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

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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.

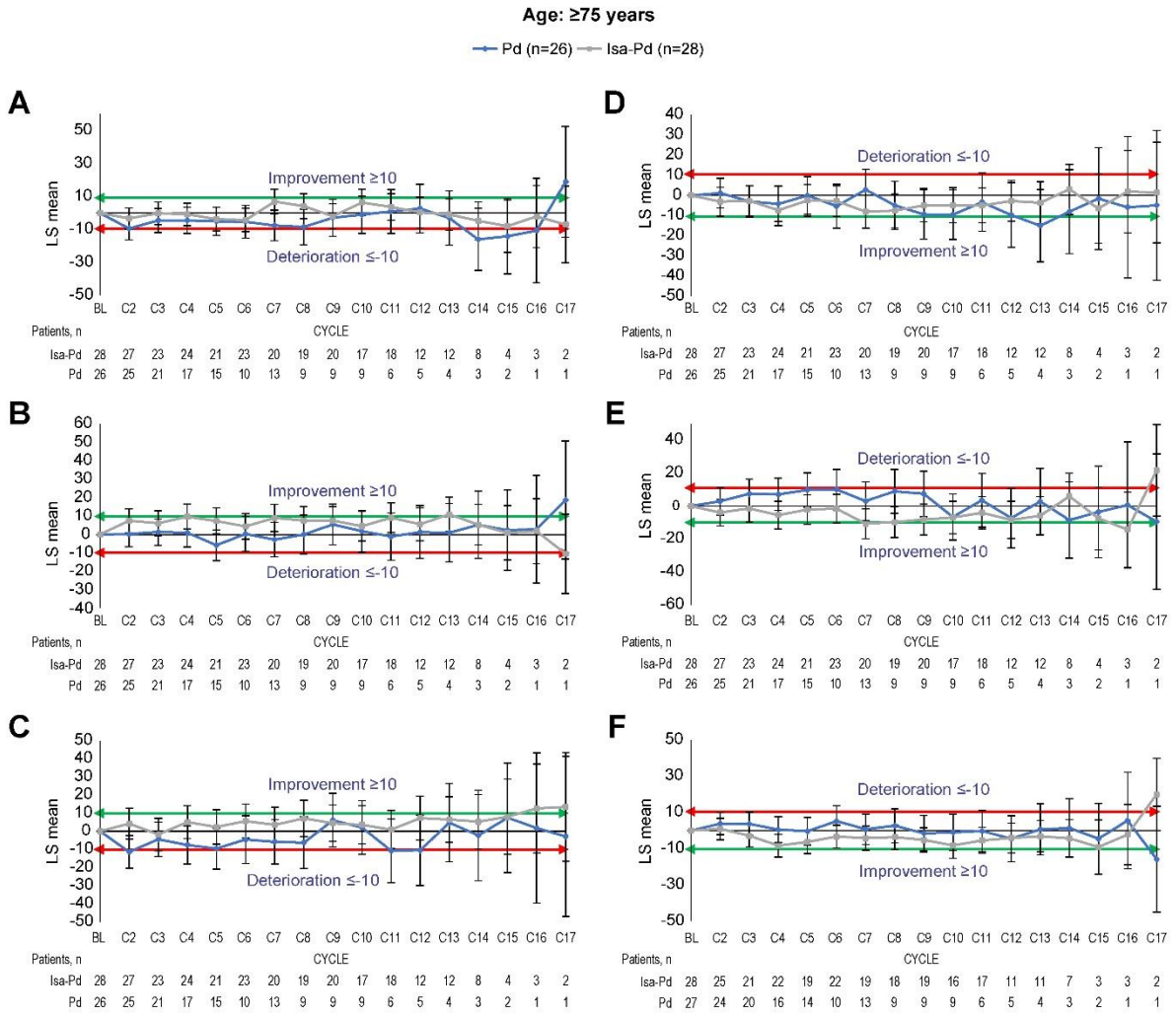
Grade 4 Thrombocytopenia, n (%)	Age ≥75 years		Age 65–74 years		Age <65 years	
	Isa-Pd (n=32)	Pd (n=28)	Isa-Pd (n=66)	Pd (n=53)	Isa-Pd (n=54)	Pd (n=68)
	6 (18.8)	3 (10.7)	13 (19.7)	9 (17.0)	6 (11.1)	10 (14.7)

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.

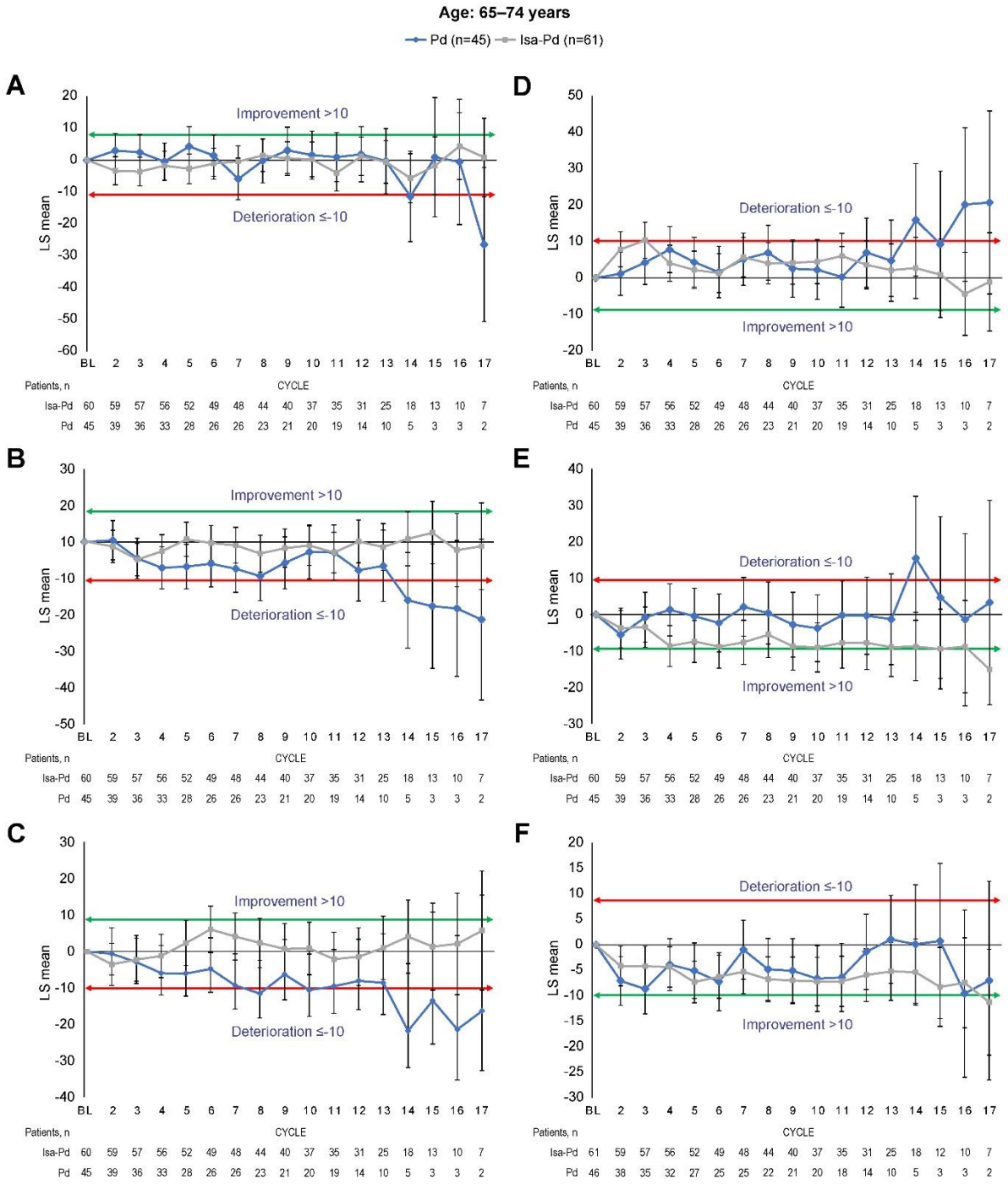
	≥75 years				65–74 years				<65 years			
	Isa-Pd (n=32)		Pd (n=28)		Isa-Pd (n=66)		Pd (n=53)		Isa-Pd (n=54)		Pd (n=68)	
Primary System Organ Class **Preferred Term, n (%)**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**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.



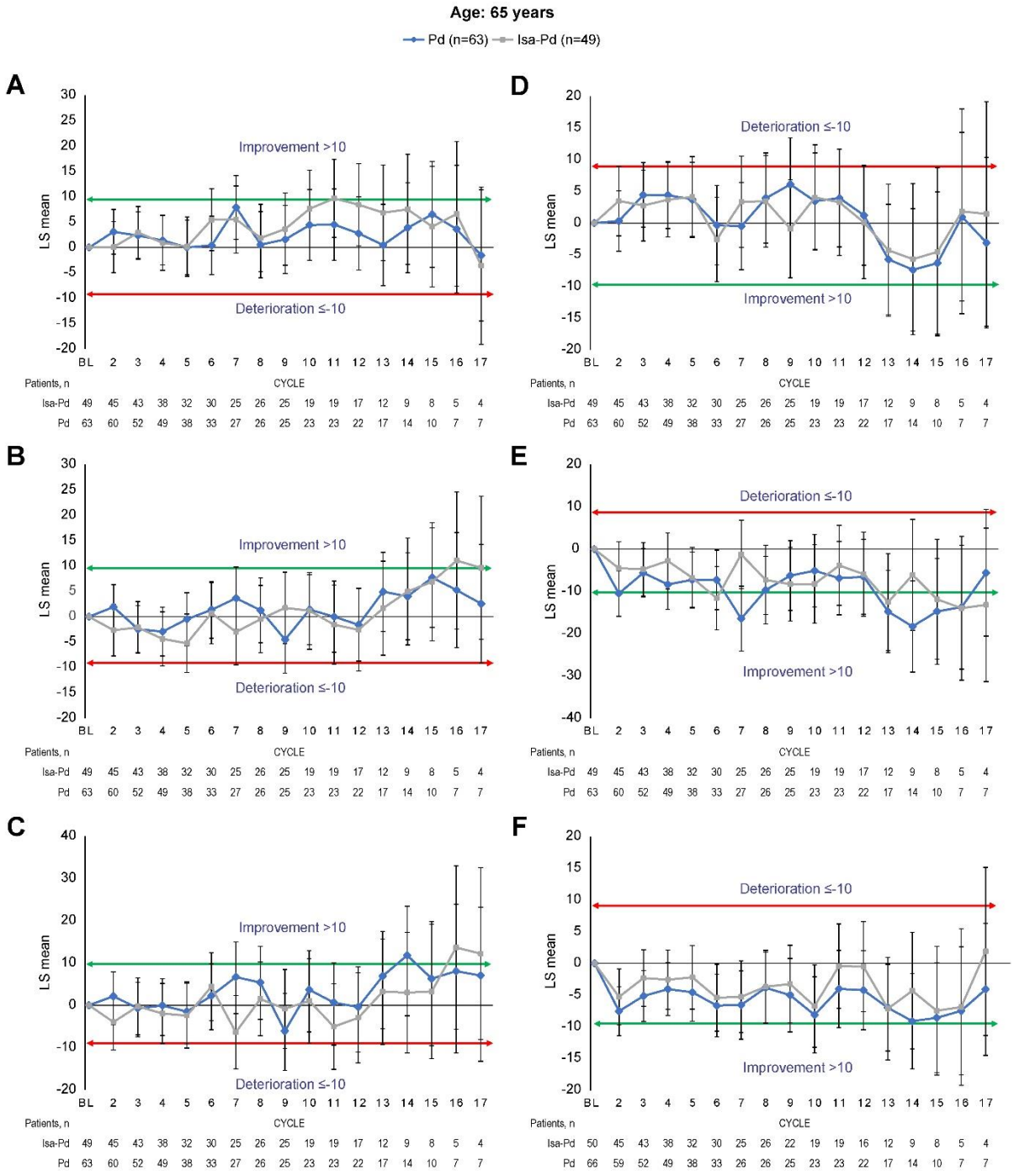
Online Supplementary Figure S1. Quality of life in the Isa-Pd and Pd arms in patients ≥75 years. Mean change from baseline for (A) Global Health Scale/Quality of Life, (B) Physical Functioning, (C) Role Functioning, (D) Fatigue, (E) C30 pain, and (F) MY20 Disease Symptoms (disease-specific pain). Graphs 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.



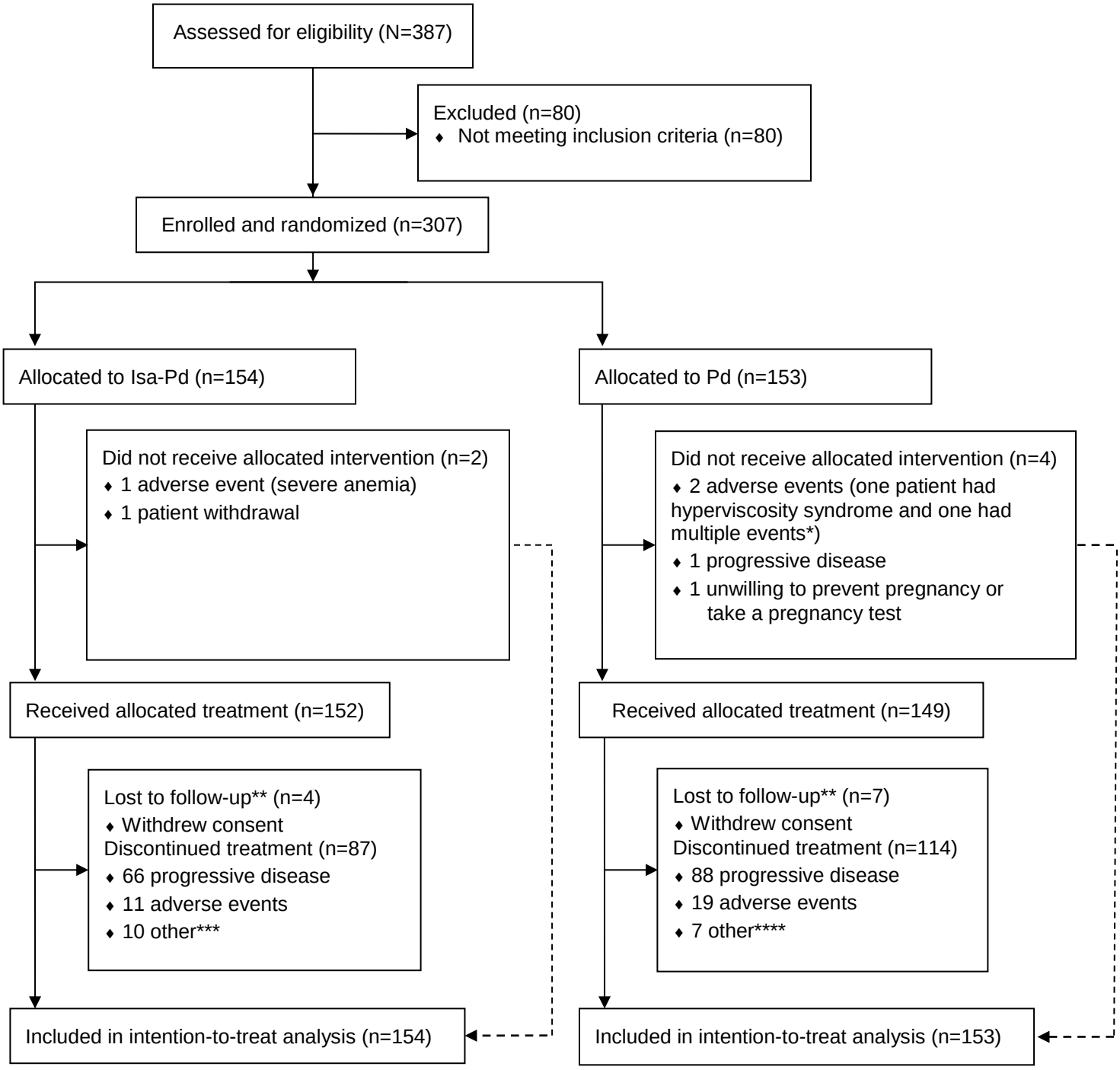
Online Supplementary Figure S2. Quality of life in the Isa-Pd and Pd arms in patients 65–74 years. (A) Mean change from baseline for Global Health Scale/Quality of Life, (B) Physical Functioning, (C) Role Functioning, (D) Fatigue, (E) C30 Pain, and (F) MY20 Disease Symptoms (disease-specific pain). Graphs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