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ORIGINAL ARTICLE

Pomalidomide, dexamethasone, and daratumumab in Japanese patients with relapsed or refractory multiple myeloma after lenalidomide-based treatment

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Abstract

In cohort C of the phase 2 MM-014 trial, the efficacy and safety of pomalidomide, dexamethasone, and daratumumab therapy were investigated in 18 Japanese patients with relapsed/refractory multiple myeloma (RRMM) after their most recent regimen of lenalidomide-based therapy (NCT01946477). Patients received oral pomalidomide (4 mg daily), oral dexamethasone (20–40 mg weekly), and intravenously infused daratumumab (16 mg/kg). Median age was 67.5 years. All patients received prior lenalidomide per protocol; 89% received prior bortezomib. Twelve patients (67%) had lenalidomide-refractory disease, and 6 (33%) had lenalidomide-relapsed disease. Ten patients (56%) had only 1 prior treatment line. As of August 3, 2020, 15 patients (83%) were still on treatment; median follow-up was 8.1 months. Three patients (17%) discontinued treatment (2 for adverse events; 1 for major protocol deviation). Overall response rate (primary endpoint) was 83% (very good partial response or better, 61%). All patients had ≥ 1 grade 3/4 treatment-emergent adverse events, most commonly neutropenia (78%; febrile, 6%), leukopenia (28%), and lymphopenia (22%). Grade 3/4 infections occurred in 17%; 11% had pneumonia. In Japanese patients with RRMM, a triplet regimen of pomalidomide, dexamethasone, and daratumumab after early-line lenalidomide treatment failure showed high efficacy and safety consistent with the known safety profile.

Keywords Pomalidomide · Daratumumab · Japan · Relapsed or refractory multiple myeloma

Introduction

Recent advances in multiple myeloma (MM) therapy have resulted in improved outcomes, yet the disease remains incurable, and nearly all patients will relapse after initial treatment [1, 2]. Lenalidomide-based therapy until disease progression is a standard of care for patients with newly diagnosed MM [3, 4]. As a result, most patients will have exhausted the benefits of lenalidomide at the time of first relapse. Although a number of treatment options are available for subsequent therapy, most studies do not include large lenalidomide-exposed or -refractory patient populations [5]. An important goal for any antimyeloma regimen in this setting is to delay relapse; patient outcomes worsen with every relapse, and the time between relapses becomes shorter with each successive line of treatment [1, 2, 5–9].

Pomalidomide is an oral immunomodulatory agent with immune-stimulating and direct tumoricidal activities [10]. In preclinical studies, pomalidomide was shown to decrease myeloma cell proliferation and reduce tumor volume in

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xenograft mouse models, specifically in the context of lenalidomide resistance [11, 12]. Importantly, in clinical trials, maintaining continuous immunomodulation with pomalidomide has also demonstrated clinical benefit in patients with lenalidomide-refractory disease [13–16]. In Japan, pomalidomide is approved for patients with relapsed or refractory MM (RRMM) whose disease did not respond to ≥ 1 standard treatment or relapsed after treatment; also, pomalidomide is recommended by the Japanese Society of Hematology guidelines as a salvage therapy for Japanese patients with RRMM [17, 18]. Currently, the Japanese Society of Hematology guidelines recommend doublet combination with dexamethasone or triplet combination with carfilzomib or bortezomib and dexamethasone as a salvage therapy with pomalidomide, although the combination with pomalidomide, carfilzomib, and dexamethasone is not approved in Japan [17, 19]. Daratumumab, an anti-CD38 monoclonal antibody, is also recommended in Japan as salvage therapy for patients with RRMM, but at this time, there is no recommendation to combine daratumumab with pomalidomide. Approved daratumumab combinations for Japanese patients with RRMM include daratumumab with dexamethasone and lenalidomide, bortezomib, or carfilzomib [20].

MM-014 is a phase 2, international, multicenter, nonrandomized trial investigating the outcomes of sequencing pomalidomide-based therapy immediately after lenalidomide-based treatment failure in patients with RRMM (NCT01946477). In an interim analysis (median follow-up, 17.2 months), the triplet combination of pomalidomide, dexamethasone, and daratumumab demonstrated an overall response rate (ORR) of 77.7% (76.2% in lenalidomide-refractory patients) in patients from the US and Canada (MM-014 DPd cohort; cohort B) who had received 1 or 2 prior lines of treatment [15]. At 1 year, 75.1% of patients were alive and had not experienced disease progression. The reported safety profile for this triplet regimen was consistent with the known toxicities of the individual agents. As an amendment to the MM-014 study, the efficacy and safety of this regimen was investigated in Japanese patients (cohort C) who were previously treated with a lenalidomide-containing regimen. This report describes the interim results of 18 patients treated in cohort C.

Materials and methods

Study design and patients

MM-014 is an open-label clinical trial with 3 cohorts conducted at 49 study sites in the United States, Canada, and Japan. Patients in cohort A received pomalidomide plus low-dose dexamethasone. Patients in cohort B (Canada and US) and cohort C (Japan) received pomalidomide, low-dose dexamethasone, and daratumumab. This analysis focuses only on cohort C. Patients were not simultaneously allocated across cohorts; rather, cohort B was added to the trial via protocol amendment after the full accrual of cohort A, and cohort C was added after the full accrual of cohort B. Data from cohorts A and B have been published [14–16].

Patients eligible for inclusion in cohort C were ≥ 18 years of age with a documented MM diagnosis, measurable disease (serum M-protein ≥ 0.5 g/dL or urine M-protein ≥ 200 mg/day) or involved free light-chain levels ≥ 100 mg/L, and Eastern Cooperative Oncology Group performance status ≤2. In addition, patients must have received 1 or 2 prior lines of treatment with a lenalidomide-containing regimen. Patients with disease that relapsed after or was refractory to lenalidomide were eligible for inclusion. Refractory disease was defined as being nonresponsive to therapy or experiencing disease progression within 60 days of the last dose of lenalidomide.

Key exclusion criteria for cohort C included prior treatment with pomalidomide or daratumumab, or hypersensitivity to thalidomide, lenalidomide, dexamethasone, or monoclonal antibodies. The following laboratory abnormalities were exclusionary criteria: absolute neutrophil count $< 1 \times 10^9$/L, platelet count $< 75 \times 10^9$/L ($< 30 \times 10^9$/L for patients in whom ≥ 50% of bone-marrow nucleated cells were plasma cells), corrected serum calcium > 2.875 mmol/L (11.5 mg/dL), hemoglobin < 80 g/L (4.9 mmol/L), aspartate aminotransferase or alanine transaminase > 3.0 × upper limit of normal, serum total bilirubin > 34.2 µmol/L (2.0 mg/dL) or 3.0 × upper limit of normal, and severe renal impairment (creatinine clearance < 30 mL/min or requiring dialysis). Patients were also excluded if they had received an allogeneic bone-marrow or peripheral blood stem cell transplant < 12 months prior to study entry and had not discontinued immunosuppressive treatment ≥ 4 weeks prior to study initiation.

This study was carried out in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guideline E6 for Good Clinical Practice. The study received approval from each institution's review board or independent ethics committee prior to study initiation and was carried out in accordance with applicable national, state, and local laws. Patients signed an informed consent document prior to undergoing any study related procedures.

All patients were treated with open-label pomalidomide, dexamethasone, and daratumumab using the following schedule for a 28-day treatment cycle: pomalidomide 4 mg/day was administered orally on days 1–21; oral dexamethasone 40 mg/day in patients aged ≤ 75 years or 20 mg/day in patients aged > 75 years was administered on days 1, 8, 15, and 22; and daratumumab was administered as an intravenous infusion at a starting dose of 16 mg/kg on days 1, 8,

15, and 22 during cycles 1 and 2. During cycles 3 through 6, daratumumab was given on days 1 and 15; for cycle 7 and subsequent cycles, daratumumab was given on day 1 until disease progression. All patients received thromboprophylaxis that included low-dose aspirin, low-molecular-weight heparin, or other equivalent antithrombotic agents. To reduce the risk of infusion reactions, it was recommended that all patients receive their protocol-specified dose of oral dexamethasone, oral acetaminophen, oral or intravenous antihistamine, and an oral leukotriene receptor antagonist approximately 1 h prior to daratumumab infusion.

Pomalidomide and dexamethasone dose modifications were permitted during the study; if pomalidomide was withheld, dexamethasone was also withheld. Daratumumab dose reductions were not allowed. In the event of grade 4 neutropenia or febrile neutropenia, the daratumumab dose was withheld, and complete blood counts were evaluated weekly. The treating physician could begin granulocyte colony-stimulating factor if the patient was not already receiving it. Absolute neutrophil counts of ≥ 1000 cells/μL were required before restarting pomalidomide. In the event of thrombocytopenia, the dose was withheld, and complete blood counts were evaluated weekly. Dosing resumed for pomalidomide at 1 dose level lower once platelet count had recovered to ≥ 50,000/μL.

Endpoints and assessments

The primary endpoint was the ORR by modified International Myeloma Working Group (mIMWG) criteria [21]. Secondary endpoints were time to response, duration of response (DOR), time to progression, progression-free survival (PFS), and overall survival.

At screening, all patients provided baseline bone-marrow aspirate and blood samples for analysis. Tumor responses were based on the investigator's assessment using local imaging review (if applicable) and central laboratory results according to mIMWG criteria. For patients with daratumumab interference on serum immunofixation (IFE), the Sebia Hydrashift 2/4 Daratumumab IFE Interference test (Norcross, GA, USA) was used to distinguish a positive serum protein electrophoresis/IFE due to the presence of daratumumab vs the presence of underlying (endogenous) monoclonal protein. Patients were considered complete responders if their positive IFE was confirmed to be daratumumab and if they met all other iMWG criteria for complete response (CR). Time to response, DOR, time to progression, and PFS were calculated based on the investigator's response assessment, and all time-to-event endpoints were estimated from the time of study enrollment, except DOR, which was calculated from the time of initial response.

Safety assessments included adverse events (AEs), physical examinations, clinical laboratory evaluations performed at a central laboratory, venous thromboembolism monitoring, pregnancy testing, and counseling. AEs were coded according to the Medical Dictionary for Regulatory Activities (MeDRA version 23). The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Once discontinued from the study treatment, patients would be followed up for ≤5 years after the last patient was enrolled (unless the follow-up was shorter due to withdrawal of consent, loss to follow-up, or death).

Statistical considerations

The safety population, defined as all enrolled patients who received ≥ 1 dose of study medication, was used for all safety analyses. The intention-to-treat population consisted of all enrolled patients, regardless of whether they received any study treatment, and was used for all efficacy analyses. The efficacy-evaluable population consisted of all enrolled patients who met eligibility criteria, received ≥ 1 dose of study medication, and had ≥ 1 postbaseline response assessment. The efficacy-evaluable population was used to provide supporting sensitivity analyses for the primary endpoint and key secondary endpoints.

Sample size determination

In this study, the primary objective was to test the hypothesis that the ORR for the triplet therapy in Japanese patients exceeded 25% using an exact 1-sided binomial test conducted at an α level of 0.025. A sample size of 17 patients was calculated to provide 80% power for an expected ORR of 60% [22]. Accounting for dropouts and non-eligibility, approximately 20 patients were expected to be enrolled in the study. The null ORR of 25% was based on Ichinohe et al. [22], and the expected 60% ORR under this triplet therapy was based on Chari et al.[23].

Analysis of the primary endpoint

The ORR was based on the best confirmed response prior to the data cutoffand was defined as the percentage of patients showing a confirmed partial response (PR) or better (CR, very good partial response [VGPR], or PR). ORR was estimated and the hypothesis of ORR exceeding 25% was evaluated using a binomial test. In addition, the 95% confidence intervals were calculated using the Clopper-Pearson exact method. The analysis of the ORR primary endpoint was used for both the intention-to-treat and efficacy-evaluable populations.

Table 1 Demographic and baseline characteristics

Characteristic	ITT population (N = 18)
Median age (range), years	67.5 (37.0–84.0)
> 65 years, *n* (%)	12 (66.6)
Male, *n* (%)	14 (77.8)
Asian ethnicity, *n* (%)	18 (100)
Median time since diagnosis (range), years	3.9 (0.7–14.8)
ECOG PS, *n* (%)	
0	16 (88.9)
1	2 (11.1)
2	0
Baseline MM stage (ISS), *n* (%)	
I	6 (33.3)
II	8 (44.4)
III	3 (16.7)
NE	1 (5.6)
Median prior antimyeloma regimens (range), *n*	3.0 (1.0–9.0)
One prior line of therapy, *n* (%)	10 (55.6)
Two prior lines of therapy, *n* (%)	8 (44.4)
Prior therapies, *n* (%)	
Immunomodulatory agent	18 (100)
Lenalidomide	18 (100)
Thalidomide	2 (11.1)
Proteasome inhibitors	16 (88.9)
Bortezomib[a]	16 (88.9)
Carfilzomib	5 (27.8)
Ixazomib	2 (11.1)
Alkylating agents	14 (77.8)
Monoclonal antibodies[b]	1 (5.6)
SCT	10 (55.6)
Disease refractory to most recent prior LEN-containing regimen, *n* (%)	12 (66.7)
Median duration of most recent prior LEN-containing regimen (range), months	32.9 (2.9–77.6)
Most recent prior LEN dose, *n* (%)	
25 mg	2 (11.1)
20 mg	1 (5.6)
15 mg	4 (22.2)
≤10 mg	11 (61.1)
Presence of selected cytogenetic abnormalities, *n* (%)	
Yes	10 (55.6)
No	7 (38.9)
Missing	1 (5.6)

ECOG PS Eastern Cooperative Oncology Group performance status, *ISS* International Staging System, *ITT* intention to treat, *LEN* lenalidomide, *MM* multiple myeloma, *NE* not evaluable, *SCT* stem cell transplant

[a] Thirteen patients received bortezomib as initial therapy: 6 patients received bortezomib, dexamethasone, and cyclophosphamide; 4 received bortezomib, lenalidomide, and dexamethasone; 1 received bortezomib and dexamethasone; 1 received bortezomib, dexamethasone, and doxorubicin; and 1 received bortezomib, melphalan, and prednisolone

[b] Elotuzumab

Results

A total of 25 patients were screened for cohort C, and 18 patients were enrolled at 7 sites in Japan. Median age was 67.5 years, and most patients (77.8%) were male (Table 1). The median time since MM diagnosis was 3.9 years. Patients had either 1 (56%) or 2 (44%) prior lines of therapy. All patients were treated with lenalidomide in the immediate prior line of therapy, and 12 (67%) had lenalidomide-refractory disease. The most recent prior lenalidomide dose was ≤10 mg in 11 patients (61%). Overall, 16 patients (89%) had received a proteasome inhibitor, and 10 patients (56%) had undergone prior stem cell transplant.

At data cutoff (August 3, 2020), 15 patients (83%) were still on treatment; 3 patients (17%) had discontinued treatment—2 due to AEs and 1 due to a protocol violation. Treatment exposure is shown in Table 2. Median duration of treatment for the triplet therapy was 6.9 months, and the median number of treatment cycles was 7. The median relative dose intensity was 0.7 for pomalidomide and dexamethasone and 0.9 for daratumumab.

At a median follow-up of 8.1 months (range 2.3–14.7 months), the ORR was 83% (95% CI, 58.6–96.4%; $P < 0.001$) in the intention-to-treat population, including 4 patients with CR (22%) and 7 with VGPR (39%) (Table 3). The clinical benefit response rate was 83% (95% CI 58.6–96.4%). Median time to response was 1.1 months (range 1.0–9.0 months). At 52 weeks, all patients were event free for PFS, and the 15 patients with response were event free for DOR. In patients who relapsed while receiving previous lenalidomide treatment, the ORR was 100% (96% CI 54.1–100.0%). In patients whose disease was refractory to previous lenalidomide treatment, the ORR was 75% (95% CI 42.8–94.5%) (Table 3). Patients with high-risk cytogenetic abnormalities achieved PR or better (i.e., presence of 17p deletion [$n = 2$; 1 CR, 1 VGPR] and 4;14 translocation [$n = 1$ PR]). No patients in the study had 14;16 translocation.

All patients in the safety population experienced ≥ 1 treatment-emergent AE (TEAE). The most frequently reported TEAEs of any grade were neutropenia (77.8%), rash (33.3%), and leukopenia, pyrexia, and infusion-related reaction (27.8% each). All patients also had ≥ 1 grade 3/4

Table 2 Treatment exposure

Median (range)	Pomalidomide ($n = 18$)	Dexamethasone ($n = 18$)	Daratumumab ($n = 18$)
Treatment duration, months[a]	6.9 (0.9–15.4)	6.9 (0.9–15.4)	6.9 (0.9–15.4)
Treatment cycles, *n*	7.0 (1.0–16.0)	7.0 (1.0–16.0)	7.0 (1.0–16.0)
Cumulative dose, mg[b]	425.5 (56.0–1 344.0)	534.0 (80.0–2 440.0)	16 478.5 (2 200.0–27 612.0)
Relative dose intensity[c]	0.7 (0.2–1.0)	0.7 (0.4–0.9)	0.9 (0.5–1.0)

[a] Treatment duration is [(last cycle end date of study treatment) minus (first cycle start date of study treatment) plus 1] divided by 30.4375

[b] Cumulative dose is total doses received during treatment phase

[c] Relative dose intensity is actual dose intensity divided by planned dose intensity

Table 3 Response (mIMWG criteria)

Response, *n* (%)	ITT population ($N = 18$)	EE population ($n = 17$)[a]	Relapsed (ITT) ($n = 6$)	Refractory (ITT) ($n = 12$)
ORR (PR or better)	15 (83.3)	14 (82.4)	6 (100)	9 (75.0)
CR	4 (22.2)	4 (23.5)	2 (33.3)	2 (16.7)
VGPR	7 (38.9)	6 (35.3)	2 (33.3)	5 (41.7)
PR	4 (22.2)	4 (23.5)	2 (33.3)	2 (16.7)
MR	0	0	0	0
SD	3 (16.7)	3 (17.6)	0	3 (25.0)
PD	0	0	0	0

CR complete response, *EE* efficacy evaluable, *ITT* intention to treat, *mIMWG* modified International Myeloma Working Group *MDS* myelodysplastic syndromes, *MM* multiple myeloma, *MR* minimal response, *ORR* overall response rate, *PD* progressive disease, *PR* partial response, *SD* stable disease, *VGPR* very good partial response

[a] One patient was excluded from the EE population because they were found to not have MM; MDS was confirmed after enrollment

Table 4 Grade 3/4 TEAEs

TEAE[a]	All patients, *n* (%) (*N* = 18)
≥ 1 grade 3/4 TEAE[b]	18 (100.0)
Hematologic TEAEs	
Neutropenia	14 (77.8)
Febrile neutropenia	1 (5.6)
Leukopenia	5 (27.8)
Lymphopenia	4 (22.2)
Anemia	1 (5.6)
Thrombocytopenia	1 (5.6)
Nonhematologic TEAEs	
Infections and infestations	3 (16.7)
Pneumonia	2 (11.1)
Influenza	1 (5.6)
Upper respiratory tract infection	1 (5.6)
Hypophosphatemia	2 (11.1)
Hyperglycemia	1 (5.6)
Erythema multiforme	1 (5.6)
Rash	1 (5.6)
Cataract	1 (5.6)
Fatigue	1 (5.6)
Hepatic function abnormal	1 (5.6)
Alanine aminotransferase increased	1 (5.6)

AE adverse event, *CTCAE* Common Terminology Criteria for Adverse Events, *MedDRA* Medical Dictionary for Regulatory Activities, *NCI* National Cancer Institute, *PT* preferred term, *SOC* system organ class, *TEAE* treatment-emergent adverse event

[a] SOCs and PTs were coded using the MedDRA Version 23.0. A patient with multiple occurrences of an AE was counted only once in the AE category

[b] NCI CTCAE Version 4.03 June 2010 for AEs

TEAE (Table 4), the most common of which were neutropenia (78%), leukopenia (28%), and lymphopenia (22%). The most common nonhematologic grade 3/4 TEAEs were pneumonia (11%) and hypophosphatemia (11%). Eight patients (44%) had ≥ 1 TEAE leading to pomalidomide dose reduction (Table 5), of which the most common was neutropenia (28%). The most common TEAEs leading to pomalidomide dose interruption included neutropenia (67%), leukopenia (17%), and rash (17%). The most common TEAE leading to dexamethasone dose interruption was neutropenia (61%). Neutropenia (78%) and infusion-related reaction (28%) were the most common TEAEs leading to daratumumab dose interruption. Two patients (11%) experienced TEAEs leading to discontinuation; 1 patient experienced pneumonia and rash, and the other patient experienced neutropenia.

Overall, 3 patients (17%) had a serious TEAE: 2 patients with pneumonia and 1 patient with tumor lysis syndrome. No patients died during the treatment period. One patient died due to progressive disease 276 days after their first dose of study treatment, but this death occurred outside of the study treatment period after the patient had initiated a subsequent antimyeloma therapy.

Discussion

The combination of pomalidomide, dexamethasone, and daratumumab demonstrated promising efficacy in this population of previously lenalidomide-treated Japanese patients with RRMM. The study met its primary endpoint with an ORR of 83% ($P < 0.001$), thus rejecting the null hypothesis (i.e., ORR ≤ 25%). These outcomes from the Japan-only cohort C of MM-014 were consistent with the results observed with pomalidomide, dexamethasone, and daratumumab in cohort B (US and Canada: ORR, 77.7%; median PFS, not reached; 1-year PFS rate, 75.1%; median follow-up, 17.2 months) [15] as well as a large European population (APOLLO: ORR, 69%; 18-month PFS rate, 42%; median follow-up, 16.9 months [24]). Furthermore, an ORR of 75% was achieved in patients whose disease was refractory to previous lenalidomide treatment. Notably, all 3 patients in this cohort with high-risk cytogenetic phenotypes achieved clinically meaningful responses (CR, VGPR, or PR), which suggests that this triplet combination could be an option for these difficult-to-treat Japanese patients; results were consistent with those in the larger MM-014 cohort B and APOLLO studies [15, 24].

Although published data from clinical trials are limited in patients with RRMM who previously received lenalidomide, in larger studies such as MM-014 cohort B [15], OPTIMISMM [13], ELOQUENT-3 [25], and APOLLO [24], triplet combinations with pomalidomide in these patients resulted in a higher ORR rate and improved PFS vs doublet combinations. Similar results were observed in a Japanese subset ($n = 17$) of OPTIMISMM [26], where ORR was 100% (VGPR or better, 58%; median PFS, 17.6 months) in 12 patients treated with pomalidomide, bortezomib, and dexamethasone compared with an ORR of 60% (VGPR or better, 20%; median PFS, 4.4 months) in 5 patients treated with bortezomib and dexamethasone. A subset analysis of the ELOQUENT-3 study also showed similar results in a Japanese subpopulation ($n = 20$), 80% of whom had disease refractory to both lenalidomide and a proteasome inhibitor [27]. In this subpopulation, an ORR of 69% and VGPR-or-better rate of 23% were achieved in patients receiving the triplet therapy ($n = 13$). The similarity of clinical outcomes among global and Japanese populations in MM-014, OPTIMISMM, and ELOQUENT-3 supports the overall findings of efficacy with these pomalidomide-based triplet combinations.

The safety profile of pomalidomide, dexamethasone, and daratumumab was consistent with the known toxicities of

Table 5 TEAEs leading to dose modification (safety population)

TEAEs, *n* (%)[a]	Pomalidomide (*n* = 18)	Dexamethasone (*n* = 18)	Daratumumab (*n* = 18)
Patients reporting ≥ 1 TEAE leading to dose reduction	8 (44.4)	9 (50.0)	NA[b]
Hematologic TEAEs	6 (33.3)	2 (11.1)	
Neutropenia	5 (27.8)	0	
Febrile neutropenia	1 (5.6)	0	
Leukopenia	1 (5.6)	0	
Lymphopenia	0	2 (11.1)	
Nonhematologic TEAEs			
Peripheral sensory neuropathy	1 (5.6)	0	
Erythema multiforme	1 (5.6)	0	
Cushingoid syndrome	0	1 (5.6)	
Fatigue	0	2 (11.1)	
ALT increased	0	1 (5.6)	
Hyperglycemia	0	2 (11.1)	
Myopathy	0	1 (5.6)	
Hiccups	0	1 (5.6)	
Patients reporting ≥ 1 TEAE leading to dose interruption	14 (77.8)	13 (72.2)	16 (88.9)
Hematologic TEAEs	13 (72.2)	13 (72.2)	15 (83.3)
Neutropenia	12 (66.7)	11 (61.1)	14 (77.8)
Leukopenia	3 (16.7)	1 (5.6)	1 (5.6)
Anemia	1 (5.6)	0	0
Febrile neutropenia	1 (5.6)	1 (5.6)	1 (5.6)
Lymphopenia	0	1 (5.6)	1 (5.6)
Nonhematologic TEAEs			
Rash	3 (16.7)	1 (5.6)	0
Erythema multiforme	1 (5.6)	0	1 (5.6)
Pneumonia	1 (5.6)	1 (5.6)	0
Upper respiratory tract infection	1 (5.6)	0	0
ALT increased	1 (5.6)	0	0
AST increased	1 (5.6)	0	0
Peripheral sensory neuropathy	1 (5.6)	1 (5.6)	1 (5.6)
Upper respiratory tract inflammation	1 (5.6)	1 (5.6)	0
Infusion related reaction	0	0	5 (27.8)
Hypotension	0	0	1 (5.6)

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *MedDRA* Medical Dictionary for Regulatory Activities, *NA* not applicable, *TEAE* treatment-emergent adverse event

[a] System organ class and preferred terms are coded using MedDRA version 23.0 and are listed in descending order of frequency for pomalidomide. A patient with multiple occurrences of an AE is counted only once in the AE category

[b] Per protocol, daratumumab dose reductions were not allowed

the individual agents and with the well-established safety profile seen in the larger MM-014 cohort B. The most common grade 3/4 hematologic TEAEs were neutropenia, anemia, and thrombocytopenia, and the most common grade 3/4 nonhematologic TEAE was pneumonia [15]. While no new safety concerns were identified, these interim results should be interpreted with caution due to the small number of patients and the shorter median follow-up (8.1 months) compared with MM-014 cohort B (17.2 months) and APOLLO (16.9 months) [15, 24]. Most TEAEs were managed with dose reductions or interruptions, but 2 patients discontinued due to neutropenia ($n = 1$) and rash ($n = 1$), indicating that patients treated with this regimen may require careful management of these AEs.

In summary, the pomalidomide, dexamethasone, and daratumumab triplet regimen demonstrated promising efficacy and a tolerable safety profile in Japanese patients with RRMM previously treated with lenalidomide. The results

suggest that continuous immunomodulation with pomalidomide-based triplets is an effective approach in patients exposed to or whose disease progressed after 1 or 2 prior lines that included lenalidomide treatment; the results support the use of pomalidomide as a foundation for combination therapy in RRMM.

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Data availability statement The Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

Declarations

Conflict of interests K. Matsue reported receiving travel funding from Celgene, a Bristol-Myers Squibb Company, and Janssen. K. Sunami reported honoraria and research funding from AbbVie, Alexion Pharma, Amgen Astellas, Bristol Myers Squibb, Celgene, a Bristol-Myers Squibb Company, Daiichi Sankyo, GlaxoSmithKline, Janssen, MSD, Novartis, Ono, Sanofi, and Takeda. M. Matsumoto reported honoraria from Janssen and Sanofi KK. J. Kuroda reported honoraria and research funding from AbbVie, Bristol Myers Squibb, Celgene, a Bristol-Myers Squibb Company, Chugai, Dainippon Sumitomo, Eizai, Janssen, Kyowa, Nippon Shinyaku, Ono, Otsuka, Sanofi, Sysmex, and Takeda. I. Sugiura reported no competing interests. H. Iwasaki reported research funding from Kyowa Kirin. W. Chung is an employee of Bristol Myers Squibb and has equity ownership in Bristol Myers Squibb. S. Kuwayama is an employee of Bristol Myers Squibb and has equity ownership in Bristol Myers Squibb. M. Nishio is an employee of Bristol Myers Squibb and has equity ownership in Bristol Myers Squibb. K. Lee is an employee of Bristol Myers Squibb and has equity ownership in Bristol Myers Squibb. S. Iida received honoraria and research funding from Celgene, a Bristol-Myers Squibb Company, Janssen, Takeda, Ono, Sanofi, and Daiichi Sankyo and research funding from Chugai, Bristol Myers Squibb, AbbVie, Kyowa Kirin, and GlaxoSmithKline.

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