities, in combination with the polypharmacy often linked to their treatment, can cause increased toxicity and decreased efficacy.[13,14] However, younger patients can also be vulnerable, and older patients can be remarkably resilient and tolerate intensive chemotherapy.[15] Thus, frailty, encompassing age and comorbidities, can be a clinically

useful criterion that is predictive of survival and toxicity outcomes and is associated with increased death rate, disease progression, and treatment discontinuation.[16] Novel therapies for patients with MM, particularly those who are older and/or frail, are required.

Exportin 1 (XPO1) is a nuclear exporter that controls the nuclear and cytoplasmic localization of most tumors suppressor proteins, IκB (the inhibitor of NF-κB), numerous RNAs, and the glucocorticoid receptor.[17,18] Selinexor forces the nuclear retention of tumor suppressor proteins and other macromolecules by preventing nuclear export without affecting import.[19,20] Overexpression of XPO1 is found in a variety of cancers including MM, and has been linked to an increase in MM bone disease and poor clinical outcomes.[4,18]

Selinexor is a potent, oral selective inhibitor of nuclear export (SINE) compound that binds to Cys528 in the cargo-binding pocket of XPO1 and blocks its function. Selinexor has been approved for the treatment of previously treated MM[4,18] as well as diffuse large B-cell lymphoma.[21,22] A recent FDA approval (December 18, 2020) was granted based on the phase 3 BOSTON trial in 402 patients with previously treated MM, which demonstrated that the triplet combination of once-weekly selinexor with bortezomib and low dose dexamethasone (XVd) was superior to the standard twice-weekly combination of bortezomib and moderate dose dexamethasone (Vd).[23]

Due to the considerable variability of comorbidities and fitness, defining optimal treatment strategies for elderly or frail patients is challenging.[24] As a consequence, these patients are less likely to receive novel agents and less likely to be included in clinical trials.[25] A number of frailty scores that support clinical decision making in patients with MM have been described,[26-30] and a simplified frailty score that distinguishes frail from non-frail patients based on the Charlson Comorbidity Index (CCI), Eastern Cooperative Oncology Group performance status score (ECOG PS), and age has recently been tested and validated as a predictor of outcome.[31,32] Here we present the results of efficacy and safety analyses of subgroups from the BOSTON study based on age and the simplified frailty score.

2 | MATERIALS AND METHODS

2.1 | Study details

Details of the BOSTON trial (ClinicalTrials.gov identifier: NCT03110562) have been previously published.[23] Patients were ≥ 18 years of age, had received 1–3 prior lines of therapy, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2, and had measurable myeloma according to the International Myeloma Working Group criteria.[33] Patients had to have acceptable hepatic, renal, and hematopoietic function. Exclusion criteria included patients who had PN grade ≥3 or grade 2 with pain, active plasma cell leukemia or systemic light chain amyloidosis and patients who had radiation, chemotherapy, or immunotherapy within 2 weeks prior to start of study. Patients could not have prior treatment with a SINE compound, active GVHD, prior ASCT within 1 month or allogenic stem cell transplantation within the 4 months prior to treatment. For study treatment, patients were randomized into two arms: The XVd arm included treatment with oral selinexor 100 mg once weekly plus bortezomib 1.3 mg/m^2 subcutaneously *once* weekly and low dose (40 mg/week) dexamethasone. In the Vd arm, patients were treated with standard bortezomib 1.3 mg/m^2 subcutaneously twice weekly with moderate dose (80 mg/week) dexamethasone until cycle nine after which bortezomib dosing was reduced to once weekly plus 40 mg of dexamethasone weekly. Patients treated with selinexor received 1–2 prophylactic anti-nausea agents. Renal function was estimated using the Cockcroft-Gault equation; impairment was defined as estimated creatinine clearance (CrCl) < 60 ml/min.

2.2 | Frailty assessment

Frailty categories were assigned as previously described,[31,32] and were based on age, CCI, and ECOG PS. Briefly, patients received score points depending on age (≤75 years = 0 points; 76–80 years = 1 point, >80 years = 2 points), CCI (≤1 = 0 points; > 1 = 1 point), and ECOG PS (0 = 0 points; 1 = 1 point; ≥2 = 2 points) and the sum of score points defined their classification as nonfrail (0–1 points) or frail (≥2 points).[31]

2.3 | Statistical analysis

Post hoc statistical analyses were performed to compare XVd versus Vd safety and efficacy in patients according to age and frailty status (<65 and ≥65 years, nonfrail and frail). Response rates were calculated applying the Cochran–Mantel–Haenszel method. The Kaplan–Meier method and log-rank test were employed for the survival analyses.

3 | RESULTS

3.1 | Baseline characteristics and demographics

Among the 402 patients (195 on XVd, 207 on Vd) enrolled in the BOSTON study, 241 (60%) were ≥65 years of age with 109 in the XVd arm; 161 patients were <65 years of age with 86 and 75 patients on the XVd and Vd arms, respectively (Figure S1). Nonfrail patients (N = 272) included 129 in the XVd arm and 143 in the Vd arm; 130 patients were considered frail with 66 in the XVd arm and 64 in the Vd arm. Frail patients had a higher median age in both treatment arms (XVd 71 years and Vd 76 years) compared to nonfrail patients (XVd 63 years and Vd 65 years). Among patients ≥65 years, 50.5% in the XVd arm and 50.0% in the Vd arm had tumors with high-risk cytogenetics, and this was 48.8% and 39.7% in patients <65. Nonfrail patients in both the XVd and Vd arm had a higher rate of tumors with high-risk cytogenetics (51.2% vs. 47.6% respectively) compared to their frail counterparts with 47% in the XVd arm and 42.2% in the Vd

TABLE 1 Patient Characteristics

Characteristic	<65 years		≥65 years		Nonfrail		Frail	
	XVd (n = 86)	Vd (n = 75)	XVd (n = 109)	Vd (n = 132)	XVd (n = 129)	Vd (n = 143)	XVd (n = 66)	Vd (n = 64)
Median Age, years (range)	57.0 (40–64)	58.0 (38–64)	71.0 (65–87)	71.5 (65–90)	63.0 (40–80)	65.0 (38–78)	71.0 (47–87)	76.0 (48–90)
Years since initial diagnosis, median (range)	3.50 (0.4–12.7)	4.13 (0.7–13.4)	3.92 (0.8–23.0)	3.16 (0.4–22.0)	3.87 (0.8–23.0)	3.85 (0.6–18.4)	3.76 (0.4–13.8)	2.86 (0.4–22.0)
High Risk Cytogenetics, n (%)	42 (48.8)	29 (38.7)	55 (50.5)	66 (50.0)	66 (51.2)	68 (47.6)	31 (47.0)	27 (42.2)
del(17p)	7 (8.1)	5 (6.7)	14 (12.8)	11 (8.3)	15 (11.6)	11 (7.7)	6 (9.1)	5 (7.8)
t(14;16)	2 (2.3)	5 (6.7)	5 (4.6)	6 (4.5)	3 (2.3)	8 (5.6)	4 (6.1)	3 (4.7)
t(4;14)	12 (14.0)	12 (16.0)	10 (9.2)	16 (12.1)	17 (13.2)	24 (16.8)	5 (7.6)	4 (6.3)
amp 1q21	33 (38.4)	18 (24.0)	47 (43.1)	53 (40.2)	54 (41.9)	50 (35.0)	26 (39.4)	21 (32.8)
R-ISS disease stage at screening, n (%)	26 (30.2)	26 (34.7)	30 (27.5)	26 (19.7)	43 (33.3)	42 (29.4)	13 (19.7)	10 (15.6)
I	47 (54.7)	38 (50.7)	70 (64.2)	87 (65.9)	69 (53.5)	80 (55.9)	48 (72.7)	45 (70.3)
II	7 (8.1)	4 (5.3)	5 (4.6)	12 (9.1)	8 (6.2)	10 (7.0)	4 (6.1)	6 (9.4)
III	6 (7.0)	7 (9.3)	4 (3.7)	7 (5.3)	9 (7.0)	11 (7.7)	1 (1.5)	3 (4.7)
Unknown								
Charlson Comorbidity Index, mean (SD)	0.6 (0.94)	0.7 (1.10)	1.1 (1.27)	1.0 (1.07)	0.4 (0.62)	0.6 (0.85)	2.0 (1.27)	1.5 (1.27)
Frail[a], n (%)	15 (17.4)	9 (12.0)	51 (46.8)	55 (41.7)	0	0	66 (100.0)	64 (100.0)
Nonfrail[a], n (%)	71 (82.6)	66 (88.0)	58 (53.2)	77 (58.3)	129 (100.0)	143 (100.0)	0	0
Creatinine Clearance, n (%)								
< 30 ml/min	0	0	3 (2.8)	10 (7.6)	1 (0.8)	0	2 (3.0)	10 (15.6)
30–60 ml/min	9 (10.5)	6 (8.0)	44 (40.4)	54 (40.9)	23 (17.8)	32 (22.4)	30 (45.5)	28 (43.8)
Number of prior lines of therapy, n (%)								
1	43 (50.0)	29 (38.7)	56 (51.4)	70 (53.0)	64 (49.6)	71 (49.7)	35 (53.0)	28 (43.8)
2	28 (32.6)	26 (34.7)	37 (33.9)	38 (28.8)	43 (33.3)	42 (29.4)	22 (33.3)	22 (34.4)
3	15 (17.4)	20 (26.7)	16 (14.7)	24 (18.2)	22 (17.1)	30 (21.0)	9 (13.6)	14 (21.9)
Prior ASCT, n (%)	41 (47.7)	37 (49.3)	35 (32.1)	26 (19.7)	64 (49.6)	59 (41.3)	12 (18.2)	4 (6.3)

[a]Based on Facon et al.[31]

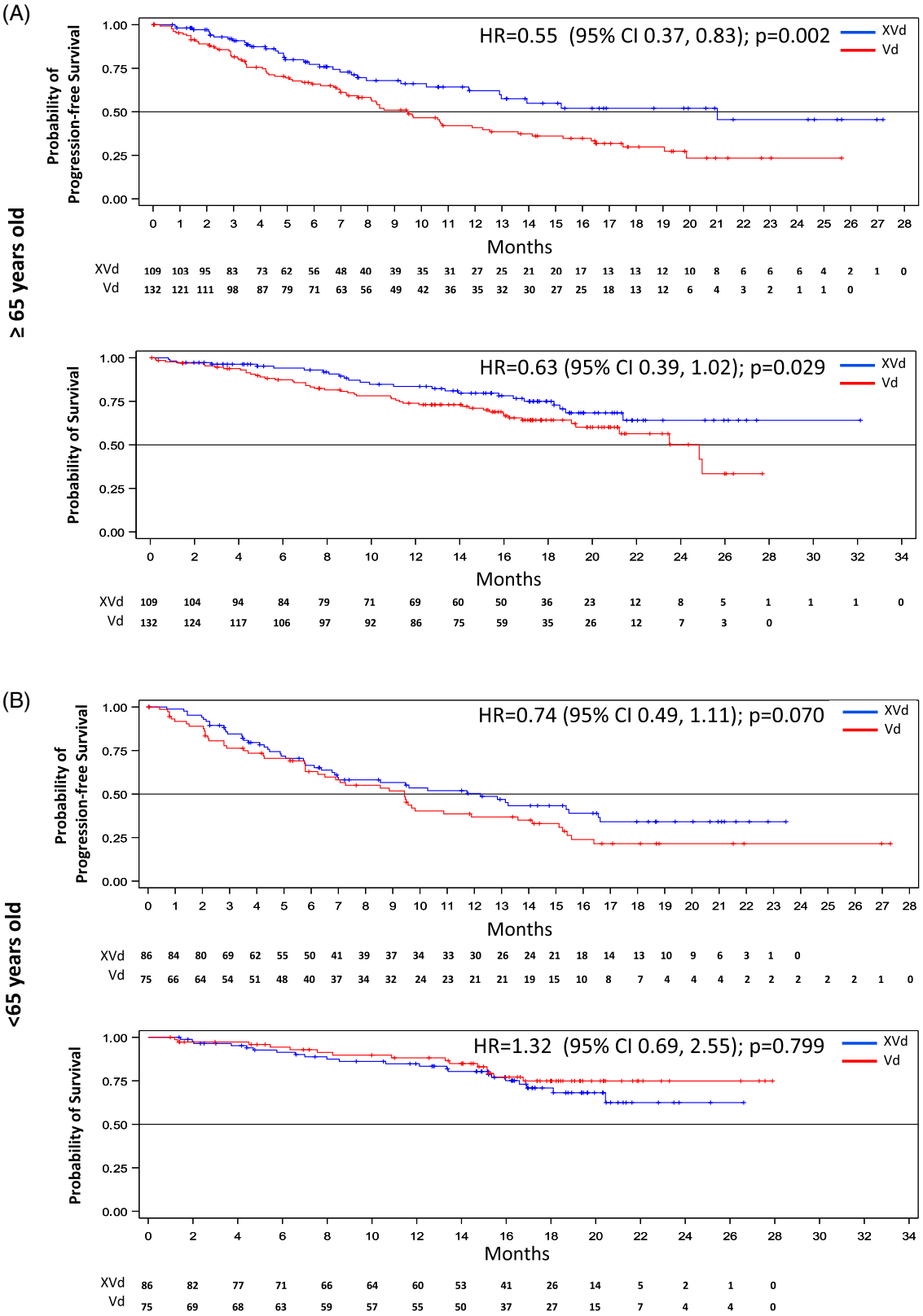

FIGURE 1 Progression-free and overall survival according to age. Kaplan–Meier curves for patients (A) under 65 years and (B) 65 years or older [Color figure can be viewed at wileyonlinelibrary.com]

arm. Frail status was higher in patients ≥65 years with 46.8% and 41.7% in the XVd and Vd arms, respectively, compared to 17.4% and 12.0% of patients <65 years.

Rates of renal impairment were similar between treatment groups but increased with age. Frail patients had a higher rate of moderate renal impairment with 3.0% in the XVd arm and 15.6% in the Vd

having a CrCl <30 ml/min as compared to 0.8% in the XVd arm and 0% in the Vd arm of the nonfrail patients. Amongst patients ≥65, 10.4% (XVd 2.8% and Vd 7.6%) had CrCl <30 ml/min, while there were none in the <65 group. A larger number of patients who were ≥65 (81.3%; XVd 40% and Vd 40.9%) or frail (89.3%; XVd 45.5% and Vd 43.8%) had mild renal impairment with CrCl between 30–60 ml/min, compared to 18.5% of patients who were <65 (XVd 10.5% and Vd 8.0%) or nonfrail (40.2%; XVd 17.8% and Vd 22.4%). Patients ≥65 were less likely to have received prior ASCT (32.1% XVd and 19.7% Vd) compared to patients <65 (47.7% XVd and 49.3% Vd. Frail patients were less likely to have undergone ASCT (18.2% XVd and 6.3% Vd) compared to nonfrail, with 49.6% XVd and 41.3% Vd. All other baseline characteristics were balanced between subgroups (Table 1).

3.2 | Efficacy

Median progression-free survival (PFS) was prolonged with XVd compared with Vd, in both age groups: ≥65 (HR, 0.55 [95% CI, 0.37–0.83] p = .002) (Figure 1(A) and Table S1) and < 65, (HR, 0. 74 [95% CI, 0.50–1.11], p = .070) (Figure 1(B) and Table S1). The same XVd versus Vd trends were observed in both the nonfrail and frail groups. Nonfrail patients had a significantly longer PFS (median 13.24 months) on XVd as compared to Vd (median 9.43 months) (HR, 0.66 [95% CI, 0.47–0.93], p = .008) (Figure 2(A)). Frail patients showed a trend towards improvement on the triplet (XVd, median 13.93 months vs. Vd, 9.46 months; HR, 0.69 [95% CI, 0.40–1.17], p = .081) (Figure 2(B)).

Treatment with Vd in patients ≥65 was associated with a lower ORR (64.4%) than treatment with XVd (76.1%) (OR, 1.77 [95% CI, 1.00–3.11], p = .024), while the ORR in those <65 years was 76.7% in the XVd arm and 58.7% in the Vd arm (OR, 2.33 [95% CI, 0.50–1.18], p = .007). Nonfrail patients had a significantly lower ORR in the Vd arm as compared with XVd: 62.9% Vd versus 79.8% XVd (OR, 2.33 [95% CI, 1.35–4.04], p = .001), whereas frail patients did not (60.9% Vd vs. 69.7 XVd; OR, 1.48 [95% CI, 0.71–3.05], p = .148).

Rates of very good partial response or better (≥VGPR) in patients ≥65 were higher in the XVd arm as compared with the Vd arm: 43.1% versus 31.1% (OR, 1.68 [95% CI, 0.99–2.86], p = .027). Treatment with XVd also resulted in a higher ≥VGPR in patients <65 compared to those treated with Vd (46.5% vs. 34.7%) (OR, 1.64 [95% CI, 0.87–3.10], p = .064) (Table S1). Frail patients had a numerically higher rate of ≥VGPR in the XVd arm than the Vd arm (36.4% vs. 29.7%) (OR, 1.35 [95% CI, 0.65–2.82], p = .210), while nonfrail patients treated with XVd had a significantly higher rate of VGPR or better compared to Vd: 48.8% vs. 33.6% (OR, 1.89 [95% CI, 1.16–3.08], p = .005) (Table S2).

The median duration of response (DOR) was not reached in patients <65 in the XVd arm and was 12.88 months in the Vd arm (HR, 0.63 [95% CI, 0.37–1.06], p = .039). Amongst the patients ≥65, the median DOR was 14 months in the XVd arm and 12.68 months in the Vd arm (HR, 0.84 [95% CI, 0.48–1.42], p = .260). Both nonfrail and frail patients tended to have longer DORs when treated with XVd as compared to Vd with HRs of 0.75 and 0.89 respectively (p = .088 for both).

Median overall survival (OS) was not reached in patients ≥65 in the XVd arm compared to the Vd arm of 24.48 months (HR, 0.63 [95% CI, 0.39–1.02], p = .029) (Figure 1(A)). Patients <65 in both treatment arms did not reach median OS (HR, 1.32 [95% CI, 0.69–2.55], p = .799) (Figure 1(B)). In both treatment arms, the median OS was not reached in nonfrail patients (HR, 0.96 [95% CI, 0.59–1.56], p = .430) (Figure 2(A)). For frail patients, the median OS was not reached in the XVd treatment arm and was 23.49 months in the Vd arm (HR, 0.62 [95% CI, 0.34–1.14], p = .061) (Figure 2(B)).

The time-to-next-treatment (TTNT) in patients ≥65 was significantly longer with XVd treatment (median 18.23 months) as compared to the Vd arm (11.73 months; HR, 0.63 [95% CI, 0.39–1.02], p = .029). In patients <65 there was a shorter median TTNT in the Vd arm as compared to the XVd arm (10.38 months vs. 15.34 months; HR, 0.69 [95% CI, 0.46–1.03], p = .035). Frail patients showed trends to improved TTNT on XVd versus Vd (HR, 0.75 [95% CI, 0.47–1.21], p = .121), while nonfrail patients had a longer TTNTs with XVd than Vd (medians 16.92 months vs. 10.81 months; HR, 0.61 [95% CI, 0.44–0.84], p = .001).

3.3 | Safety

The majority of patients experienced at least one treatment-emergent adverse event (TEAE). Overall, both hematological and non-hematological grade ≥ 3 TEAEs were observed more frequently in patients treated with XVd compared to those treated with Vd across all age and frailty groups analyzed (Table 2). However, grade ≥ 3 TEAEs were not observed more often in older compared to younger patients, nor in the frail compared to the nonfrail group. Incidence of AEs from pneumonia in the XVd arm was 2.3% in nonfrail patients and 3.5% in <65 as compared to 5.5% in patients ≥65 and 9.1% in frail.

Rates of PN were consistently lower on XVd than on Vd: Amongst patients ≥65 years, PN of any grade was lower in the XVd arm (32.1%) compared to the Vd arm (46.5%); (OR 0.57 [95%CI 0.34–0.97], p = .017), including a lower incidence of grade 3 PN (XVd 3.7% vs. Vd 11.6%). Patients <65 followed a similar trend of PN AEs of any grade: 32.6% in the XVd arm and 48.0% in the Vd arm (OR 0.42 [95% CI 0.21–0.82], p = .006). Frail patients had a significantly lower rate of PN AEs of any grade when treated with XVd compared to Vd: 27.3% versus 50.0% (OR 0.36 [95%CI 0.17–0.76], p = .003). The same trend was observed in nonfrail patients with PN AEs of any grade, with a rate of 34.9% in the XVd arm versus 45.8% in the Vd arm (OR 0.61 [95%CI 0.37–0.99], p = .024). Grade 3 PN AEs were only reported in the Vd arm in frail patients with an incidence of 14.5%. Nonfrail patients had similar rates of grade 3 PN AEs in both arms: XVd 6.2% versus Vd 6. 3%.

Serious adverse events (SAEs) occurred more frequently in the XVd arm versus the Vd arm in all age and frailty subgroups analyzed

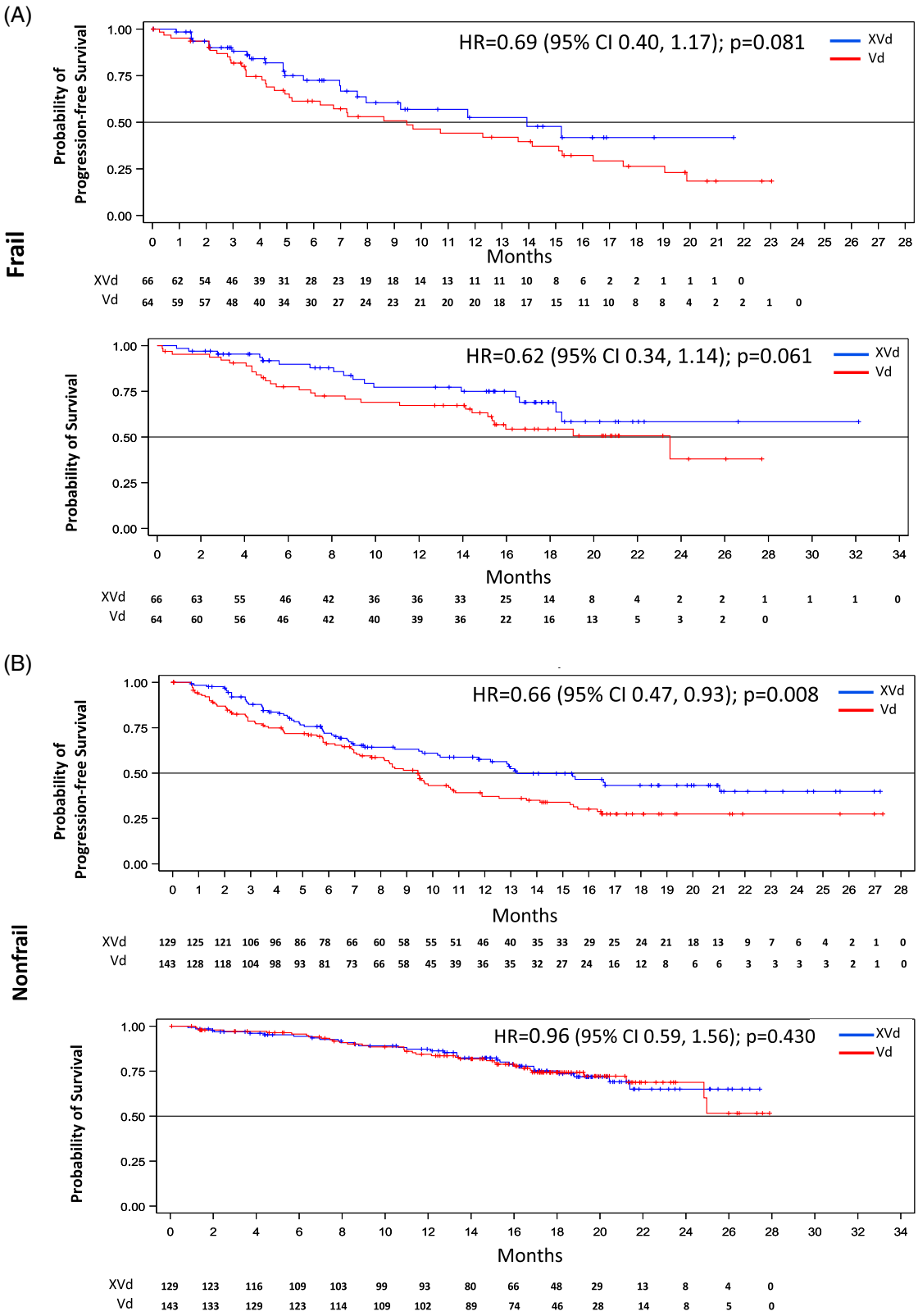

FIGURE 2 Progression-free and overall survival according to frailty status. Kaplan–Meier curves for (A) frail and (B) nonfrail patients [Color figure can be viewed at wileyonlinelibrary.com]

and were observed more often in patients ≥65 years and frail patients (Table 2). However, SAEs from pneumonia trended slightly lower in patients receiving XVd compared to Vd in both the nonfrail patients (8.5% vs. 11.3%) and in patients ≥65 (10.1% vs. 13.2%).

TABLE 2 Treatment-emergent adverse events in patients according to age and frailty

	<65 years		≥65 years		Nonfrail		Frail	
	XVd (n = 86)	Vd (n = 75)	XVd (n = 109)	Vd (n = 129)	XVd (n = 129)	Vd (n = 142)	XVd arm (n = 66)	Vd arm (n = 62)
Grade ≥ 3 Adverse Events, n (%)								
Thrombocytopenia	51 (59.3)	23 (30.7)	66 (60.6)	32 (24.8)	81 (62.8)	39 (27.5)	36 (54.5)	16 (25.8)
Anemia	35 (40.7)	18 (24.0)	36 (33.0)	29 (22.5)	46 (35.7)	32 (22.5)	25 (37.9)	15 (24.2)
Neutropenia	16 (18.6)	2 (2.7)	13 (11.9)	10 (7.8)	20 (15.5)	9 (6.3)	9 (13.6)	3 (4.8)
Leukopenia	7 (8.1)	0	3 (2.8)	3 (2.3)	6 (4.7)	2 (1.4)	4 (6.1)	1 (1.6)
Lymphopenia	5 (5.8)	3 (4.0)	6 (5.5)	1 (0.8)	10 (7.8)	4 (2.8)	1 (1.5)	0
Fatigue	34 (39.5)	13 (17.3)	48 (44.0)	24 (18.6)	55 (42.6)	28 (19.7)	27 (40.9)	9 (14.5)
Asthenia	20 (23.3)	10 (13.3)	28 (25.7)	17 (13.2)	24 (18.6)	18 (12.7)	24 (36.4)	9 (14.5)
Hyponatremia	7 (8.1)	2 (2.7)	8 (7.3)	1 (0.8)	10 (7.8)	3 (2.1)	5 (7.6)	0
Nausea	41 (47.7)	8 (10.7)	57 (52.3)	12 (9.3)	65 (50.4)	15 (10.6)	33 (50.0)	5 (8.1)
Vomiting	20 (23.3)	2 (2.7)	20 (18.3)	7 (5.4)	25 (19.4)	7 (4.9)	15 (22.7)	2 (3.2)
Diarrhea	34 (39.5)	16 (21.3)	29 (26.6)	35 (27.1)	43 (33.3)	33 (23.2)	20 (30.3)	18 (29.0)
Serious treatment-emergent adverse events	40 (46.5)	19 (25.3)	61 (56.0)	58 (45.0)	62 (48.1)	47 (33.1)	39 (59.1)	30 (48.4)
Dose Reduction	60 (69.8)	37 (49.3)	81 (74.3)	67 (51.9)	93 (72.1)	71 (50.0)	48 (72.7)	33 (53.2)
Discontinuation	11 (12.8)	7 (9.3)	30 (27.5)	25 (19.4)	28 (21.7)	22 (15.5)	13 (19.7)	10 (16.1)

Treatment with XVd was associated with a higher rate of AEs leading to dose reduction or treatment discontinuation compared to the Vd arm in patients <65 and ≥65 years, with higher rates of treatment discontinuation in the older group (Table 2). Patients in the XVd arm had a higher rate of dose reduction or discontinuation due to TEAEs as compared to the Vd arm in both frail and nonfrail groups, but rates were similar in frail and nonfrail patients (Table 2). There were six deaths due to TEAEs in patients <65 (XVd, n = 6 [two deemed to be treatment-related]) and 17 in patients ≥65 (XVd, n = 6; Vd, n = 11 [two and one treatment-related, respectively]). Similarly, there were nine (XVd, n = 8 [four treatment-related]; Vd, n = 1) in nonfrail patients, and 14 (XVd, n = 4; Vd, n = 10 [one treatment-related]) in frail patients.

4 | DISCUSSION

The BOSTON study compared the standard twice weekly Vd regimen to the novel once weekly XVd regimen in patients with previously treated MM. Here we have assessed the impact of age and frailty on efficacy and safety across the study. For all key efficacy outcomes analyzed including OS, XVd was superior to Vd in patients ≥65 years. In patients <65 years old, ORR and TTNT were significantly improved with XVd, while median PFS and ≥VGPR rate were compatible with trends to improved outcomes with XVd but did not meet prespecified significance criteria. In nonfrail patients, XVd was superior to Vd in terms of PFS, ORR, ≥VGPR and TTNT. While the benefits of XVd were less robust in frail patients, PFS, ORR, ≥VGPR, and OS were still numerically higher compared to Vd, and comparable with nonfrail patients and the entire ITT population. Thus, while the efficacy benefits of XVd over Vd are observed in both younger and older patients, and in those that are nonfrail or frail, improvements with XVd are more marked in older patients and in nonfrail patients. At present, we do not have an explanation for these findings. By and large, the safety profile of XVd in patients ≥65 was similar to that of younger patients, and, similarly, frail patients did not experience increased clinically meaningful toxicity compared to nonfrail patients except for a slightly higher rate of pneumonia. Importantly, the lower PN rate associated with XVd versus Vd across the entire population[34] was observed in both age groups analyzed, as well as in frail and nonfrail patients. Together, the findings indicate that the combination of weekly selinexor with weekly bortezomib and dexamethasone as used in the BOSTON trial is effective and safe in patients <65 and ≥65 years of age, and in nonfrail and frail patients.

While triplet regimens have improved median PFS and demonstrate deeper responses than doublets in patients with newly diagnosed MM, they often have toxicity profiles and AEs that may not be well tolerated for populations with already impaired health, as in those patients that are frail and/or elderly. In addition, many triplet regimens require twice weekly and/or prolonged clinic visits to receive parenteral agents. For example, in the SWOG S077 study, combining bortezomib, lenalidomide and dexamethasone (VRd) had increased toxicity versus Rd, particularly grade ≥3 PN AEs.[35] In the phase III ENDURANCE trial, which compared the triplets VRD and KRd (carfilzomib-lenalidomide-dexamethasone), subgroup analyses including age has not revealed differences in median PFS, however a significantly higher incidence of cardio-pulmonary and renal toxicities was observed on the KRd arm.[36] Daratumumab, lenalidomide, and

dexamethasone (DRd) provides a marked PFS benefit over Rd in older populations with main adverse events consisting of neutropenia and respiratory infections, along with infusion reactions occurring in 41%[37]; the use of subcutaneous daratumumab[38,39] and prophylactic leukotriene blockade can attenuate the infusion reactions. Thus, the weekly XVd triplet, which does not require prolonged parenteral administration, has demonstrated a manageable safety profile in older and frail patients with mostly grade 1 or 2 AEs and tolerability similar to that in younger and nonfrail populations.

The current results were based on post hoc analyses as frailty status at baseline in the BOSTON study was not a prespecified subgroup in the statistical plan. However, all components of the frailty score determinations were collected prior to study entry and specified in the protocol. The frailty algorithm by Facon et al[31] utilized in this analysis was successful in the prediction of efficacy outcomes via frailty status for newly diagnosed MM in the FIRST (MM-020) study.[31]

It may also be important to note that CCI scores are dependent on medical coding rules based on medical history, provided by the clinical site for the BOSTON study, and that medical histories could be incomplete. Although these potential limitations could impact frailty classification, they would likely apply across both arms of the study and can be expected to be insubstantial in the context of a trial. While a number of scores have been reported to provide accurate assessments of frailty that are valuable in clinical decision making and outcome prediction,[25-30] some require assessments that are not yet carried out widely in routine practice and in clinical trials, and their relative utility has not been determined in head-to-head comparisons. Thus, one key advantage of the validated frailty score used here is its relative simplicity and thus applicability. Consistent with general medical practice and results of other studies, the data obtained here aligned with expected reduced efficacy and increased toxicity seen in frail patient populations. These findings were comparable to the known safety profiles previously reported of selinexor, bortezomib, and dexamethasone alone or in combination.[22]

In conclusion, the use of once weekly selinexor with weekly bortezomib and dexamethasone in older and frail patient populations is effective, safe, tolerated, and manageable.

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CONFLICT OF INTEREST

Holger W. Auner reports an advisory role for Takeda and Karyopharm; grant from Amgen; and a speaker's bureau role for Janssen. Nizar J. Bahlis reports grants and personal fees from Celgene; personal fees from Janssen, Amgen, Takeda, Abbvie, GSK and Karyopharm. Maria Gavriatopoulou reports receiving honoraria from Amgen, Karyopharm Therapeutics, Takeda, Genesis Pharma, and Janssen-Cilag. Sosana Delimpasi has received honoraria from Janssen, Takeda, Amgen, and Celgene. Ivan Spicka reports personal fees from Janssen-Cilag, Takeda, Sanofi Aventis and Novartis; personal fees and non-financial support from Colgene, BMS and Amgen. Iryna Kriachok reports a consulting role, an advisory role, and a speaker's bureau role for Takeda, Janssen, Roche, Abbvie and MSD; Travel support by Takeda, MSD, Roche, Abbvie and Janssen. Roman Hajek has had a consultant or advisory relationship with Janssen, Amgen, Celgene, AbbVie, BMS, Novartis, PharmaMar, and Takeda; has received honoraria from Janssen, Amgen, Celgene, BMS, PharmaMar, and Takeda; and has received research funding from Janssen, Amgen, Celgene, BMS, Novartis, and Takeda. Christopher P. Venner has received honoraria from BMS/Celgene, Janssen, Sanofi, Amgen, GSK, and Takeda. Mamta Garg reports support for attending conferences from Takeda; an advisory role for Amgen, Takeda, Jansen, Novartis and Celgene; and a speaker's bureau role for Janssen. Hang Quach reports grants from and an advisory board role for Amgen, Celgene, Karyopharm, GlaxoSmithKline; non-financial support and research drug supply from Sanofi; an advisory board role for Janssen Cilag and Specialized therapeutics. Sundar Jagannath reports consulting services for AbbVie, Bristol-Myers Squibb, Janssen Pharmaceuticals, Merck & Co. Philip Moreau reports personal fees from Celgene, Amgen, Takeda, Janssen and Abbvie. Moshe Levy reports receiving consulting fees and lecture fees from Takeda, Celgene, Seattle Genetics, AbbVie, Jazz Pharmaceuticals, Gilead Sciences, Bristol-Myers Squibb, Amgen, Spectrum Pharmaceuticals, and Janssen. Larry D. Anderson, Jr. reports honoraria from advisory board activity from the following: GSK, Amgen, Janssen, BMS/Celgene, Karyopharm, and Oncopeptides. Thierry Facon reports an advisory board role for Karyopharm, Amgen, Roche and Oncopeptides; an advisory board role and a speaker bureau role for Janssen, Celgene/BMS, and Takeda. Maria Victoria Mateos has served as member of advisory boards or received honoraria from Janssen, BMS-Celgene, Takeda, Amgen, Sanofi, Oncopeptides, GSK, Adaptive, Pfizer, Regeneron, Roche and Sea-Gen. Yi Chai, Melina Arazy, Jatin Shah and Michael G. Kauffman are salaried employees and stockholders of Karyopharm Therapeutics Inc. Sharon Shacham reports being employed by and owning stock in Karyopharm Therapeutics, holding patents (8 999 996, 9 079 865, 9 714 226, PCT/US12/048319, and I574957) on hydrazide-containing nuclear transport modulators and uses, and holding pending patents (PCT/US12/048319, 499/2012, PI20102724, and 2 012 000 928) on hydrazide-containing nuclear transport modulators and uses. Paul G. Richardson reports receiving grant support and honoraria from Oncopeptides, Celgene, and Takeda, grant support from Bristol-Myers Squibb, and honoraria from Amgen, Janssen, and Karyopharm Therapeutics.

DATA AVAILABILITY STATEMENT

Karyopharm Therapeutics agrees to share individual participant data that underlie the results reported in this article (after deidentification), including the study protocol and statistical analysis plan. Data availability will begin 9 months after publication and will be available 36 months after publication. To gain access, data requestors should submit a proposal to medicalinformation@karyopharm.com. Proposals

will be reviewed by an independent review committee identified for this purpose.

ETHICS STATEMENT

The study was approved and performed in accordance with the International Conference on Harmonization, the Guidelines for Good Clinical Practice, appropriate regulatory requirements, and with approval of institutional review boards at individual enrolling institutions. All patients provided written informed consent before study start.

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SUPPORTING INFORMATION

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

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