Isatuximab-Pomalidomide-Dexamethasone Versus Pomalidomide-Dexamethasone in East Asian Patients With Relapsed/Refractory Multiple Myeloma: ICARIA-MM Subgroup Analysis

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Abstract

Data from the phase III ICARIA-MM study in patients with relapsed/refractory multiple myeloma demonstrated significant improvements in progression-free survival and response rates with isatuximab plus pomalidomide and dexamethasone (Isa-Pd) versus pomalidomide and dexamethasone. This predefined subgroup analysis confirmed the efficacy and safety of Isa-Pd in Japanese, Korean, and Taiwanese patients, supporting the use of this treatment combination in East Asia.

Background: In the pivotal phase III, randomized, multicenter ICARIA-MM study (NCT02990338), isatuximab plus pomalidomide and dexamethasone (Isa-Pd) improved progression-free survival and overall response rate versus pomalidomide and dexamethasone (Pd) in the overall population of patients with relapsed/refractory multiple myeloma. **Patients and Methods:** In this predefined subgroup analysis, efficacy, and safety between East Asian patients and the overall population were assessed. **Results:** In total, 36 East Asian patients were included (Japanese, n = 13; Korean, n = 9; Taiwanese, n = 14). At a median follow-up of 11.6 months, median progression-free survival was not reached (95% confidence interval [CI] 5.80–not calculable) in the Isa-Pd arm and was 7.9 months (95% CI 2.90–not calculable) in the Pd arm. The hazard ratio for the between-group difference was 0.52 (95% CI 0.19-1.39), which was similar to the overall population (hazard ratio, 0.60; 95% CI 0.44-0.82). No new safety signals were observed, except that a higher

Abbreviations: AE, adverse event; ASCT, autologous stem cell transplantation; CI, confidence interval; CR, complete response; CrCl, creatinine clearance; HR, hazard ratio; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IR, infusion-related reaction; Isa-Pd, isatuximab plus pomalidomide and dexamethasone; ISS, international staging system; ITT, intention-to-treat; MM, multiple myeloma; MRD, minimal residual disease; NC, not calculable; ORR, overall response rate; Pd, pomalidomide and dexamethasone; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; RDI, relative dose intensity; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; VGPR, very good partial response.

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proportion of patients in the East Asian population experienced Grade ≥ 3 neutropenia compared with the overall population. **Conclusion:** These results confirm the efficacy of Isa-Pd in East Asian patients with relapsed/refractory multiple myeloma, and the related safety data are consistent with those observed in the overall population and are manageable.

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Introduction

Multiple myeloma (MM) is a neoplastic plasma cell disorder and is the second most common hematologic malignancy.[1] MM occurs most frequently in individuals aged > 65 years,[2] and while treatment options are available, there is currently no cure for this disease. Combinations of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) are currently the mainstay of treatment, but patients still experience disease relapse and ultimately become refractory to these drugs. Outcomes for patients with relapsed/refractory MM (RRMM) are poor, with overall survival for patients refractory to IMiD and PI treatment being ≤ 9 months.[3,4] There remains considerable unmet need for effective combination therapies that provide improved outcomes for patients with RRMM.

CD38 is a multifunctional surface glycoprotein that is highly expressed on malignant plasma cells, and therefore represents a promising therapeutic target.[5,6] The anti–CD38 monoclonal antibody daratumumab has become a widely used therapeutic agent in the treatment of RRMM, either alone or in combination with an IMiD or PI.[7] Isatuximab is an anti–CD38 monoclonal antibody that binds to a specific epitope on human CD38[8] and induces multiple antitumor effects, including antibody-dependent cellular cytotoxicity, complement-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and homotypic aggregation-associated cell death without Fc-mediated cross-linkage.[9,10] In a phase I study that evaluated 84 patients with RRMM, isatuximab demonstrated a manageable safety profile and promising clinical activity. At ≤ 5 mg/kg (n = 21), 10 mg/kg (n = 49), and 20 mg/kg (n = 14) doses, the overall response rate (ORR) was 10%, 25%, and 21%, respectively, and the clinical benefit rate was 14%, 29%, and 36%, respectively.[8] In a phase I/II study that evaluated 36 Japanese patients with RRMM treated with isatuximab 10 mg/kg (n = 3) and 20 mg/kg (n = 33), the ORR was 66.7% and 36.4%, and the clinical benefit rate was 66.7% and 54.5%, respectively.[11] While isatuximab monotherapy has shown acceptable safety profile and promising clinical outcomes, the cytotoxic effect of isatuximab on MM cells can be augmented by the addition of pomalidomide.[9] Furthermore, recent clinical trials assessing isatuximab in combination with pomalidomide plus dexamethasone or lenalidomide plus dexamethasone have observed manageable safety profiles and favorable efficacy outcomes in patients with RRMM.[12-14] Collectively, these observations indicate the therapeutic potential of isatuximab combination therapies for the treatment of patients with RRMM. Accordingly, isatuximab in combination with pomalidomide and dexamethasone has been approved in a number of countries, including Japan, Taiwan, and the Republic of Korea for the treatment of adult patients with RRMM who have received at least 2 prior therapies, including lenalidomide and a PI.[15]

The ICARIA-MM study was a phase III, randomized, controlled, multicenter trial which evaluated the efficacy and safety of isatuximab plus pomalidomide and dexamethasone (Isa-Pd) versus pomalidomide and dexamethasone (Pd) in RRMM.[13,16] Compared with Pd, Isa-Pd significantly improved progression-free survival (PFS; 6.5 vs. 11.5 months, respectively; stratified hazard ratio [HR], 0.596; 95% confidence interval [CI] 0.44-0.81; $P = .001$) and ORR (35% vs. 60%, respectively) in the overall population. The ICARIA-MM study included patients enrolled from 3 East Asian countries (Japan, Republic of Korea, and Taiwan). The incidence of MM is known to vary with ethnicity and is lower in Asian populations compared with Western populations.[17] However, epidemiologic studies show that MM incidence rates are increasing in Asian populations,[18,19] owing to improved detection, true increases in disease prevalence, and increases in life expectancy.[20] While there are no known defining clinical characteristics of MM between Asian and Western populations, the median age of Asian patients with MM is lower and the incidence of advanced disease is higher, compared with Western populations.[17,21] Despite the introduction of novel drugs for the treatment of MM in Asian populations, there is still a need to optimize current treatments and develop drug combinations that will prove efficacious in this population.[22,23]

The objective of this predefined subgroup analysis was to examine the efficacy and safety of Isa-Pd in East Asian patients, including a separate analysis of Japanese patients, and to compare findings with the overall population of the ICARIA-MM study.

Subjects and Methods

Study Design and Patients

The ICARIA-MM study was a prospective, randomized, open-label, active-controlled, multicenter, phase III study conducted at 102 sites in 24 countries, with an enrollment period between January 10, 2017, and February 2, 2018. The study protocol was approved by the institutional review boards and independent ethics committees at all participating institutions and the study adhered to the Declaration of Helsinki and relevant local guidelines for clinical trials. The trial is registered at ClinicalTrials.gov; identifier NCT02990338.

The study design has previously been described.[13,16] Briefly, eligible patients had RRMM, had received at least 2 prior lines of treatment, had not responded to treatment with lenalidomide and a PI (bortezomib, carfilzomib, or ixazomib), alone or in combina-

tion, had measurable disease (serum M protein ≥ 0.5 g/dL and/or urine M protein ≥ 200 mg/24 h), and were refractory to the most recent line of treatment. RRMM was diagnosed using the International Myeloma Working Group (IMWG) criteria.[24] Patients were excluded if they were refractory to prior anti–CD38 monoclonal antibody treatment had received prior treatment with pomalidomide, had ongoing toxicity (Grade > 1) from prior antimyeloma therapy, had active primary amyloid-light chain amyloidosis, or had concomitant plasma cell leukemia. All patients provided written informed consent.

Randomization and Dosing

Following enrollment, patients were randomized (1:1) to receive either Isa-Pd or Pd. Randomization was performed using interactive technology and stratified according to the number of previous lines of treatment (2-3 vs. > 3) and age (< 75 vs. ≥ 75 years). Treatment assignment was unmasked for patients and study personnel but was masked for those involved in analyzing the results.

Patients in the Isa-Pd arm received isatuximab (10 mg/kg intravenously on days 1, 8, 15, and 22 in the first 28-day cycle, then on days 1 and 15 in subsequent cycles), pomalidomide (4 mg orally on days 1-21 in each cycle), and dexamethasone (40 mg [20 mg for patients ≥ 75 years] orally or intravenously on days 1, 8, 15, and 22 in each cycle). Patients in the Pd arm received pomalidomide and dexamethasone at the same dose and schedule as in the Isa-Pd arm. Patients in both treatment arms received thromboprophylaxis of either aspirin or low molecular-weight heparin. Patients in the Isa-Pd arm received premedication prior to each isatuximab infusion, which included ranitidine (50 mg), paracetamol (650-1000 mg), diphenhydramine (25-50 mg), and dexamethasone (40 mg [20 mg for patients ≥ 75 years]). Dose reduction was permitted for pomalidomide and dexamethasone, but not for isatuximab.

Endpoints and Assessments

The primary endpoint was PFS, defined as the time from randomization to first documentation of progressive disease, as determined by the institutional response committee, or death from any cause.

The key secondary endpoints for this analysis included the assessment of ORR, time to response, duration of response, and safety. Overall survival was not calculated in this analysis due to the limited number of events (including no deaths being recorded in the Japanese population). Response and disease progression were assessed based on the IMWG response criteria.[24] Bone marrow samples were collected for the assessment of minimal residual disease (MRD), which was determined using the Adaptive clonoSEQ Assay (version 2.0; Adaptive Biotechnologies, Seattle, WA). Bone marrow aspirate samples were collected at screening, at the time of complete response (CR) confirmation, or if clinically indicated. Up to a total of 3 on-treatment samples were collected at 3-month intervals if the patient was determined MRD-positive. Cytogenetic analysis (by fluorescent in-situ hybridization) was performed centrally. High-risk genetic status was defined as del(17p), t(4;14), or t(14;16), with cut-offs of 50%, 30%, and 30%, respectively. Safety assessments included adverse events (AEs) and treatment-emergent AEs (TEAEs), laboratory parameters, vital signs, Eastern Cooperative Oncology Group performance status, and physical examination. All AEs were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analyses

The predefined subgroup analysis reported here was conducted using 36 patients enrolled from East Asian countries (Japan, n = 13 patients at 8 sites; Republic of Korea, n = 9 patients at 5 sites; Taiwan, n = 14 patients at 4 sites). In addition, data from Japanese patients in the East Asian population were analyzed separately. All efficacy endpoints were analyzed in the intention-to-treat (ITT) population, the data cut-off for the analysis was October 11, 2018. All safety data were collected for any patient in the ITT population who received at least 1 dose of the study treatment. PFS was analyzed using the Kaplan-Meier method. Hazard ratios (HRs) were estimated using the stratified Cox proportional hazards model in the overall population. Treatment arms were compared using a 1-sided log-rank test stratified by prior lines of treatment and age. The proportions of patients achieving a response were compared using the stratified Cochran-Mantel-Haenszel test. No inferential statistics were performed on other secondary endpoints, and these are summarized descriptively.

Results

The results of the ICARIA-MM study in the overall population have previously been reported[13] but have been included here for comparison with the findings of this subanalysis.

Patients

In total, 307 patients were enrolled and assigned study treatment in the ICARIA-MM study, which included 36 patients from East Asia (Pd, n = 15; Isa-Pd, n = 21; Figure 1). Of these East Asian patients, 13 were from Japan (Pd, n = 4; Isa-Pd, n = 9), 9 from Republic of Korea (Pd, n = 3; Isa-Pd, n = 6), and 14 from Taiwan (Pd, n = 8; Isa-Pd, n = 6).

Patient characteristics are summarized in Table 1. Most characteristics in the Japanese and East Asian populations were similar to the overall population, however, there were some differences between treatment arms. Of note, while the number of prior treatment lines was similar between treatment arms, Japanese and East Asian patients treated with Isa-Pd had shorter duration since initial diagnosis (3.4 and 3.6 years, respectively) compared with those treated with Pd (6.3 and 6.0 years, respectively). All patients had previously received treatment with PI and IMiD, and most had received prior treatment with an alkylating agent. The majority of patients were refractory to treatment with IMiD, lenalidomide, PI, or a combination of IMiD and PI, and to their previous regimen (Table 1).

Treatments

Dose exposure to study drugs is summarized in Table 2. Median treatment duration was similar between the Isa-Pd and Pd arms for all study populations (approximately 40 weeks), with the exception of the Pd arm in the overall population which was shorter (24 weeks). The median relative dose intensity (RDI) of isatuximab was ≥ 92% for all study populations. The median RDI of

Table 1 Key Patient Demographics and Baseline Clinical Characteristics (ITT Population)

	Japan (n = 13)		East Asia[a] (n = 36)		Overall (N = 307)	
	Isa-Pd (n = 9)	Pd (n = 4)	Isa-Pd (n = 21)	Pd (n = 15)	Isa-Pd (n = 154)	Pd (n = 153)
Female	3 (33.3)	2 (50.0)	5 (23.8)	7 (46.7)	65 (42.2)	83 (54.2)
Age, y						
Median (range)	67.0 (61-81)	65.5 (41-85)	66.0 (47-81)	64.0 (41-85)	68.0 (36-83)	66.0 (41-86)
< 65	2 (22.2)	2 (50.0)	8 (38.1)	9 (60.0)	54 (35.1)	70 (45.8)
65 to < 75	5 (55.6)	1 (25.0)	9 (42.9)	5 (33.3)	68 (44.2)	54 (35.3)
≥ 75	2 (22.2)	1 (25.0)	4 (19.0)	1 (6.7)	32 (20.8)	29 (19.0)
CrCl < 60 mL/min/1.73 m^2[b]	2 (22.2)	2 (50.0)	4 (19.0)	4 (26.7)	54 (35.5)	46 (30.9)
Y since initial diagnosis, median (range)	3.4 (0.8-7.2)	6.3 (1.6-10.3)	3.6 (0.8-8.5)	6.0 (1.1-10.3)	4.5 (0.6-18.4)	4.1 (0.5-20.5)
Type of myeloma at diagnosis						
IgA	0 (0.0)	1 (25.0)	5 (23.8)	5 (33.3)	34 (22.1)	41 (26.8)
IgG	7 (77.8)	3 (75.0)	13 (61.9)	10 (66.7)	102 (66.2)	100 (65.4)
Light chain ($\kappa + \lambda$)	2 (22.2)	0 (0.0)	3 (14.3)	0 (0.0)	15 (9.7)	11 (7.2)
ISS stage at diagnosis						
I	3 (33.3)	1 (25.0)	3 (14.3)	5 (33.3)	36 (23.4)	41 (26.8)
II	5 (55.6)	1 (25.0)	9 (42.9)	7 (46.7)	49 (31.8)	48 (31.4)
III	1 (11.1)	2 (50.0)	6 (28.6)	3 (20.0)	42 (27.3)	44 (28.8)
Cytogenetic risk at baseline[c]						
High	1 (11.1)	2 (50.0)	3 (14.3)	2 (13.3)	24 (15.6)	36 (23.5)
Standard	7 (77.8)	2 (50.0)	14 (66.7)	9 (60.0)	103 (66.9)	78 (51.0)
Missing	1 (11.1)	0 (0.0)	4 (19.0)	4 (26.7)	27 (17.5)	39 (25.5)
Disease characteristics						
Beta 2-microglobulin (mg/L), median (range)[d]	2.1 (1.8-8.0)	4.3 (1.8-5.8)	3.0 (1.5-10.5)	3.4 (1.0-5.8)	3.4 (0.4-27.0)	3.8 (0.7-54.7)
Albumin (g/L), median (range)	37.0 (32.0-45.0)	36.5 (30.0-40.0)	37.0 (24.0-45.0)	39.0 (30.0-50.0)	37.0 (16.0-48.7)	37.9 (16.5-50.0)
Bone marrow plasma cells (%), median (range)	10.4 (0.0-23.6)	12.5 (2.0-34.0)	14.9 (0.0-92.2)	20.4 (0.0-90.0)	25.0 (0.0-100.0)	29.0 (0.0-93.0)
Measurable serum M protein	7 (77.8)	4 (100)	18 (85.7)	13 (86.7)	103 (66.9)	107 (69.9)
Bone lesions[e,f]	6 (66.7)	3 (75.0)	14 (66.7)	10 (66.7)	103 (67.3)	101 (67.8)
Soft tissue plasmacytoma[e]	1 (11.1)	0 (0.0)	3 (14.3)	0 (0.0)	14 (9.1)	10 (6.5)
Prior lines of therapy, median (range)	2.0 (2.0-5.0)	3.5 (2.0-5.0)	3.0 (2.0-7.0)	3.0 (2.0-6.0)	3.0 (2.0-11.0)	3.0 (2.0-10.0)
Prior regimens, median (range)	5.0 (2.0-7.0)	5.0 (3.0-5.0)	5.0 (2.0-10.0)	5.0 (2.0-9.0)	4.0 (2.0-13.0)	4.0 (2.0-11.0)
Prior treatment						
Alkylating agent	5 (55.6)	4 (100.0)	16 (76.2)	13 (86.7)	139 (90.3)	148 (96.7)
PI	9 (100.0)	4 (100.0)	21 (100.0)	15 (100.0)	154 (100.0)	153 (100.0)
IMiD	9 (100.0)	4 (100.0)	21 (100.0)	15 (100.0)	154 (100.0)	153 (100.0)
Refractory to treatment						
IMiD	8 (88.9)	3 (75.0)	20 (95.2)	14 (93.3)	147 (95.5)	144 (94.1)
Lenalidomide	8 (88.9)	3 (75.0)	20 (95.2)	13 (86.7)	144 (93.5)	140 (91.5)
PI	8 (88.9)	3 (75.0)	17 (81.0)	8 (53.3)	118 (76.6)	115 (75.2)
IMiD + PI	7 (77.8)	3 (75.0)	16 (76.2)	8 (53.3)	113 (73.4)	110 (71.9)
Last regimen	9 (100.0)	4 (100.0)	21 (100.0)	15 (100.0)	150 (97.4)	151 (98.7)
Prior ASCT	3 (33.3)	2 (50.0)	10 (47.6)	7 (46.7)	83 (53.9)	90 (58.8)

Abbreviations: ASCT = autologous stem cell transplantation; CrCl = creatinine clearance; IMiD = immunomodulatory drug; Isa-Pd = isatuximab-pomalidomide-dexamethasone; ISS = international staging system; ITT = intention-to-treat; Pd = pomalidomide-dexamethasone; PI = proteasome inhibitor. Note: Data are shown as n (%) or n/N (%) unless otherwise stated.
[a] East Asian population included patients in the Japanese population;
[b] Assessed in all treated population;
[c] Cytogenetics by central laboratory: cut-off values were 50% for del(17p), 30% for t(4,14), and 30% for t(14,16);
[d] All Pd population (n = 150);
[e] As assessed by internal response council;
[f] All Pd population (n = 149).

Figure 1 Patient disposition. [a]Data cut-off October 11, 2018. AE = adverse event; Isa-Pd; isatuximab-pomalidomide-dexamethasone; Pd = pomalidomide-dexamethasone; PD = progressive disease.

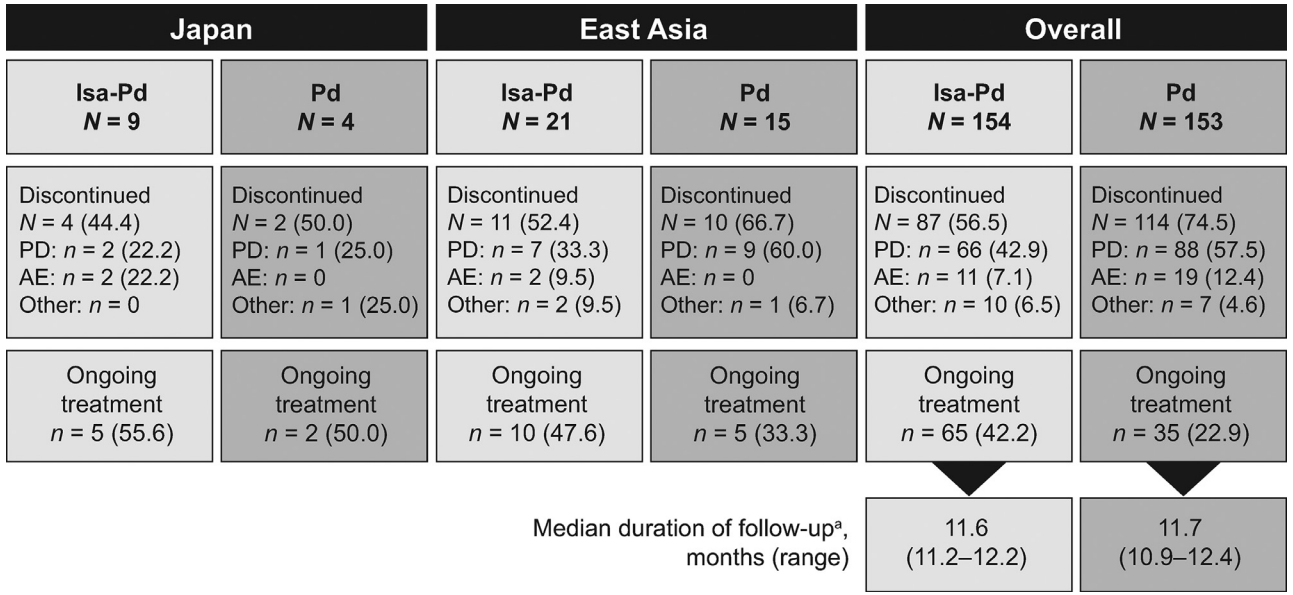
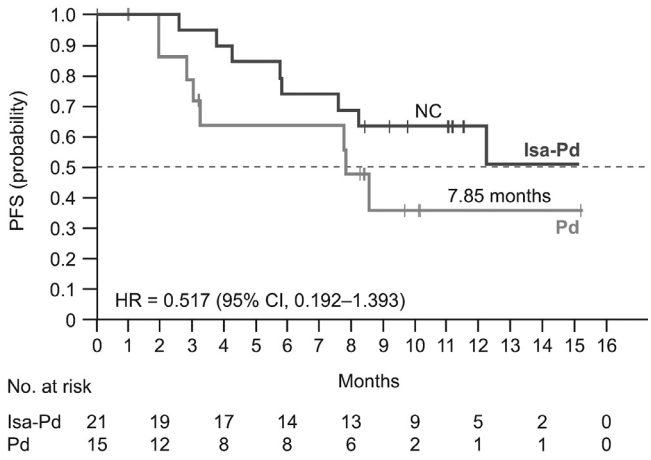


Table 2 Exposure to Study Drugs (all Treated Population)

	Japan (n = 13)		East Asia (n = 36)		Overall (N = 307)	
	Isa-Pd (n = 9)	Pd (n = 4)	Isa-Pd (n = 21)	Pd (n = 15)	Isa-Pd (n = 152)	Pd (n = 149)
Treatment duration, wk, median (range)	40.0 (28.6-69.9)	39.4 (8.0-49.3)	41.0 (4.0-69.9)	39.1 (8.0-69.0)	41.0 (1.3-76.7)	24.0 (1.0-73.7)
RDI, %, median (range)						
Isatuximab	91.9 (83.7-98.3)	..	95.6 (75.0-100.5)	..	92.3 (19.7-111.1)	..
Pomalidomide	63.3 (36.7-96.2)	94.1 (47.5-97.4)	87.2 (36.7-100.0)	94.4 (47.5-100.2)	85.1 (22.9-103.7)	93.3 (37.2-118.5)
Dexamethasone	84.0 (37.4-98.4)	82.6 (45.0-97.4)	93.3 (37.4-100.0)	95.7 (45.0-100.0)	87.8 (15.9-130.0)	96.3 (30.3-300.0)
Pomalidomide dose reductions, n (%)	6 (66.7)	1 (25.0)	9 (42.9)	3 (20.0)	65 (42.8)	36 (24.2)
Dexamethasone dose reductions, n (%)	4 (44.4)	2 (50.0)	5 (23.8)	4 (26.7)	50 (32.9)	38 (25.5)

Data are shown as n (%) unless otherwise stated. Abbreviations: Isa-Pd = isatuximab-pomalidomide-dexamethasone; Pd = pomalidomide-dexamethasone; RDI = relative dose intensity.

Figure 2 Kaplan-Meier plots of progression-free survival in East Asian patients. CI = confidence interval; HR = hazard ratio; Isa-Pd = isatuximab-pomalidomide-dexamethasone; NC = not calculable; Pd = pomalidomide-dexamethasone; PFS = progression-free survival.



pomalidomide was lower in the Isa-Pd arm of the Japanese population (63.3%), due to a higher rate of pomalidomide dose reduction (66.7%), compared with other subgroups. The median RDI of dexamethasone was lower in the Japanese population (in both Isa-Pd and Pd arms) compared with other subgroups; a higher rate of dexamethasone dose reduction was noted in the Japanese population. At data cut-off, approximately half of the patients in the Isa-Pd arm (in Japanese, East Asian, and overall populations) and the Pd arm in the Japanese population were still receiving treatment, while a lower proportion of patients in the Pd arm in the East Asian (33.3%) and overall (22.9%) populations were still receiving treatment (Figure 1).

Progression-free Survival and Treatment Response

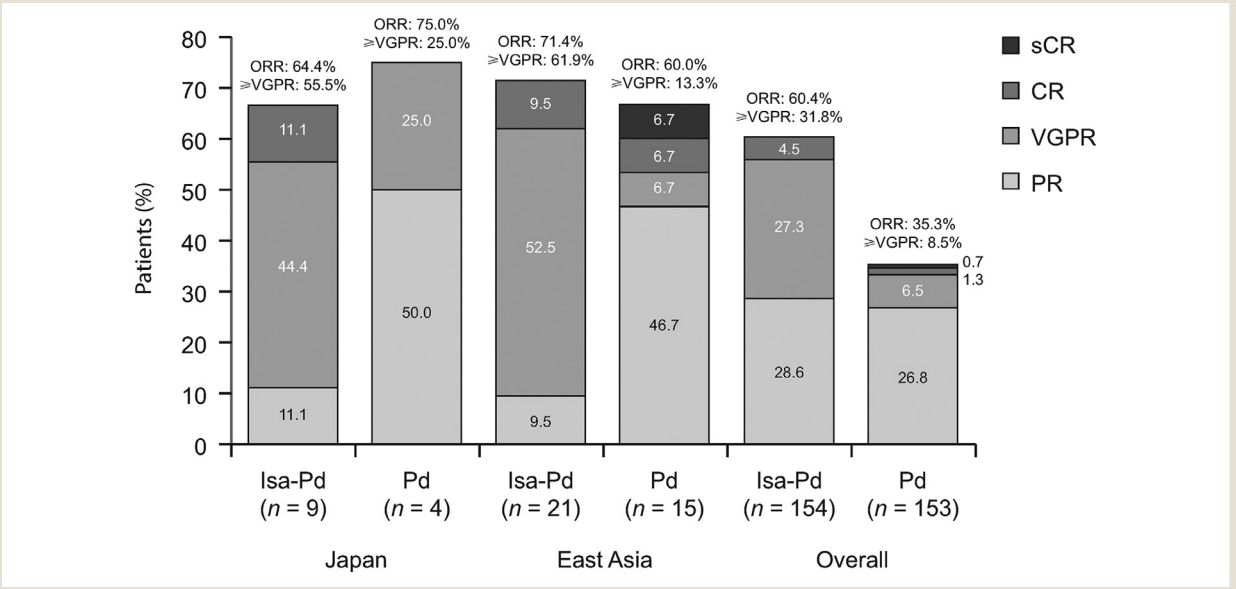
At a median follow-up of 11.6 months (interquartile range, 10.1-13.9), in the East Asian population, median PFS was not reached (95% confidence interval [CI] 5.8-not calculable) in the Isa-Pd arm and was 7.9 months (95% CI 2.9-not calculable) in the Pd arm (Figure 2). The HR for PFS, for Isa-Pd versus Pd, was similar in the East Asian population (HR, 0.52; 95% CI 0.19-1.39) compared with the overall population (HR, 0.60; 95% CI 0.44-0.82). In a sensitivity analysis based on investigator assessment using M protein and imaging locally in the East Asian population, median PFS was 12.3 months in the Isa-Pd arm (95% CI 7.425-not calculable) and 8.6 months in the Pd arm (95% CI 2.168-not calculable). The HR for PFS by investigator, for Isa-Pd versus Pd, was 0.543 (95% CI 0.213-1.384) in the East Asian population, compared with 0.602 (95% CI 0.444-0.816) in the overall population. PFS is not reported separately for the Japanese population due to a limited number of cases of disease worsening in this population at the data cut-off.

A summary of responses is provided in Figure 3 and Table 4. ORR was higher in the Isa-Pd arm versus Pd arm in the East Asian population (71.4% vs. 60.0%, respectively) and the overall population (60.4% vs. 35.3%, respectively), but this was reversed in the Isa-Pd arm versus Pd arm in the Japanese population (64.4% vs 75.0%, respectively; Figure 3). More patients achieved a very good partial response (VGPR) or better in the Isa-Pd arm versus Pd arm for all study populations (Isa-Pd: Japanese, 55.5%; East Asian, 61.9%; overall, 31.8% vs. Pd: Japanese, 25.0%; East Asian, 13.3%; overall, 8.5%). The median time to first response was shorter in the Isa-Pd arm versus the Pd arm (approximately 30 vs. 60 days) for all study populations (Table 4). The median time to first VGPR or better was similar between the Isa-Pd and Pd arms in the East Asian (121.0 days for both) and overall (88.0 and 90.0 days, respectively) populations, but was shorter in the Isa-Pd arm versus the Pd arm in the Japanese population (121.0 vs. 152.0 days, respectively; Table 4).

Minimal Residual Disease

By protocol, MRD samples were collected in case of investigator-assessed CR or if clinically indicated. As a result, in the East Asian population, MRD samples from just 4 patients were available for analysis, all in the Isa-Pd arm, of which samples from 3 patients were from the Japanese population. No samples were available from patients in the Pd arm of the East Asian population. In the overall population, MRD samples were analyzed from 16 patients (Isa-Pd, n = 14; Pd, n =2). In the Isa-Pd arm of the East Asian population, MRD negativity was confirmed in 3 of 21 patients (14.3%) at 10^{-4} and 10^{-5}, and 1 of 21 patients (4.8%) at 10^{-6}. In the Isa-Pd arm of the Japanese population, MRD negativity was confirmed in 2 of 9 patients (22.2%) at 10^{-4} and 10^{-5}. In the Isa-Pd arm of the overall population, MRD negativity was confirmed in 10 of 154 patients (6.5%) at 10^{-4}, 8 of 154 patients (5.2%) at 10^{-5}, and 2 of 154 (1.3%) patients at 10^{-6}. MRD negativity was not confirmed in either patient (0/2) in the Pd arm of the overall population (0.0%). The median time to first MRD negativity, at a sensitivity of 10^{-5}, was 267 days (range, 216-316 days) and 264 days (range, 146-316)

Figure 3 Best responses and time to responses (by independent review committee review). CR = complete response; Isa-Pd = isatuximab-pomalidomide-dexamethasone; ORR = overall response rate; Pd = pomalidomide-dexamethasone; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.



for the Isa-Pd arm in the East Asian and overall populations, respectively.

Safety

TEAEs are summarized in Table 3. The proportions of patients reporting any TEAE were similar between treatment arms and study populations, (≥ 98.0% for all), while the proportions of patients reporting any Grade ≥ 3 TEAE were higher in the Isa-Pd arm versus Pd arm in the East Asian (90.5% vs. 73.3%) and overall (86.6% vs. 70.5%) populations but not in the Japanese population (88.9% vs. 100%). The incidence of serious drug-related TEAEs was higher in the Isa-Pd arm versus Pd arm in the Japanese (22.2% vs. 0.0%), East Asian (19.0% vs. 6.7%), and overall (35.5% vs. 16.1%) populations. A higher proportion of patients discontinued due to TEAEs in the Isa-Pd arm versus Pd arm in the overall population. In the Japanese and East Asian populations, a higher proportion of patients discontinued study treatment due to TEAEs in the Isa-Pd arm versus Pd arm (22.2% vs. 0.0% and 9.5% vs. 0.0%, respectively). There were no deaths due to TEAEs or treatment-related TEAEs in the Japanese population. One death due to TEAE was reported in the Isa-Pd arm of the East Asian population, however, this was not considered treatment-related. Deaths due to TEAEs were reported in 12 and 14 patients in the Isa-Pd and Pd arms of the overall population, respectively. Of these, 1 death (< 1%) in the Isa-Pd arm was due to treatment-related TEAE (sepsis) while 2 deaths (1%) reported in the Pd arm (pneumonia and urinary tract infection) were due to treatment-related TEAEs.

Neutropenia was the most frequently reported TEAE in both treatment arms and in all study populations, and most incidences of neutropenia were Grade ≥ 3 (Table 3). Infusion-related reactions (IRs) were commonly reported in the Isa-Pd arm in all study populations (36.8%-57.1%). Most reported IRs were Grade 1 or 2. Most IRs occurred during the first infusion with few patients reporting IRs at subsequent infusions. No consistent pattern was observed in the proportion of patients reporting upper respiratory tract infections. The proportion of patients reporting pneumonia was similar between all study populations and treatment arms (15.4%-22.2%). There were no occurrences of patient-reported pneumonia in the Pd arm of the Japanese population.

An overview of the hematologic laboratory parameters assessed is provided in Figure S1, and additional details are included in the Supporting Materials (Doc S1).

Discussion

The current predefined subgroup analysis is the first to assess the efficacy and safety of Isa-Pd in East Asian patients with RRMM.[13] Our findings are consistent with those reported for the overall population in the ICARIA-MM study and support the use of this treatment combination for Japanese, Taiwanese, and Korean patients with RRMM.

In the East Asian population, a clinically meaningful improvement in PFS was observed with Isa-Pd versus Pd, with Kaplan-Meier curves showing an early and sustained separation that translated to a 48.3% reduction in the risk of disease progression or death, which was similar to the improvement observed in the overall population (40.4%).[13] Median PFS was not reached in the Isa-Pd arm of the East Asian population when assessed by the institutional response committee. A sensitivity analysis based on investigator assessment

Table 3 Summary of Treatment-emergent Adverse Events (all Treated Population)

	Japan				East Asia				Overall			
	Isa-Pd (n = 9)		Pd (n = 4)		Isa-Pd (n = 21)		Pd (n = 15)		Isa-Pd (N = 152)		Pd (N = 149)	
Any TEAE	9 (100.0)		4 (100.0)		21 (100.0)		15 (100.0)		151 (99.3)		146 (98.0)	
Grade ≥ 3 TEAE	8 (88.9)		4 (100.0)		19 (90.5)		11 (73.3)		132 (86.8)		105 (70.5)	
Treatment-related Grade ≥ 3 TEAE	8 (88.9)		4 (100.0)		15 (71.4)		10 (66.7)		109 (71.7)		71 (47.7)	
Serious TEAE	4 (44.4)		0 (0.0)		9 (42.9)		4 (26.7)		94 (61.8)		80 (53.7)	
Serious drug-related TEAE	2 (22.2)		0 (0.0)		4 (19.0)		1 (6.7)		54 (35.5)		24 (16.1)	
Any TEAE leading to definitive discontinuation	2 (22.2)		0 (0.0)		2 (9.5)		0 (0.0)		11 (7.2)		19 (12.8)	
	Isa-Pd (n = 9)		Pd (n = 4)		Isa-Pd (n = 21)		Pd (n = 15)		Isa-Pd (N = 152)		Pd (N = 149)	
Preferred term	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Neutropenia	7 (77.8)	7 (77.8)	3 (75.0)	3 (75.0)	15 (71.4)	15 (71.4)	6 (40.0)	6 (40.0)	71 (46.7)	70 (46.1)	50 (33.6)	48 (32.2)
IR	4 (44.4)	0 (0.0)	0 (0.0)	0 (0.0)	12 (57.1)	0 (0.0)	0 (0.0)	0 (0.0)	56 (36.8)	4 (2.6)	2 (1.3)	0 (0.0)
URTI	1 (11.1)	0 (0.0)	1 (25.0)	0 (0.0)	6 (28.6)	1 (4.8)	4 (26.7)	0 (0.0)	43 (28.3)	5 (3.3)	26 (17.4)	1 (0.7)
Diarrhea	1 (11.1)	0 (0.0)	1 (25.0)	0 (0.0)	3 (14.3)	0 (0.0)	3 (20.0)	0 (0.0)	39 (25.7)	3 (2.0)	29 (19.5)	1 (0.7)
Bronchitis	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	36 (23.7)	5 (3.3)	13 (8.7)	1 (0.7)
Pneumonia	2 (22.2)	2 (22.2)	0 (0.0)	0 (0.0)	5 (23.8)	4 (19.0)	3 (20.0)	3 (20.0)	31 (20.4)	25 (16.4)	26 (17.4)	23 (15.4)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (14.3)	0 (0.0)	1 (6.7)	0 (0.0)	26 (17.1)	6 (3.9)	32 (21.5)	0 (0.0)
Back pain	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (14.3)	0 (0.0)	1 (6.7)	0 (0.0)	25 (16.4)	3 (2.0)	22 (14.8)	2 (1.3)
Constipation	1 (11.1)	0 (0.0)	2 (50.0)	0 (0.0)	4 (19.0)	0 (0.0)	4 (26.7)	0 (0.0)	24 (15.8)	0 (0.0)	26 (17.4)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (19.0)	2 (9.5)	1 (6.7)	1 (6.7)	23 (15.1)	5 (3.3)	27 (18.1)	4 (2.7)
Dyspnea	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (14.3)	1 (4.8)	2 (13.3)	1 (6.7)	23 (15.1)	6 (3.9)	15 (10.1)	2 (1.3)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	1 (6.7)	0 (0.0)	23 (15.1)	0 (0.0)	14 (9.4)	0 (0.0)

Data are n (%). Abbreviations: Isa-Pd = isatuximab-pomalidomide-dexamethasone; IR = infusion-related reaction; Pd = pomalidomide-dexamethasone; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection.

Table 4 Summary of Responses in the All-treated Population and in Responders in the Intention-to-treat Population

	Japan		East Asia		Overall	
All Treated Population	**Isa-Pd (n = 9)**	**Pd (n = 4)**	**Isa-Pd (n = 21)**	**Pd (n = 15)**	**Isa-Pd (N = 152)**	**Pd (N = 149)**
PR or better	6 (66.7)	3 (75.0)	15 (71.4)	9 (60.0)	93 (61.2)	54 (36.2)
VGPR or better	5 (55.6)	1 (25.0)	13 (61.9)	2 (13.3)	49 (32.2)	13 (8.7)
Time to first response, d, median (range)	30.5 (29-60)	68.0 (30-154)	32.0 (29-97)	59.0 (30-154)	35.0 (29-138)	58.0 (29-172)
Time to best response, d, median (range)	146.5 (30-218)	152.0 (30-154)	121.0 (30-237)	59.0 (30-172)	76.0 (29-324)	85.0 (29-384)
Time to first VGPR, d, median (range)	121.0 (29-206)	152.0 (152-152)	121.0 (29-237)	121.0 (90-152)	88.0 (29-324)	90.0 (29-237)
CR	1 (11.1)	0 (0.0)	2 (9.5)	1 (6.7)	7 (4.6)	3 (2.0)
Time to CR, d, median (range)	218.0 (218-218)	NC	153.0 (88-218)	172.0 (172-172)	173.0 (88-324)	240.0 (172-384)
Responders	**Isa-Pd (n = 6)**	**Pd (n = 3)**	**Isa-Pd (n = 15)**	**Pd (n = 9)**	**Isa-Pd (N = 93)**	**Pd (N = 54)**
Time to first response, d, median (range)	30.5 (29-60)	68.0 (30-154)	32.0 (29-97)	59.0 (30-154)	35.0 (29-198)	58.0 (29-172)
Time to best response, d, median (range)	146.5 (30-218)	152.0 (30-154)	121.0 (30-237)	59.0 (30-172)	76.0 (29-324)	85.0 (29-384)

Data are shown as n (%) unless otherwise stated. Abbreviations: CR = complete response; Isa-Pd = isatuximab-pomalidomide-dexamethasone; NC = not calculable; Pd = pomalidomide-dexamethasone; PR = partial response; VGPR = very good partial response.

observed a longer median PFS in the Isa-Pd arm (12.3 months) compared with the Pd arm (8.6 months) of the East Asian population. This observation is in line with the median PFS based observed in the sensitivity analysis of the overall Isa-Pd and Pd arms (11.1 months and 6.5 months, respectively).[13] The median time to first response was shorter in the Isa-Pd arm versus Pd arm (approximately 30 vs. 60 days) for all study populations, suggesting a quick onset of action of this triplet combination therapy in patients with RRMM. Higher proportions of Japanese and East Asian patients achieved VGPR or better in the Isa-Pd arm versus Pd arm (55.6% vs. 25.0% and 61.9% vs. 13.3%, respectively). The proportion of patients achieving VGPR or higher in the overall Isa-Pd arm was 32.2%.

Although patients in the Isa-Pd arms of the East Asian and Japanese populations were heavily pre treated (median of 2 or 3 prior lines of therapy, respectively), MRD negativity at 10^{-5} was observed in 22.2% of Japanese patients and 14.3% of East Asian patients in the Isa-Pd arm. In a subanalysis from the Phase III POLLUX study, MRD negativity at 10^{-5} was achieved in 21.2% of East Asian patients and 23.8% of Japanese patients following treatment with daratumumab, lenalidomide, and dexamethasone.[25] Of note, East Asian and Japanese patients in the POLLUX study had received fewer prior lines of treatment (median of 1 and 2 prior lines of treatment, respectively) and were either lenalidomide-naïve or lenalidomide-sensitive, so any potential differences between the studies should be interpreted with caution. Interestingly, the proportions of East Asian and Japanese patients achieving MRD negativity at 10^{-5} in the current study were higher than that observed in the overall Isa-Pd arm (5.2%). While this observation suggests a deeper response of Isa-Pd in the East Asian and Japanese populations compared with the overall population, the small sample size of these subpopulations suggests that further investigations with larger samples sizes are required. However, collectively, these observations suggest that the triplet Isa-Pd combination therapy is able to induce a deeper response than the doublet Pd therapy in patients with RRMM.

The patient population in this study was comparable with data obtained from real-world patients with RRMM in Japan and elsewhere,[21,26,27] highlighting the potential generalizability of the ICARIA-MM results to the wider RRMM population both in East Asia and globally.

Similar to the overall population, Isa-Pd treatment in East Asian patients with RRMM demonstrated a manageable safety profile, and TEAEs were generally similar between the Isa-Pd and Pd arms. The most common TEAEs in the East Asian and Japanese populations were neutropenia, IRs, and upper respiratory tract infections, similar to those observed in the overall population.[13] While the incidence of IRs was higher in the Isa-Pd arm of the East Asian population compared with the Pd arm of the overall population, most were Grade 1 or 2, and the pattern of onset was similar between these 2 arms, with most patients reporting IRs at first infusion only and fewer patients exhibiting IRs at subsequent infusions. These observations are consistent with those previously reported following treatment with isatuximab, either alone or in combination with other agents.[8,14] In the current subanalysis, IRs were reported in a higher proportion of Japanese (44.4%) and East Asian (57.1%) patients receiving Isa-Pd treatment, compared with those previously reported in Japanese (35.0%) and East Asian (49.0%) patients receiving daratumumab plus lenalidomide and dexamethasone.[25] The cause of this discrepancy is unclear, but given the small sample sizes of both the Japanese and East Asian populations in these subanalyses, further study in a larger East Asian population is warranted.

In the Japanese population, a lower RDI of pomalidomide and dexamethasone was observed in the Isa-Pd arm, while a lower RDI of dexamethasone was observed in the Pd arm, compared with the East Asian and overall populations. The lower RDI can be attributed to the higher rate of pomalidomide and dexamethasone dose reductions in the Japanese population. A higher proportion of Japanese patients experienced treatment-related Grade $\geq$ 3 TEAEs ($\geq$ 88.9%), compared with the East Asian and overall populations (47.7%-71.7%), which may have accounted for the increased dose reductions in this population. Previously, a higher rate of Grade 3/4 thrombocytopenia and a lower rate of Grade 3/4 thromboembolic events were observed in Asian MM patients treated with lenalidomide and dexamethasone, compared with Western patients,[28] suggesting that Asian patients may tolerate IMiDs differ-

ently to Western patients. However, the Asian population assessed in that study did not include Japanese patients and in the current subanalysis, TEAEs were generally similar between the East Asian, which included Japanese patients, and overall populations. Therefore, it is unclear why a higher number of dose reductions in the current subanalysis occurred in the Japanese population, although such an observation could arise due to differences in the management of AEs between populations. Further studies are warranted to assess potential differences in the tolerability of IMiDs between East Asian, including Japanese patients, and Western populations.

A previously published phase Ib study assessing isatuximab in combination with lenalidomide plus dexamethasone reported an ORR of 56% and PFS of 8.5 months in patients with RRMM.[12] Additionally, another phase Ib study assessing isatuximab in combination with Pd reported an ORR of 62% and PFS of 17.6 months.[14] Patients in both trials had received ≥ 2 prior anti–MM regimens and were refractory to the prior therapy. These observations are consistent with the findings of the current study and the published primary study,[13] and indicate the utility of isatuximab combination therapies in patients with previously-treated RRMM. Other combination therapies involving monoclonal antibodies have also shown promise in the treatment of patients with RRMM. Daratumumab in combination with bortezomib plus dexamethasone[29] or lenalidomide plus dexamethasone[30] have demonstrated improved clinical efficacy compared with a single agent treatment. Additionally, elotuzumab with pomalidomide plus dexamethasone[31] or lenalidomide plus dexamethasone[32] have shown improved clinical outcomes in patients with RRMM, compared with pomalidomide plus dexamethasone or lenalidomide plus dexamethasone, respectively. Subanalyses of East Asian and Japanese populations within these clinical trials have also suggested that efficacy and safety outcomes following treatment with daratumumab plus lenalidomide and dexamethasone or elotuzumab plus lenalidomide and dexamethasone are consistent with global cohort data.[25,33] Collectively, although different treatment combinations have been analyzed in different patient populations (ie, generally a later treatment line is reported here), these observations support the use of monoclonal antibody combination therapies in patients with RRMM and also suggest that efficacy and safety outcomes are consistent between the East Asian and overall populations.

The limitations of the global study have previously been described.[13] Additional limitations of this predefined subanalysis include the small sample size which limited statistical comparisons between treatment arms. The restricted number of patients available for inclusion in this subgroup analysis may also have resulted in undue magnification of incidental differences between arms and populations, including the higher ORR rate with Pd in Asian patients (60.0%) and Japanese patients (75.0%) compared with the overall population (35.3%). Another limitation was that randomization was not stratified by center/region, resulting in an imbalance of patients randomized to the Isa-Pd and Pd arms. This was particularly apparent in the Japanese population where the Pd arm included only 4 patients, compared with 9 patients in the Isa-Pd arm.

In conclusion, this predefined subgroup analysis of the ICARIA-MM study confirmed the efficacy and safety of Isa-Pd in East Asian and Japanese patients, consistent with observations from the overall population.[13] These findings support the role of isatuximab, in combination with Pd, in the treatment of East Asian patients with RRMM to improve clinical outcomes for a population which otherwise has few therapeutic options and a poor prognosis.

Clinical Practice Points

- The pivotal phase III ICARIA-MM study demonstrated that isatuximab plus pomalidomide and dexamethasone (Isa-Pd) improved progression-free survival and overall response rate versus pomalidomide and dexamethasone (Pd) in patients with relapsed/refractory multiple myeloma (RRMM).
- The current predefined subgroup analysis is the first to assess the efficacy and safety of Isa-Pd in East Asian patients with RRMM. A clinically meaningful improvement in progression-free survival was observed with Isa-Pd versus Pd, with an early and sustained separation in Kaplan-Meier curves that translated to a 48.3% reduction in the risk of disease progression or death. Higher proportions of patients achieved very good partial response or better in the Isa-Pd arm versus Pd arm.
- Isa-Pd treatment in East Asian patients with RRMM demonstrated a manageable safety profile, consistent with the overall ICARIA-MM study data.
- The patient population in this study was comparable with data obtained from real-world patients with RRMM in Japan and elsewhere, highlighting the potential generalizability of the ICARIA-MM results to the wider RRMM population both in East Asia and globally.

Disclosure

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Author Contributions

KS confirms that he had full access to the data in the study and final responsibility for the decision to submit for publication.

Data Availability

Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2022.04.005.

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