Isatuximab-pomalidomide-dexamethasone *versus* pomalidomide-dexamethasone in patients with relapsed and refractory multiple myeloma: final overall survival analysis

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Abstract

The primary and prespecified updated analyses of ICARIA-MM (*clinicaltrial gov. Identifier: NCT02990338*) demonstrated improved progression-free survival (PFS) and a benefit in overall survival (OS) was reported with the addition of isatuximab, an anti-CD38 monoclonal antibody, to pomalidomide-dexamethasone (Pd) in patients with relapsed/refractory multiple myeloma. Here, we report the final OS analysis. This multicenter, randomized, open-label, phase III study included patients who had received and failed ≥2 previous therapies, including lenalidomide and a proteasome inhibitor. Between January 10, 2017, and February 2, 2018, 307 patients were randomized (1:1) to isatuximab-pomalidomide-dexamethasone (Isa-Pd; N=154) or Pd (N=153), stratified based on age (<75 *vs.* ≥75 years) and number of previous lines of therapy (2-3 *vs.* >3). At data cutoff for the final OS analysis after 220 OS events (January 27, 2022), median follow-up duration was 52.4 months. Median OS was 24.6 months (95% confidence interval [CI]: 20.3-31.3) with Isa-Pd and 17.7 months (95% CI: 14.4-26.2) with Pd (hazard ratio=0.78; 95% CI: 0.59-1.02; 1-sided *P*=0.0319). Despite subsequent daratumumab use in the Pd group and its potential benefit on PFS in the first subsequent therapy line, median PFS2 was significantly longer with Isa-Pd *versus* Pd (17.5 *vs.* 12.9 months; log-rank 1-sided *P*=0.0091). In this analysis, Isa-Pd continued to be efficacious and well tolerated after follow-up of approximately 52 months, contributing to a clinically meaningful, 6.9-month improvement in median OS in patients with relapsed/refractory multiple myeloma.

Introduction

Multiple myeloma (MM) primarily remains an incurable disease, and although novel agents have improved response and survival rates, almost all patients relapse either on or after these treatments.[1-4] Treatment choice for relapsed and refractory MM (RRMM) is determined by refractoriness and exposure to prior drugs.[5]

Due to the need for novel treatments for RRMM, monoclonal antibodies targeting CD38 have emerged, such as daratumumab and isatuximab.[6-9] Isatuximab is a monoclonal antibody targeting a specific epitope of the human cell-surface antigen CD38, which is widely and uniformly expressed on myeloma cells.[10-12]

Isatuximab was investigated in combination with pomalidomide and dexamethasone (Pd) in a phase III, randomized, multicenter, open-label trial (ICARIA-MM; *clinicaltrials gov. Identifier: NCT02990338*).[13] After a median follow-up of 11.6 months, median progression-free survival (PFS) was 11.5 (95% confidence interval [CI]: 8.9-13.9) months with isatuximab–pomalidomide–dexamethasone (Isa-Pd) and 6.5 (95% CI: 4.5-8.3) months with Pd alone.[13] Median overall survival (OS) was not reached in either treatment arm (hazard ratio [HR]=0.687; 95% CI: 0.461-1.023; *P*=0.0631).[13] Results from a prespecified updated analysis at 24 months after the primary analysis reported a median OS of 24.6 months (95% CI: 20.3-31.3) with Isa-Pd *versus* 17.7 months (95% CI: 14.4-26.2) months with Pd (HR=0.76, 95% CI: 0.57-1.01).[14]

Based on the primary results of ICARIA-MM, isatuximab has been approved in several countries in combination with Pd for adult patients with RRMM who have received ≥2 previous therapies, including lenalidomide and a proteasome inhibitor (PI).[11,15]

This analysis of ICARIA-MM reports the final OS, conducted when 220 deaths occurred.

Methods

Study design and participants

ICARIA-MM is a prospective, multicenter, randomized, open-label, parallel-group phase III study conducted at 102 sites in 24 countries (*Online Supplementary Appendix*, page 2-3). Detailed inclusion and exclusion criteria, study design, randomization and masking, and procedures have been previously described and are detailed in the *Online Supplementary Appendix*, page 4-7.[13,14]

Briefly, eligible patients were ≥18 years old, had RRMM, received ≥2 previous therapies, and had failed therapy with lenalidomide and a PI (alone or in combination). Failure to therapy included progression on or within 60 days, intolerance to lenalidomide or the PI, or disease progression within 6 months after achieving at least a partial response (PR). Patients refractory to previous anti-CD38 therapy, with prior pomalidomide exposure, with an Eastern Cooperative Oncology Group Performance Status >2, an ongoing toxic effect grade >2 from previous therapy (grade according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03), with active primary amyloid light-chain amyloidosis, or concomitant plasma cell leukemia were excluded.

The trial complied with the International Conference on Harmonization Good Clinical Practice Guideline and the Declaration of Helsinki. All participating institutional review boards and ethics committees approved the study protocol, and patients provided written informed consent.

Randomization and masking

Following eligibility confirmation, patients were randomized using an interactive response technology (IRT) system in a 1:1 ratio to the Isa-Pd (isatuximab) arm or to the Pd (control) arm. Randomization was stratified by age (<75 *vs.* ≥75 years) and number of previous lines of therapy (2 or 3 *vs.* >3).

Procedures

Intravenous isatuximab 10 mg/kg was administered on days 1, 8, 15, and 22 of cycle 1 and days 1 and 15 for subsequent cycles. Intravenous or oral dexamethasone 40 mg (20 mg if age ≥75 years) was administered on days 1, 8, 15, and 22, and oral pomalidomide 4 mg was administered on days 1-21. Premedication and isatuximab preparation were described previously.[13,14]

Outcomes

The primary endpoint of ICARIA-MM was PFS as determined by the IRC. No PFS per IRC update is provided based on this additional follow-up. Key secondary endpoints include overall response rate (ORR) and OS. ORR was defined as the proportion of patients with complete response (CR), stringent CR, very good partial response (VGPR), and PR as best overall response, assessed by IRC using the International Myeloma Working Group criteria. No updated ORR per IRC is provided. OS was defined as the time from the date of randomization to date of death from any cause. If death was not observed before the analysis data cutoff date, OS was censored at the last date that the patient was known to be alive or at the cutoff date, whichever was first. Exploratory endpoints included PFS2, ORR on further therapy (best overall response reported by the investigator), PFS on the first line of further therapy, and time to next treatment (TTNT). Additional definitions and methods are detailed in the *Online Supplementary Appendix*, page 4-7 and have been defined previously.[14,16]

Statistical analysis

Based on the primary efficacy endpoint (PFS) using the assumptions that the control arm had a median PFS of 4.0 months; the Isa-Pd arm was assessed to have 40%

risk reduction in HR *versus* control, corresponding to an improvement in the true median PFS time from 4.0 to 6.67 months; and a log-rank test at a 1-sided 2.5% significance level, a total of 162 PFS events were calculated to be needed to achieve 90% power for the study. Based on these assumptions, 220 deaths were needed to achieve 80% power for the study.

For the final analysis, a data cutoff date of March 14, 2022, was selected, and data were included up to this date (last patient last visit). Per protocol, the cutoff date for the final OS analysis was to occur when 220 OS events had been observed. The 220th OS event occurred on January 27, 2022, and this date was considered to be the OS cutoff date for the primary OS analysis.

Efficacy analyses were conducted using the intention-to-treat (ITT) population, defined as patients who provided signed informed consent and were allocated a randomization number by the IRT. Safety was assessed in all patients from the ITT population who received at least a partial dose of study treatment. Patients were considered lost to follow-up if the last contact was ≥8 weeks prior to the data cutoff.

OS was analyzed using the Kaplan-Meier method and corresponding 95% CI, which was calculated with log-log transformation of survival function and the method devised by Brookmeyer and Crowley. HR and corresponding 95% CI are calculated from a Cox proportional hazards model, stratified by age and number of previous lines of therapy. Prespecified analyses were completed for updated PFS by investigator assessment (sensitivity analysis), PFS on subsequent therapy or death, and PFS on the first line of subsequent therapy (separate summaries for subsequent therapy with/without daratumumab-based therapy), and TTNT using OS analysis methods. *P* values for exploratory endpoints are provided for descriptive purposes only. Additional statistical methods have been described previously.[14,16] All statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC) or R (version 3.4.3; R Foundation, Vienna, Austria). Since the updated analysis, no additional amendments to the protocol have been made. This study is registered with *clinicaltrials gov. Identifier: NCT02990338*.

Results

Between January 10, 2017, and February 1, 2018, 387 patients were screened and 307 were randomized (Isa-Pd, 154; control, 153) at 102 sites in 24 countries. Cutoff for the first OS interim analysis, at the time of the primary PFS analysis, was October 11, 2018 (reported previously).[13] Cutoff for the preplanned second interim analysis was October 1, 2020 (reported previously).[14] Cutoff for the final OS analysis was January 27, 2022, per protocol (Figure 1). Data cutoff for last patient last visit was March 14, 2022.

Baseline characteristics were similar in both arms, as previously published and briefly shown in Table 1. All patients previously received PI and IMiD agents.

Median treatment duration was 11.0 (range, 2.6-12.4) months among patients receiving Isa-Pd and 5.5 (range, 4.4-21.8) months among patients receiving Pd. At data cutoff (March 14, 2022), 16 (10.4%) patients receiving Isa-Pd and three (2.0%) patients receiving Pd remained on treatment. The most frequent reason for definitive discontinuation was progressive disease (isatuximab, 65.6%; control, 76.5%).

After a median follow-up of 52.4 months, median PFS per investigator assessment (ignoring symptomatic deterioration) showed consistent improvement with longer follow-up (Isa-Pd: 11.1 months, 95% CI: 7.8-13.8; Pd: 5.9 months, 95% CI: 4.5-7.9; HR=0.57, 95% CI: 0.44-0.73; 1-sided *P*<0.0001; *Online Supplementary Figure S1*).

The prespecified required number of 220 OS events occurred on January 27, 2022, which was the analysis cutoff date. Of the 220 deaths, 106 (68.8%) occurred in the Isa-Pd arm and 114 (74.5%) in the Pd arm. Median OS was 24.6 months (95% CI: 20.3-31.3) in the Isa-Pd group and 17.7 months (95% CI: 14.4-26.2) in the Pd group (HR=0.78, 95% CI: 0.59-1.02; 1-sided *P*=0.0319; Figure 2). Early separation was observed in the OS curves between arms; however, because the 1-sided *P* value for statistical significance was set to 0.02 based on the previous interim analysis, the current analysis did not cross the level of significance. Censored patients (Isa-Pd: 48/154 [31%]; Pd: 39/153 [26%]) remained alive at data cutoff (Isa-Pd: 39/48 [81%]; Pd: 31/39 [80%]), were alive at the last contact before the cutoff date (1/48 [2%]; 0/39), or were lost to follow-up (8/48 [17%]; 8/39 [21%]). Subgroup analyses of OS are shown in *Online Supplementary Figure S2*.

Among patients receiving subsequent anti-myeloma therapy, daratumumab was given to 23 (23%) of 102 patients in the Isa-Pd group and 71 (60%) of 119 patients in the Pd group (*Online Supplementary Table S3*). In order to estimate the treatment effect in the absence of a switch to subsequent anti-cancer therapy with daratumumab, sensitivity analyses using the RPSFT model were performed, with overall similar results (HR=0.706, 95% CI: 0.538-0.926) to the ITT estimate, in favor of the Isa-Pd arm (HR=0.776, 95% CI: 0.594-1.015; *Online Supplementary Appendix*, page 17). An OS sensitivity analysis was conducted to assess the impact of death due to coronavirus disease 2019 infection, with similar results to the ITT estimate (*Online Supplementary Appendix*, page 18).

Overall, 102 (66%) of 154 patients in the Isa-Pd group and 119 (78%) of 153 patients in the Pd group received subsequent anti-myeloma therapy. Median TTNT was longer with isatuximab (15.5 months, 95% CI: 12.1-19.8) *versus* Pd (8.9 months, 95% CI: 6.3-11.5; 1-sided *P*<0.0001; Figure 3). Median PFS on subsequent therapy or death (PFS2) was longer in the Isa-Pd group (17.5 months, 95% CI: 14.9-19.2) *versus* Pd (12.9 months, 95% CI: 10.1-16.6; 1-sided *P*=0.0091; Figure 2).

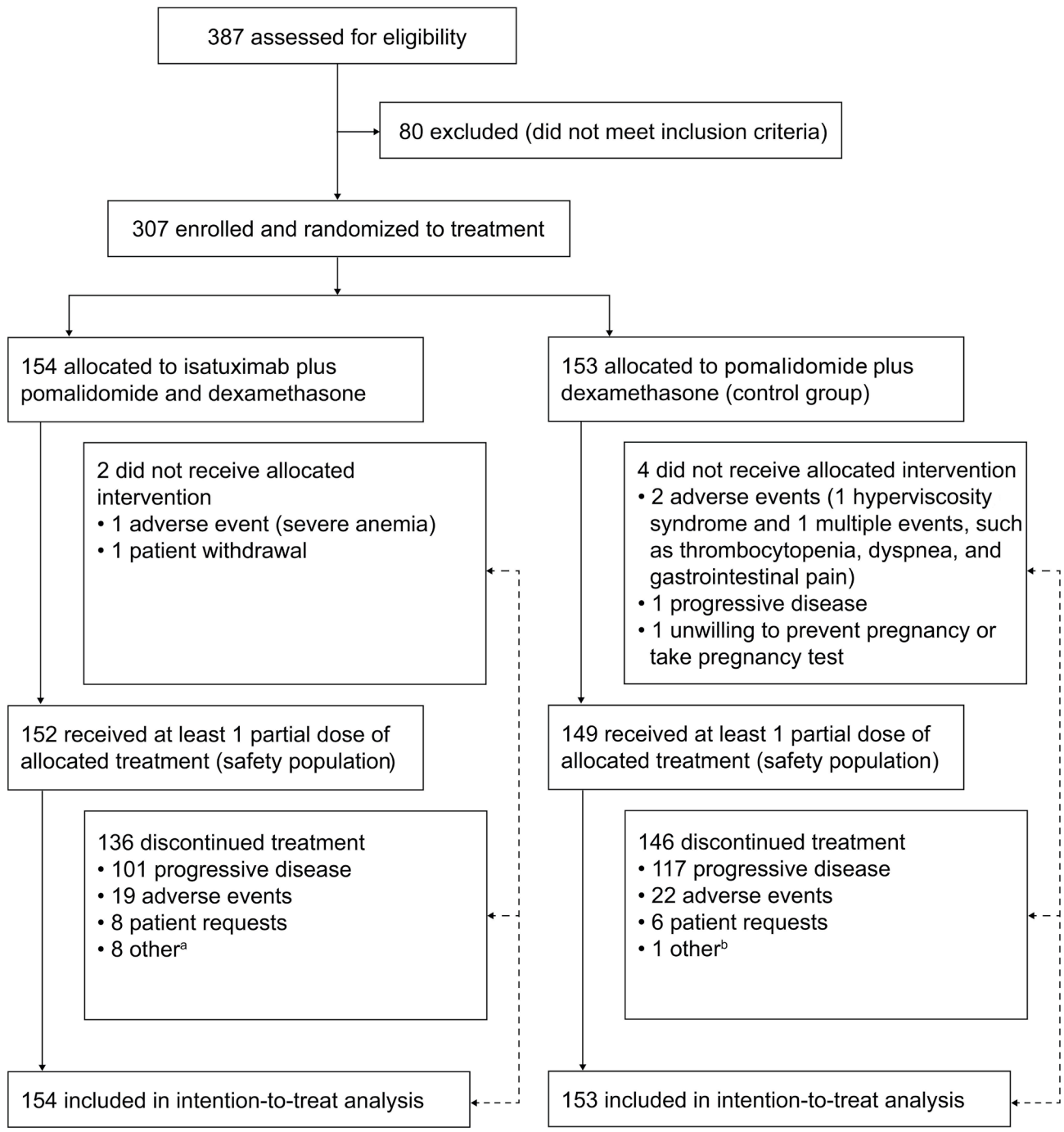

Figure 1. Trial profile as of data cutoff for the final overall survival analysis. [a]Investigator decision due to free light chain increase (N=3), physician's decision (suspected progression, N=1), unconfirmed progression (N=1), poor compliance to protocol (N=1), investigator decided to switch treatment to daratumumab-pomalidomide-dexamethasone (N=1), investigator kept the same isatuximab-pomalidomide-dexamethasone (Isa-Pd) combination off protocol, as the product is available commercially (N=1). [b]Physician decision. OS: overall survival.

The proportional hazard assumption was met (Schoenfeld residuals test) for the following Cox models: PFS by investigator (P=0.89), OS (P=0.28), TTNT (P=0.44), and PFS2 (P=0.42).

The ORR was higher with Isa-Pd *versus* Pd, consistent with the primary analysis and second interim analysis (*Online Supplementary Table S2; Online Supplementary Figure S3*). Deeper responses were also observed with Isa-Pd *versus* Pd. Minimal residual disease negativity was observed in ten (6%) patients in the Isa-Pd group at the 10^{-5} sensitivity level (18 patients with data available) but in no patients in the Pd group (3 patients with data available; *data not shown*). More patients in the Isa-Pd group *versus* the Pd group received subsequent alkylating agents, PI, corticosteroids, and other treatments (i.e., investigational anti-neoplastic drugs, cisplatin, etoposide, and stem cells), whereas IMiD agents were administered to a similar proportion of patients in both groups (*Online Supplementary Table S3*).

Exploratory analysis of ORR, CR, VGPR, or PR on selected subsequent therapies with/without daratumumab are shown in Figure 4 and *Online Supplementary Figure S4*. Among non-daratumumab-based regimens, non-IMiD-based regimens *versus* IMiD-based regimens led to better response rates with Isa-Pd (28/71 [39%] *vs.* 3/27 [11%]). Per the inclusion criteria, patients previously failed treatment with lenalidomide and a PI.

ORR with subsequent daratumumab in any subsequent line was lower for patients in the Isa-Pd group (5/21 [24%]) *vs.* the Pd group (23/57 [40%]); however, rates of ≥VGPR were similar (3/21 [14%] *vs.* 10/57 [18%]). Daratumumab in combination led to improvements in both arms (Isa-Pd: 4/14 [29%]; Pd: 13/29 [45%]) *versus* daratumumab monotherapy

Table 1. Baseline demographic and patient characteristics of the intention-to-treat population.

Characteristic	Isa-Pd N=154	Pd N=153
Age in years		
Median (IQR)	68 (60-74)	66 (59-71)
<65, N (%)	54 (35)	70 (46)
65–75, N (%)	68 (44)	54 (35)
≥75, N (%)	32 (21)	29 (19)
Sex, N (%)		
Female	65 (42)	83 (54)
Male	89 (58)	70 (46)
Ethnicity, N (%)		
Hispanic or Latino	4 (3)	3 (2)
Not Hispanic or Latino	130 (84)	134 (88)
Unknown	2 (1)	2 (1)
Not reported	18 (12)	14 (9)
History of asthma or COPD, N (%)	16 (10)	17 (11)
eGFR <60 mL/min/1.73 m^2, N/N (%)	55/142 (39)	49/145 (34)
Previous autologous stem-cell transplantation, N (%)	83 (54)	90 (59)
Time since initial diagnosis in years, median (IQR)	4.5 (2.6-7.2)	4.1 (2.9-7.0)
Type of myeloma at diagnosis, N (%)		
IgA	34 (22)	41 (27)
IgG	102 (66)	100 (65)
Light chain (κ+λ)	15 (10)	11 (7)
Other	2 (1)	0
ISS stage at study entry, N (%)		
Stage I	64 (42)	51 (33)
Stage II	53 (34)	56 (37)
Stage III	34 (22)	43 (28)
Unknown	3 (2)	3 (2)
Cytogenetic risk at baseline,[a] N (%)		
High	24 (16)	36 (24)
Standard	103 (67)	78 (51)
Missing	27 (18)	39 (25)
Number of previous lines of therapy, median (IQR)	3 (2-4)	3 (2-4)
Previous therapy, N (%)		
Alkylating agent	139 (90)	148 (97)
Proteasome inhibitors	154 (100)	153 (100)
Immunomodulatory agents	154 (100)	153 (100)
Refractory to treatment, N (%)		
Last line of therapy	150 (97)	151 (99)
Immunomodulatory agent	147 (95)	144 (94)
Lenalidomide	144 (94)	140 (92)
Proteasome inhibitor	118 (77)	115 (75)
Lenalidomide and proteasome inhibitor	111 (72)	107 (70)
Lenalidomide last line	93 (60)	88 (58)

Cytogenetic analysis was performed by fluorescence *in situ* hybridization by a central laboratory with cutoff of 50% for del(17p) and 30% for t(4;14) and t(14;16). [a]High-risk cytogenetic status was defined as the presence of at least del(17p), t(4;14), or t(14;16) chromosomal abnormalities. COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; IgA: immunoglobulin A; IgG: immunoglobulin G; Isa-Pd: isatuximab-pomalidomide-dexamethasone; ISS: International Staging System (ISS staging is derived based on the combination of serum β2-microglobulin and albumin); Pd: pomalidomide-dexamethasone.

± steroids (*Online Supplementary Figure S4*). Some patients receiving daratumumab, alone or in combination, as a first subsequent line of therapy achieved ≥VGPR, even after receiving prior isatuximab study therapy (2/8 patients [25%]) with a short washout period (median, 13 days) (Figure 4).

Among patients receiving non-daratumumab–based therapy, median PFS on the first line of subsequent therapy was similar in the Isa-Pd group (4.6 months, 95% CI: 3.1-6.6 in 69/93 [74%] patients receiving subsequent non-daratumumab therapy) *versus* the Pd group (5.2 months, 95%

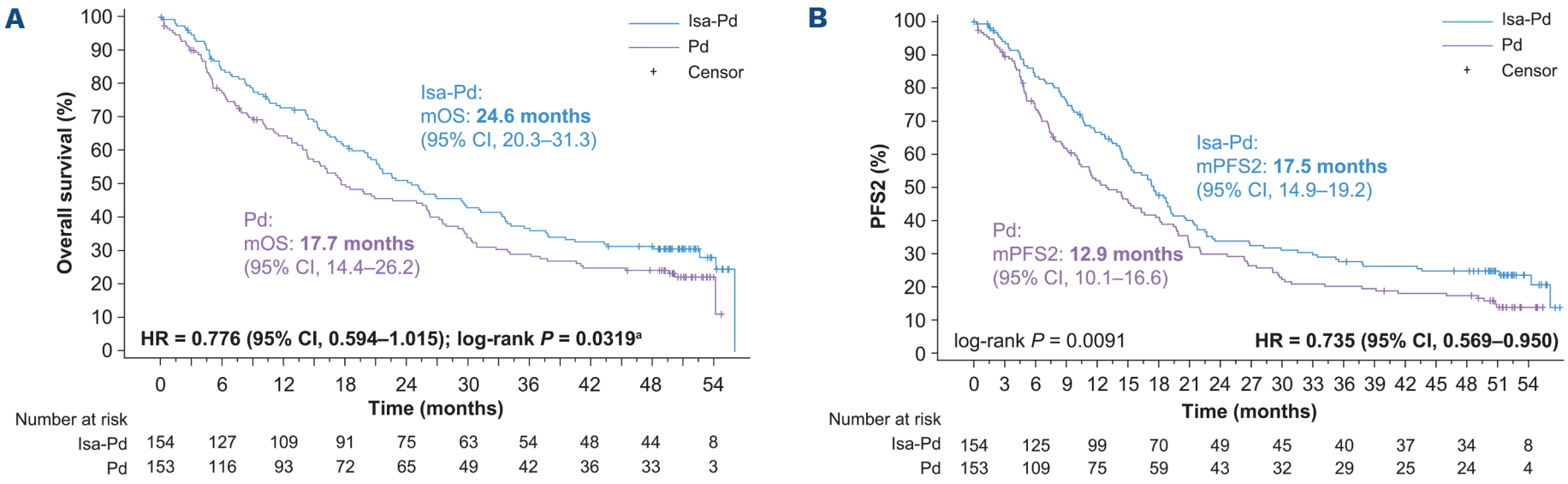

Figure 2. Overall survival and progression-free survival on subsequent therapy or death in the intention-to-treat population. (A) Kaplan–Meier analysis of overall survival (OS) after 220 events. Patients who were alive at the cutoff date (January 27, 2022), alive at the last contact before the cutoff date, or lost to follow-up were censored. (B) Kaplan-Meier analysis of time from randomization to disease progression on subsequent therapy or death, as assessed by investigators. [a]The 1-sided log-rank *P* value is provided for descriptive purposes. Patients who did not experience an event were censored (denoted by crosses). Hazard ratio (HR) and corresponding 95% confidence intervals (CI) are from a Cox proportional hazard model, stratified by age and number of previous lines of therapy. Isa-Pd: isatuximab-pomalidomide-dexamethasone; mOS: median overall survival; mPFS2: median progression-free survival on subsequent therapy or death; OS: overall survival; Pd: pomalidomide-dexamethasone; PFS: progression-free survival; PFS2: progression-free survival on subsequent therapy or death.

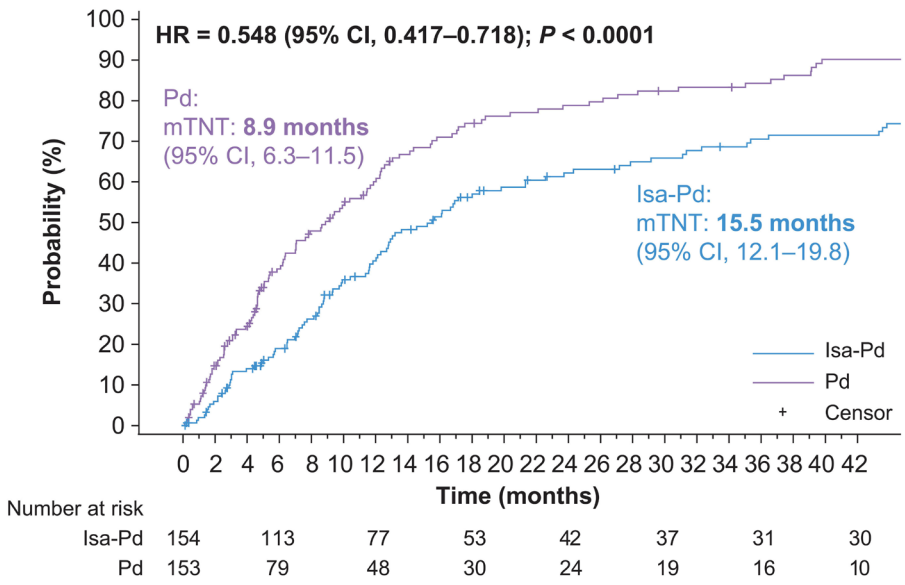

Figure 3. Time to next treatment (intention-to-treat population). Kaplan-Meier analysis of time to next treatment, as reported by investigators. Patients who did not proceed to subsequent anti-myeloma treatment before the cutoff date were censored. Median follow-up was 52.4 months. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) are from a Cox proportional hazard model stratified by age and number of previous lines of therapy. Isa-Pd: isatuximab-pomalidomide-dexamethasone; mTNT: median time to next treatment; Pd: pomalidomide-dexamethasone.

CI: 3.8-7.3 in 43/67 [64%] patients receiving subsequent non-daratumumab therapy) (*Online Supplementary Figure S5*). However, among patients receiving daratumumab-based therapy as the first subsequent line (N=9; Pd: N=52), median PFS was lower with Isa-Pd (Isa-Pd: 2.2 months, 95% CI: 0.03-7.4 in 7/9 [78%] patients receiving subsequent daratumumab) *versus* Pd (5.7 months, 95% CI: 3.8-10.8 in 39/52 [75%] patients receiving subsequent daratumumab) (*Online Supplementary Figure S5*). The median time between the last dose of investigational medicinal product and the first subsequent therapy with daratumumab was shorter in the Isa-Pd group (N=9; 13 days; range, 2-100 days) *versus* the Pd group (N=52; 22 days; range, 1-822 days; *data not shown; post hoc*).

With longer follow-up, no new safety concerns were identified with Isa-Pd. The overall safety summary is in *Online Supplementary Table S4*, and the most frequently reported treatment-emergent adverse events (TEAE) are in Table 2. Compared with the Pd group, the Isa-Pd group, respectively, had longer cumulative exposure to treatment (216.1 *vs.* 137.3 patient-years) and a larger median number of cycles started per patient (11; interquartile range [IQR], 4-22.5 *vs.* 6; IQR, 3-13; *Online Supplementary Table S1*). In the safety population, 70 (46%) of 152 patients had pomalidomide dose reductions and 62 (41%) had dexamethasone dose reductions in the isatuximab group *versus* 40 (27%) of 149 patients with pomalidomide dose reductions and 45 (30%) with dexamethasone reductions in the Pd group (*Online Supplementary Table S1*). The most frequently reported grade ≥3 TEAE in the Isa-Pd and Pd groups were neutropenia (77 [51%] of 152 *vs.* 52 [35%] of 149), pneumonia (35 [23%] *vs.* 31 [21%]), and thrombocytopenia (20 [13%] *vs.* 18 [12%]; *Online Supplementary Table S6*). TEAE reported in ≥10% of patients and ≥5% higher with isatuximab are shown in *Online Supplementary Table S5*. TEAE reported in ≥5% of patients are shown in *Online Supplementary Table S7*. Infusion reactions (IR) were reported with Isa-Pd (2 patients in the Pd group experienced IR upon subsequent daratumumab therapy), and all were reversible; only one IR has been reported since the primary analysis (cycle 19;

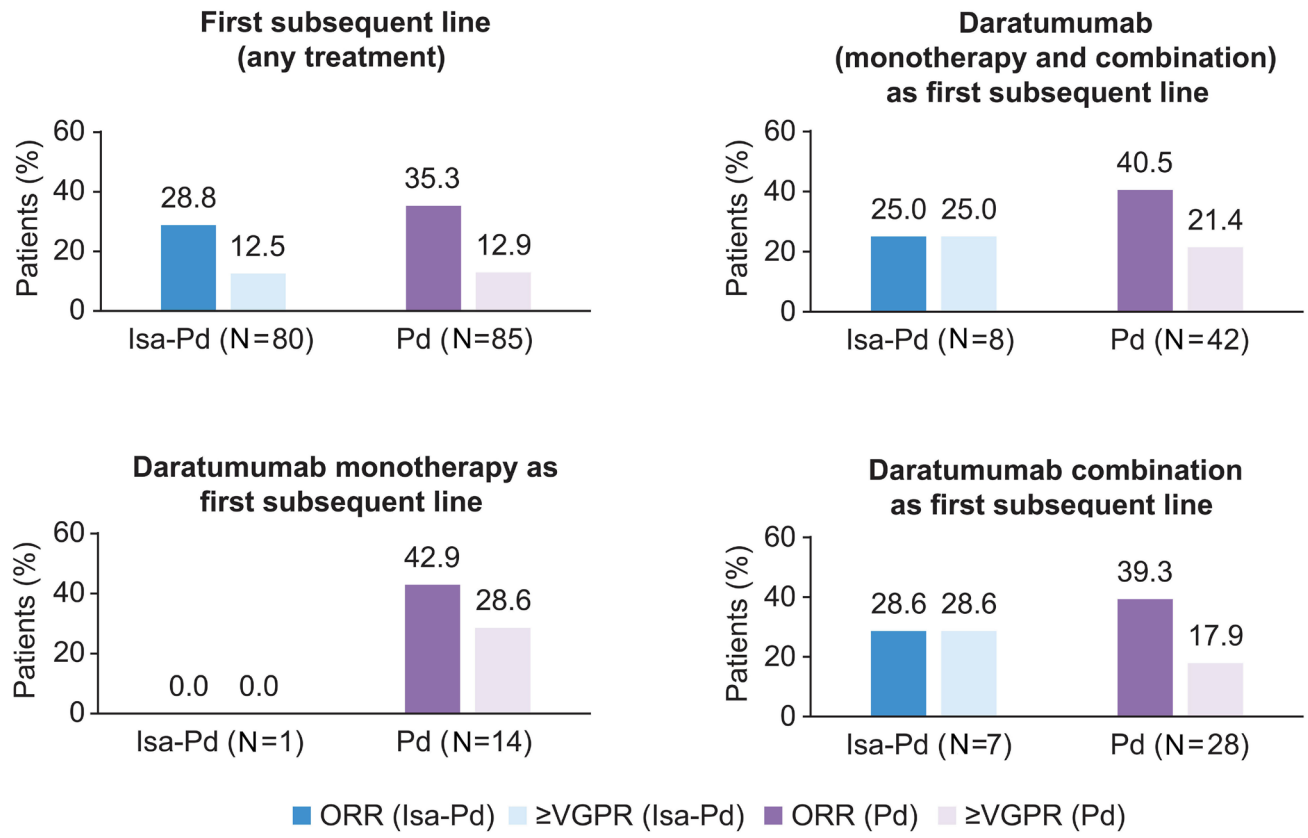

Figure 4. Exploratory analysis of response rate on first subsequent therapy,* intention-to-treat population. *Median washout period between therapies was 13 (range, 2-100) days for the isatuximab group and 22 (range, 1-822) days for the control group. Isa-Pd: isatuximab-pomalidomide-dexamethasone; ORR: overall response rate; Pd: pomalidomide-dexamethasone; VGPR: very good partial response or better.

data not shown), whereas all others were reported in the first three infusions. Grade 3/4 IR were reported in four (3%) of 152 patients. Hematologic laboratory abnormalities are shown in *Online Supplementary Table S8*. SPM occurred in ten (7%) of 152 patients in the Isa-Pd group and three (2%) of 149 in the Pd group (*Online Supplementary Appendix page 21*). Of these, three (Isa-Pd) occurred during the post-treatment period.

Treatment-emergent serious AE (SAE) occurred in 112 (74%) of 152 patients in the Isa-Pd group and 91 (61%) of 149 in the Pd group (*Online Supplementary Table S9*). Pneumonia was the most frequent SAE (all grades, both groups), reported in 35 (23%) of 152 patients in the Isa-Pd group and 31 (21%) of 149 in the Pd group. TEAE with a fatal outcome were reported in 23 (15%) of 152 patients in the Isa-Pd group and 19 (13%) of 149 in the Pd group. There were two (1%) treatment-related deaths in the Isa-Pd group (sepsis, 1; cerebellar infarction, 1) and two (1%) in the Pd group (pneumonia, 1; urinary tract infection, 1; *data not shown*). Overall, 108 (71%) patients in the Isa-Pd group and 113 (76%) in the Pd group died during the on- or post-treatment period due to disease progression (Isa-Pd: 76 [50%]; Pd: 81 [54%]), AE (7 [5%] *vs.* 8 [5%]), or other causes (25 [16%] *vs.* 24 [16%]; *data not shown*).

Dose reductions for pomalidomide and dexamethasone due to TEAE were more frequent in the Isa-Pd arm *versus* the Pd arm (pomalidomide reductions in 115/152 [76%] patients *vs.* 70/149 [47%] patients; dexamethasone reductions in 104 [68%] patients *vs.* 76 [51%] patients) and were primarily due to infections and neutropenia (*data not shown*). Definitive treatment discontinuation due to TEAE was infrequent and occurred at similar rates in both treatment arms (19/152 [13%] patients in the Isa-Pd group *vs.* 22/149 [15%] patients in the Pd group; *Online Supplementary Table S10*).

Discussion

This final OS analysis of ICARIA-MM showed a clinically meaningful benefit with a 6.9-month improvement in median OS with the addition of isatuximab to Pd (HR=0.78; log-rank 1-sided *P*=0.0319). Because the 1-sided *P* value for statistical significance was set to 0.02 due to α level spent at previous interim analyses, the current analysis did not cross the level of significance; however, early separation was observed in the OS curves between arms. The more frequent use of subsequent daratumumab in the control group (59.7% *vs.* 22.5% [isatuximab group]) may have led to a diminished treatment effect between the two arms after daratumumab use and affected the power to detect statistically significant OS in the ITT analysis, given the planned number of events and sample size, which was supported by sensitivity analyses to estimate the OS treatment effect in the absence of daratumumab therapy using the RPSFT model that demonstrated a better estimate *versus* the ITT estimate, with overall similar results (HR=0.706, 95% CI: 0.538-0.926) in favor of the Isa-Pd arm (described in the *Online Supplementary Appendix,* page 17).

The RPSFT analysis estimated a counterfactual factor and indicated there was a gain in survival time of the patients

Table 2. Treatment-emergent adverse events, safety population.

TEAE, N (%)	Isatuximab group N=152		Control group N=149	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any class	151 (99)	138 (91)	146 (98)	113 (76)
Neutropenia	79 (52)	77 (51)	54 (36)	52 (35)
Infusion-related reaction	57 (37.5)	4 (3)	2 (1)	0
Upper respiratory tract infection	54 (36)	5 (3)	31 (21)	4 (3)
Diarrhea	48 (32)	3 (2)	33 (22)	2 (1)
Pneumonia	42 (28)	35 (23)	38 (26)	31 (21)
Bronchitis	41 (27)	8 (5)	17 (11)	1 (<1)
Back pain	30 (20)	4 (3)	25 (17)	2 (1)
Fatigue	30 (20)	6 (4)	32 (22)	0
Edema peripheral	30 (20)	2 (1)	18 (12)	0
Constipation	27 (18)	0	30 (20)	0

Adverse events (AE) occurring in 20% or more of patients in any group are reported. TEAE: treatment-emergent AE.

in the control arm after switching to daratumumab.

Long-term outcome measures showed continuous overall benefit for patients randomized to isatuximab *versus* control treatment, suggesting the prolonged benefit of isatuximab use in earlier lines without inducing more resistant disease refractory to subsequent treatments. There was a significant TTNT delay in the Isa-Pd group *versus* the Pd group (15.5 *vs.* 8.9 months). Despite subsequent daratumumab use in the Pd group and its potential benefit on PFS in the first subsequent therapy line, median PFS2 was significantly longer with Isa-Pd *versus* Pd (17.5 *vs.* 12.9 months; log-rank 1-sided *P*=0.0091). Based on these data, anti-CD38 therapy should be used as early as possible during the treatment continuum.

Extended follow-up to approximately 52 months revealed continued efficacy and tolerability of the isatuximab regimen, representing an important option for patients who are refractory to other treatments, such as lenalidomide. At study entry, approximately 95% of patients were refractory to IMiD agents (93% to lenalidomide, specifically). Looking at all non-daratumumab-based therapies in any subsequent line, non-IMiD- *versus* IMiD-based regimens appear to have better response rates after isatuximab. Similar rates of ≥VGPR were seen between groups regardless of subsequent regimens.

More patients in the control group received subsequent therapy and subsequent daratumumab therapy, as more patients in the Isa-Pd arm were still receiving study treatment at data cutoff. As expected, ORR were higher with subsequent daratumumab therapy after Pd *versus* Isa-Pd; however, ≥VGPR rates were similar. Daratumumab-based combination therapy led to improved responses in both arms *versus* monotherapy. Patients receiving daratumumab alone or in combination as first subsequent line of therapy achieved ≥VGPR, even after Isa-Pd therapy with a short washout period. Patients who received daratumumab after Isa-Pd had shorter PFS than those who did not receive subsequent daratumumab; however, only nine patients received daratumumab after the isatuximab combination. No cross-resistance to regimens without daratumumab was observed in the isatuximab group *versus* the control group. In a study examining the use of isatuximab following daratumumab, improved responses were observed among those patients with longer intervals from the last daratumumab dose to the first isatuximab dose, with a disease control rate of 58.3% (last dose ≥6 months) *versus* 26.4% (last dose <6 months).[17] Although limited by small sample size and open-label nature of the study, these results provide initial information on potential efficacy differences related to treatment sequencing. Additional studies are needed to better understand the optimal sequencing and timing of isatuximab and daratumumab in patients with RRMM.

After a follow-up of approximately 52 months, more patients remained on treatment in the Isa-Pd *versus* Pd group. The proportion of patients discontinuing due to AE was similar in both arms, indicating no increased risk with the addition of isatuximab resulting from longer exposure in the isatuximab group. Importantly, the overall safety profile observed with Isa-Pd was not different from previous analyses of ICARIA-MM.[13,14] At this final analysis, SPM were reported in 7% of patients in the isatuximab group, consistent with the second interim analysis,[14] similar to the cumulative incidence of SPM in patients with MM at 10 years (7.4%),[18] and with ranges reported in RRMM registry studies.[19] Furthermore, SPM occurrence did not have a detrimental impact on OS in patients receiving Isa-Pd,

supporting the overall favorable benefit of the regimen.

Although cross-trial comparisons must be conducted with caution, final OS analysis of the phase II ELOQUENT-3 trial demonstrated that elotuzumab, a monoclonal antibody targeting signaling lymphocytic activation molecule F7, in combination with Pd, significantly improved OS after a minimum follow-up of 45 months.[20] The proportion of patients with International Staging System Stage 3 at study entry (12% *vs.* 22%) in the triplet combination groups was substantially lower in ELOQUENT-3 than in ICARIA-MM. Among relevant adverse prognostic factors, there was a trend toward more patients with gain(1q21) in the Isa-Pd (49.4%) *versus* Pd arm (39%) in ICARIA-MM; the proportion of patients with gain(1q21) in the elotuzumab and Pd arms was similar in ELOQUENT-3.[21] There were more patients aged >65 years in the Isa-Pd (64.9%) *versus* Pd arm (54.2%), whereas it was balanced between the elotuzumab and Pd arms (63% *vs.* 61%).[21] The use of subsequent anti-CD38 therapy was balanced between the two arms in ELOQUENT-3 (53.3% in the elotuzumab arm *vs.* 49.2% in the Pd arm), which may have impacted OS. Results from the phase III APOLLO trial investigating daratumumab–pomalidomide–dexamethasone *versus* Pd demonstrated clinically meaningful OS benefit with the daratumumab combination (34.4 *vs.* 23.7 months; HR=0.82, 95% CI: 0.61-1.11; not statistically significant), with a HR similar to that observed in ICARIA-MM (HR=0.78, 95% CI: 0.59-1.02).[22] Patients in APOLLO received fewer prior lines of therapy and were less refractory *versus* patients in the ICARIA-MM study (median prior lines, 2 *vs.* 3; 80% *vs.* 94% refractory to lenalidomide; 48% *vs.* 77% refractory to a PI; 42% *vs.* 72% refractory to both lenalidomide and a PI). Long-term follow-up of the OPTIMISMM trial investigating pomalidomide-bortezomib-dexamethasone *versus* bortezomib-dexamethasone demonstrated a slight trend toward OS benefit (35.6 *vs.* 31.6 months, HR=0.94, 95% CI: 0.77-1.15; not statistically significant).[23,24] These findings combined with the clinically meaningful OS benefit demonstrated in ICARIA-MM with the Isa-Pd combination indicate the value of treating patients with RRMM using a regimen that includes pomalidomide and a monoclonal antibody.

Limitations of the current study include its open-label nature, the absence of patients refractory to previous daratumumab therapy, and the imbalance of the subsequent use of daratumumab that may have affected the power to detect statistically significant OS. Other limitations of OS analyses in general include the decreased number of deaths compared with cases of disease progression at any time point and the resulting decreased power of OS analysis; the influence of competing risks of death and crossover therapy on patient survival time; and the fact that median OS is approximately 1 year longer than median PFS, wherein several lines of therapy can impact OS with lesser effects of the initial experiment.[25]

In summary, the final OS analysis of this large, multicenter study confirmed that Isa-Pd continued to be efficacious and well tolerated after follow-up of approximately 52 months, contributing to a clinically meaningful benefit with a 6.9-month improvement in median OS, further supporting its position as a standard-of-care therapy for patients with RRMM and informing real-world practice.[26]

Disclosures

PGR reports research funding from Bristol Myers Squibb/Celgene, Karyopharm, Oncopeptides, and Takeda and participation on an entity's board of directors or advisory committee for AstraZeneca, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Karyopharm, Oncopeptides, Protocol Intelligence, Regeneron, Secura Bio, Sanofi, and Takeda. AP reports honoraria from AbbVie, Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, Sanofi, and Takeda. JS-M reports honoraria from AbbVie, Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Haemalogix, Janssen, Karyopharm, Merck Sharp & Dohme, Novartis, Regeneron, Roche, Sanofi, SecuraBio, and Takeda. MB reports honoraria from Amgen, Celgene, Janssen, Sanofi, and Takeda and participation on an entity's board of directors or advisory committee for Amgen, Janssen, Oncopeptides, and Takeda. IS reports honoraria from Amgen, Bristol Myers Squibb, Celgene, Janssen-Cilag, Novartis, PharmaMar, Sanofi, and Takeda. FS reports research funding from Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, and Targovax; honoraria from AbbVie, Amgen, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Janssen, Novartis, Oncopeptides, Pfizer, Sanofi, SkyliteDX, and Takeda; and participation on an entity's board of directors or advisory committee for AbbVie, Celgene, GlaxoSmithKline, Janssen, Oncopeptides, Sanofi, and Takeda. PM reports honoraria from AbbVie, Amgen, Celgene, GlaxoSmithKline, Janssen, and Sanofi. MAD reports honoraria from Amgen, BeiGene, Bristol Myers Squibb, Janssen, and Takeda. JM reports honoraria from Amgen, Bristol Myers Squibb/Celgene, Takeda, Janssen, and Sanofi and participation on an entity's board of directors or advisory committees for Amgen, Bristol Myers Squibb/Celgene, Janssen, Oncopeptides, Sanofi, and Takeda. MC reports consulting fees from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, and Sanofi and honoraria from Amgen, Bristol Myers Squibb/Celgene, GlaxoSmithKline, Janssen, and Sanofi. SM, FD, RZ, and MCM are employees of Sanofi and may hold stock and/or stock options. KCA reports consulting fees from AstraZeneca, Janssen, Pfizer, and Precision Biosciences. XL, S-YH, and HMP have no conflicts of interest to disclose.

Contributions

PGR, AP, JS-M, MB, IS, XL, FS, PM, MAD, S-YH, JM, MC, and HMP were investigators in the study and contributed to data acquisition. PGR and AP were co-primary investigators of the ICARIA-MM study. PGR, SM, RZ, FD, and MCM contributed to the analysis, verification, and interpretation of data for the work. KCA was the chairman of the study Steering Committee. All authors revised the work for important intellectual content and assume responsibility for data integrity and the

decision to submit this manuscript for publication, had full access to the study data, edited and reviewed manuscript drafts, and approved the final version for submission.

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Data-sharing statement

Qualified researchers can request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report forms, 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 are at: https://www.vivli.org.

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