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Isatuximab plus pomalidomide and dexamethasone in elderly patients with relapsed/refractory multiple myeloma: ICARIA-MM subgroup analysis

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Multiple myeloma (MM) typically affects elderly patients, with a median age at diagnosis of 69 years.[1] Treatment of elderly patients is challenging due to frailty, comorbidities, and decreased resilience to treatment-related toxicity.[2] Furthermore, advanced age negatively impacts the prognosis of patients with MM.[3,4] Considering these challenges, the development of new, well tolerated treatment options for this age group is needed.

Isatuximab is a monoclonal antibody that targets a specific epitope on CD38 and triggers MM cell death via multiple mechanisms.[5-7] Isatuximab-irfc is approved in the United States for use in combination with pomalidomide and dexamethasone (Pd) to treat relapsed/refractory MM (RRMM) patients who have received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor.[8]

ICARIA-MM (NCT02990338) was a randomized, open-label, multicenter phase 3 study of isatuximab in combination with Pd (Isa-Pd) that showed significantly improved progression-free survival (PFS) in heavily treated patients with RRMM with a manageable safety profile compared with Pd alone.[9,10] Due to its prognostic relevance, age (<75 *versus* ≥75 years) was one of the stratification factors in ICARIA-MM. As the population <75 years was very large, it was further divided into 65–74 and <65 years subpopulations in this pre-specified subgroup analysis of ICARIA-MM, comparing efficacy and safety in these three age groups.

Patient baseline characteristics divided by age group are shown in Table 1, and were generally balanced across arms.

Median PFS was significantly prolonged with Isa-Pd and was similar in all three age subgroups (Figure 1A-C): ≥75 years, 11.40 months (Isa-Pd; n=32) *versus* 4.47 months (Pd; n=29), hazard ratio (HR) 0.479; 95% confidence interval (CI) 0.242–0.946; 65–74 years, 11.57 months (Isa-Pd; n=68) *versus* 8.58 months (Pd; n=54), HR 0.638; 95% CI 0.385–1.059; and <65 years, 11.53 (Isa-Pd; n=54) *versus* 5.03 months (Pd; n=70), HR 0.656; 95% CI 0.401–1.074.

The overall response rate (ORR) was also improved with Isa-Pd *versus* Pd in all three age subgroups (Figure 1D): ≥75 years, 53.1% *versus* 31.0% (odds ratio [OR] 2.52; 95% CI 0.79–8.26); 65–74 years, 64.7% *versus* 38.9% (OR 2.88; 95% CI 1.29–6.46); and <65 years, 59.3% *versus* 34.3% (OR 2.79; 95% CI 1.26–6.20). Across age groups, the proportion of patients who achieved ≥very good partial response (VGPR) was consistently higher with Isa-Pd *versus* Pd (Figure 1D): ≥75 years, 31.2% *versus* 0% (OR not calculable); 65–74 years, 32.3% *versus* 13.0% (OR 3.21; 95% CI 1.17–9.70); and <65 years 31.5% *versus* 8.6% (OR 4.90; 95% CI 1.64–16.35).

Eight patients in the Isa-Pd arm had minimal residual disease (MRD) negativity (at 10^{-5} assessed by next-generation sequencing); two were ≥75 years, two 65–74 years, and four <65 years. No patients in the Pd arm achieved MRD negativity.

In patients ≥75 years, 8/32 (25.0%) Isa-Pd *versus* 15/29 (51.7%) Pd died. Median overall survival (OS) in this patient population was not reached in Isa-Pd and was 10.3 months in Pd with a CI for HR that does not cross 1 (HR 0.40; 95% CI 0.17–0.96). Among patients 65–74 years, median OS was not reached in the Isa-Pd arm and was 14.5 months in the Pd arm (HR 0.75; 95% CI 0.38–1.45). Median OS was not reached for either treatment arm in patients <65 years (HR 0.85; 95% CI 0.46–1.59).

Multivariate analyses adjusting PFS and OS for International Staging System (ISS) stage at study entry in the three age groups were performed and suggest that the imbalance in ISS stage at study entry did not influence the treatment effect in favor of Isa-Pd for PFS or OS outcomes (*Online Supplementary Table 1*).

Health-related quality of life (QoL) parameters were better maintained in the Isa-Pd arm among patients aged ≥75 years, *versus* 65–74 years and <65 years (*Online Supplementary Figures S1*, *S2* and *S3*, respectively), as demonstrated by the results of Global Health Status/Quality of Life, Physical Functioning and Role Functioning scores and no worsening of Fatigue, C30 Pain, and MY20 Disease Symptoms. The maintenance of QoL in elderly MM patients is important because (i) while younger

patients with MM are usually more concerned with achieving a complete response or MRD negativity, older patients desire to have their disease controlled while maintaining their QoL;[11] and (ii) MM-related complications tend to be more severe and debilitating in older patients, and therefore treatments that preserve QoL are desired in this patient group.[2]

As indicated in *Online Supplementary Table S2*, a longer treatment duration was observed for Isa-Pd *versus* Pd, independent of age. In the Isa-Pd arm, longer treatment exposure and higher numbers of cycles started were observed in patients ≥75 years compared with the other two age groups. Additionally, a tendency towards lower relative dose intensity was observed for patients ≥75, followed by patients aged 65–74 and <65 years in both treatment arms.

The number of patients with any treatment-emergent adverse event (TEAE) was similar in Isa-Pd *versus* Pd (Table 2). The incidences of Grade ≥3 TEAEs, serious TEAEs, and discontinuations due to TEAEs were higher in patients ≥75 years compared with younger patients with both Isa-Pd and Pd, but there was no increase in fatal TEAEs in Isa-Pd or impact on median treatment duration (*Online Supplementary Table 2*). The most common any-grade non-hematologic TEAEs with Isa-Pd were infusion reactions (IRs), regardless of age group (Table 2). IRs were mostly Grade 1–2, reversible, and occurred with the first infusion. Interestingly, fewer IRs were observed in patients ≥75 years (28.1%) compared with 65–74 years (36.4%) or <65 years (42.6%). The underlying mechanism of anti-CD38 IRs is not currently understood; it is possible that the cytokine release by responsible immune cell subset(s) is less pronounced in elderly patients due to their impaired immune function.

The most common Grade ≥3 non-hematologic TEAE was pneumonia, regardless of patient age or treatment group (Table 2). In Isa-Pd, the incidence of pneumonia was lower in patients ≥75 (12.5%), followed by those <65 (16.7%) and 65–74 years (27.3%). This might be explained by a higher percentage of older patients receiving prophylactic antibiotic treatment (*Online Supplementary Table S3*). With Isa-Pd, TEAEs with the

greatest difference in incidence for patients ≥75 *versus* <65 years were IRs (28.1% *versus* 42.6%) and acute kidney injury (15.6% *versus* 1.9%; compared to 10.7% *versus* 5.9% in the Pd group, possibly because elderly patients have less renal buffer).

Hematological laboratory abnormalities were assessed during the study (Table 2) and were recorded as TEAEs only if they were serious or led to study treatment modification or discontinuation. Grade 3–4 neutropenia was more common with Isa-Pd than Pd, regardless of age group (Table 2). Grade 3–4 anemia was more common in older patients and was observed in comparable rates in both arms, except for patients aged 65–74 years. Patients ≥75 years required more red blood cell transfusions and treatment with erythropoiesis-stimulating agents than younger patients, with older Pd patients requiring these interventions more than Isa-Pd patients (*Online Supplementary Table S4*). Grade 4 thrombocytopenia was similar between arms across age groups, except for patients ≥75 years (18.8% with Isa-Pd *versus* 10.7% with Pd, *Online Supplementary Table S5*). The need for platelet transfusions was low for all subpopulations and treatment arms. Neutropenia and infections were reversible and manageable with supportive care (granulocyte-colony stimulating factor/granulocyte-macrophage colony-stimulating factor and antibiotics, respectively).

As shown in *Online Supplementary Table S6*, the majority of TEAEs leading to treatment discontinuation were Grade ≥3. Infections were the most common TEAEs leading to treatment discontinuation in patients ≥75 years in both arms: 9.4% in Isa-Pd and 14.3% in Pd. In the Isa-Pd arm, 1 patient aged 65–74 (1.5%) and 2 aged <65 years (3.7%) discontinued treatment due to general disorders. For patients aged 65–74 and <65 years in the Pd arm, thrombocytopenia was the most frequent TEAE leading to treatment discontinuation (5.7% and 5.9%, respectively).

One limitation of the current ICARIA-MM sub-analysis is that the subgroup of patients ≥75 years in ICARIA-MM was about half the size of the other two age groups. Comorbidities and other illnesses that frequently accompany elderly patients may have compromised their eligibility for the study. However, the same limitation is present in

many MM clinical trials.[12] Nonetheless, both study arms had around 20% of patients aged ≥75 years and the oldest patient enrolled in ICARIA-MM was 86 years old, a very advanced age for a third-line trial. Furthermore, the ICARIA-MM study did not assess frailty.[13]

In contrast to the general observation of negative prognosis of elderly age in MM, the addition of isatuximab to pomalidomide and dexamethasone improved PFS, ORR, ≥VGPR rates, and OS rates in elderly patients, consistent with the benefit observed in the overall ICARIA-MM study population. Moreover, isatuximab was well tolerated in older patients (≥75 years), with a numerically longer treatment duration compared with younger patients and with no increase in fatal TEAEs in Isa-Pd *versus* Pd. A consistent trend toward higher rates of serious TEAEs and discontinuation due to TEAEs in patients ≥75 years was evident in both arms. Such results further support the use of Isa-Pd in RRMM patients regardless of age.

Authors Contributions

FC, the funder's clinical study director, was responsible for the ICARIA-MM study oversight. PGR was a coprimary investigator of this study. FHS, PGR, TF, AA, AS, AJ, KS, LF, C-KM and SBr were investigators in the study and contributed to data acquisition. PGR, FC and SL-G designed the study. SG and PLL processed the health-related quality of life data and performed the analysis. SL-G, FC, HvdV and SBe contributed to the analysis and interpretation of data for the work. 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; and edited, and reviewed manuscript drafts, and approved the final version for submission.

Disclosures

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Data sharing

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.clinicalstudydatarequest.com.

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Tables

Table 1. Baseline patient characteristics at study entry by age group in the intent-to-treat population.

	≥75 years (n=61)		65–74 years (n=122)		<65 years (n=124)	
	Isa-Pd (n=32)	Pd (n=29)	Isa-Pd (n=68)	Pd (n=54)	Isa-Pd (n=54)	Pd (n=70)
Age (years)						
Mean (SD)	77.9 (2.0)	78.3 (3.2)	69.4 (2.9)	69.0 (2.5)	56.5 (5.9)	57.0 (6.1)
Median (range)	77 (75–83)	78 (75–86)	69 (65–74)	69 (65–74)	57.5 (36–64)	58 (41–64)
MM subtype, n (%)						
IgG	21 (65.6)	22 (75.9)	45 (66.2)	32 (59.3)	38 (70.4)	47 (67.1)
IgA	9 (28.1)	4 (13.8)	17 (25.0)	19 (35.2)	7 (13.0)	18 (25.7)
IgM	0	0	1 (1.5)	0	1 (1.9)	0
Kappa light chain only	1 (3.1)	2 (6.9)	2 (2.9)	1 (1.9)	5 (9.3)	4 (5.7)
Lambda light chain only	1 (3.1)	1 (3.4)	3 (4.4)	2 (3.7)	3 (5.6)	1 (1.4)
ISS stage[*], n (%)						
Stage I	7 (21.9)	4 (13.8)	31 (45.6)	18 (33.3)	26 (48.1)	29 (41.4)
Stage II	12 (37.5)	12 (41.4)	22 (32.4)	23 (42.6)	19 (35.2)	21 (30.0)
Stage III	13 (40.6)	12 (41.4)	14 (20.6)	13 (24.1)	7 (13.0)	18 (25.7)
Unknown	0	1 (3.4)	1 (1.5)	0	2 (3.7)	2 (2.9)
ECOG performance status, n (%)						
0	9 (28.1)	14 (48.3)	24 (35.3)	18 (33.3)	22 (40.7)	37 (52.9)
1	18 (56.3)	8 (27.6)	36 (52.9)	31 (57.4)	29 (53.7)	29 (41.4)
2	5 (15.6)	7 (24.1)	8 (11.8)	5 (9.3)	3 (5.6)	4 (5.7)
Cytogenetic risk[†], n (%)						
High-risk CA	7 (21.9)	11 (37.9)	9 (13.2)	6 (11.1)	8 (14.8)	19 (27.1)
Standard-risk CA	20 (62.5)	9 (31.0)	47 (69.1)	32 (59.3)	36 (66.7)	37 (52.9)
Unknown or missing	5 (15.6)	9 (31.0)	12 (17.6)	16 (29.6)	10 (18.5)	14 (20.0)
Number of patients with medical history of						
Asthma or COPD, n (%)	5 (15.6)	5 (17.2)	7 (10.3)	8 (14.8)	4 (7.4)	4 (5.7)
Number of patients with renal impairment[‡], n (%)	30 (93.8)	27 (93.1)	63 (92.6)	51 (94.4)	49 (90.7)	67 (95.7)
eGFR, n (%)						
≥60-<90 mL/min/1.73 m² (mild impairment)	10 (33.3)	11 (40.7)	31 (49.2)	25 (49.0)	20 (40.8)	33 (49.3)
≥45-<60 mL/min/1.73 m²	13 (43.3)	9 (33.3)	14 (22.2)	12 (23.5)	8 (16.3)	11 (16.4)
≥30-<45 mL/min/1.73 m²	6 (20.0)	5 (18.5)	7 (11.1)	4 (7.8)	6 (12.2)	7 (10.4)
≥15-<30 mL/min/1.73 m² (severe impairment)	0	1 (3.7)	0	0	1 (2.0)	0
Number of prior lines of therapy						
Median (range)	3 (2–11)	3 (2–10)	3 (2–8)	3 (2–6)	3 (2–10)	3 (2–7)
Prior therapy, n (%)						
Alkylating agent	27 (84.4)	29 (100)	60 (88.2)	51 (94.4)	52 (96.3)	68 (97.1)
Proteasome inhibitor	32 (100)	29 (100)	68 (100)	54 (100)	54 (100)	70 (100)

Lenalidomide	32 (100)	29 (100)	68 (100)	54 (100)	54 (100)	70 (100)
Refractory status, n (%)						
Lenalidomide refractory	7 (21.9)	3 (10.3)	1 (1.5)	7 (13.0)	2 (3.7)	2 (2.9)
PI refractory	6 (18.8)	4 (13.8)	7 (10.3)	9 (16.7)	6 (11.1)	8 (11.4)
Lenalidomide and PI refractory	3 (9.4)	0	0	3 (5.6)	1 (1.9)	1 (1.4)

CA: chromosomal abnormalities; COPD: chronic obstructive pulmonary disease; d: dexamethasone; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; Ig: immunoglobulin; Isa: isatuximab; ISS: International Staging System; MM: multiple myeloma; P: pomalidomide; PI: proteasome inhibitor; SD: standard deviation.

*ISS staging was derived based on the combination of serum β2-microglobulin and albumin
†High risk CA was defined as the presence of del(17p), and/or t(4;14), and/or t(14;16) by fluorescence in situ hybridization. Cytogenetics was performed by a central laboratory with a cut-off of analyzed plasma cells 50% for del(17p), and 30% of analyzed plasma cells for t(4;14) and t(14;16)
‡Renal impairment was defined as eGFR <60mL/min/1.73 m^2 as determined using the Modification of Diet in Renal Disease (MDRD) equation

Table 2. Most common TEAEs and hematological laboratory abnormalities while on treatment by patient age group and treatment arm in the safety population.

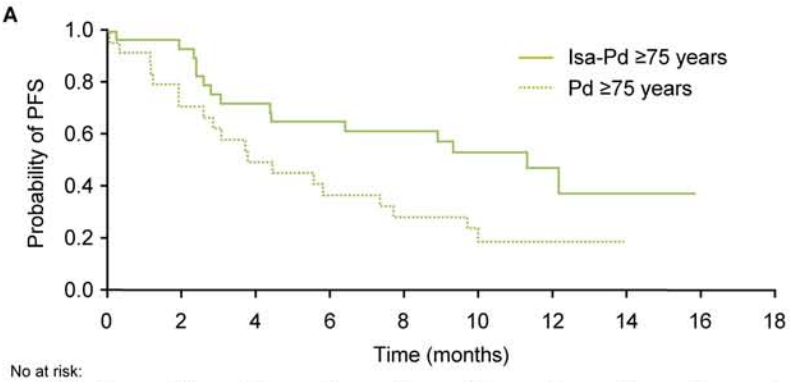
	≥75 years (n=60)		65–74 years (n=119)		<65 years (n=122)	
	Isa-Pd (n=32)	Pd (n=28)	Isa-Pd (n=66)	Pd (n=53)	Isa-Pd (n=54)	Pd (n=68)
Any TEAE*, n (%)	32 (100)	28 (100)	66 (100)	52 (98.1)	53 (98.1)	66 (97.1)
Infections	26 (81.3)	19 (67.9)	57 (86.4)	30 (56.6)	40 (74.1)	47 (69.1)
Upper respiratory tract infection	10 (31.3)	1 (3.6)	22 (33.3)	8 (15.1)	11 (20.4)	17 (25.0)
Pneumonia	4 (12.5)	2 (7.1)	18 (27.3)	7 (13.2)	9 (16.7)	17 (25.0)
Blood and lymphatic system disorders	22 (68.8)	15 (53.6)	38 (57.6)	25 (47.2)	29 (53.7)	25 (36.8)
Neutropenia	17 (53.1)	13 (46.4)	30 (45.5)	18 (34.0)	24 (44.4)	19 (27.9)
Thrombocytopenia	6 (18.8)	3 (10.7)	9 (13.6)	7 (13.2)	4 (7.4)	8 (11.8)
Gastrointestinal disorders	19 (59.4)	17 (60.7)	33 (50.0)	23 (43.4)	29 (53.7)	34 (50.0)
Diarrhea	12 (37.5)	7 (25.0)	14 (21.2)	10 (18.9)	13 (24.1)	12 (17.6)
Constipation	4 (12.5)	7 (25.0)	11 (16.7)	7 (13.2)	9 (16.7)	12 (17.6)
Musculoskeletal disorders	19 (59.4)	13 (46.4)	38 (57.6)	29 (54.7)	29 (53.7)	32 (47.1)
Back pain	6 (18.8)	6 (21.4)	10 (15.2)	4 (7.5)	9 (16.7)	12 (17.6)
Arthralgia	4 (12.5)	1 (3.6)	7 (10.6)	7 (13.2)	5 (9.3)	5 (7.4)
Others						
Fatigue	19 (59.4)	20 (71.4)	35 (53.0)	30 (56.6)	28 (51.9)	39 (57.4)
Acute kidney injury	5 (15.6)	3 (10.7)	1 (1.5)	1 (1.9)	1 (1.9)	4 (5.9)
Infusion reaction	9 (28.1)	0	24 (36.4)	1 (1.9)	23 (42.6)	1 (1.5)
Grade ≥3 TEAE†, n (%)	30 (93.8)	21 (75.0)	56 (84.8)	40 (75.5)	46 (85.2)	44 (64.7)
Infections	15 (46.9)	10 (35.7)	30 (45.5)	14 (26.4)	20 (37.0)	21 (30.9)
Upper respiratory tract infection	1 (3.1)	0	1 (1.5)	1 (1.9)	3 (5.6)	0
Pneumonia	4 (12.5)	2 (7.1)	14 (21.2)	7 (13.2)	7 (13.0)	14 (20.6)
Blood and lymphatic system disorders	22 (68.8)	15 (53.6)	36 (54.5)	22 (41.5)	29 (53.7)	22 (41.5)
Neutropenia	16 (50.0)	13 (46.4)	30 (45.5)	17 (32.1)	24 (44.4)	18 (26.5)
Thrombocytopenia	5 (15.6)	3 (10.7)	9 (13.6)	7 (13.2)	4 (7.4)	8 (11.8)
Gastrointestinal disorders	3 (9.4)	0	2 (3.0)	2 (3.8)	4 (7.4)	1 (1.5)
Diarrhea	1 (3.1)	0	1 (1.5)	1 (1.9)	1 (1.9)	0
Constipation	0	0	0	0	0	0
Musculoskeletal disorders	2 (6.3)	2 (7.1)	3 (4.5)	3 (5.7)	7 (13.0)	3 (4.4)
Back pain	0	1 (3.6)	1 (1.5)	0	2 (3.7)	1 (1.5)
Arthralgia	2 (6.3)	0	1 (1.5)	1 (1.9)	1 (1.9)	0
Others						
Fatigue	2 (6.3)	0	3 (4.5)	0	1 (1.9)	0
Acute kidney injury	2 (6.3)	2 (7.1)	1 (1.5)	1 (1.9)	1 (1.9)	3 (4.4)
Infusion reaction	1 (3.1)	0	2 (3.0)	0	1 (1.9)	0
Grade 5 (fatal) TEAE	2 (6.3)	4 (14.3)	3 (4.5)	5 (9.4)	6 (11.1)	4 (5.9)
Serious TEAE	22 (68.8)	16 (57.1)	41 (62.1)	32 (60.4)	31 (57.4)	32 (47.1)
TEAE leading to definitive discontinuation	5 (15.6)	4 (14.3)	2 (3.0)	8 (15.1)	4 (7.4)	7 (10.3)
Hematologic laboratory abnormalities‡ (Grade 3-4)						
Neutropenia	28 (87.5)	18 (64.3)	53 (80.3)	38 (71.7)	48 (88.9)	47 (69.1)
Anemia	14 (43.8)	12 (42.9)	20 (30.3)	11 (20.8)	14 (25.9)	18 (26.5)
Thrombocytopenia	11 (34.4)	8 (28.6)	20 (30.3)	13 (24.5)	16 (29.6)	15 (22.1)

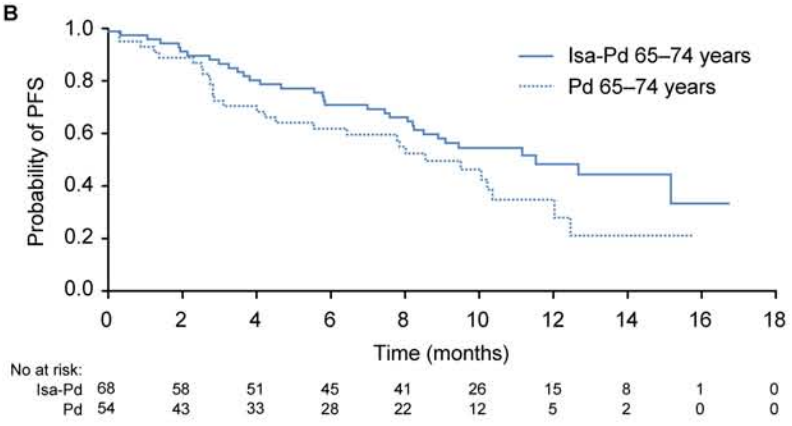
d: dexamethasone; Isa: isatuximab; P: pomalidomide; TEAE: treatment-emergent adverse effect.

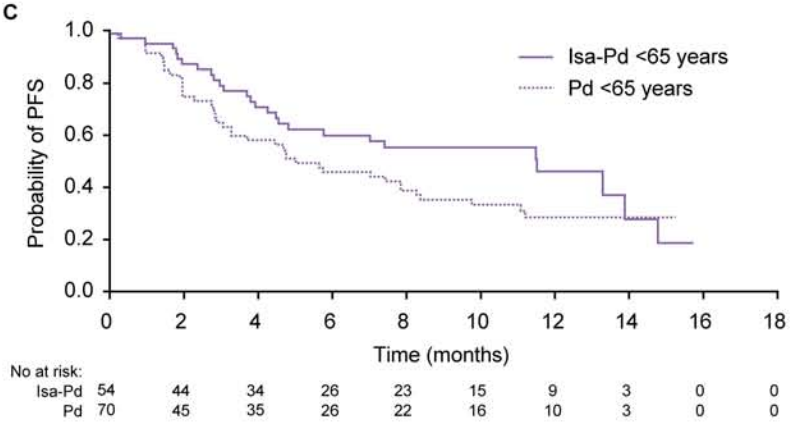
*System Organ Class with TEAEs with an incidence of ≥15%
†System Organ Class with Grade ≥3 TEAEs with an incidence of ≥10%
‡Derived from clinical laboratory analysis, including complete blood count, neutrophil count, platelet count, and hemoglobin values. Clinical laboratory abnormalities were recorded as TEAEs only if they were serious or led to study treatment modification or discontinuation.

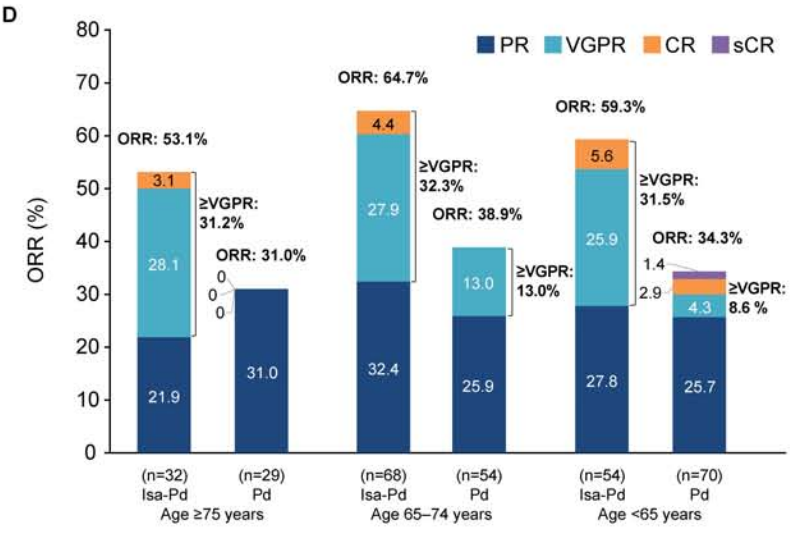
Figure Legend

Figure 1: Progression-free survival in the Isa-Pd and Pd arms in (A) patients ≥75 years, (B) 65–74 years, and (C) <65 years. Response to therapy in the Isa-Pd and Pd arms by patient age group (D). A–C. Kaplan–Meier analysis of progression-free survival as assessed by an Independent Response Committee. Hazard ratio and corresponding 95% confidence intervals are from a Cox proportional hazard model. **D.** Overall response rate (ORR) by patient age group as assessed by an Independent Response Committee using the IMWG uniform response criteria for evaluating MM response. A stratified Cochran-Mantel-Haenszel chi-square test measured treatment differences in ORR and rates of very good partial response (VGPR) or better and complete response (CR) or better. CR: complete response; d: dexamethasone; IMWG: International Myeloma Working Group; Isa: isatuximab; MM: multiple myeloma; P: pomalidomide; PFS: progression-free survival; PR: partial response; sCR: stringent complete response.


A
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0.0
Isa-Pd ≥75 years
Pd ≥75 years
0 2 4 6 8 10 12 14 16 18
Time (months)
No at risk:
Isa-Pd 32 27 21 18 17 11 6 3 0 0
Pd 29 17 12 9 7 5 2 0 0 0


B
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0.0
Isa-Pd 65–74 years
Pd 65–74 years
0 2 4 6 8 10 12 14 16 18
Time (months)
No at risk:
Isa-Pd 68 58 51 45 41 26 15 8 1 0
Pd 54 43 33 28 22 12 5 2 0 0


C
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0.0
Isa-Pd <65 years
Pd <65 years
0 2 4 6 8 10 12 14 16 18
Time (months)
No at risk:
Isa-Pd 54 44 34 26 23 15 9 3 0 0
Pd 70 45 35 26 22 16 10 3 0 0


D
ORR (%)
80
70
60
50
40
30
20
10
0
PR
VGPR
CR
sCR
ORR: 53.1%
3.1
28.1
21.9
≥VGPR: 31.2%
ORR: 31.0%
0
0
0
31.0
ORR: 64.7%
4.4
27.9
32.4
≥VGPR: 32.3%
ORR: 38.9%
13.0
25.9
≥VGPR: 13.0%
ORR: 59.3%
5.6
25.9
27.8
≥VGPR: 31.5%
ORR: 34.3%
1.4
2.9
4.3
25.7
≥VGPR: 8.6 %
(n=32) Isa-Pd
(n=29) Pd
Age ≥75 years
(n=68) Isa-Pd
(n=54) Pd
Age 65–74 years
(n=54) Isa-Pd
(n=70) Pd
Age <65 years

Supplementary Appendix

Methods

Study design

ICARIA-MM was a prospective, randomized, open-label, active-controlled, multicenter, Phase 3 study of patients with relapsed/refractory multiple myeloma (RRMM).(1, 2) The protocol was approved by institutional review boards and independent ethics committees of all participating institutions, and was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline. All patients provided written informed consent. The detailed study design was published previously.(2) Briefly, RRMM patients who had received ≥2 prior lines of therapy, and had failed therapy with lenalidomide and a proteasome inhibitor given alone or in combination were enrolled. Eligible patients had RRMM, received ≥2 prior lines, and had not responded to therapy with lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) given alone or in combination. Patients also needed to have measurable disease defined as a serum monoclonal protein concentration of at least 0.5 g/dL, or a urine monoclonal protein concentration of at least 200 mg/24 h, and be refractory to their last line of treatment. Patients were required to have adequate hematological, hepatic, and renal function (estimated glomerular filtration rate ≥30 mL/min per 1.73 m^2 as per modification of diet in the renal disease study equation). Patients with asthma or chronic obstructive pulmonary disease were not excluded. Patients were excluded if they were refractory to previous therapy with an anti-CD38 monoclonal antibody treatment, had previous treatment with pomalidomide, or an ongoing toxic effect worse than Grade 1 from previous antimyeloma therapy. Patients with active primary amyloid-light chain amyloidosis, or concomitant plasma cell leukemia were also excluded.(1)

Procedures

All eligible patients were randomized 1:1 according to the number of prior lines of therapy (2–3 *versus* >3) and age (<75 years or ≥75 years). Patients in the isatuximab

(Isa) plus pomalidomide and dexamethasone (Pd) arm received isatuximab 10 mg/kg intravenously (days 1, 8, 15, 22 in the first 28-day cycle; days 1, 15 in subsequent cycles), in combination with pomalidomide 4 mg orally (days 1 to 21 each cycle), and dexamethasone 40 mg (20 mg for ≥75 years old) orally or intravenously (days 1, 8, 15, 22 each cycle). Patients in the Pd arm received pomalidomide and dexamethasone in the same schedule. Therapy continued until disease progression, unacceptable toxicity, or consent withdrawal (*Online Supplementary Figure S4*).

Outcomes

The patient-reported outcome data were collected electronically on day 1 of each treatment cycle. The primary endpoint was progression-free survival (PFS), assessed by an Independent Response Committee. Key secondary endpoints were overall response rate (ORR) and overall survival (OS). Minimal residual disease (at 10^{-5} assessed by next-generation sequencing) was evaluated in case of investigator-assessed complete response. Treatment-emergent adverse events (TEAEs) were graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. Hematological laboratory abnormalities were derived from laboratory analysis, including complete blood count, neutrophil count, platelet count, and hemoglobin values. Health-related quality of life (QoL), impact of symptoms and health utility/status were assessed using EORTC QLQ-C30, QLQ-MY20 and EQ-5D-5L. Data from the C30 Global Health Status/Quality of Life, Physical Functioning, Role Functioning, Fatigue, C30 Pain (“Have you had pain?”, “Pain interfered with daily activities?”) and MY20 Disease Symptom (measuring disease-specific pain, including: “Had bone aches or pain?”, “Had pain in your back?”, “Had pain in your hip?”, “Had pain in arm or shoulder?”, “Had pain in chest?”, “Pain increased with activity?”) domains were assessed, based on QoL conceptual models in RRMM.(3-5) Clinically meaningful improvement (reduction in pain) at 10-point minimal clinically important difference was achieved for Isa-Pd older patients at cycle 7 (n=20). It should be noted that as the sample sizes for later cycles (e.g. after cycle 12) are small; caution should be used before drawing any meaningful conclusions based on later cycles. Of note, there was no difference in age group compliance for QoL parameters (expected *versus* received),

with a high overall compliance (completion rates at each cycle for each arm and age group were ≥90%).

Statistical analyses

All efficacy analyses were conducted in the intent-to-treat population, while TEAEs and QoL analyses were conducted in the safety population, and divided by three age groups: ≥75, 65–74, and <65 years. PFS was analyzed using the Kaplan-Meier method, hazard ratios (HR) were estimated using a Cox proportional hazards model, and groups were compared using a log-rank test. ORRs and rates of very good partial response or better and complete response or better were compared using a Cochran Mantel-Haenszel test. For the QoL analysis, change from baseline was analyzed using a mixed-effect model repeated measures approach within each treatment arm at each cycle. Missing data were handled using a maximum-likelihood procedure.

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Online Supplementary Table S1. Multivariate analysis adjusting progression-free survival and overall survival for International Staging System at study entry by age group in the intent-to-treat population.

	≥75 years (n=60)	65–74 years (n=119)	<65 years (n=122)
PFS			
Adjusted* HR (95% CI)	0.457 (0.227–0.919)	0.631 (0.379–1.048)	0.669 (0.403–1.111)
Unadjusted HR (95% CI)	0.479 (0.242–0.946)	0.638 (0.385–1.059)	0.656 (0.401–1.074)
OS			
Adjusted* HR (95% CI)	0.405 (0.168–0.975)	0.776 (0.396–1.521)	0.968 (0.513–1.824)
Unadjusted HR (95% CI)	0.404 (0.171–0.956)	0.746 (0.383–1.450)	0.854 (0.459–1.590)

CI: confidence interval; HR: hazard ratio; ISS: International Staging System; OS: overall survival; PFS: progression-free survival.

*: Adjusted on ISS stage at study entry

Online Supplementary Table S2. Treatment duration by patient age group in the safety population.

	≥75 years (n=60)		65–74 years (n=119)		<65 years (n=122)	
	Isa-Pd (n=32)	Pd (n=28)	Isa-Pd (n=66)	Pd (n=53)	Isa-Pd (n=54)	Pd (n=68)
Median duration of treatment exposure, weeks	46.5	19.8	42.6	30.1	32.5	23
(range)	(3.1–74.1)	(1.7–64.6)	(1.3–76.7)	(1.3–73.7)	(4.0–72.1)	(1.0–67.6)
Median number of cycles started by patient	11	5	10	7	8	6
(range)	(1.0–18.0)	(1.0–16.0)	(1.0–19.0)	(1.0–18.0)	(1.0–18.0)	(1.0–17.0)
Median duration of Isa exposure, weeks	46.5	–	42.1	–	31.9	–
(range)	(1.0–74.1)	–	(1.0–75.1)	–	(2.0–72.1)	–
Median number of Isa cycles started by patient	11	–	10	–	8	–
(range)	(1.0–18.0)	–	(1.0–19.0)	–	(1.0–18.0)	–
Median Isa RDI, %	89.2	–	93.3	–	93.6	–
(range)	(20.0–106.1)	–	(19.7–111.1)	–	(52.6–104.0)	–
Median duration of P exposure, weeks	40.8	19.8	41.6	30.1	31.9	23
(range)	(2.0–74.0)	(1.7–64.6)	(1.3–75.1)	(1.3–73.7)	(3.9–72.1)	(0.9–67.6)
Median number of P cycles started by patient	9.5	5	10	7	7	6
(range)	(1.0–18.0)	(1.0–16.0)	(1.0–18.0)	(1.0–18.0)	(1.0–18.0)	(1.0–17.0)
Median P RDI, %	82.3	79.4	85.1	92.9	86.3	94.4
(range)	(32.3–97.8)	(40.4–100.0)	(22.9–103.7)	(37.2–118.5)	(39.4–100.0)	(61.9–100.0)
Median duration of d exposure, weeks	46.1	19.1	41.6	26	31.4	22.9
(range)	(2.1–74.0)	(1.0–64.6)	(1.0–76.7)	(1.0–73.7)	(3.0–72.1)	(1.0–65.9)
Median number of d cycles started by patient	11	5	10	7	8	6
(range)	(1.0–18.0)	(1.0–16.0)	(1.0–19.0)	(1.0–18.0)	(1.0–18.0)	(1.0–17.0)
Median d RDI, % (range)	84.8	90.9	87.1	95.6	91	98.7
(range)	(44.0–100.0)	(45.0–300.0)	(15.9–103.2)	(30.3–105.0)	(27.1–130.0)	(49.3–102.1)

d: dexamethasone; Isa: isatuximab; P: pomalidomide; RDI: relative dose intensity.

Online Supplementary Table S3. Percentage of patients receiving concomitant prophylactic antibiotic treatment by age group in the intent-to-treat population.

Any prophylactic antibiotic treatment, n (%)	Age ≥75 years		Age 65–74 years		Age <65 years	
	Isa-Pd (n=32)	Pd (n=29)	Isa-Pd (n=68)	Pd (n=54)	Isa-Pd (n=54)	Pd (n=70)
	20 (62.5)	13 (44.8)	44 (64.7)	34 (63.0)	32 (59.3)	39 (55.7)

d: dexamethasone; Isa: isatuximab; P: pomalidomide.

Online Supplementary Table S4. Patients who needed red blood cells transfusion and treatment with erythropoiesis stimulating agents by age group in the safety population.

Treatment, n (%)	≥75 years (n=60)		65–74 years (n=119)		<65 years (n=122)	
	Isa-Pd (n=32)	Pd (n=28)	Isa-Pd (n=66)	Pd (n=53)	Isa-Pd (n=54)	Pd (n=68)
Any red blood cells transfusion	11 (34.4)	13 (46.4)	22 (33.3)	18 (34.0)	13 (24.1)	20 (29.4)
Blood, whole	0	3 (10.7)	3 (4.5)	1 (1.9)	0	2 (2.9)
Erythrocytes	1 (3.1)	2 (7.1)	5 (7.6)	2 (3.8)	3 (5.6)	5 (7.4)
Red blood cells	8 (25.0)	7 (25.0)	12 (18.2)	13 (24.5)	9 (16.7)	12 (17.6)
Red blood cells, concentrated	3 (9.4)	1 (3.6)	3 (4.5)	3 (5.7)	1 (1.9)	1 (1.5)
Red blood cells, leucocyte depleted	0	0	0	0	1 (1.9)	0
Any ESA	6 (18.8)	7 (25.0)	11 (16.7)	10 (18.9)	8 (14.8)	8 (11.8)
Darbepoetin alfa	2 (6.3)	2 (7.1)	2 (3.0)	2 (3.8)	3 (5.6)	4 (5.9)
Epoetin alfa	3 (9.4)	3 (10.7)	8 (12.1)	5 (9.4)	5 (9.3)	1 (1.5)
Epoetin beta	0	0	0	3 (5.7)	0	1 (1.5)
Epoetin zeta	1 (3.1)	0	1 (1.5)	1 (1.9)	0	2 (2.9)
Erythropoietin	0	2 (7.1)	0	1 (1.9)	0	0
Any red blood cells transfusion and ESA	1 (3.1)	6 (21.4)	6 (9.1)	7 (13.2)	3 (5.6)	1 (1.5)

d: dexamethasone; ESA: erythropoiesis stimulating agent; Isa: isatuximab; P: pomalidomide.

Online Supplementary Table S5. Abnormal thrombocytopenia laboratory parameters (Grade 4) during treatment by patient age group in the safety population.

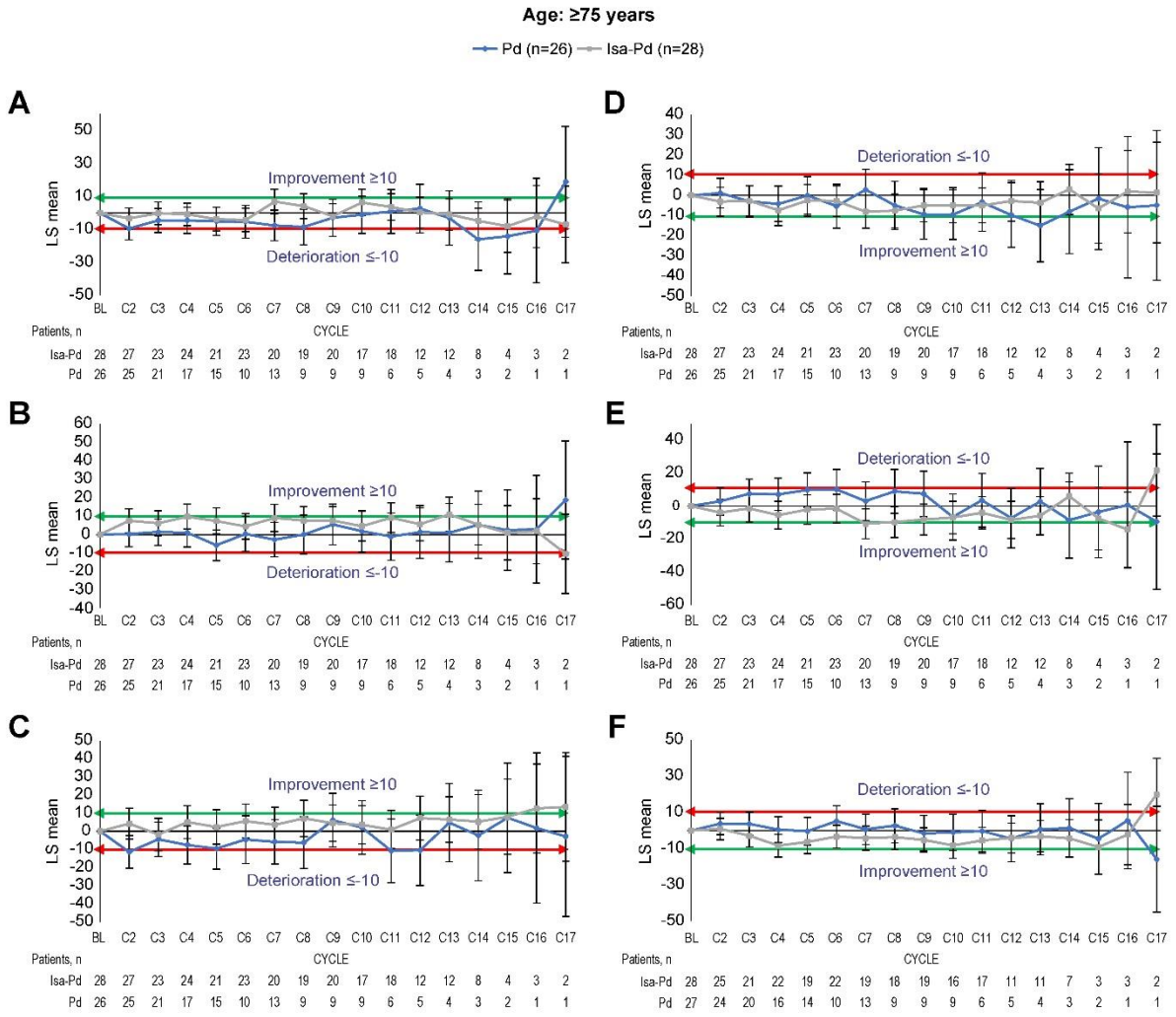
Grade 4 Thrombocytopenia, n (%)	Age ≥75 years		Age 65–74 years		Age <65 years	
	Isa-Pd (n=32)	Pd (n=28)	Isa-Pd (n=66)	Pd (n=53)	Isa-Pd (n=54)	Pd (n=68)
	6 (18.8)	3 (10.7)	13 (19.7)	9 (17.0)	6 (11.1)	10 (14.7)

d: dexamethasone; Isa: isatuximab; P: pomalidomide.

Online Supplementary Table S6. Patients with TEAEs leading to definitive treatment discontinuation by patient age group and treatment arm in the safety population.

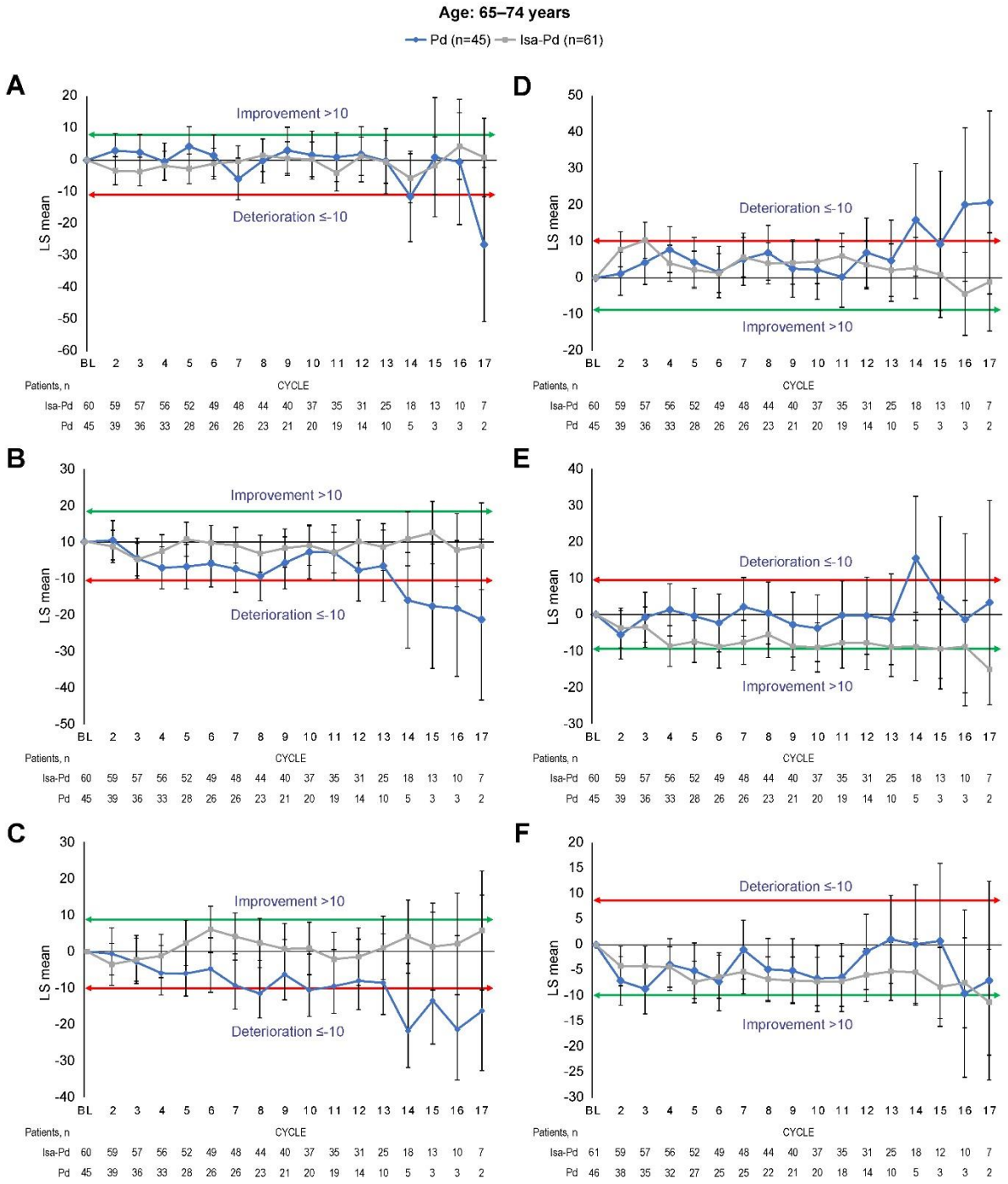
	≥75 years				65–74 years				<65 years			
	Isa-Pd (n=32)		Pd (n=28)		Isa-Pd (n=66)		Pd (n=53)		Isa-Pd (n=54)		Pd (n=68)	
Primary System Organ Class **Preferred Term, n (%)**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Any class	5 (15.6)	5 (15.6)	4 (14.3)	4 (14.3)	2 (3.0)	2 (3.0)	8 (15.1)	7 (13.2)	4 (7.4)	4 (7.4)	7 (10.3)	7 (10.3)
Infections and infestations	3 (9.4)	3 (9.4)	4 (14.3)	4 (14.3)	0	0	2 (3.8)	1 (1.9)	1 (1.9)	1 (1.9)	2 (2.9)	2 (2.9)
Atypical pneumonia	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0
Bronchopulmonary aspergillosis	1 (3.1)	1 (3.1)	0	0	0	0	0	0	0	0	0	0
Echinococciasis	0	0	0	0	0	0	1 (1.9)	0	0	0	0	0
Medical device site infection	1 (3.1)	1 (3.1)	0	0	0	0	0	0	0	0	0	0
Pneumonia	0	0	1 (3.6)	1 (3.6)	0	0	1 (1.9)	1 (1.9)	0	0	1 (1.5)	1 (1.5)
Pneumonia influenzal	1 (3.1)	1 (3.1)	0	0	0	0	0	0	0	0	0	0
Pneumonia streptococcal	0	0	1 (3.6)	1 (3.6)	0	0	0	0	0	0	0	0
Sepsis	0	0	1 (3.6)	1 (3.6)	0	0	0	0	0	0	0	0
Septic shock	0	0	1 (3.6)	1 (3.6)	0	0	0	0	0	0	1 (1.5)	1 (1.5)
Neoplasms benign, malignant and unspecified (include cysts and polyps)	0	0	0	0	1 (1.5)	1 (1.5)	0	0	0	0	0	0
Myelodysplastic syndrome	0	0	0	0	1 (1.5)	1 (1.5)	0	0	0	0	0	0
Blood and lymphatic system disorders	1 (3.1)	1 (3.1)	0	0	0	0	3 (5.7)	3 (5.7)	0	0	4 (5.9)	4 (5.9)
Neutropenia	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0	1 (1.5)	1 (1.5)
Thrombocytopenia	1 (3.1)	1 (3.1)	0	0	0	0	3 (5.7)	3 (5.7)	0	0	4 (5.9)	4 (5.9)
Nervous system disorders	0	0	0	0	0	0	2 (3.8)	2 (3.8)	0	0	0	0
Hemorrhage intracranial	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0	0	0
Spinal subdural hematoma	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0	0	0
Hepatobiliary disorders	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0
Hepatic failure	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0
Decubitus ulcer	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0
General disorders and administration site conditions	1 (3.1)	1 (3.1)	0	0	1 (1.5)	1 (1.5)	1 (1.9)	1 (1.9)	2 (3.7)	2 (3.7)	1 (1.5)	1 (1.5)
Death	0	0	0	0	1 (1.5)	1 (1.5)	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)	0	0
General physical health deterioration	1 (3.1)	1 (3.1)	0	0	0	0	0	0	0	0	0	0
Multiple organ dysfunction syndrome	0	0	0	0	0	0	0	0	1 (1.9)	1 (1.9)	0	0
Sudden death	0	0	0	0	0	0	0	0	0	0	1 (1.5)	1 (1.5)

d: dexamethasone; Isa: isatuximab; P: pomalidomide; TEAE: treatment-emergent adverse effect.



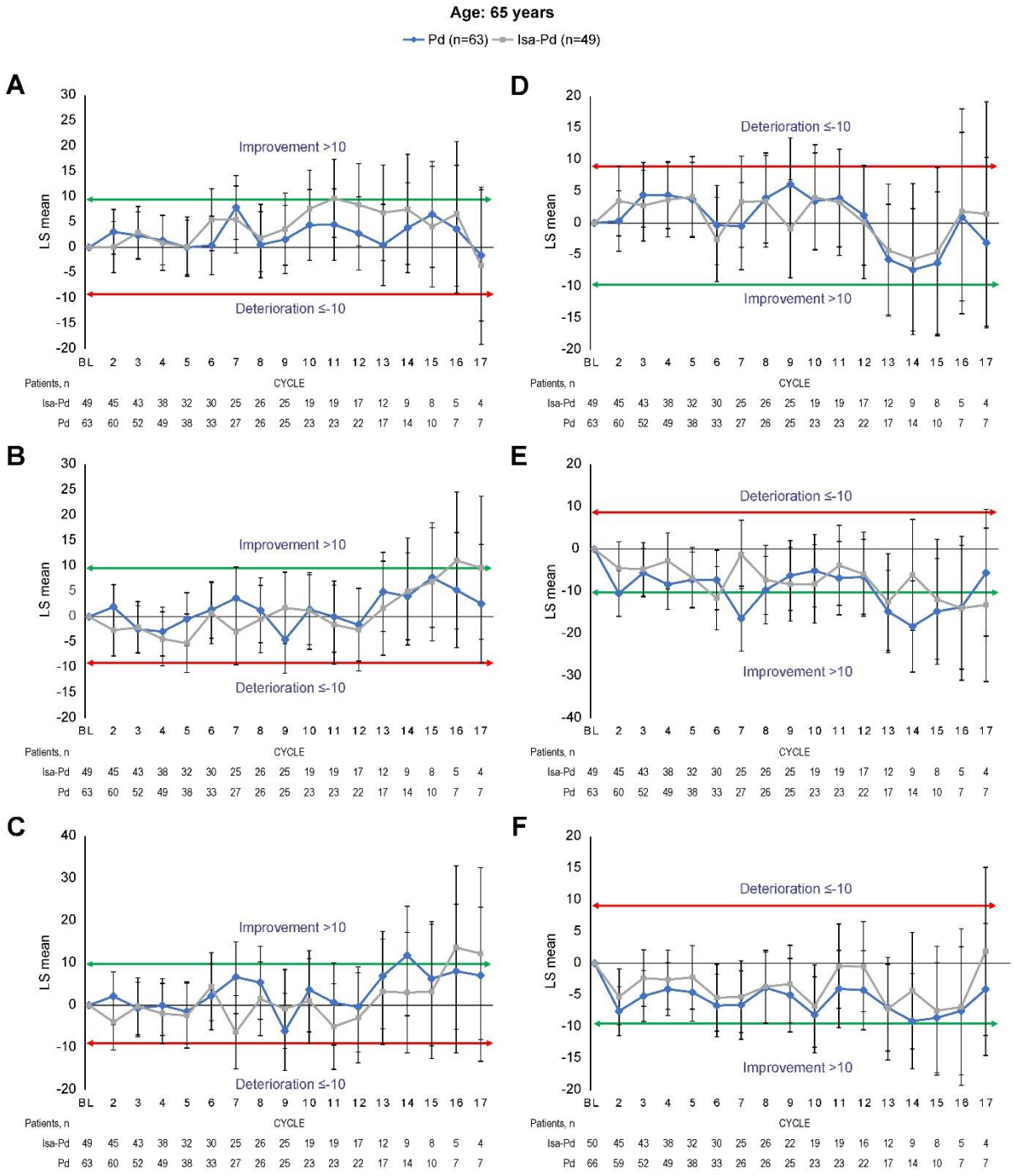
Online Supplementary Figure S1. Quality of life in the Isa-Pd and Pd arms in patients ≥75 years. Mean change from baseline for (A) Global Health Scale/Quality of Life, (B) Physical Functioning, (C) Role Functioning, (D) Fatigue, (E) C30 pain, and (F) MY20 Disease Symptoms (disease-specific pain). Graphs show the mean change from baseline for each cycle for patients aged ≥75 years (n=29 for the Isa-Pd arm and n=26 for the Pd control arm). Grey square represents the mean change from baseline for Isa-Pd and blue diamond for patients in Pd arm. Error bars represent 95% confidence intervals. Tables describe the sample size for each cycle in the Isa-Pd and Pd arms. A 10-point minimal clinical important difference was used to show clinically meaningful improvement and deterioration for all C30 and MY20 Quality of Life,

functional, and symptom domains. Higher scores in Global Health Scale/Quality of Life, Physical Functioning and Role Functioning represent greater functioning and better quality of life, whereas higher scores in Pain, Fatigue, and Disease Symptoms represent higher symptom burden. BL: baseline; C: cycle; d: dexamethasone; Isa: isatuximab; LS: least squares; P: pomalidomide.



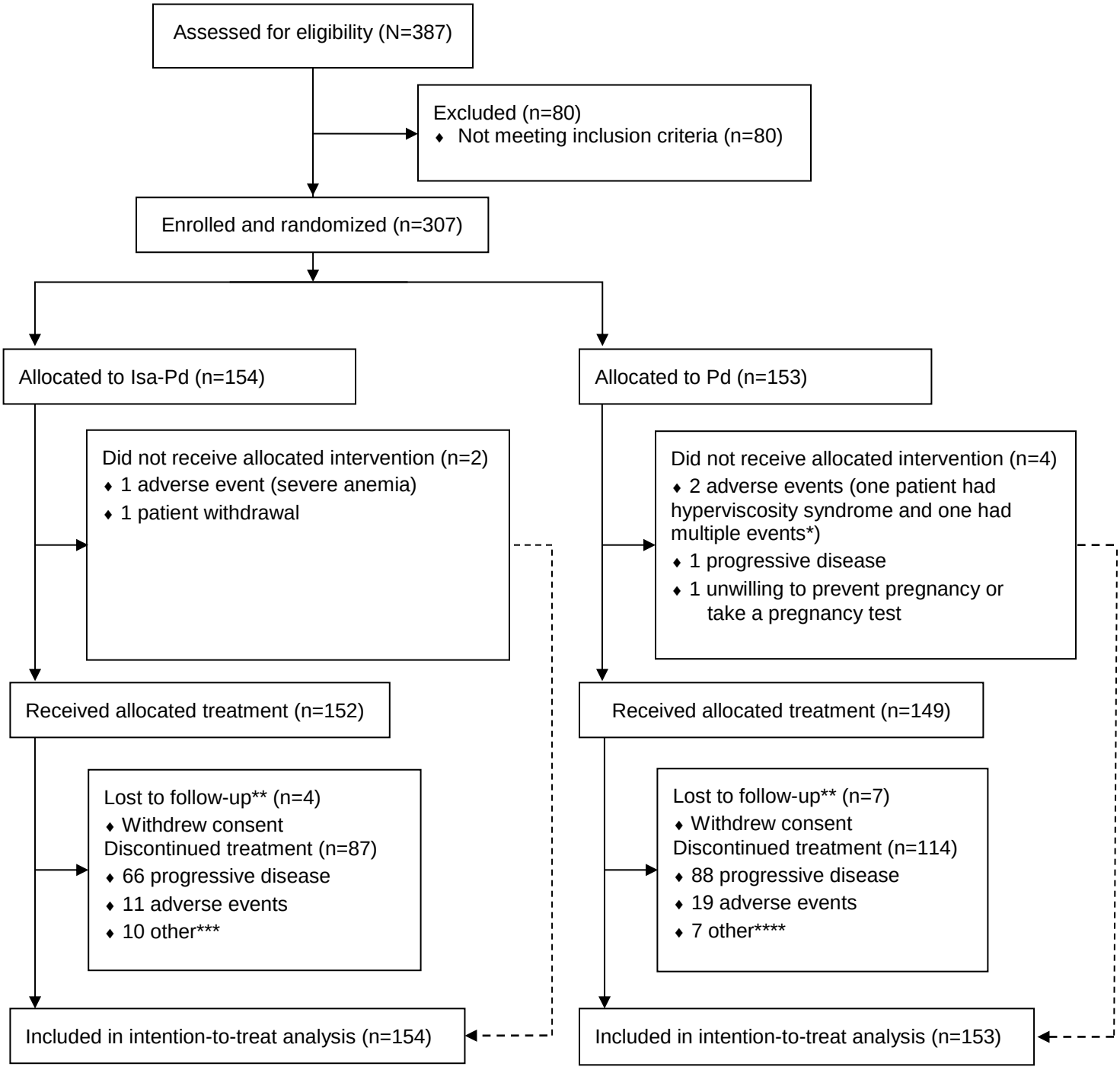
Online Supplementary Figure S2. Quality of life in the Isa-Pd and Pd arms in patients 65–74 years. (A) Mean change from baseline for Global Health Scale/Quality of Life, (B) Physical Functioning, (C) Role Functioning, (D) Fatigue, (E) C30 Pain, and (F) MY20 Disease Symptoms (disease-specific pain). Graphs show the mean change from baseline for each cycle for patients aged 65–74 years

(n=61 for the Isa-Pd arm and n=45 for the Pd control arm). Grey square represents the mean change from baseline for Isa-Pd and blue diamond for patients in Pd arm. Error bars represent 95% confidence intervals. Tables describe the sample size for each cycle in the Isa-Pd and Pd arms. A 10-point minimal clinical important difference was used to show clinically meaningful improvement and deterioration for all C30 and MY20 Quality of Life, functional, and symptom domains. Higher scores in Global Health Scale/Quality of Life, Physical Functioning and Role Functioning represent greater functioning and better quality of life, whereas higher scores in Pain, Fatigue, and Disease Symptoms represent higher symptom burden. BL: baseline; C: cycle; d: dexamethasone; Isa: isatuximab; LS: least squares; P: pomalidomide.



Online Supplementary Figure S3. Quality of life in the Isa-Pd and Pd arms in patients <65 years. (A) Mean change from baseline for Global Health Scale/Quality of Life, (B) Physical Functioning, (C) Role Functioning, (D) Fatigue, (E) C30 Pain,

and (F) MY20 Disease Symptoms (disease-specific pain). Graphs show the mean change from baseline for each cycle for patients aged <65 years (n=49 for the Isa-Pd arm and n=63 for the Pd control arm). Grey square represents the mean change from baseline for Isa-Pd and blue diamond for patients in Pd arm. Error bars represent 95% confidence intervals. Tables describe the sample size for each cycle in the Isa-Pd and Pd arms. A 10-point minimal clinical important difference was used to show clinically meaningful improvement and deterioration for all C30 and MY20 Quality of Life, functional, and symptom domains. Higher scores in Global Health Scale/Quality of Life, Physical Functioning and Role Functioning represent greater functioning and better quality of life, whereas higher scores in Pain, Fatigue, and Disease Symptoms represent higher symptom burden. BL: baseline; C: cycle; d: dexamethasone; Isa: isatuximab; LS: least squares; P: pomalidomide.



Online Supplementary Figure S4. ICARIA-MM flow diagram. *Thrombocytopenia, dyspnea, and gastrointestinal pain. **Greater than 8 weeks between last contact and analysis cutoff date. ***Five patient decision to withdraw; one poor compliance to protocol; four principal investigator decision (one to switch treatment to daratumumab

plus pomalidomide plus dexamethasone; three discontinued because of increase in serum free light chain concentrations). ****Six patient decision to withdraw; one physician decision to withdraw the patient. d: dexamethasone; Isa: isatuximab; P: pomalidomide.