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Pomalidomide-bortezomib-dexamethasone in relapsed or refractory multiple myeloma: Japanese subset analysis of OPTIMISMM

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Abstract

In the phase 3 OPTIMISMM trial, pomalidomide, bortezomib and dexamethasone (PVd) significantly improved the progression-free survival (PFS) and the overall response rate (ORR) vs bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma. All patients were previously treated with lenalidomide (70% refractory to lenalidomide) and had received one to three prior regimens. Here we report the first efficacy and safety analysis of PVd vs Vd in Japanese patients with relapsed or refractory multiple myeloma. Seventeen patients enrolled in the OPTIMISMM trial in Japan. With a median follow-up of 14.8 months, the median PFS was 17.6 months with PVd (n = 12) vs 4.4 months with Vd (n = 5), and the ORR was 100% vs 60.0%, respectively. The safety profile was as expected for PVd. Toxicities were managed with dose reductions and interruptions, and no patients discontinued PVd due to treatment-emergent adverse events. These results are consistent with those in the overall OPTIMISMM patient population and confirm the clinical benefit of PVd in Japanese patients.

KEYWORDS

Japan, lenalidomide refractory, OPTIMISMM, pomalidomide, relapsed or refractory multiple myeloma

1 | INTRODUCTION

Despite treatment advances, multiple myeloma (MM) remains an incurable disease, and nearly all patients experience relapse.[1,2] With each successive treatment, response depth and duration decrease, due to increased genetic heterogeneity and development of more aggressive disease that is increasingly resistant to available treatment options.[3,4]

Lenalidomide is a standard treatment for newly diagnosed MM and early-line relapsed or refractory multiple myeloma (RRMM).[5] The use

of lenalidomide-based treatments in these settings and until disease progression has increased the prevalence of patients refractory to lenalidomide at first or second relapse.[5] In Japan, lenalidomide-based and bortezomib-based regimens are among the recommended therapy options for patients with RRMM.[2] Even though there are several newly approved regimens for RRMM, data on novel combinations of immunomodulatory agents and/or proteasome inhibitors in Japanese patients with RRMM are needed to help inform treatment decisions.[6]

Pomalidomide is an oral immunomodulatory agent with direct tumoricidal and immune-enhancing activities.[7] In preclinical studies conducted in lenalidomide-resistant models of MM, pomalidomide-based treatment decreased proliferation and induced apoptosis in cell lines and significantly reduced tumor volume compared with lenalidomide in xenograft mice.[8,9] Pomalidomide therapy has also previously demonstrated clinical benefit in lenalidomide-refractory patients.[10-12]

In Japan, pomalidomide is approved for patients with RRMM who did not respond to at least one standard treatment or relapsed after treatment and is recommended by the Japanese Society of Hematology guidelines as a salvage therapy.[2,13] Currently, these guidelines recommend carfilzomib, pomalidomide and dexamethasone as a salvage therapy in Japanese patients with RRMM, but there are no clinical trial data for this treatment in Japanese patients, and it is not covered by the national healthcare insurance system in Japan.[2]

The randomized, open-label, phase 3 OPTIMISMM trial was the first prospective trial of a pomalidomide-based triplet regimen designed to specifically address the therapeutic needs of patients previously treated with lenalidomide early in their treatment course (one to three prior regimens).[14] Pomalidomide, bortezomib and dexamethasone (PVd) significantly improved the progression-free survival (PFS) (median, 11.2 vs 7.1 months; hazard ratio [HR], 0.61 [95% confidence interval [CI]: 0.49-0.77]; $P < 0.0001$) and the overall response rate (ORR) (82.2% vs 50.0%; odds ratio, 5.02 [95% CI: 3.35-7.52]; $P < 0.0001$) compared with bortezomib and dexamethasone (Vd) in the intent-to-treat (ITT) population (median 2 prior lines of therapy; 70% lenalidomide refractory). The safety profile of PVd was consistent with the adverse event (AE) profile of each constituent agent. These results supported an indication for PVd in Japan for the treatment of patients with RRMM who have received ≥1 prior standard treatment regimen.[13]

Treatment patterns can differ due to multiple factors, including genetics and local guidelines. Given the proven clinical benefit of novel triplet regimens, including PVd, we investigated whether outcomes in Japanese patients were consistent with the global OPTIMISMM study population.[14] Here we report the first analysis of the efficacy and safety of PVd vs Vd in Japanese patients with RRMM.

2 | MATERIALS AND METHODS

2.1 | Patients

Seventeen patients from Japan were enrolled in the OPTIMISMM trial (ClinicalTrials.gov identifier NCT01734928). Study design, eligibility criteria, procedures, outcomes and statistical analyses were described previously.[14] Briefly, adult patients diagnosed with MM and who had measurable disease, had received one to three prior regimens, including ≥2 cycles of lenalidomide treatment, and had disease progression were enrolled in the study. Patients refractory to lenalidomide, including those who received lenalidomide in the last prior regimen, were eligible for the study. Patients refractory to bortezomib, consisting of bortezomib-pretreated patients who had progressed on bortezomib administered at <1.3 mg/m^{2}of body surface area or once weekly, were also eligible. Patients exposed to bortezomib were excluded from the study if they had progressive disease during treatment or within 60 days of the last dose of a bortezomib-containing regimen administered at the most intensive bortezomib schedule of 1.3 mg/m^2 of body surface area twice weekly.

2.2 | Study design and treatment

Patients were randomized (1:1) to receive PVd or Vd, administered in 21-day cycles until disease progression or unacceptable toxicity. Pomalidomide was given orally at 4 mg/day on days 1-14 (PVd arm only). Bortezomib 1.3 mg/m^2 was given subcutaneously on days 1, 4, 8 and 11 of cycles 1-8 and on days 1 and 8 of cycle 9 and beyond. Dexamethasone 20 mg/day (10 mg/day if patient was aged > 75 years) was given orally on days of and after bortezomib administration.

The protocol was approved by the institutional review board or the central or local ethics committee at each participating site. Patients provided written informed consent. The study conformed to the principles of Good Clinical Practice according to the International Conference on Harmonisation requirements and the Declaration of Helsinki.

2.3 | Study endpoints and assessments

The primary endpoint was PFS in the ITT population, assessed by an independent review committee. Prespecified secondary endpoints included: ORR, evaluated according to International Myeloma Working Group criteria; overall survival (OS); duration of response (DOR); and safety. Time to response (TTR) was a prespecified exploratory endpoint. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0 or higher) and were summarized by system organ class and preferred term.

2.4 | Statistical analysis

Efficacy analyses, except for DOR, were adjusted by stratification factors that included age (≤75 vs >75 years), number of prior antimyeloma regimens (1 vs >1) and concentration of β_2-microglobulin at screening (<3.5 vs ≥3.5 to ≤5.5 vs >5.5 mg/L).

PFS was estimated using the Kaplan-Meier method. Data were not mature for the planned interim analysis of OS at the time of data cutoff (26 October 2017). The treatment effect (measured by HR and 95% CI) was estimated using a stratified Cox proportional hazards model. A stratified Cochran-Mantel-Haenszel test was used to compare responses.

3 | RESULTS

3.1 | Patients

Of 559 patients enrolled worldwide, 17 were randomized in Japan: 12 patients to PVd and 5 to Vd (Table 1). In general, baseline

TABLE 1 Patient demographics and baseline characteristics

Characteristic	PVd (n = 12)	Vd (n = 5)	ITT population (N = 559)
Age, median (range), years	72 (60-83)	73 (69-76)	68 (27-89)
Age groups, n (%)			
≤65 years	1 (8)	0	243 (43)
>65 years	11 (92)	5 (100)	316 (57)
Male, n (%)	7 (58)	4 (80)	302 (54)
ECOG performance status, n (%)			
0	11 (92)	5 (100)	286 (51)
1	1 (8)	0	240 (43)
ISS stage at study entry, n (%)[a]			
I	10 (83)	4 (80)	287 (51)
II	2 (17)	1 (20)	175 (31)
Albumin, median (range), g/dL	4.1 (3.5-4.8)	3.6 (3.5-4.2)	4.0 (1.9-5.2)
β2-microglobulin, median (range), mg/L	2.1 (1.4-4.0)	2.5 (1.6-4.4)	3.4 (0.9-16.7)
CrCl < 60 mL/min, n (%)	7 (58)	2 (40)	167 (30)
Time since diagnosis, median (range), years	3.3 (1.7-8.0)	2.1 (0.4-4.3)	4.2 (0.2-25.9)
High-risk of cytogenetic abnormalities, n (%)[b]	1 (8)[c]	1 (20)[c]	110 (20)
Number of prior lines of therapy, median (range)	1 (1-2)	1 (1-2)	2 (1-4)
1 prior line, n (%)	8 (67)	3 (60)	226 (40)
2 prior lines, n (%)	4 (33)	2 (40)	221 (40)
Prior therapy, n (%)			
Lenalidomide	12 (100)	5 (100)	559 (100)
Bortezomib	8 (67)	3 (60)	404 (72)
Prior stem cell transplant, n (%)	5 (42)	2 (40)	324 (58)
Last prior treatment, n (%)			
Corticosteroids	12 (100)	5 (100)	533 (95)
Lenalidomide	12 (100)	5 (100)	487 (87)
Bortezomib	6 (50)	2 (40)	186 (33)
Alkylating agents	6 (50)	1 (20)	230 (41)
Monoclonal antibodies	1 (8)	0	16 (3)
Refractory disease, n (%)			
Lenalidomide	8 (67)	5 (100)	391 (70)
Lenalidomide in last prior regimen	8 (67)	5 (100)	345 (62)
Bortezomib	1 (8)	1 (20)	56 (10)

Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; ITT, intent-to-treat; PVd pomalidomide, bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

[a]ISS was calculated using baseline values of albumin and β2-microglobulin.

[b]High risk was defined as presence of ≥1 of the following cytogenetic abnormalities: del(17p) (including monosomy 17), t(4;14) and/or t(14;16).

[c]The patient had del(17p).

characteristics of the Japanese subgroup were similar to those of the overall OPTIMISMM patient population.[14] The median age was 72 years (range, 60-83 years), and median time since diagnosis was 3.1 years (range, 0.4-8.0 years). Patients in both arms had a median of one prior line of therapy (range, one to two). Prior therapies included bortezomib in 67% vs 60% of patients in the PVd vs Vd arm, respectively. A total of 13 patients (76%) were lenalidomide refractory (n = 8 in the PVd and n = 5 in the Vd arm), all of whom were refractory to lenalidomide as their last prior regimen.

At the data cutoff (26 October 2017), treatment was ongoing in 7 patients (58%) in the PVd arm and 1 patient (20%) in the Vd arm. Progressive disease was the main reason for treatment discontinuation, reported in 4 patients (33%) in the PVd arm and 3 patients (60%) in the Vd arm. Other reasons for discontinuation included withdrawal of consent (PVd) and AE (Vd).

The median treatment duration was 14.5 months with PVd vs 4.0 months with Vd. The median number of cycles was 20.5 (range, 6-29 cycles) with PVd vs 6.0 (range, 4-11 cycles) with Vd.

3.2 | Efficacy

Median PFS (95% CI) was 17.6 months (5.7–not evaluable) with PVd vs 4.4 months (1.4-8.2) with Vd; median follow-up was 14.8 months (range, 6.1-20.2 months).

The ORR with PVd was 100% vs 60% in the Vd arm. PVd led to deeper responses than Vd, with higher rates of complete response (CR) or better (n = 3 [25%] vs n = 0) and very good partial response (VGPR) or better (n = 7 [58%] vs n = 1 [20%]). The median TTR was 0.8 months (range, 0.7-2.1 months) with PVd vs 1.5 months (range, 0.9-2.1 months) with Vd. The median DOR was 16.8 months in the PVd arm vs 7.4 months in the Vd arm. The PFS benefit with PVd was evident in patients with good responses. In the 3 patients who achieved CR, duration of PFS was 19.2, 17.4 and 12.3 months; in 3 of 4 patients with a best response of VGPR, the duration of PFS was 18.7, 17.2 and 9.7 months (Figure 1).

3.3 | Adverse events

The most common treatment-emergent adverse events (TEAEs) reported in ≥15% of patients in any treatment arm are shown in Table 2. Similar to the safety data in the ITT population, the most frequent grade 3/4 hematologic TEAEs were neutropenia (n = 6 [50%] with PVd vs n = 0 with Vd) and thrombocytopenia (n = 2 [17%] with PVd vs n = 1 [20%] with Vd).[14] The most common grade 3/4 nonhematologic toxicities were infections, reported in 5 patients (42%) (n = 2 [17%] with pneumonia) in the PVd arm and 2 patients (40%) in the Vd arm. No patients experienced febrile neutropenia or infections with concurrent grade 3/4 neutropenia. Moreover, no grade 3/4 events of deep vein thrombosis or pulmonary embolism were observed. A total of 4 patients (33%) in the PVd arm vs 1 patient (20%) in the Vd arm had ≥1 drug-related serious TEAE, mostly consisting of infections. No treatment-related deaths were reported. One patient died because of myeloma progression (PVd arm).

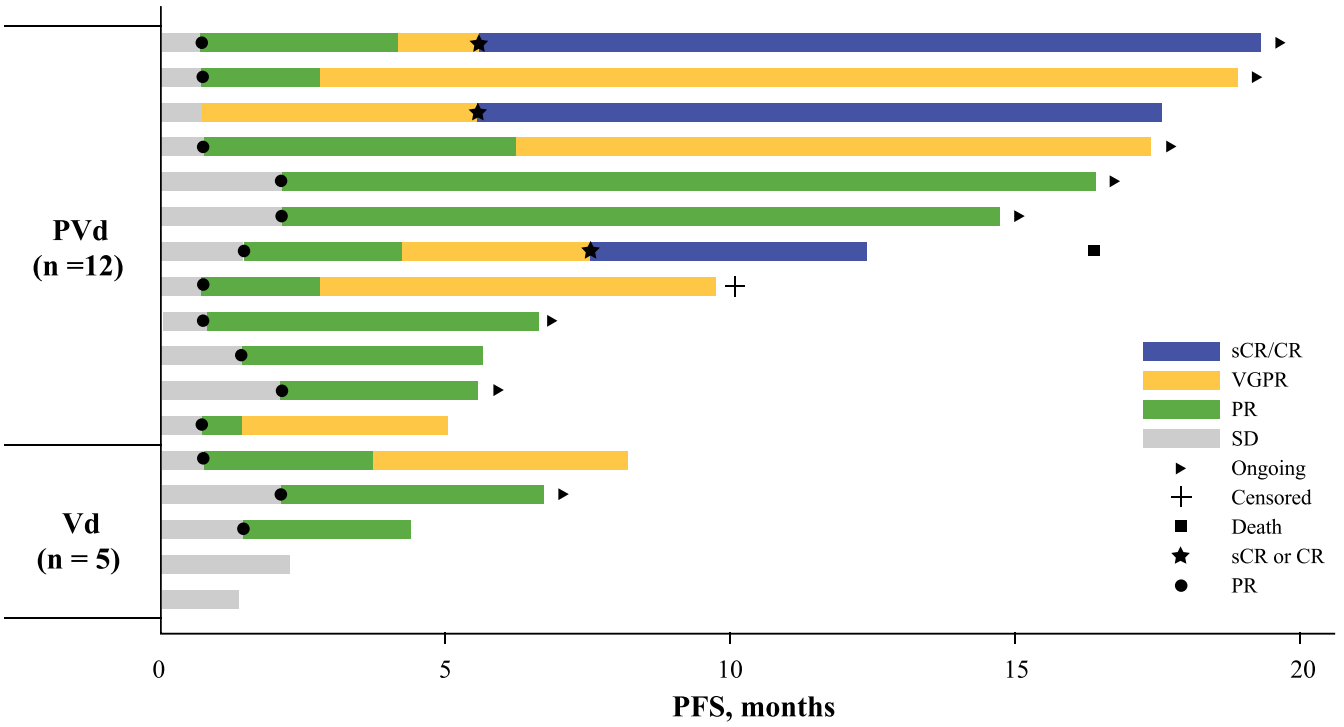

FIGURE 1 Swimmers plot of progression-free survival by response of patients treated with PVd or Vd. CR, complete response; PFS, progression-free survival; PR, partial response; PVd, pomalidomide, bortezomib and dexamethasone; sCR, stringent complete response; SD, stable disease; Vd, bortezomib and dexamethasone; VGPR, very good partial response

TABLE 2 TEAE in ≥15% of patients in either arm

Event, n (%)	PVd (n = 12)		Vd (n = 5)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hematologic TEAE				
Neutropenia	6 (50)	6 (50)	0	0
Leukopenia	3 (25)	2 (17)	0	0
Thrombocytopenia	2 (17)	2 (17)	1 (20)	1 (20)
Anemia	1 (8)	0	1 (20)	1 (20)
Nonhematologic TEAE				
Infections[a]	10 (83)	5 (42)	3 (60)	2 (40)
Viral upper respiratory tract infection	5 (42)	0	0	0
Pharyngitis	4 (33)	0	1 (20)	0
Bronchitis	2 (17)	1 (8)	2 (40)	1 (20)
Influenza	2 (17)	0	0	0
Pneumonia	2 (17)	2 (17)	0	0
Escherichia bacteremia	0	0	1 (20)	1 (20)
Peripheral sensory neuropathy	9 (75)	0	4 (80)	0
Constipation	4 (33)	0	0	0
Malaise	4 (33)	0	1 (20)	0
Back pain	3 (25)	0	0	0
Cataract	3 (25)	1 (8)	0	0
Diarrhea	3 (25)	1 (8)	2 (40)	0
Injection site erythema	2 (17)	0	0	0
Edema peripheral	2 (17)	0	0	0
Pyrexia	2 (17)	0	0	0
Diabetes mellitus	2 (17)	0	0	0
Arthropod bite	2 (17)	0	0	0
Rash	2 (17)	0	0	0
Oropharyngeal pain	2 (17)	0	0	0
Nausea	1 (8)	0	1 (20)	0
Hematuria	1 (8)	1 (8)	1 (20)	0
Hyperglycemia	0	0	1 (20)	1 (20)
Hyponatremia	0	0	1 (20)	1 (20)
Insomnia	0	0	1 (20)	0

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

[a]In the PVd arm, infections included 1 (8%) case each of any grade conjunctivitis, gastroenteritis, myringitis, nail candida, oral candidiasis, skin candida, tinea pedis, muscle abscess (grade 3/4) and *Pneumocystis jirovecii* pneumonia (grade 3/4).

Ten patients (83%) in the PVd vs 4 patients (80%) in the Vd arm had dose reductions due to ≥1 TEAE, primarily caused by peripheral sensory neuropathy (n = 4 vs n = 3). Five patients had the pomalidomide dose reduced due to ≥1 TEAE, with two of these due to thrombocytopenia (Table 3). Eleven (92%) vs 4 patients (80%) in the PVd vs Vd arm had dose interruptions due to ≥1 TEAE, mostly infections (n = 7 vs n = 2) and peripheral sensory neuropathy (n = 3 vs n = 4). Pomalidomide dose interruptions due to ≥1 TEAE occurred primarily due to infections (n = 7), with no interruptions caused by peripheral sensory neuropathy. No patients discontinued pomalidomide due to TEAEs.

4 | DISCUSSION

In this highly lenalidomide-refractory (76%) Japanese subgroup of the phase 3 OPTIMISMM trial, PVd demonstrated a manageable safety profile and improved PFS and ORR vs Vd. Furthermore, PVd resulted in deeper responses that were associated with longer PFS. These outcomes with PVd are the first reported in Japanese patients and support its clinical utility for the treatment of RRMM in this patient population.

Outcomes from the Japanese subgroup are consistent with the overall study population of OPTIMISMM.[14] Both duration and number of cycles with PVd treatment were greater in Japanese patients compared with the patients in the overall population, whereas treatment exposure with Vd was generally similar between the two patient populations. Furthermore, the addition of pomalidomide to Vd led to a greater increase in median PFS in the Japanese subgroup than the overall population (a 13.2-month vs a 4.1-month increase over Vd alone, respectively). In Japanese patients, the ORR in both treatment arms was also numerically higher than in the overall population, whereas the depth of response with each regimen was similar between patient populations (≥VGPR rate was 58% with PVd vs 20% with Vd in Japanese patients and 53% vs 18%, respectively, in the overall population). The numerically better outcomes reported with PVd treatment were achieved in a patient population that was less pretreated and had a lower disease burden (as evidenced by a better Eastern Cooperative Oncology Group performance status and International Staging System stage at baseline) than the overall OPTIMISMM population. However, considering the limited number of patients in the Japanese subgroup, it is difficult to specify the exact reason for improved outcomes with PVd between the two patient populations. Please note, these comparisons are only descriptive and are not supported statistically. Consequently, these results do not indicate the superiority of PVd treatment in Japanese patients compared with the overall population.

The safety profile of PVd in Japanese patients was consistent with that of the overall population, with neutropenia and infections reported as the most common grade 3/4 TEAEs associated with PVd.[14] The main cause of dose reduction for any drug was peripheral sensory neuropathy, likely related to bortezomib. Infections and peripheral sensory neuropathy were the main reasons for any drug interruptions, with pomalidomide dose interruptions primarily due to infections. Because no patients discontinued PVd treatment due

TABLE 3 Dose modifications due to TEAE

Event, n (%)	PVd (n = 12)		Vd (n = 5)
	Any drug	Pomalidomide	Any drug
Discontinuations	0	0	1 (20)[a]
Reductions[b]	10 (8)	5 (42)	4 (80)
Due to peripheral sensory neuropathy	4 (33)	1 (8)	3 (60)
Due to thrombocytopenia	2 (17)	2 (17)	0
Due to infections	2 (17)	1 (8)[c]	0
Due to diabetes mellitus	2 (17)	0	0
Due to diarrhea	2 (17)	1 (8)	0
Interruptions[b]	11 (92)	11 (92)	4 (80)
Due to infections	7 (58)	7 (58)[d]	2 (40)
Bronchitis	2 (17)	2 (17)	1 (20)
Influenza	2 (17)	2 (17)	0
Pneumonia	2 (17)	2 (17)	0
Due to peripheral sensory neuropathy	3 (25)	0	4 (80)
Due to diarrhea	2 (17)	1 (8)	2 (40)

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

[a]Due to bronchitis.

[b]Reductions and interruptions that occurred in ≥2 patients in either arm are shown. A patient with multiple occurrences of the same preferred term was counted only once in that preferred term.

[c]Due to *Pneumocystis jirovecii* pneumonia.

[d]Pomalidomide dose interruptions due to infections included 1 case each of muscle abscess, *Pneumocystis jirovecii* pneumonia and viral upper respiratory tract infection.

to TEAEs, this regimen may be considered tolerable, with a manageable safety profile in Japanese patients.

To our knowledge, this is the first Japanese subanalysis of a phase 3 randomized clinical trial of patients with RRMM who received previous treatment with lenalidomide, the majority of whom were lenalidomide refractory. Other published studies of triplet regimens in Japanese patients include ELOQUENT-2 (elotuzumab, lenalidomide and dexamethasone) and POLLUX (daratumumab, lenalidomide and dexamethasone).[15,16] However, these phase 3 trials excluded lenalidomide-refractory patients; in POLLUX, only 14% of patients were previously treated with lenalidomide (not specified in ELOQUENT-2).

In a recent subanalysis of the randomized phase 2 ELOQUENT-3 trial, the efficacy and safety of elotuzumab, pomalidomide and dexamethasone (EPd) vs Pd in lenalidomide-refractory Japanese patients were reported.[17] The ELOQUENT-3 Japanese subgroup included 20 patients (EPd, n = 13; Pd, n = 7), nearly the same size of the group in OPTIMISMM (PVd, n = 12; Vd, n = 5). All patients in both studies were previously treated with lenalidomide, with 100% and 76% refractory to lenalidomide, respectively. Japanese patients in ELOQUENT-3 were treated in later relapse (median of three prior lines of therapy [range, two to eight]) than those in OPTIMISMM (median of one prior line of therapy [range, one to two]). Both pomalidomide-based triplets demonstrated improved ORR (ELOQUENT-3: 69% EPd vs 29% Pd) and deeper responses (≥VGPR, 23% EPd vs 14% Pd) vs their doublet comparator. Because of differences in patient populations and study designs, cross-trial comparisons should be made with caution. As such, the higher ORR and greater depth of response achieved with PVd in the OPTIMISMM study vs EPd in ELOQUENT-3 may reflect the earlier line treatment and lower proportion of lenalidomide-refractory patients.[17] Although further investigation is warranted, these data suggest that administration of PVd therapy in early line RRMM may maximize the depth of response and delay progression. Any grade neutropenia was experienced by 31% and 50% of Japanese patients treated with EPd and PVd in the two trials, respectively. As the rate was higher with PVd, patients treated with this regimen may require careful management of neutropenia.

In summary, these findings add to the expanding body of evidence on the advantages of pomalidomide-based triplet regimens in Japan. The results of this analysis are relevant to clinical practice, as they support the use of PVd as a new treatment option in patients with RRMM in Japan, including those who are refractory to lenalidomide.

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