Pomalidomide, Bortezomib, and Dexamethasone in Lenalidomide-Pretreated Multiple Myeloma: A Subanalysis of OPTIMISMM by Frailty and Bortezomib Dose Adjustment

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Abstract

This subanalysis of OPTIMISMM demonstrates that patients who received pomalidomide, bortezomib, and dexamethasone (PVd) had a higher ORR and longer median PFS vs. bortezomib and dexamethasone, regardless of frailty. Bortezomib dose adjustment allowed longer PVd treatment, with improved efficacy and fewer discontinuations. Therefore, these data support the use of PVd for the treatment of relapsed/refractory multiple myeloma in frail patients.

Introduction: A proportion of patients with multiple myeloma (MM) are older and/or have comorbidities, requiring dose adjustments. Data from OPTIMISMM (NCT01734928) supported the use of pomalidomide, bortezomib, and dexamethasone (PVd) for treating relapsed/refractory MM. This subanalysis of OPTIMISMM assessed outcome by frailty and/or bortezomib dose adjustment. **Methods:** Patient frailty (nonfrail vs. frail) was classified using age, Charlson Comorbidity Index, and Eastern Cooperative Oncology Group performance status. Data from patients requiring a bortezomib dose reduction, interruption, and/or withdrawal during PVd treatment were assessed. **Results:** Among 559 patients, 93 of 281 (33.1%) and 93 of 278 (33.5%) patients who received PVd and bortezomib and dexamethasone (Vd), respectively, were frail. Overall response rate (ORR) and median progression-free survival (PFS) were higher in nonfrail vs. frail with PVd treatment (ORR, 82.8% vs. 79.6%; PFS, 14.7 vs. 9.7 months); significantly higher than with Vd regardless of frailty.

Abbreviations: AE, adverse event; CCI, Charlson Comorbidity Index; CI, confidence interval; CR, complete response; DoT, duration of treatment; ECOG, Eastern Cooperative Oncology Group; IMWG, International Myeloma Working Group; ISS, International Staging System; ITT, intent-to-treat; Kd, carfilzomib plus dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; MM, multiple myeloma; NCCN, National Comprehensive Cancer Network; NE, not evaluable; OR, odds ratio; ORR, overall response rate; OS, overall survival; Pd, pomalidomide and dexamethasone; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; PVd, pomalidomide, bortezomib, and dexamethasone; Rd, lenalidomide and dexamethasone; Rd-R, lenalidomide and dexamethasone induction–lenalidomide maintenance; RR, relapsed/refractory; sCR, stringent complete response; SD, stable disease; TEAE, treatment-emergent adverse event; Vd, bortezomib and dexamethasone; XVd, selinexor, bortezomib, and dexamethasone.

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Submitted: Aug 16, 2023; Revised: Oct 6, 2023; Accepted: Oct 26, 2023; Epub: 8 November 2023

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https://doi.org/10.1016/j.clml.2023.10.009

Grade ≥ 3 treatment-emergent adverse events (TEAEs) were higher with PVd vs. Vd, regardless of frailty. Discontinuations of PVd were lower in nonfrail vs. frail patients (19.2% vs. 30.1%); the median duration of treatment was similar (DoT; 8.8 vs. 8.9 months, respectively). Patients who received PVd with a bortezomib dose adjustment (n = 240) had a longer median DoT (9.3 vs. 4.5 months) and PFS (12.1 vs. 8.4 months) vs. those without. **Conclusion:** Frail patients treated with PVd demonstrated a higher ORR and a longer PFS and DoT vs. Vd, despite a higher frequency of grade ≥ 3 TEAEs leading to pomalidomide, bortezomib, and/or dexamethasone discontinuation. Therefore, PVd treatment may improve patient outcomes, regardless of frailty.

Clinical Lymphoma, Myeloma and Leukemia, Vol. 24, No. 3, 165–176
Keywords: Charlson Comorbidity Index, dose modifications, ECOG PS, immunomodulatory agent, relapsed/refractory multiple myeloma

Introduction

Multiple myeloma (MM) remains incurable and follows a relapsing-remitting cycle.[1,2] Despite significant advances in therapy, particularly the introduction of immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies, patients with relapsed/refractory MM (RRMM) typically have poorer outcomes following each subsequent treatment.[1-3] In newly diagnosed MM, lenalidomide now forms part of the standard of care as a component of triplet regimens or as maintenance therapy.[3,4] This has resulted in a population of patients with MM who are refractory to lenalidomide early in their treatment due to remaining on lenalidomide until disease progression.[5] As patients with MM will inevitably relapse, there is a need for novel therapies/combinations to improve outcomes.[1,2]

Pomalidomide is an oral drug of the same class as lenalidomide that has demonstrated direct tumoricidal and immunomodulatory activity in lenalidomide-refractory MM.[6-10] In patients with lenalidomide-refractory MM, pomalidomide in combination with dexamethasone (Pd) is a standard treatment option that received approval in the USA and EU following the randomized phase III MM-003 trial and now forms the backbone of multiple triplet regimes.[3,7,8,10-12] Approved triplet regimens with a Pd backbone include elotuzumab-Pd (ELOQUENT 3), daratumumab-Pd (APOLLO), and isatuximab-Pd (ICARIA); trials supporting these approvals demonstrated a median progression-free survival (PFS) of approximately 10-13 months in patients with double-refractory disease.[13-15]

OPTIMISMM (NCT01734928) was a randomized, open-label, phase III trial comparing the efficacy and safety of pomalidomide in conjunction with bortezomib and dexamethasone (PVd) vs. bortezomib and dexamethasone (Vd) alone in which 70% of patients were lenalidomide refractory.[16] This trial enrolled 559 patients and, after a median follow-up of 15.9 months, demonstrated significant improvements with PVd vs. Vd for the primary endpoint of PFS (11.2 vs. 7.1 months, $P < .0001$) and the secondary endpoint of overall response rate (ORR) (82.2% vs. 50.0%). Based on these results, PVd has been approved in the EU for the treatment of patients with MM who have received ≥ 1 prior regimen including lenalidomide.[11]

Despite high response rates among patients with MM treated with standard-of-care triplet regimens, patients with MM are mostly older (median age at diagnosis was 69 years)[17] and/or frail (reduced performance status and/or presence of comorbidities), resulting in difficulty tolerating triplet regimens. Therefore, it is recommended that frail patients begin treatment using a doublet regimen, with a reduced dose version of bortezomib, lenalidomide, and dexamethasone, the only triplet specifically recommended by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).[3] However, despite guidance recommending treatment with doublet rather than triplet regimens, dose adjustments may be required to improve treatment tolerability in patients receiving triplet regimens and to optimize clinical benefit. Additionally, there are limited data on the effect of dose adjustments on survival outcomes, with many studies only reporting that dose adjustments occurred and not their effects on patient outcomes. This subanalysis of OPTIMISMM investigated the efficacy and safety of PVd vs. Vd in frail and nonfrail patients with RRMM who received PVd and in those who received a bortezomib dose adjustment.

Patients and Methods

Patients

As previously reported,[16] key inclusion criteria for enrollment included age ≥ 18 years with measurable MM, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2, receipt of 1-3 prior lines of therapy (including lenalidomide for ≥ 2 consecutive cycles), and documented disease progression during or after the last antimyeloma therapy. Patients were excluded if they had documented progressive disease (PD) during treatment or within 60 days of the last dose of a bortezomib-containing regimen or had been previously treated with pomalidomide.

All patients gave written informed consent. The study was conducted in accordance with the principles of Good Clinical Practice according to the International Conference on Harmonisation and the Declaration of Helsinki. The study protocol was approved by the institutional review board or central or local ethics committee at each participating study site.

Treatment

Eligible patients were randomized 1:1 to receive either Vd or PVd in 21-day cycles. All patients received bortezomib 1.3 mg/m^2 intravenously or subcutaneously on days 1, 4, 8, and 11 for cycles 1-8 and days 1 and 8 for each subsequent cycle and dexamethasone 20

mg (10 mg if age > 75 years) orally on days 1, 2, 4, 5, 8, 9, 11, and 12 for cycles 1-8 and days 1, 2, 8, and 9 for each subsequent cycle. Patients assigned to PVd also received pomalidomide 4 mg orally on days 1-14 of each cycle. Patients remained on treatment until PD or unacceptable toxicity. During the PFS follow-up phase, patients who did not experience PD, but permanently discontinued treatment, were continuously followed until PD.

Frailty Analysis

Patient frailty scores were derived using the frailty algorithm developed for the frailty subanalysis of the FIRST trial (Supplemental Table 1).[18] In this algorithm, frailty scores were calculated using age (0 if ≤ 75 years, 1 if 76-80 years, 2 if > 80 years), Charlson Comobidity Index (CCI) (0 if ≤ 1, 1 if > 1), and ECOG PS (0 if 0, 1 if 1, 2 if ≥ 2). Scores of 0 classified patients as fit, 1 as intermediate, and ≥ 2 as frail, and patients were subsequently grouped as nonfrail for scores < 2 and frail for scores ≥ 2.

Dose Adjustment

Patients who received PVd could have any of the following types of bortezomib dose adjustments (not mutually exclusive): any dose reduction (defined as a reduction of the planned bortezomib dose [ie, 1.3 mg/m^2], except for the per-protocol planned reduction in dose from twice weekly to weekly after cycle 8), any dose interruption (defined as skipping the bortezomib dose intermittently), or dose discontinuation after a given cycle (defined as permanently stopping bortezomib treatment). In all instances, pomalidomide was still administered.

Endpoints and Assessments

The endpoints of the post hoc frailty subanalysis were PFS, ORR, and safety (treatment-emergent adverse events [TEAEs], grade ≥ 3 TEAEs, and TEAEs leading to treatment discontinuation) in each frailty subgroup (frail or nonfrail). PFS was assessed using International Myeloma Working Group (IMWG) criteria and Food and Drug Administration censoring rules. Response assessments were conducted at the start of each treatment cycle using IMWG criteria and determined by the Independent Response Adjudication Committee. ORR was defined as all patients with a partial response or better. Adverse events (AEs) were assessed from the signing of consent to 28 days after the last dose of any study drug, were coded using Medical Dictionary for Regulatory Activities 20.0, and were graded using National Cancer Institute Common Terminology Criteria for Adverse Events 4.03 or higher. AEs of interest in this subanalysis included cardiac failure, ischemic heart disease, acute renal failure, peripheral neuropathy, hypertension, and neutropenia.

Statistical Considerations

The intent-to-treat (ITT) population included all randomized patients, the frailty-analysis population included all ITT patients with a baseline frailty status, and the frailty safety population included all frailty-analysis patients who received ≥ 1 dose of study medication. The frailty assessment was undertaken on the ITT population. Baseline demographics and characteristics, ORR, and PFS were determined using the frailty analysis population and safety was analyzed using the frailty safety population.

The bortezomib dose adjustment population included all randomized patients who received ≥ 1 dose of study medication. Baseline demographics and characteristics, ORR, PFS, and TEAEs were assessed by treatment group and bortezomib dose adjustment type. An additional analysis also assessed frailty in this population.

Patient demographics and baseline disease characteristics were collected at screening and summarized. Median PFS and 95% confidence intervals (CIs) were estimated using Kaplan–Meier plots. Hazard ratios and *P* values were estimated using a stratified Cox proportional hazards regression analysis, with treatment arm (PVd vs. Vd) by frailty subgroup as a covariate and number of prior anti-MM regimens (1 vs. > 1) and β2-microglobulin level at screening (< 3.5 mg/L, ≥ 3.5 to ≤ 5.5 mg/L, and > 5.5 mg/L) as stratification factors. ORR odds ratio along with 95% CI and *P* values were calculated using a stratified Cochran–Mantel–Haenszel test, with the number of prior anti-MM regimens (1 vs. > 1) and β2-microglobulin level at screening (< 3.5 mg/L, ≥ 3.5 to ≤ 5.5 mg/L, and > 5.5 mg/L) as stratification factors.

Results

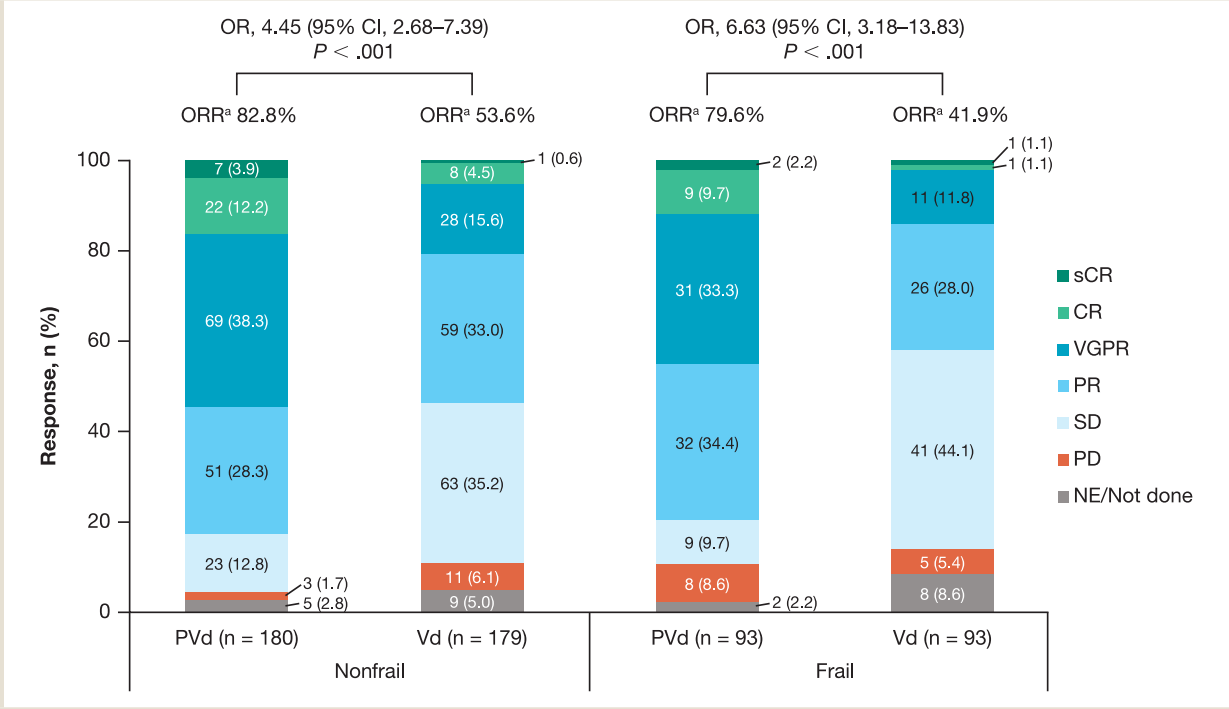
Patient Disposition and Characteristics

In total, 559 patients were included in the ITT population. Of the 281 patients randomized to PVd, 93 were defined as frail and 180 as nonfrail; of the 278 randomized to Vd, 93 were defined as frail and 179 as nonfrail (Supplemental Figure 1). There were 8 patients in the PVd group and 6 in the Vd group who were missing a frailty status and were not included in the analyses. Baseline characteristics were mostly consistent between treatment groups within each frailty subgroup (Supplemental Table 2).

At the data cutoff (October 26, 2017), in patients randomized to PVd, 65 (36.1%) nonfrail and 24 (25.8%) frail patients remained on treatment; 34 (19.0%) nonfrail and 9 (9.7%) frail patients randomized to Vd remained on treatment. Treatment discontinuations in patients randomized to PVd occurred in 115 (63.9%) nonfrail and 69 (74.2%) frail patients; 145 (81%) nonfrail and 84 (90.3%) frail patients randomized to Vd discontinued treatment. The most common reason for treatment discontinuation was PD, occurring in 71 (39.4%) nonfrail and 38 (40.9%) frail patients who received PVd and in 82 (45.8%) nonfrail and 49 (52.7%) frail patients who received Vd, respectively.

In patients randomized to PVd, 240 (86.3%) required a bortezomib dose adjustment, with a median time to first bortezomib dose adjustment of 1.5 (range, 0.1-16.5) months. There were 148 (53.2%) patients who required a dose reduction, 181 (65.1%) who required a dose interruption, 83 (29.9%) who discontinued bortezomib, and 33 (11.9%) who had all 3 types of adjustment (Supplemental Figure 2). Of the 233 patients with a bortezomib dose adjustment and available frailty status, 152 (65.2%) were nonfrail and 81 (34.8%) were frail. Baseline characteristics were generally consistent between patients who had a dose adjustment and those without an adjustment (Supplemental Table 3).

Figure 1 ORR by frailty level. ORR was defined as PR or better (ie, sCR, CR, VGPR, and PR). Abbreviations: CI, confidence interval; CR = complete response; NE = not evaluable; OR = odds ratio; ORR = overall response rate; PD = progressive disease; PR = partial response; PVd = pomalidomide, bortezomib, and dexamethasone; sCR = stringent complete response; SD = stable disease; Vd = bortezomib and dexamethasone; VGPR = very good partial response.



Efficacy

At data cutoff, the median follow-up was 16.2 (range, 0.1-57.4) months for PVd and 15.7 (range, 0.0-53.7) months for Vd. Frailty status did not affect the median follow-up time for PVd (nonfrail, 16.5 [range, 0.1-52.2] months; frail, 15.1 [range, 5.4-57.4] months) or Vd (nonfrail, 15.7 [range, 0.0-53.7] months; frail, 15.4 [range, 0.2-43.4] months). The ORR was significantly greater in nonfrail patients treated with PVd than with Vd (82.8% vs. 53.6%; odds ratio [OR], 4.45; $P < .001$) (Figure 1). The ORR was also significantly greater in frail patients who received PVd compared with Vd (79.6% vs. 41.9%; OR, 6.63; $P < .001$). More patients who received PVd achieved at least a very good partial response or better (nonfrail, 54.4%; frail, 45.2%) compared with Vd (nonfrail, 20.7%; frail, 14.0%). Median PFS was significantly longer with PVd vs. Vd in both nonfrail (14.7 vs. 8.3 months; $P < .001$) and frail (9.7 vs. 5.1 months; $P = .006$) patients (Figure 2). Patients who received PVd had a longer median (range) duration of treatment (DoT) than Vd, regardless of frailty (PVd, 8.8 [0.3-34.3] and 8.9 [0.3-43.7] months in nonfrail and frail patients, respectively; Vd, 5.7 [0.1-38.4] and 4.3 [0.1-24.3] months). Additionally, patients who received PVd had a shorter median (range) time to response compared with Vd, regardless of frailty (PVd, 0.9 [0.7-5.7] and 1.0 [0.7-5.4] months in nonfrail and frail patients, respectively; Vd, 1.4 [0.7-6.8] and 1.4 [0.7-3.8] months). However, differences in median follow-up time between treatment arms were not accounted for when determining DoT.

Patients treated with PVd with a dose adjustment had a higher ORR than those without an adjustment (85.4% vs. 68.4%, respectively; Figure 3) and a longer median PFS (12.1 vs. 8.4 months, respectively). Patients treated with PVd with a dose adjustment also had a significantly higher ORR compared with Vd (85.4% vs. 51.5%; OR, 6.16 [95% CI, 3.91-9.72]; $P < .001$), reduced risk of progression or death (HR, 0.57 [95% CI, 0.45-0.72]; $P < .001$), and a substantially longer median (range) DoT (9.3 [0.3-43.7] vs. 5.0 [0.1-38.4] months; Figures 3 and 4). In contrast, patients treated with PVd without a bortezomib dose adjustment did not have a significantly different ORR compared with Vd (68.4% vs. 51.5%; OR, 2.19 [95% CI, 0.99-4.83]; $P = .055$) or risk of progression or death (HR, 0.94 [95% CI, 0.59-1.50]; $P = .807$), while DoT was similar (4.5 [0.3-28.8] vs. 5.0 [0.1-38.4] months). Additionally, nonfrail patients who received PVd and had a bortezomib dose adjustment had a 40% lower risk of progression or death compared with patients who received Vd (HR, 0.60 [95% CI, 0.41-0.89]; $P = .011$; Figure 5A); however, patients without an adjustment did not have a statistically significant difference in the risk of progression or death compared with Vd (HR, 1.56 [95% CI, 0.71-3.42]; $P = .269$). Frail patients who received PVd had a lower risk of progression or death compared with Vd regardless

Figure 2 PFS with PVd vs. Vd in (A) nonfrail and (B) frail patients. Abbreviations: CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; PVd = pomalidomide, bortezomib, and dexamethasone; Vd = bortezomib and dexamethasone.

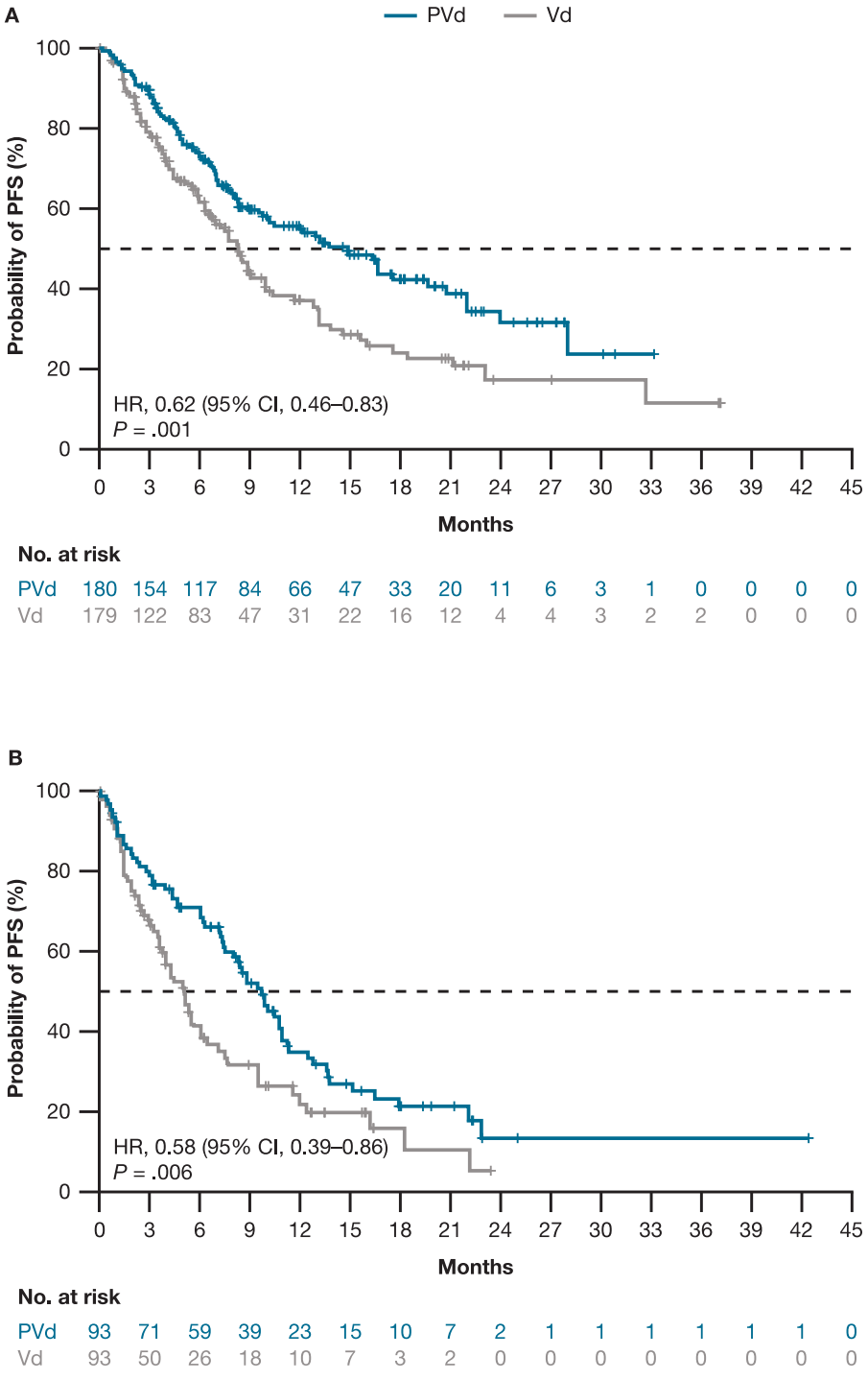
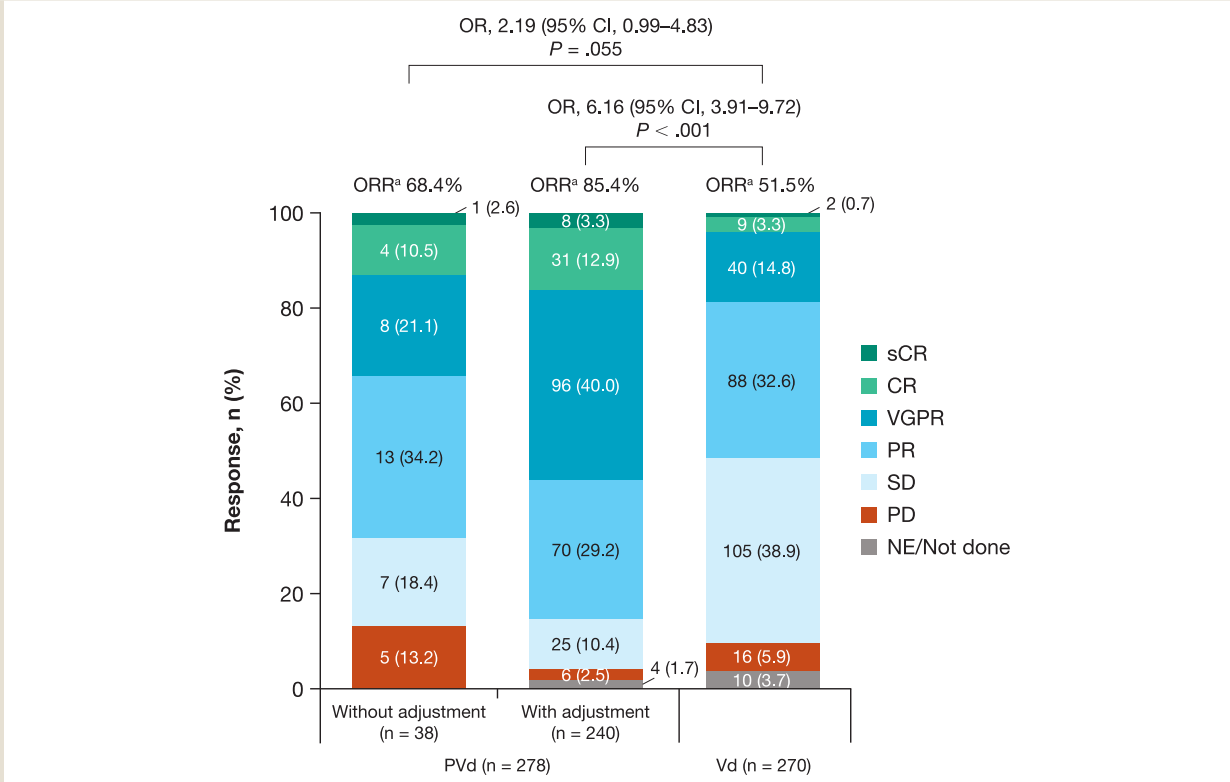


Figure 3 ORR for PVd with and without a bortezomib dose adjustment compared with Vd. [a]ORR is defined as at least a partial response or better (ie, sCR, CR, VGPR, and PR). Abbreviations: CI = confidence interval; CR = complete response; NE = not evaluable; OR = odds ratio; ORR = overall response rate; PD = progressive disease; PR = partial response; PVd = pomalidomide, bortezomib, and dexamethasone; sCR = stringent complete response; SD = stable disease; Vd = bortezomib and dexamethasone; VGPR = very good partial response.



of bortezomib dose adjustment (with adjustment, HR 0.58 [95% CI, 0.42-0.79]; without adjustment, HR 0.78 [95% CI, 0.42-1.44]; Figure 5B); however, only those treated with PVd with a dose adjustment demonstrated a significantly lower risk (with adjustment, $P <$ .001; without adjustment, $P = .427$). The frequency of dose adjustments between frail and nonfrail patients was comparable.

Safety

Overall safety by treatment arm has been published previously.[16] The majority of patients who received PVd or Vd experienced at least 1 TEAE (Table 1). Across both treatment arms, rates of grade ≥ 3 TEAEs were lower in nonfrail patients (PVd, 88.1%; Vd, 61.3%) compared with frail patients (PVd, 96.8%; Vd, 87.9%).

The most common grade ≥ 3 TEAE of interest was neutropenia, which was experienced by more patients who received PVd than Vd regardless of frailty (PVd: nonfrail, 45.8%; frail, 40.9% vs. Vd: nonfrail, 9.8%; frail, 11%). Similarly, grade ≥ 3 peripheral neuropathy was experienced by more patients who received PVd than Vd but was similar across frailty status (PVd: nonfrail, 11.3%; frail, 11.8% vs. Vd: nonfrail, 5.2%; frail, 5.5%). Patients with ≥ 1 TEAE leading to discontinuation of any study drug (pomalidomide, bortezomib, and/or dexamethasone) were higher in patients who received PVd vs. Vd for both nonfrail (26.6% vs. 18.5%, respectively) and frail patients (35.5% vs. 20.9%, respectively). Discontinuations of any study drug due to grade ≥ 3 TEAEs in patients treated with PVd were lower in nonfrail vs. frail patients (19.2% vs. 30.1%); in contrast, discontinuations for Vd were similar irrespective of frailty (nonfrail, 18.5%; frail, 20.9%).

The proportions of patients who received PVd and experienced any-grade or grade ≥ 3 TEAEs were similar regardless of bortezomib dose adjustment (without adjustment vs. with adjustment: any grade, 100.0% vs. 99.6%; grade ≥ 3, 89.5% vs. 90.4%; Table 2). The frequency of grade ≥ 3 TEAEs of interest was greater in patients who were treated with PVd and had a dose adjustment compared with patients without an adjustment. The most notable difference between groups was in the proportion of patients with or without a dose adjustment who experienced peripheral neuropathy (12.5% vs. 2.6%). Patients with a dose adjustment had a lower rate of discontinuation of any study drug due to grade 3/4 TEAEs vs. those without an adjustment (21.3% vs. 28.9%), although the rate of any-grade TEAEs leading to any study drug discontinuation was similar between groups (without adjustment, 31.6%; with adjustment, 28.3%). Finally, frail patients who received PVd were more likely to discontinue any study drug compared with nonfrail patients

Figure 4 Probability of PFS for PVd with and without a bortezomib dose adjustment compared with Vd. [a]HR and *P* value compared PVd with adjustment vs. Vd; [b]HR and *P* value compared PVd without adjustment vs. Vd. Abbreviations: CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; PVd = pomalidomide, bortezomib, and dexamethasone; Vd = bortezomib and dexamethasone.

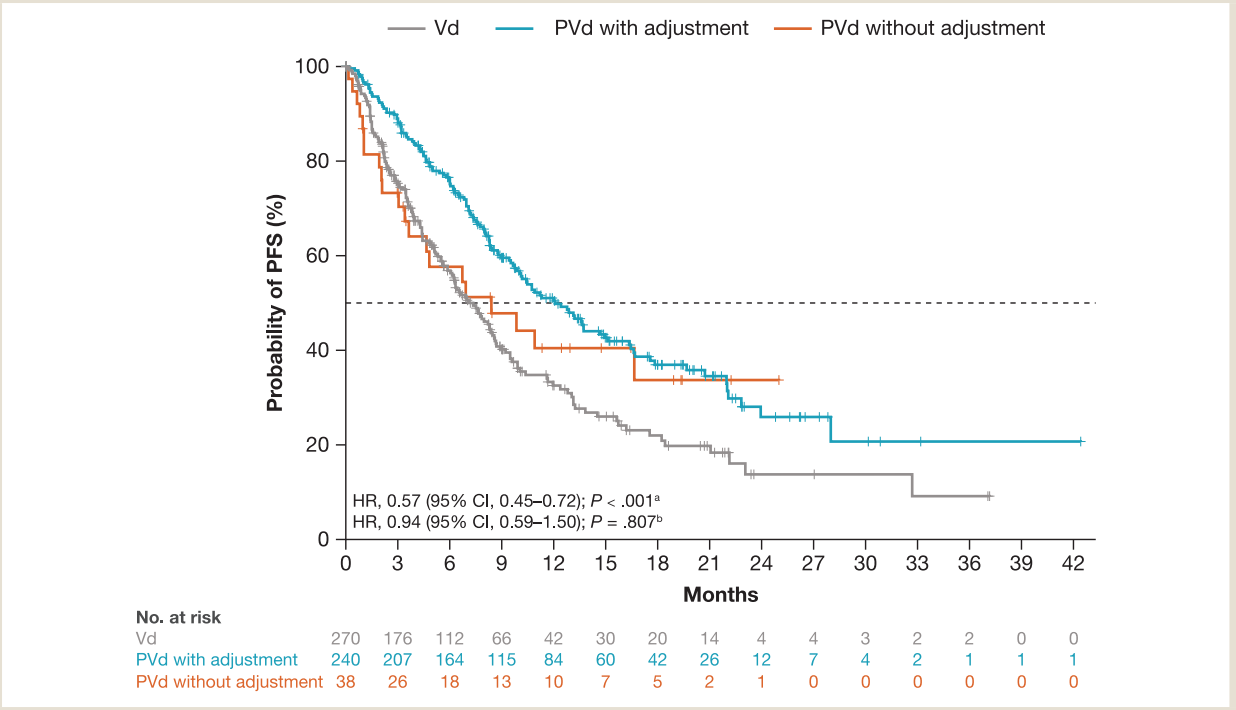


Table 1 TEAEs by Frailty

TEAE, n (%)	Nonfrail		Frail	
	PVd (n = 177)	Vd (n = 173)	PVd (n = 93)	Vd (n = 91)
Patients with at least 1 TEAE	176 (99.4)	169 (97.7)	93 (100.0)	89 (97.8)
Patients with at least 1 grade ≥ 3 TEAE	156 (88.1)	106 (61.3)	90 (96.8)	80 (87.9)
Grade ≥ 3 TEAEs of interest				
Neutropenia	81 (45.8)	17 (9.8)	38 (40.9)	10 (11)
Peripheral neuropathy	20 (11.3)	9 (5.2)	11 (11.8)	5 (5.5)
Hypertension	8 (4.5)	3 (1.7)	0 (0)	1 (1.1)
Acute renal failure	7 (4.0)	2 (1.2)	2 (2.2)	4 (4.4)
Cardiac failure	1 (0.6)	3 (1.7)	5 (5.4)	1 (1.1)
Ischemic heart disease	0 (0)	1 (0.6)	2 (2.2)	0 (0)
Patients with at least 1 TEAE leading to discontinuation of any study drug	47 (26.6)	32 (18.5)	33 (35.5)	19 (20.9)
Patients with at least 1 grade ≥ 3 TEAE leading to discontinuation of any study drug	34 (19.2)	32 (18.5)	28 (30.1)	19 (20.9)

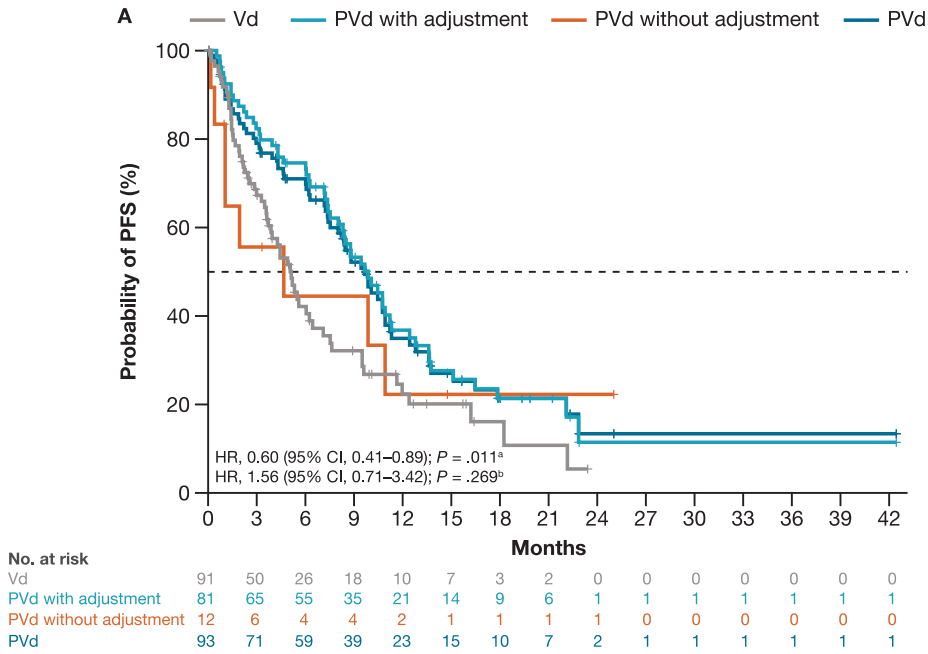
Abbreviations: PVd = pomalidomide, bortezomib, and dexamethasone; TEAE = treatment-emergent adverse event; Vd = bortezomib and dexamethasone.

due to any-grade TEAE (without adjustment, 50.0% vs. 24.0%; with adjustment, 33.0% vs. 27.0%) or grade 3/4 TEAE (without adjustment, 50.0% vs. 20.0%; with adjustment, 27.2% vs. 19.1%), regardless of bortezomib adjustment status.

Discussion

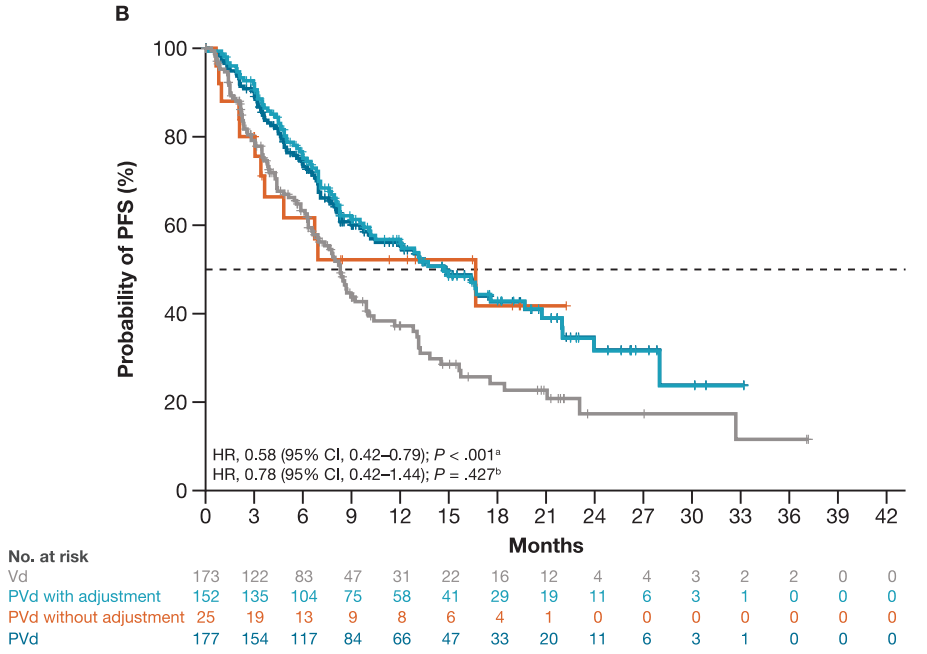
Despite significant advances in the treatment of MM, the disease remains incurable with significant barriers to treating patients as they tend to be older and are more likely to have a reduced perfor-

Figure 5 Probability of PFS for PVd with and without a bortezomib dose adjustment compared with Vd in (A) nonfrail and (B) frail patients. [a]HR and *P* value compared PVd with adjustment vs. Vd; [b]HR and *P* value compared PVd without adjustment vs. Vd. Abbreviations: CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; PVd = pomalidomide, bortezomib, and dexamethasone; Vd = bortezomib and dexamethasone.



No. at risk

Vd	91	50	26	18	10	7	3	2	0	0	0	0	0	0	0
PVd with adjustment	81	65	55	35	21	14	9	6	1	1	1	1	1	1	1
PVd without adjustment	12	6	4	4	2	1	1	1	1	0	0	0	0	0	0
PVd	93	71	59	39	23	15	10	7	2	1	1	1	1	1	1



No. at risk

Vd	173	122	83	47	31	22	16	12	4	4	3	2	2	0	0
PVd with adjustment	152	135	104	75	58	41	29	19	11	6	3	1	0	0	0
PVd without adjustment	25	19	13	9	8	6	4	1	0	0	0	0	0	0	0
PVd	177	154	117	84	66	47	33	20	11	6	3	1	0	0	0

Table 2 TEAEs for PVd Following a Bortezomib Dose Adjustment

TEAE, n (%)	PVd Without an Adjustment			PVd With an Adjustment			Vd		
	Nonfrail (n = 25)	Frail (n = 12)	Total (n = 38)[a]	Nonfrail (n = 152)	Frail (n = 81)	Total (n = 240)[a]	Nonfrail (n = 173)	Frail (n = 91)	Total (n = 270)[a]
Patients with at least 1 TEAE	25 (100.0)	12 (100.0)	38 (100.0)	151 (99.3)	81 (100.0)	239 (99.6)	169 (97.7)	89 (97.8)	264 (97.8)
Patients with at least 1 grade ≥ 3 TEAE	21 (84.0)	12 (100.0)	34 (89.5)	135 (88.8)	78 (96.3)	217 (90.4)	106 (61.3)	80 (87.9)	190 (70.4)
Grade ≥ 3 TEAEs of interest									
Neutropenia	10 (40.0)	4 (33.0)	14 (36.8)	71 (46.7)	34 (42.0)	105 (43.8)	17 (9.8)	10 (11.0)	17 (8.5)
Peripheral neuropathy	1 (4.0)	0	1 (2.6)	19 (12.5)	11 (13.6)	30 (12.5)	9 (5.2)	5 (5.5)	14 (5.2)
Hypertension	1 (4.0)	0	1 (2.6)	7 (4.6)	0	7 (2.9)	3 (1.7)	1 (1.1)	4 (1.5)
Acute renal failure	0	0	0	7 (4.6)	2 (2.5)	10 (4.2)	2 (1.2)	4 (4.4)	6 (2.2)
Cardiac failure	0	0	0	1 (0.7)	5 (6.2)	6 (2.5)	3 (1.7)	1 (1.1)	4 (1.5)
Ischemic heart disease	0	0	0	0	2 (2.5)	2 (0.8)	1 (0.6)	0	1 (0.4)
Patients with at least 1 TEAE leading to discontinuation of any study drug	6 (24.0)	6 (50.0)	12 (31.6)	41 (27.0)	27 (33.0)	68 (28.3)	32 (18.5)	19 (20.9)	51 (18.9)
Patients with at least 1 grade ≥ 3 TEAE leading to discontinuation of any study drug	5 (20.0)	6 (50.0)	11 (28.9)	29 (19.1)	22 (27.2)	51 (21.3)	32 (18.5)	19 (20.9)	51 (18.9)

Abbreviations: PVd = pomalidomide, bortezomib, and dexamethasone; TEAE = treatment-emergent adverse event; Vd = bortezomib and dexamethasone.
[a] There was 1 patient who received PVd without adjustment, 7 patients who received PVd with adjustment, and 6 patients who received Vd who did not have frailty scores.

mance status or comorbidities. For these reasons, the NCCN guidelines recommend that frail patients, or patients with a poor performance status, are initially treated with a doublet regimen, with a third drug added if their performance status improves.[3] As lenalidomide has become heavily used in early treatment lines in combination with dexamethasone as one of the preferred doublet regimens for frail patients, the OPTIMISMM trial aimed to address the needs of patients with early lenalidomide-refractory disease requiring subsequent therapy. In this subanalysis of OPTIMISMM in patients who received PVd, frailty did not appear to impact response rates negatively but did shorten the median PFS. Although frail patients who received PVd had higher rates of grade ≥ 3 TEAEs and discontinuations, DoT was similar (8.8 vs. 8.9 months) when compared with nonfrail patients.

Multiple scoring systems are used to assess frailty, and survival outcomes (PFS and overall survival [OS]) for frail patients, are poor vs. nonfrail patients. The IMWG developed a scoring system for classifying patients as frail or nonfrail in 2015, which used age, comorbidities (CCI), patient-evaluated self-care (Katz Activities of Daily Living scale), and household management (Lawton Instrumental Activities of Daily Living scale).[19] However, as the Activities of Daily Living scales may not be included as assessments in clinical trials, the frailty scoring system developed during a subanalysis of the FIRST trial used ECOG PS as an alternative since it is widely assessed in clinical trials for determining the day-to-day functions of patients.[18] In addition to the FIRST trial, the frailty scoring system based on ECOG PS was used to assess treatment by frailty subgroups in multiple clinical trials, including ASPIRE, ENDEAVOR, ARROW, ALCYONE, and BOSTON.[18,20-22] These trials demonstrated that frail patients consistently experience poorer survival outcomes (PFS and OS) compared with nonfrail patients, except for the BOSTON trial which demonstrated a similar PFS but shorter OS.

In OPTIMISMM, patients treated with PVd had a longer median PFS compared with those who received Vd, irrespective of patient frailty. Both nonfrail and frail patients treated with PVd had a higher ORR vs. Vd. Further, the risk of disease progression or death reduced in nonfrail and frail patients was 38% and 42% lower vs. Vd, respectively. However, frail patients treated with PVd were more likely to discontinue due to TEAEs than those receiving Vd, possibly due to the addition of a third drug. Additionally, more patients who received PVd compared with Vd experienced grade ≥ 3 neutropenia, regardless of frailty. However, the DoT in patients treated with PVd was similar across frailty groups and was longer than in patients treated with Vd in either frailty status.

Patients who received PVd and required a dose adjustment had a higher ORR and a longer median PFS compared with those without an adjustment. Both nonfrail and frail patients benefitted from a dose adjustment, although there was a greater reduction in risk of progression or death in frail patients with an adjustment vs. those without compared with patients who received Vd. Patients who received a dose adjustment stayed on treatment for longer and were less likely to discontinue due to grade ≥ 3 TEAEs, except for frail patients who were more likely to discontinue treatment regardless of dose adjustments. However, the proportion of frail patients who discontinued due to grade ≥ 3 TEAEs appeared to be reduced by dose adjustments, although interpretation is limited by the small number of patients without a dose adjustment.

The results from this subanalysis demonstrate that the use of PVd did not negatively affect outcomes in frail patients and support the use of this triplet regimen in this population despite the higher treatment burden. Adjusting the dose of bortezomib in patients who received PVd did not reduce the efficacy of PVd vs. Vd. Rather, dose adjustments appeared to allow longer and more continuous PVd treatment, with fewer treatment discontinuations, which may be more important for maintaining efficacy. However, patients with

better response and who remained on treatment longer had an extended period in which they may have received dose adjustments compared with patients who relapsed earlier in their treatment. OS data were immature and remained blinded at data cutoff; as such, understanding of the long-term benefits of triplet PVd over Vd in frail patients was limited.

Frailty analyses have been conducted previously in clinical trials. However, due to variations in patient population, treatments, and frailty groups analyzed, direct comparisons are difficult to make. In contrast to OPTIMISMM, the FIRST trial, in which the frailty algorithm used for this subanalysis was developed, enrolled patients with newly diagnosed MM who were treated with lenalidomide and dexamethasone.[18] As a result, PFS in the FIRST trial was significantly longer than in OPTIMISMM. However, the FIRST trial showed a similar trend with a reduced median PFS in frail patients compared with nonfrail patients (19.4 vs. 24.0 months, $P < .0001$). Furthermore, the FIRST trial reported a similar trend in the safety results to this subanalysis, with more frail than nonfrail patients experiencing grade ≥ 3 TEAEs and discontinuing earlier.

In other trials where the frailty algorithm developed in the FIRST trial was used to assess patients with RRMM, treatment options and comparison populations varied depending on the trial. The BOSTON trial compared frail vs. nonfrail patients who received selinexor plus Vd, which demonstrated a similar median PFS regardless of frailty status (nonfrail, 13.2 months; frail, 13.9 months).[22] Further, grade ≥ 3 treatment-related AEs and AEs leading to dose reductions or discontinuations were also similar in nonfrail and frail patients. In 3 further trials, patients were defined as fit or frail (rather than nonfrail or frail) and treated with carfilzomib, lenalidomide, and dexamethasone (KRd; ASPIRE) or carfilzomib plus dexamethasone (Kd; ENDEAVOR or ARROW); frail patients had a lower median PFS compared with fit patients in all 3 trials.[20] In ASPIRE, frail patients who received KRd had similar levels of grade ≥ 3 TEAEs and TEAEs leading to discontinuation compared with nonfrail patients. In ENDEAVOR, patients treated with Kd had similar levels of grade ≥ 3 TEAEs regardless of frailty status but higher levels of discontinuation in frail patients. Patients treated with Kd in ARROW demonstrated higher rates of both grade ≥ 3 TEAEs and TEAEs leading to discontinuation in frail patients vs. fit patients. However, the DoT in all 3 trials was lower for frail patients compared with fit patients. Despite the different patient populations and treatments, the results from the frailty analyses of ASPIRE, ENDEAVOR, and ARROW demonstrate similar trends in PFS as OPTIMISMM but differ with regard to safety.

There are limited data on the effect of bortezomib dose adjustment on survival outcomes. However, the results of this study align with previous reports. In a study investigating the effect of dose adjustments on the efficacy of bortezomib, melphalan, and prednisone (VMP), 85% of patients required a VMP dose reduction resulting in 78% of patients completing treatment. The outcomes demonstrated no significant differences in PFS ($P = .581$) or OS ($P = .138$) for patients with a higher vs. a lower total dose of VMP (≥ 52.1 mg/m^2 vs. < 52.1 mg/m^2; range, 33.8-67.5 mg/m^2).[23] In the MC0789 trial, which used pomalidomide and dexamethasone in patients with RRMM, 51% of patients required a dexamethasone adjustment. Compared with patients without a dose adjustment, a dexamethasone dose adjustment resulted in a longer mean treatment duration (339 vs. 124 days, $P < .0001$), a higher probability of responding as assessed by univariate or multivariate analysis (both $P < .001$), and a significantly improved OS at 1, 3, and 5 years ($P < .001$).[24]

In another study comparing continuous lenalidomide and dexamethasone (Rd) vs. Rd induction (9 cycles) with lenalidomide maintenance (Rd-R), outcomes for patients with the preplanned dose reduction in the Rd-R arm were not negatively impacted. The event-free survival with Rd-R vs. Rd was 10.4 vs. 6.9 months ($P = .02$); median PFS was 20.2 vs. 18.3 months ($P = .16$) and 3-year OS was 74% vs. 63% ($P = .06$).[25] Further, in an earlier study comparing high-dose vs. low-dose dexamethasone for Rd, patients receiving the low-dose Rd regimen had a greater 1-year OS (96% vs. 87%, $P = .0002$) resulting in all patients moving over to this regimen.[26] Results from these studies, along with improvements in patient outcomes following dose adjustment of bortezomib in the PVd arm of this study, suggest that an attenuated PVd regimen may be beneficial in patients who cannot tolerate the full regimen dose. For example, the attenuation of the triplet regimen lenalidomide, bortezomib, and dexamethasone (RVD lite) proved effective in older, transplant-ineligible patients with newly diagnosed MM.[27]

Therefore, this subanalysis of OPTIMISMM is important in expanding the understanding of dose adjustments on outcomes and demonstrates the potential importance of dose adjustments for improving survival. This further strengthens the value of trial findings as they relate to real-world practice,[28] although the trial was limited by the lack of adjustment to account for differences in follow-up time when analyzing the DoT and safety data. Additionally, data on whether patients received a bortezomib dose adjustment before or after response were not available, which may introduce bias if some patients died or progressed before dose adjustment; data on dose adjustments for dexamethasone or pomalidomide were also not available. Finally, the long-term effectiveness of bortezomib dose adjustment was difficult to determine due to the lack of mature OS data.

Conclusion

This subanalysis of OPTIMISMM demonstrated that PVd was an effective treatment option compared with Vd, with higher ORR and median PFS values in lenalidomide-pretreated patients with RRMM regardless of frailty. Frail patients treated with PVd demonstrated a longer PFS, higher ORR, and longer DoT vs. Vd, despite higher frequency of grade ≥ 3 TEAEs and discontinuations. Additionally, bortezomib dose adjustment appeared to enable longer treatment duration with PVd, which may potentially improve patient outcomes. Overall, these findings support the use of PVd in both frail and nonfrail patients with RRMM, with dose adjustments resulting in longer treatment durations and potentially improving patient outcomes.

Clinical Practice Points

What is already known about this subject?

- The primary analysis of OPTIMISMM demonstrated support for the use of pomalidomide, bortezomib,

and dexamethasone (PVd) in the treatment of patients with lenalidomide-pretreated relapsed/refractory multiple myeloma (RRMM), resulting in the approval of PVd in the European Union.

What are the new findings?

- This subanalysis demonstrated a higher response rate and longer progression-free survival with PVd compared with bortezomib and dexamethasone (Vd), supporting the use of PVd for the treatment of frail patients with lenalidomide-pretreated RRMM. Further, bortezomib dose adjustments may further improve patient outcomes.

How might it impact on clinical practice in the foreseeable future?

- In patients who received PVd, the results from OPTIMISMM demonstrated that frail patients had a higher percentage of treatment-emergent adverse events compared with nonfrail patients or patients who received Vd. However, the duration of treatment was similar to nonfrail patients who received PVd and longer than those who received Vd. Therefore, suggesting that despite the increased treatment burden with a triplet vs. doublet regimen, frail patients benefitted and tolerated the addition of a third agent.
- Further, the use of a triplet regimen in conjunction with dose adjustments may enable frail patients to remain on treatment longer, leading to improved survival outcomes.

Data Availability Statement

The Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Author Contributions

Albert Oriol: Conceptualization, Investigation, Writing—Reviewing and Editing. Meletios Dimopoulos: Conceptualization, Investigation, Writing—Reviewing and Editing. Fredrik Schjesvold: Conceptualization, Investigation, Writing—Reviewing and Editing. Meral Beksac: Conceptualization, Investigation, Writing—Reviewing and Editing. Thierry Facon: Conceptualization, Investigation, Writing—Reviewing and Editing. Sujith Dhanasiri: Conceptualization, Formal Analysis, Writing—Reviewing and Editing. Shien Guo: Conceptualization, Formal Analysis, Writing—Reviewing and Editing. Yutian Mu: Conceptualization, Formal Analysis, Writing—Reviewing and Editing. Kevin Hong: Conceptualization, Investigation, Writing—Reviewing and Editing. Christian Gentili: Conceptualization, Formal Analysis, Writing—Reviewing and Editing. Monica Galli: Conceptualization, Writing—Reviewing and Editing. Munci Yagci: Conceptualization, Investigation, Writing—Reviewing and Editing. Alessandra Larocca: Conceptualization, Investigation, Writing—Reviewing and Editing. Paul Richardson: Conceptualization, Investigation, Writing—Reviewing and Editing. Katja Weisel: Conceptualization, Investigation, Writing—Reviewing and Editing.

Disclosure

The study was supported by Celgene, a Bristol-Myers Squibb company. All the authors contributed to and approved the manuscript. Professional medical writing support for this manuscript was provided by Joels Wilson-Nieuwenhuis, PhD, of Caudex, a division of IPG Health Medical Communications, funded by Bristol Myers Squibb.

A.O. reports honoraria from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, and Sanofi; and advisory board participation with Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, and Sanofi. M.D. reports honoraria from AbbVie, Amgen, Beigene, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Menarini, Regeneron, Sanofi, and Takeda. F.S. reports research funding from Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, and Targovax; honoraria from Amgen, AbbVie, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Janssen, Novartis, Oncopeptides, Pfizer, Sanofi, SkyliteDX, and Takeda; and advisory board participation with AbbVie, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, and Takeda. M.B. reports consulting fees from Janssen, Menarini, and Sanofi; and honoraria from Janssen and Takeda. T.F. has nothing to disclose. S.D. reports employment and stock with Bristol Myers Squibb. S.G. reports consulting fees from Bristol Myers Squibb. Y.M. reports consulting fees from Bristol Myers Squibb. K.H. reports employment and stock with Bristol Myers Squibb. C.G. reports employment and stock with Bristol Myers Squibb. M.G. reports honoraria from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Sanofi, and Takeda. M.Y. has nothing to disclose. A.L. reports honoraria advisory board participation with Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen-Cilag, Karyopharm, Oncopeptides, Sanofi, and Takeda. P.R. reports research funding from Bristol Myers Squibb/Celgene, Karyopharm, Oncopeptides, and Takeda; consulting fees from AstraZeneca, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Karyopharm, Oncopeptides, Sanofi, and Takeda. K.W. reports research funding from AbbVie, Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, and Sanofi; honoraria from AbbVie, Adaptive, Amgen, AstraZeneca, BeiGene, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Karyopharm, Novartis, Oncopeptides, Pfizer, Roche, Sanofi, Stemline, and Takeda; and consulting fees from AbbVie, Adaptive, Amgen, BeiGene, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Karyopharm, Oncopeptides, Pfizer, Roche, Sanofi, and Takeda.

Acknowledgments

The authors thank the patients and families who made this study possible and the clinical study teams who partichipated in the trial.

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Supplementary material

Table S1 Frailty algorithm[a]

Factor	Score
Age	
≤ 75 years	0
76–80 years	1
> 80 years	2
CCI	
≤ 1	0
> 1	1
ECOG PS	
0	0
1	1
≥ 2	2
Sum of scores (1)	
Fit	0
Intermediate	1
Frail	≥ 2
Sum of scores (2)	
Nonfrail	0–1
Frail	≥ 2

Abbreviations: CCI = Charlson Comorbidity Index; ECOG PS = Eastern Cooperative Oncology Group performance status.
[a] Frailty algorithm is from Facon T, et al. *Leukemia*. 2020;34:224–233.[18]

Figure S1 Patient disposition by frailty.
There were 14 patients with no comorbidities who were missing CCI score, and thus frailty status.
Abbreviations: CCI = Charlson Comorbidity Index; ITT = intent-to-treat; PVd = pomalidomide, bortezomib, and dexamethasone; Vd = bortezomib and dexamethasone.

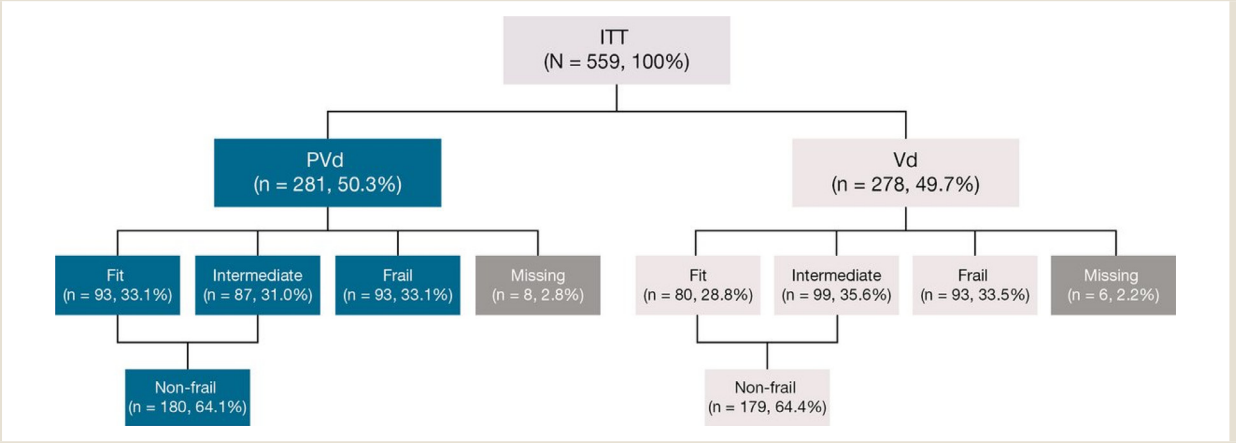

Table S2 Baseline demographics and disease characteristics

Characteristics	Nonfrail		Frail	
	PVd (n = 180)	Vd (n = 179)	PVd (n = 93)	Vd (n = 93)
Age, median (range), years	64.5 (38.0–79.0)	64.0 (27.0–80.0)	74.0 (54.0–87.0)	72.0 (45.0–89.0)
Age group, n (%)				
≤ 75 years	176 (97.8)	170 (95.0)	52 (55.9)	56 (60.2)
76–80 years	4 (2.2)	9 (5.0)	30 (32.3)	20 (21.5)
>80 years	0 (0)	0 (0)	11 (11.8)	17 (18.3)
Male, n (%)	96 (53.3)	92 (51.4)	53 (57.0)	51 (54.8)
ECOG PS, n (%)				
0	135 (75.0)	129 (72.1)	9 (9.7)	5 (5.4)
1	45 (25.0)	50 (27.9)	73 (78.5)	66 (71.0)
2	0 (0)	0 (0)	11 (11.8)	22 (23.7)
CCI group, n (%)				
0	142 (78.9)	139 (77.7)	21 (22.6)	18 (19.4)
1	38 (21.1)	40 (22.3)	72 (77.4)	75 (80.6)
ISS stage,[a] n (%)				
I	43 (23.9)	40 (22.3)	21 (22.6)	12 (12.9)
II	47 (26.1)	42 (23.5)	24 (25.8)	24 (25.8)
III	34 (18.9)	34 (19.0)	26 (28.0)	18 (19.4)
Missing	55 (30.6)	55 (30.7)	21 (22.6)	39 (41.9)
Time since MM diagnosis, median (range), years	4.2 (0.2–19.1)	4.6 (0.4–21.8)	3.6 (0.9–25.9)	4.0 (0.6–14.7)
Number of prior treatment lines, n (%)				
1	75 (41.7)	75 (41.9)	34 (36.6)	39 (41.9)
2	70 (38.9)	70 (39.1)	41 (44.1)	32 (34.4)
3[b]	35 (19.4)	33 (18.4)	18 (19.4)	22 (23.7)
Refractory to prior lenalidomide, n (%)	133 (73.9)	116 (64.8)	63 (67.7)	70 (75.3)
β2-microglobulin level at screening, n (%)				
< 3.5 mg/L	111 (61.7)	110 (61.5)	39 (41.9)	33 (35.5)
≥ 3.5 to ≤ 5.5 mg/L	49 (27.2)	49 (27.4)	28 (30.1)	30 (32.3)
> 5.5 mg/L	20 (11.1)	20 (11.2)	26 (28.0)	30 (32.3)

Abbreviations: CCI = Charlson Comobidity Index; ECOG PS = Eastern Cooperative Oncology Group performance status; ISS = International Staging System; MM = multiple myeloma; PVd = pomalidomide, bortezomib, and dexamethasone; Vd = bortezomib and dexamethasone.
[a] There were 1 frail PVd patient, 1 nonfrail PVd patient, and 8 nonfrail Vd patients with an unknown ISS stage;
[b] There was 1 nonfrail Vd patient who had > 3 prior lines of treatment.

Table S3 Baseline characteristics for PVd following a bortezomib dose adjustment

	PVd (n = 278)		
Characteristic[a]	**Without adjustment (n = 38)**	**With adjustment (n = 240)**	**Vd (n = 270)**
Age, median (range), years	66.5 (38.0–80.0)	68.0 (29.0–87.0)	68.0 (27.0–89.0)
Male	20 (52.6)	134 (55.8)	143 (53.0)
ECOG PS			
0	19 (50.0)	128 (53.3)	135 (50.0)
1	18 (47.4)	102 (42.5)	114 (42.2)
2	1 (2.6)	10 (4.2)	21 (7.8)
Cytogenetic risk			
High risk[b]	9 (23.7)	51 (21.3)	48 (17.8)
Standard risk	16 (42.1)	119 (49.6)	131 (48.5)
Unknown/missing	13 (34.2)	70 (29.2)	91 (33.7)
ISS stage			
I	10 (26.3)	55 (22.9)	47 (17.4)
II	7 (18.4)	64 (26.7)	67 (24.8)
III	11 (28.9)	49 (20.4)	51 (18.9)
Unknown/missing	10 (26.3)	72 (30.0)	105 (38.9)
Time since MM diagnosis, median (range), years	3.8 (1.1–25.9)	4.0 (0.2–19.9)	4.4 (0.4–21.8)
Number of prior treatment lines, median (range)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–4.0)
Refractory to prior lenalidomide	23 (60.5)	174 (72.5)	186 (68.9)
β_2-microglobulin at screening			
$<$ 3.5 mg/L	23 (60.5)	131 (54.6)	144 (53.3)
$\geq$ 3.5–$\leq$ 5.5 mg/L	11 (28.9)	67 (27.9)	78 (28.9)
$>$ 5.5 mg/L	4 (10.5)	42 (17.5)	48 (17.8)
Frailty status,[c,d] **n**			
Frail	12 (32.4)	81 (34.8)	91 (34.5)
Nonfrail	25 (67.6)	152 (65.2)	173 (65.5)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; ISS = International Staging System; MM = multiple myeloma; PVd = pomalidomide, bortezomib, and dexamethasone; Vd = bortezomib and dexamethasone.
[a] All values are n (%) unless otherwise stated;
[b] Includes del 17p, t(4;14), and t(14;16);
[c] There was 1 patient who received PVd without adjustment, 7 patients who received PVd with adjustment, and 6 patients who received Vd who did not have frailty scores;
[d] Percentages are based on patients with available frailty status (PVd without adjustment, n = 37; PVd with adjustment, n = 233; Vd, n = 264).

Figure S2 [a]Patients could have a bortezomib dose adjustment of 3 (not mutually exclusive) types; [b]Dose reduction was defined as a reduction of the planned bortezomib dose (ie, 1.3 mg/m2) in any of the treatment cycles where pomalidomide was still administered; [c]Dose interruption was defined as skipping the bortezomib dose intermittently in any of the treatment cycles where pomalidomide was still administered; [d]Dose discontinuation was defined as permanently stopping bortezomib treatment after a given cycle during subsequent treatment cycles where pomalidomide was still administered.
Patient disposition by bortezomib dose adjustment in PVd. Abbreviations: PVd = pomalidomide, bortezomib, and dexamethasone; Vd = bortezomib and dexamethasone.