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

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Received: October 4, 2023.
Accepted: January 24, 2024.
Early view: February 1, 2024.

https://doi.org/10.3324/haematol.2023.284325

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Supplementary methods

Please see the previously published ICARIA protocol for additional methodology details [1].

Study design and participants

Inclusion and exclusion criteria have been previously reported [1].

Eligible patients:

a) Aged 18 years or older or country's legal age of majority if the legal age was >18 years
b) Had documented diagnosis of multiple myeloma with evidence of measurable disease:
- Serum M-protein ≥0.5 g/dL measured using serum protein immunoelectrophoresis and/or
- Urine M-protein ≥200 mg/24 h measured using urine protein immunoelectrophoresis

c) Had received at least 2 previous lines of treatment, which included at least 2 consecutive cycles of lenalidomide and a proteasome inhibitor (PI) (bortezomib, carfilzomib, or ixazomib), given alone or in combination
d) Had failed therapy with lenalidomide and a PI given alone or in combination defined by any of the following (failure to lenalidomide and a PI may have occurred at any line of therapy):
- Progression had occurred while on or within 60 days from end of the treatment with lenalidomide and/or a PI
- In case of previous response ≥partial response to lenalidomide and/or a PI, patient had progressed within 6 months after discontinuation of the treatment
- Patients who had developed intolerable toxicity after a minimum of 2 consecutive cycles of a regimen containing lenalidomide and a PI alone or in combination. Intolerance was defined as below:
    1. For PI-containing regimens: Any toxicity leading to discontinuation of a PI, like ≥Grade 2 peripheral neuropathy or ≥Grade 2 neuropathic pain. Peripheral neuropathy must be ≤Grade 1 before study entry (according to National Cancer Institute Common Terminology for Adverse Events (v4.03)
    2. For lenalidomide-containing regimens: Any toxicity leading to discontinuation of lenalidomide, like Grade 3 rash. Rash could not be Grade 4 and other non-hematologic toxicities could not be Grade 4. All non-hematologic toxicities had to be ≤Grade 1 before study entry

e) Patients had to have progressed on or within 60 days after end of the previous therapy before study entry (i.e., refractory to the last line of treatment). This patient population included the following 2 categories:
- Refractory disease: Patients who were refractory to all previous lines of treatment but had achieved at least a minimal response in 1 previous line
- Relapsed and refractory disease: Patients who were relapsed from at least 1 previous line of treatment and refractory to the last line of treatment. Patients could have been refractory to other previous line/lines of treatment. Patients had to have achieved a minimal response or better to at least 1 of the previous lines of treatment (i.e., primary refractory disease was not eligible)

f) Patients had given voluntary written informed consent before performance of any study-related procedures not part of normal medical care, with the understanding that consent could have been withdrawn by the patient at any time without prejudice to his/her medical care

Exclusion criteria included:

a) Refractoriness to previous anti-CD38 monoclonal antibody therapy
b) Previous treatment with pomalidomide
c) Any anti-myeloma drug treatment within 14 days before randomization, including dexamethasone
d) Prior allogenic hematopoietic stem cell transplant with active graft vs. host disease any grade and/or were under immunosuppressive treatment within the last 2 months
e) Any major procedure within 14 days before the initiation of the study treatment: Plasmapheresis, major surgery (kyphoplasty was not considered a major procedure), radiotherapy
f) Patient who had received any other investigational drugs or prohibited therapy for this study within 28 days or 5 half-lives from randomization, whichever was longer
g) Eastern Cooperative Oncology Group Performance Status >2
h) Platelets <75 000 cells/μL if <50% of bone marrow nucleated cells were plasma cells and <30 000 cells/μL if ≥50% of bone marrow nucleated cells were plasma cells. Platelet transfusion was not allowed within 3 days before the screening hematological test
i) Absolute neutrophil count <1000 μ/L (1 × 109/L). The use of granulocyte colony stimulating factor was not allowed to reach this level
j) Creatinine clearance <30 mL/min (Modification of Diet in Renal Disease equation)
k) Total bilirubin >2× upper limit of normal
l) Corrected serum calcium >14 mg/dL (>3.5 mmol/L)
m) Aspartate aminotransferase and/or alanine aminotransferase >3× upper limit of normal
n) Significant cardiac dysfunction; myocardial infarction within 12 months; unstable, poorly controlled angina pectoris
o) Diagnosed or treated for another malignancy within 3 years prior to randomization with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy
p) Known to be human immunodeficiency virus positive or to have hepatitis A, B, or C active infection
q) Malabsorption syndrome or any condition that could have significantly impacted the absorption of pomalidomide
r) Active primary amyloid-light amyloidosis (evidence of end organ damage or receiving treatment for amyloidosis)
s) Concomitant plasma cell leukemia
t) Any severe acute or chronic medical condition that would have impaired the ability of the patient to participate in the study or interfered with interpretation of study results (e.g., systemic infection unless specific anti-infective therapy was employed) or patient was unable to comply with the study procedures

Procedures

In the isatuximab–pomalidomide–dexamethasone (Isa-Pd) arm, patients received isatuximab 10 mg/kg intravenously (days 1, 8, 15, and 22 of the first 28-day cycle; days 1 and 15 of subsequent cycles), combined with the approved dosing and schedules of pomalidomide 4 mg orally (days 1–21 of each cycle) and dexamethasone 40 mg (20 mg for patients ≥75 years of age) orally or intravenously (days 1, 8, 15, and 22 of each cycle). For isatuximab infusions, patients were pre-medicated with an H2 blocker, diphenhydramine (25–50 mg or equivalent), and paracetamol (650–1000 mg). A single administration of dexamethasone (intravenous or oral) was used for study treatment and pre-medication. For patients who did not experience an infusion reaction to any of the first 4 isatuximab administrations, pre-medication could be discontinued at the investigator's discretion. No post-infusion bronchodilator or corticosteroid

prophylaxis was required following isatuximab infusion. In the pomalidomide–dexamethasone (Pd) arm, patients received pomalidomide and dexamethasone according to the same schedule as the Isa-Pd arm. All patients received thromboprophylaxis with low-molecular-weight heparin or aspirin. Therapy continued until disease progression, unacceptable toxicity, or withdrawal of consent. Dose adjustments (and reductions for pomalidomide and dexamethasone) were permitted for adverse reactions in both arms, but isatuximab dose reductions were not allowed.

Patients discontinued if they withdrew consent; if, in the investigator's opinion, continuation of the study treatment would be detrimental to the patient's well-being (such as disease progression, unacceptable adverse event, poor compliance to the study protocol, or any other reason that prevented further administration of study treatment); or if the patient was lost to follow-up. For patients who progressed on study treatment, subsequent therapy decisions were at the investigator's discretion.

Primary and secondary efficacy assessments were undertaken on day 1 of each treatment cycle, unless otherwise specified:

- Serum and 24-h urine M-protein quantification by local and central laboratory. At screening and at cycle 1, day 1 (if applicable), immunoelectrophoresis and immunofixation were done. After cycle 1, day 1, immunofixation was done in case of undetectable M-protein (serum and urine). If urine M-protein was not measurable at cycle 1, its qualification was performed every 3 cycles and to confirm complete response
- Free light chain quantification by local laboratory; free light chain quantitation performed by central laboratory to confirm complete response
- Quantitative immunoglobulins (local and central laboratory)
- Bone marrow aspiration (or biopsy as clinically indicated) at baseline for disease assessment (local laboratory) and cytogenetic abnormality analysis (central laboratory), and then to confirm complete response (local laboratory):
    - Cytogenetics were assessed during screening by a central laboratory by fluorescence in situ hybridization testing of purified CD138+ plasma cells and results reported with a cutoff of 50% for del(17p) and 30% for t(4;14) or t(14;16). These cutoff values correspond to prognostic thresholds, which are more stringent than positivity thresholds. High-risk cytogenetic status was defined as del(17p), t(4;14), or t(14;16)
- Bone disease assessment:
    - Skeletal survey (including skull, spine, all long bones, pelvis, and chest) or low-dose whole-body computed tomography scan at baseline, then once a year and anytime during the study if clinically indicated
- Extramedullary disease (plasmacytoma) assessment:
    - If known or documented extramedullary disease (plasmacytoma) at baseline, computed tomography scan or magnetic resonance imaging was done at baseline and repeated every 12 weeks (±1 week) and if clinically indicated
    - If no previous positive image for extramedullary disease, computed tomography scan, or magnetic resonance imaging was done in case of suspicion of progression or if clinically indicated

Safety assessments were performed throughout study treatment (at each visit on days 1, 8, 15, and 22 of cycle 1; days 1 and 15 of subsequent cycles; and at 30 days after last treatment administration). Following 30 days of follow-up, ongoing treatment-related adverse events (AEs), all ongoing serious AEs (regardless of the relationship with study treatment), and all new related AEs (regardless of seriousness),

were followed up until resolution or stabilization. Patients who discontinued study treatment without progressive disease were followed monthly for safety and efficacy until disease progression was confirmed. Patients with progressive disease were followed every 3 months until death. AEs were qualified and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

In addition to efficacy and safety data, details of subsequent anti-myeloma therapy and second primary malignancies were collected.

Protocol

There have been no major deviations of the protocol since the publication of the updated analysis and no additional protocol updates [2].

Definitions

Intent-to-treat population: All patients with a signed informed consent and who were allocated a randomization number by the interactive response technology, regardless of whether the patient was treated

Non-progressive disease: Defined as having M-protein below the level of eligibility at baseline, not meeting the criteria for progressive disease or complete response

Overall response rate (ORR): Defined as the proportion of patients with a complete response, stringent complete response, partial response, and very good partial response (as assessed by the investigator for this second interim analysis)

Overall survival (OS): Defined as the time from the date of randomization to the date of death from any cause

Progression-free survival (PFS): Defined as the time from the date of randomization to the date of first documentation of progressive disease (as reported by the investigator), or the date of death from any cause, whichever occurred first

PFS on first line of subsequent therapy: Defined as the time from the start date of the first line of subsequent therapy to the date of the first documentation of progressive disease (as reported by the investigator) after initiation of the first line of subsequent therapy or death from any cause, whichever happened first. If the first line of subsequent therapy included daratumumab, the start date of the first line of subsequent therapy was defined as the start date of daratumumab

PFS2: Defined as the time from the date of randomization to the date of the first documentation of progressive disease (as reported by the investigator) after initiation of subsequent anti-myeloma treatment or death from any cause, whichever happened first

Poor prognosis: Includes patients in all the following groups: patients aged ≥75 years, patients who have received >3 prior lines of therapy, patients with renal function <60 mL/min/1.73 m^2, patients with International Staging System Stage III and revised International Staging System Stage III at study entry, and patients with high-risk cytogenetics

Prior treatment failure: Defined as meeting 1 of the following:

1. Progression while on or within 60 days from the end of treatment with lenalidomide and/or a proteasome inhibitor (PI)
2. If the previous response is at least a partial response to lenalidomide and/or a PI, the patient must have progressed within 6 months after discontinuation of treatment
3. Patients who develop intolerable toxicity after a minimum of 2 consecutive cycles of a regimen containing lenalidomide and a PI (bortezomib, carfilzomib, ixazomib) alone or in combination. Intolerance was defined as:
    a. PI-containing regimens: Any toxicity leading to discontinuation of a PI (e.g., Grade ≥2 peripheral neuropathy or neuropathic pain). Peripheral neuropathy must be Grade ≤1 before study entry (according to the US National Institute of Cancer Common Terminology Criteria for Adverse Events v4.03)
    b. Lenalidomide-containing regimens: Any toxicity leading to discontinuation of lenalidomide (e.g., Grade 3 rash). Rash and any other non-hematologic adverse events

must not have been Grade 4 at any time. All non-hematologic adverse events must be Grade ≤1 before study entry

Safety population: Includes patients from the intent-to-treat population who actually received at least 1 dose or part of a dose of the study treatments

Stable disease: Defined as not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease. Two consecutive assessments were required

Time to next treatment (TTNT): Defined as the time from randomization to the start of subsequent anti-myeloma treatment

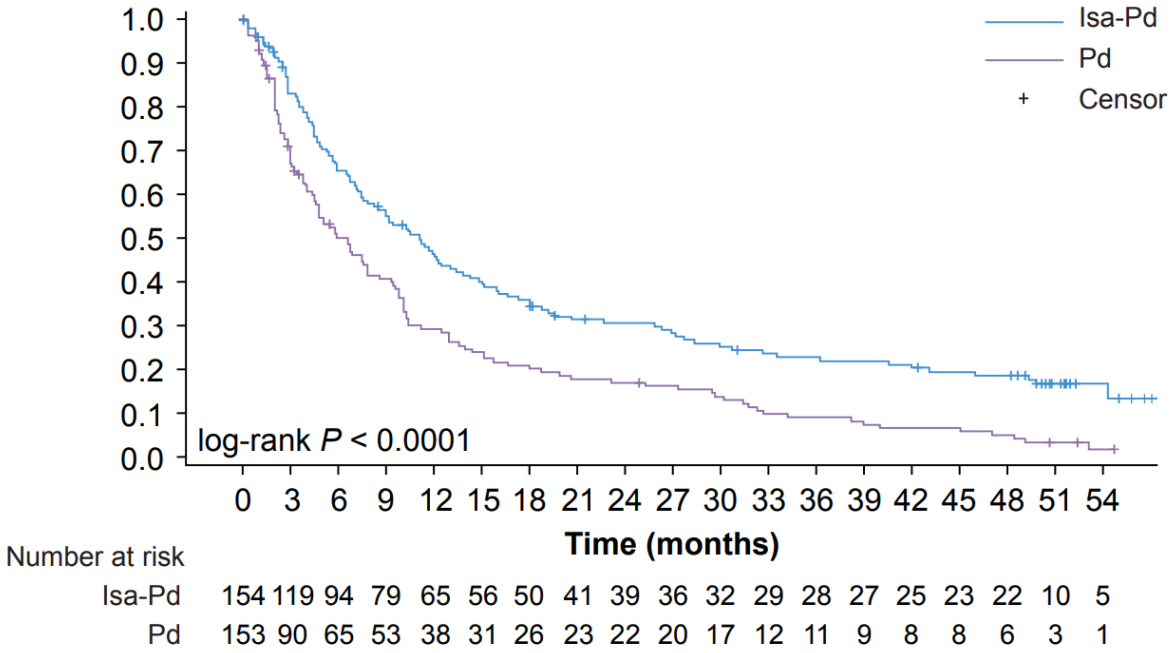
Supplementary results

Supplementary Table 1. Exposure to study treatments (safety population).

	Isa-Pd (*n* = 152)	**Pd (*n* = 149)**
Treatment duration, weeks	47.57 (1.3–245.6)	24.0 (1–241.6)
Number of cycles started per patient	11 (1–59)	6 (1–58)
Relative dose intensity, %		
Isatuximab	91.28 (19.7–111.1)	NA
Pomalidomide	81.39 (22.9–103.7)	91.29 (37.2–118.5)
Dexamethasone	83.67 (13.6–130.0)	95.63 (30.3–300.0)
Pomalidomide dose reductions		
≥1 dose reduction	70 (46.1)	40 (26.8)
≥2 dose reductions	28 (18.4)	10 (6.7)
≥3 dose reductions	9 (5.9)	0
Pomalidomide dose intensity, mg/week	17.09 (4.8–21.8)	19.17 (7.8–24.9)
Dexamethasone dose reductions	62 (40.8)	45 (30.2)

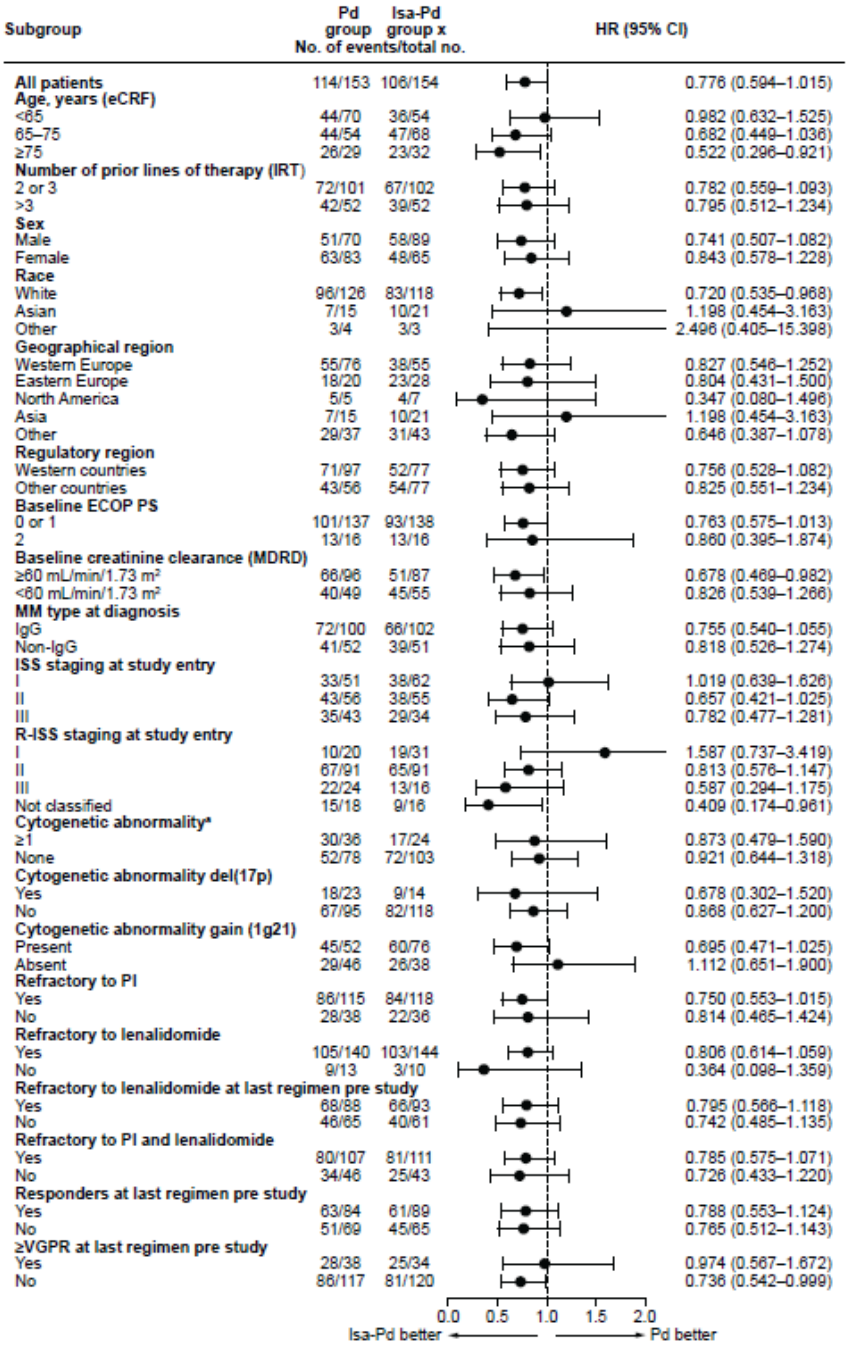
Isa-Pd isatuximab–pomalidomide–dexamethasone, *NA* not applicable, *Pd* pomalidomide–dexamethasone. Data are median (range) or *n* (%).

Supplementary Figure 1. Investigator-assessed PFS (intention-to-treat population).



Kaplan–Meier analysis of PFS, based on disease assessment by investigators and ignoring symptomatic deterioration. Patients who did not experience a PFS event before the cutoff date or the date of initiation of subsequent anti-myeloma treatment were censored. Median follow-up was 52.4 months. One-sided *P* value is from 1-sided log rank test stratified by age and number of previous lines of therapy. *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *Pd* pomalidomide–dexamethasone, *PFS* progression-free survival.

Supplementary Figure 2. Subgroup analysis of OS (intention-to-treat population).



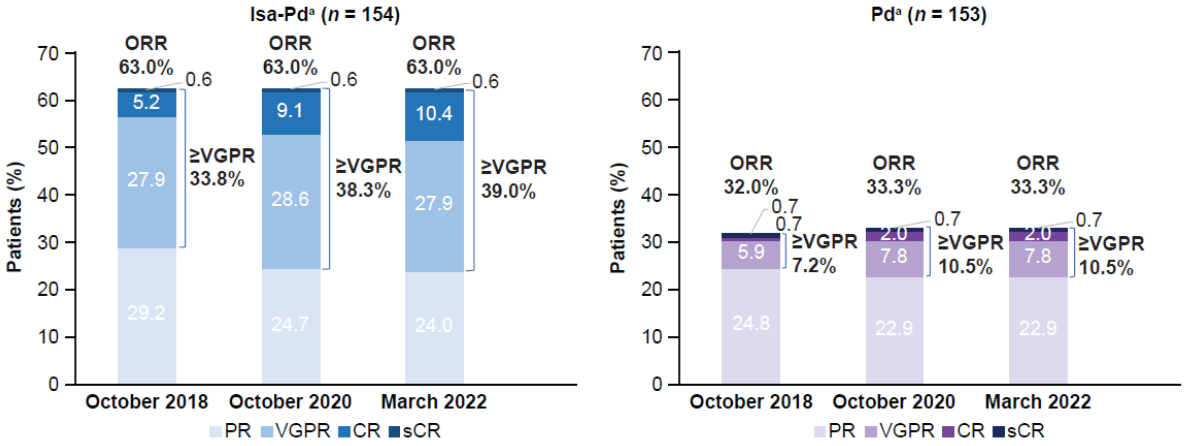
CI confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *eCRF* electronic case report form, *HR* hazard ratio, *IgG* immunoglobulin G, *IRT* interactive response technology, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *ISS* International Staging System, *MDRD* Modification of Diet in Renal Disease, *MM* multiple myeloma, *OS* overall survival, *Pd* pomalidomide–dexamethasone, *PI* proteasome inhibitor, *R-ISS* revised International Staging System.
[a]Cytogenetics by central laboratory cutoffs of 30% for t(4;14) and t(14;16) and 50% for del(17p). Cutoff date January 27, 2022.

Supplementary Table 2. Investigator-assessed response to therapy (intention-to-treat population).

	Isa-Pd (*n* = 154)	**Pd (*n* = 153)**
Best overall response		
sCR	1 (<1)	1 (<1)
CR[a]	16 (10)	3 (2)
VGPR	43 (28)	12 (8)
PR	37 (24)	35 (23)
MR	9 (6)	19 (12)
Stable disease	33 (21)	51 (33)
Non-progressive disease	0	0
Progressive disease	8 (5)	15 (10)
Unconfirmed progressive disease	2 (1)	4 (3)
Not evaluable/not assessed	5 (3)	13 (8)
Overall response		
Responders (sCR, CR[a], VGPR, or PR)	97 (63)	51 (33)
95% CI[b]	55–71	26–41
VGPR or better	60 (39)	16 (10)
95% CI[b]	31–47	6–16
Clinical benefit		
Responders (MR or better)	106 (69)	70 (46)
95% CI[b]	61–76	38–54

CI confidence interval, *CR* complete response, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *MR* minimal response, *Pd* pomalidomide–dexamethasone, *PR* partial response, *sCR* stringent complete response, *VGPR* very good partial response.
Data are *n* (%) unless otherwise specified.
[a]Data not adjusted for isatuximab interference in M-protein measurement by serum immunofixation.
[b]Estimated using Clopper–Pearson method.

Supplementary Figure 3. Response to therapy, as assessed by the investigator at the time of the primary analysis, second interim analysis, and final analysis (intention-to-treat population).



CR complete response, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *ORR* overall response rate, *Pd* pomalidomide–dexamethasone, *PR* partial response, *sCR* stringent complete response, *VGPR* very good partial response.

Responses were assessed by the investigator.

[a]Data not adjusted for isatuximab interference in M-protein measurement by serum immunofixation.

Supplementary Table 3. Subsequent therapy anti-myeloma treatments in any subsequent line of therapy (intention-to-treat population).

	Isa-Pd (*n* = 154)	**Pd (*n* = 153)**
Any further anti-myeloma treatment[a]	102 (66.2)	119 (77.8)
Number of further regimens	2.0 (1–8)	1.0 (1–8)
Number of further regimens		
1	46 (45.1)	60 (50.4)
2	18 (17.6)	25 (21.0)
≥3	38 (37.3)	34 (28.6)
Main further anti-myeloma treatments[b]		
Alkylating agents	71 (69.6)	57 (47.9)
Proteasome inhibitors	70 (68.6)	69 (58.0)
Immunomodulatory agents	34 (33.3)	39 (32.8)
Lenalidomide	16 (15.7)	15 (12.6)
Pomalidomide	18 (17.6)	20 (16.8)
Thalidomide	6 (5.9)	7 (5.9)
HDAC inhibitors	4 (3.9)	5 (4.2)
Anthracyclins	8 (7.8)	11 (9.2)
Corticosteroids	88 (86.3)	94 (79.0)
Monoclonal antibodies	28 (27.5)	75 (63.0)
Daratumumab	23 (22.5)	71 (59.7)
Vinca alkaloids	2 (2.0)	3 (2.5)
Anti-BCMA	7 (6.9)	5 (4.2)
Other	36 (35.3)	24 (20.2)
CAR T cells NOS	1 (1.0)	2 (1.7)
Investigational anti-neoplastic drugs	6 (5.9)	3 (2.5)
Stem cells NOS	6 (5.9)	3 (2.5)
Cisplatin	7 (6.9)	2 (1.7)
Etoposide	10 (9.8)	3 (2.5)
Selinexor	6 (5.9)	6 (5.0)
Venetoclax	6 (5.9)	4 (3.4)

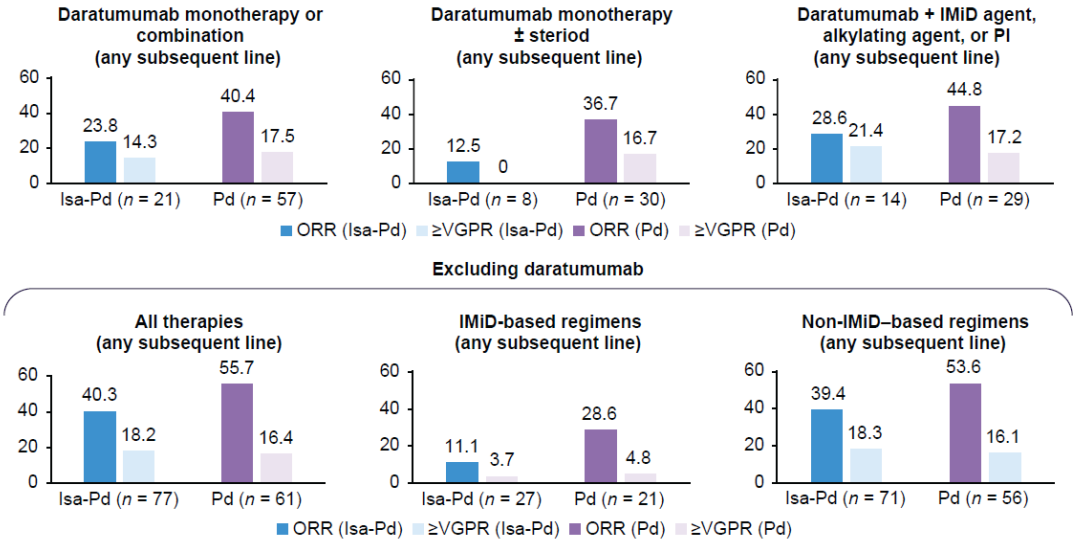
BCMA B-cell maturation antigen, *CAR* chimeric antigen receptor, *HDAC* histone deacetylase, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *NOS* not otherwise specified, *Pd* pomalidomide–dexamethasone.

Data are *n* (%) or median (range).

[a]Calculated out of 154 (Isa-Pd) and 153 (Pd) patients. All other calculations based on patients receiving further anti-myeloma treatment in the Isa-Pd (*n* = 102) and Pd (*n* = 119) arms.

[b]Main subsequent anti-myeloma therapy was chosen by investigators, based on currently available therapy, which could be standard of care of experimental agents in clinical studies. There were no protocol specifications or restrictions in the choice of subsequent therapy.

Supplementary Figure 4. Response rate on selected subsequent anti-myeloma drug combinations in any subsequent line (intention-to-treat population).



IMiD immunomodulatory agent, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *ORR* overall response rate, *Pd* pomalidomide–dexamethasone, *PI* proteasome inhibitor, *≥VGPR* very good partial response or better.

Sensitivity analyses to estimate the overall survival treatment effect in the absence of subsequent daratumumab therapy

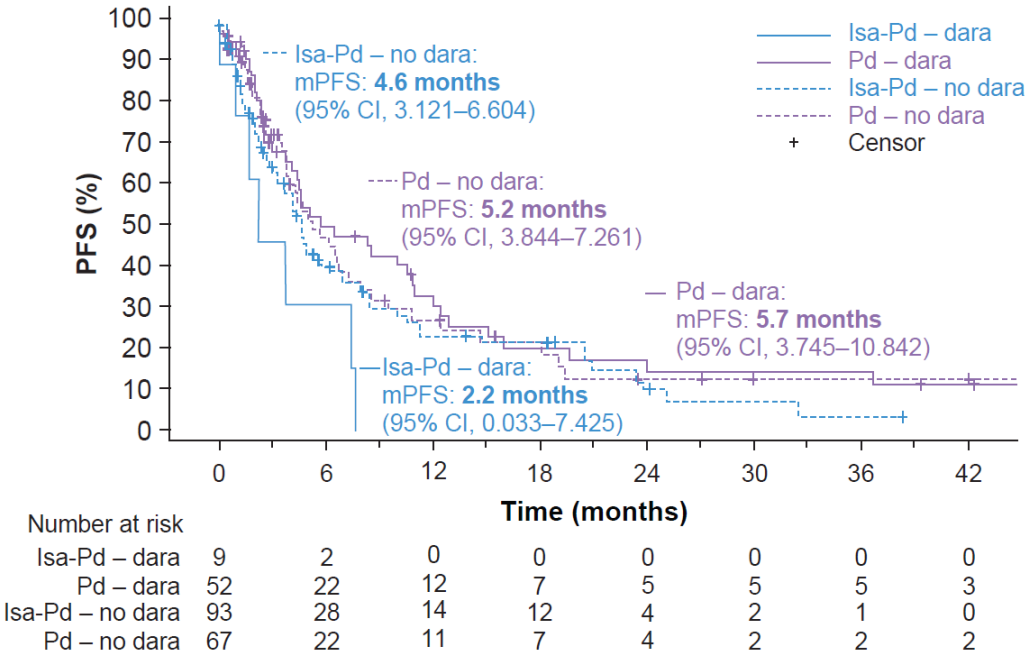
Rank-preserving structural failure time analysis

In the rank-preserving structural failure time method, a multiplicative factor is used to estimate the gain or loss in survival time from switching to daratumumab; the survival duration of patients is then reconstructed and re-censored as if they had never received daratumumab. The stratified hazard ratio from the rank-preserving structural failure time analysis was 0.706 (95% confidence interval, 0.538–0.926), which is slightly better than the intention-to-treat estimate of 0.776 (95% confidence interval, 0.594–1.015). This method makes the strong assumption of a constant treatment effect over time.

Sensitivity analyses to estimate impact of death due to coronavirus disease 2019 infection

There were 52 (34%) patients censored in the isatuximab group and 39 (26%) patients censored in the control arm. There were 4 reported deaths due to coronavirus disease 2019 infection, all in the isatuximab group. The stratified hazard ratio was 0.759 (95% confidence interval, 0.580–0.994), which is slightly better than the intention-to-treat estimate of 0.776 (95% confidence interval, 0.594–1.015).

Supplementary Figure 5. PFS on first subsequent therapy (intention-to-treat population).



Kaplan–Meier analysis of PFS on first subsequent therapy as assessed by investigators at a median follow-up time of 52.4 months. Patients who did not experience a PFS event on first subsequent therapy were censored. *CI* confidence interval, *Dara* daratumumab, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, m*PFS* median progression-free survival, *Pd* pomalidomide–dexamethasone, *PFS* progression-free survival.

Supplementary Table 4. Updated overall safety summary (safety population).

	Isa-Pd (*n* = 152)	**Pd (*n* = 149)**
Any TEAE	151 (99)	146 (98)
Any Grade ≥3 TEAE	138 (91)	113 (76)
Any treatment-related[a] Grade ≥3 TEAE	115 (76)	75 (50)
Any Grade 5 TEAE[b]	15 (10)	16 (11)
Any treatment-emergent SAE[c]	112 (74)	91 (61)
Any TEAE leading to definitive treatment discontinuation	19 (13)	22 (15)

COVID-19 coronavirus disease 2019, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *Pd* pomalidomide–dexamethasone, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event. Data are *n* (%).

[a]Treatment-related TEAEs are TEAEs related to at least 1 drug of the combination.

[b]TEAEs with a fatal outcome during the treatment period, including disease progression (*n* = 6), COVID-19 pneumonia (*n* = 1), influenzal pneumonia (*n* = 1), sepsis (*n* = 1), metastatic malignant melanoma (*n* = 1), cerebellar infarction (*n* = 1), arteriosclerosis coronary artery (*n* = 1), hepatic failure (*n* = 1), death (*n* = 2), and multiple organ dysfunction syndrome (*n* = 1) with Isa-Pd; disease progression (*n* = 5), sepsis (*n* = 1), COVID-19 (*n* = 1), pneumonia (*n* = 1), septic shock (*n* = 2), urinary tract infection (*n* = 1), intracranial hemorrhage (*n* = 1), myocardial infarction (*n* = 1), death (*n* = 1), and sudden death (*n* = 1) with Pd.

[c]When adjusted for difference in exposure, the event rate per patient-year was 1.04 in the Isa-Pd group and 0.95 in the control group (data not shown).

Safety

The rates of thrombocytopenia and neutropenia based on laboratory result analysis were similar between groups, although Grade 3–4 events were slightly more common with isatuximab–pomalidomide–dexamethasone (Isa-Pd) than with pomalidomide–dexamethasone (Pd; Supplementary Table 10). Granulocyte colony stimulating factor was used in 109/152 (72%) patients in the Isa-Pd group and in 82/149 (55%) in the control group (data not shown).

Second primary malignancies were observed during treatment or the post-treatment period in 10/152 (7%) patients in the Isa-Pd arm and 3/149 (2%) patients in the Pd arm. In the Isa-Pd arm, there were 6/152 (4%) patients with skin cancer, 3/152 (2%) patients with non-skin solid tumors (one of whom also had reported skin cancer), and 1/152 (<1%) patient with a hematological malignancy (myelodysplastic syndrome; data not shown). In the Pd arm, 3/149 (2%) patients had skin cancer.

Supplementary Table 5. TEAEs (all grades) in ≥10% of patients and ≥5% higher in the isatuximab group by primary system organ class and preferred term (safety population).

	Isa-Pd (*n* = 152)	**Pd (*n* = 149)**
Infections and infestations	126 (83)	103 (69)
Bronchitis	41 (27)	17 (11)
Upper respiratory tract infection[a]	79 (52)	52 (35)
Pneumonia[b]	55 (36)	45 (30)
Blood and lymphatic system disorders	97 (64)	68 (46)
Febrile neutropenia	18 (12)	5 (3)
Neutropenia	79 (52)	54 (36)
Metabolism and nutrition disorders	37 (24)	22 (15)
Decreased appetite	18 (12)	8 (5)
Respiratory, thoracic, and mediastinal disorders	69 (45)	50 (34)
Dyspnea[c]	29 (19)	18 (12)
Gastrointestinal disorders	86 (57)	81 (54)
Diarrhea	48 (32)	33 (22)
Nausea	24 (16)	14 (9)
Vomiting	20 (13)	6 (4)
General disorders and administration site conditions	91 (60)	91 (61)
Edema peripheral	30 (20)	18 (12)

CMQ Company MedDRA Query, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *MedDRA* Medical Dictionary for Regulatory Activities, *Pd* pomalidomide–dexamethasone, *SMQ* Standardized MedDRA Query, *TEAE* treatment-emergent adverse event.

Data are *n* (%) of patients.

[a]The selection of preferred terms is based on CMQ 'Upper respiratory tract infections'.

[b]Pneumonia includes TEAEs in the narrow SMQ Infective pneumonia.

[c]Dyspnea includes Dyspnea, Dyspnea exertional, Dyspnea at rest.

Supplementary Table 6. Most common TEAEs of Grade ≥3 (in ≥5% of patients in either arm) by preferred term (safety population).

	Isa-Pd (*n* = 152)	**Pd (*n* = 149)**
Neutropenia	77 (51)	52 (35)
Pneumonia	35 (23)	31 (21)
Thrombocytopenia	20 (13)	18 (12)
Febrile neutropenia	18 (12)	5 (3)
Disease progression	10 (7)	9 (6)
Lower respiratory tract infection	8 (5)	4 (3)
Urinary tract infection	8 (5)	2 (1)
Bronchitis	8 (5)	1 (<1)

Isa-Pd isatuximab–pomalidomide–dexamethasone, *Pd* pomalidomide–dexamethasone, *TEAE* treatment-emergent adverse event.
Data are *n* (%) of patients.

Supplementary Table 7. TEAEs in 5% or more patients in any group by primary system organ class and preferred term (safety population).

	Isa-Pd (*n* = 152)		**Pd (*n* = 149)**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any class	151 (99)	138 (91)	146 (98)	113 (76)
Infections and infestations	126 (83)	80 (53)	103 (69)	57 (38)
Bronchitis	41 (27)	8 (5)	17 (11)	1 (<1)
Gastroenteritis	7 (5)	2 (1)	5 (3)	1 (<1)
Influenza	12 (8)	5 (3)	8 (5)	1 (<1)
Lower respiratory tract infection	12 (8)	8 (5)	9 (6)	4 (3)
Nasopharyngitis	23 (15)	0	10 (7)	0
Oral herpes	10 (7)	0	3 (2)	0
Pneumonia	42 (28)	35 (23)	38 (26)	31 (21)
Respiratory tract infection	8 (5)	2 (1)	7 (5)	2 (1)
Upper respiratory tract infection	54 (36)	5 (3)	31 (21)	4 (3)
Urinary tract infection	19 (13)	8 (5)	14 (9)	2 (1)
Blood and lymphatic system disorders	97 (64)	95 (63)	68 (46)	63 (42)
Anemia	8 (5)	7 (5)	2 (1)	1 (<1)
Febrile neutropenia	18 (12)	18 (12)	5 (3)	5 (3)
Neutropenia	79 (52)	77 (51)	54 (36)	52 (35)
Thrombocytopenia	21 (14)	20 (13)	18 (12)	18 (12)
Metabolism and nutrition disorders	37 (24)	15 (10)	22 (15)	8 (5)
Decreased appetite	18 (12)	2 (1)	8 (5)	1 (<1)
Psychiatric disorders	31 (20)	6 (4)	33 (22)	6 (4)
Confusional state	7 (5)	1 (<1)	5 (3)	1 (<1)
Insomnia	15 (10)	2 (1)	14 (9)	3 (2)
Nervous system disorders	68 (45)	14 (9)	49 (33)	10 (7)
Dizziness	10 (7)	0	5 (3)	0
Headache	16 (11)	1 (<1)	9 (6)	0
Peripheral sensory neuropathy	18 (12)	1 (<1)	11 (7)	0
Tremor	13 (9)	3 (2)	7 (5)	1 (<1)
Eye disorders	24 (16)	7 (5)	21 (14)	6 (4)
Cataract	15 (10)	7 (5)	11 (7)	4 (3)
Cardiac disorders	34 (22)	12 (8)	9 (6)	5 (3)
Atrial fibrillation	10 (7)	3 (2)	3 (2)	1 (<1)
Vascular disorders	28 (18)	7 (5)	19 (13)	7 (5)
Hypertension	11 (7)	5 (3)	8 (5)	3 (2)
Hypotension	7 (5)	1 (<1)	3 (2)	2 (1)
Respiratory, thoracic, and mediastinal disorders	69 (45)	14 (9)	50 (33)	10 (7)
Cough	14 (9)	0	12 (8)	1 (<1)
Dyspnea	25 (16)	7 (5)	15 (10)	2 (1)
Oropharyngeal pain	12 (8)	0	4 (3)	0
Productive cough	8 (5)	0	3 (2)	0

	Isa-Pd (*n* = 152)		Pd (*n* = 149)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Gastrointestinal disorders	86 (57)	13 (9)	81 (54)	5 (3)
Abdominal distension	7 (5)	0	3 (2)	0
Abdominal pain	8 (5)	0	6 (4)	0
Constipation	27 (18)	0	30 (20)	0
Diarrhea	48 (32)	3 (2)	33 (22)	2 (1)
Nausea	24 (16)	0	14 (9)	0
Stomatitis	10 (7)	1 (<1)	4 (3)	0
Vomiting	20 (13)	2 (1)	6 (4)	0
Skin and subcutaneous tissue disorders	50 (33)	3 (2)	37 (25)	1 (<1)
Pruritus	9 (6)	0	11 (7)	0
Rash	11 (7)	0	8 (5)	0
Musculoskeletal and connective tissue disorders	97 (64)	16 (11)	78 (52)	9 (6)
Arthralgia	22 (15)	3 (2)	20 (13)	1 (<1)
Back pain	30 (20)	4 (3)	25 (17)	2 (1)
Bone pain	13 (9)	2 (1)	13 (9)	2 (1)
Muscle spasms	17 (11)	1 (<1)	16 (11)	0
Muscular weakness	14 (9)	1 (<1)	8 (5)	0
Musculoskeletal chest pain	15 (10)	0	7 (5)	0
Myalgia	12 (8)	0	5 (3)	0
Pain in extremity	12 (8)	0	5 (3)	0
Pathological fracture	13 (9)	5 (3)	9 (6)	4 (3)
Renal and urinary disorders	22 (15)	10 (7)	23 (15)	12 (8)
Acute kidney injury	9 (6)	4 (3)	8 (5)	6 (4)
General disorders and administration site conditions	91 (60)	29 (19)	91 (61)	20 (13)
Asthenia	24 (16)	5 (3)	29 (20)	4 (3)
Disease progression	10 (7)	10 (7)	9 (6)	9 (6)
Fatigue	30 (20)	6 (4)	32 (22)	0
Influenza like illness	8 (5)	1 (<1)	5 (3)	0
Edema peripheral	30 (20)	2 (1)	18 (12)	0
Peripheral swelling	7 (5)	2 (1)	0	0
Pyrexia	25 (16)	4 (3)	21 (14)	2 (1)
Investigations	22 (15)	5 (3)	15 (10)	4 (3)
Weight decreased	10 (7)	0	2 (1)	0
Injury, poisoning and procedural complications	77 (51)	9 (6)	19 (13)	3 (2)
Fall	12 (8)	0	9 (6)	1 (<1)
Infusion reaction	57 (38)	4 (3)	2 (1)	0

Isa-Pd isatuximab–pomalidomide–dexamethasone, *Pd* pomalidomide–dexamethasone, *TEAE* treatment-emergent adverse event.
Data are *n* (%) of patients.

Supplementary Table 8. Hematologic laboratory abnormalities (safety population with at least 1 post-baseline assessment).

	Isa-Pd (*n* = 152)			**Pd (*n* = 147)**		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Neutropenia	146 (96)	33 (22)	96 (63)	138 (94)	57 (39)	48 (33)
Thrombocytopenia	128 (84)	23 (15)	29 (19)	119 (81)	15 (10)	22 (15)
Anemia	152 (100)	53 (35)	0	145 (99)	42 (29)	0

Isa-Pd isatuximab–pomalidomide–dexamethasone, *Pd* pomalidomide–dexamethasone.
Data are *n* (%) of patients.

Supplementary Table 9. Treatment-emergent SAEs with an incidence ≥2% in any treatment group by primary system organ class and preferred term (safety population).

	Isa-Pd (*n* = 152)		**Pd (*n* = 149)**	
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Any class	112 (74)	107 (70)	91 (61)	82 (55)
Infections and infestations	76 (50)	72 (47)	56 (38)	53 (36)
Pneumonia	35 (23)	32 (21)	31 (21)	29 (20)
Bronchitis	7 (5)	7 (5)	1 (<1)	1 (<1)
Lower respiratory tract infection	7 (5)	7 (5)	3 (2)	3 (2)
Urinary tract infection	7 (5)	7 (5)	2 (1)	2 (1)
Pneumonia bacterial	5 (3)	5 (3)	1 (<1)	1 (<1)
Influenza	4 (3)	4 (3)	2 (1)	1 (<1)
Pneumocystis jirovecii pneumonia	4 (3)	4 (3)	5 (3)	5 (3)
Sepsis	4 (3)	4 (3)	2 (1)	2 (1)
Septic shock	1 (<1)	1 (<1)	4 (3)	4 (3)
Upper respiratory tract infection	1 (<1)	1 (<1)	5 (3)	4 (3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	7 (5)	6 (4)	2 (1)	1 (<1)
Squamous cell carcinoma of skin	4 (3)	2 (1)	0	0
Blood and lymphatic system disorders	19 (13)	19 (13)	12 (8)	11 (7)
Febrile neutropenia	10 (7)	10 (7)	5 (3)	5 (3)
Neutropenia	5 (3)	5 (3)	2 (1)	2 (1)
Metabolism and nutrition disorders	10 (7)	9 (6)	6 (4)	5 (3)
Hypercalcemia	2 (1)	1 (<1)	3 (2)	3 (2)
Nervous system disorders	10 (7)	8 (5)	7 (5)	5 (3)
Syncope	4 (3)	4 (3)	1 (<1)	1 (<1)
Respiratory, thoracic, and mediastinal disorders	10 (7)	9 (6)	9 (6)	8 (5)
Dyspnea	4 (3)	3 (2)	2 (1)	1 (<1)
Musculoskeletal and connective tissue disorders	17 (11)	12 (8)	7 (5)	5 (3)
Pathological fracture	7 (5)	4 (3)	4 (3)	3 (2)
Renal and urinary disorders	10 (7)	6 (4)	10 (7)	8 (5)
Acute kidney injury	6 (4)	3 (2)	6 (4)	4 (3)
Renal failure	1 (<1)	1 (<1)	3 (2)	3 (2)
General disorders and administration site conditions	22 (15)	20 (13)	15 (10)	14 (9)
Disease progression	9 (6)	9 (6)	8 (5)	8 (5)
Pyrexia	5 (3)	3 (2)	2 (1)	1 (<1)
General physical health deterioration	1 (<1)	1 (<1)	3 (2)	3 (2)

	Isa-Pd (*n* = 152)		Pd (*n* = 149)	
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Injury, poisoning and procedural complications	12 (8)	9 (6)	4 (3)	2 (1)
Infusion-related reaction	6 (4)	4 (3)	1 (<1)	0

Isa-Pd isatuximab–pomalidomide–dexamethasone, *Pd* pomalidomide–dexamethasone, *SAE* serious adverse event.
Data are *n* (%) of patients.

Supplementary Table 10. TEAEs leading to definitive treatment discontinuation by primary system organ class and preferred term (safety population).

	Isa-Pd (*n* = 152)		**Pd (*n* = 149)**	
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Any class	19 (13)	19 (13)	22 (15)	21 (14)
Infections and infestations	9 (6)	9 (6)	9 (6)	8 (5)
Pneumonia	2 (1)	2 (1)	3 (2)	3 (2)
Atypical pneumonia	1 (<1)	1 (<1)	0	0
Bronchopulmonary aspergillosis	1 (<1)	1 (<1)	0	0
COVID-19 pneumonia	1 (<1)	1 (<1)	0	0
Medical device site infection	1 (<1)	1 (<1)	0	0
Meningitis cryptococcal	1 (<1)	1 (<1)	0	0
Pneumonia influenzal	1 (<1)	1 (<1)	0	0
Pyoderma	1 (<1)	1 (<1)	0	0
COVID-19	0	0	1 (<1)	1 (<1)
Echinococciasis	0	0	1 (<1)	0
Pneumonia streptococcal	0	0	1 (<1)	1 (<1)
Sepsis	0	0	1 (<1)	1 (<1)
Septic shock	0	0	2 (1)	2 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1)	2 (1)	0	0
Metastases to liver	1 (<1)	1 (<1)	0	0
Myelodysplastic syndrome	1 (<1)	1 (<1)	0	0
Blood and lymphatic system disorders	1 (<1)	1 (<1)	7 (5)	7 (5)
Thrombocytopenia	1 (<1)	1 (<1)	7 (5)	7 (5)
Neutropenia	0	0	2 (1)	2 (1)
Nervous system disorders	1 (<1)	1 (<1)	2 (1)	2 (1)
Cerebellar infarction	1 (<1)	1 (<1)	0	0
Hemorrhage intracranial	0	0	1 (<1)	1 (<1)
Spinal subdural hematoma	0	0	1 (<1)	1 (<1)
Eye disorders	0	0	1 (<1)	1 (<1)
Vision blurred	0	0	1 (<1)	1 (<1)
Cardiac disorders	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Arteriosclerosis coronary artery	1 (<1)	1 (<1)	0	0
Myocardial infarction	0	0	1 (<1)	1 (<1)
Hepatobiliary disorders	1 (<1)	1 (<1)	0	0
Hepatic failure	1 (<1)	1 (<1)	0	0
Skin and subcutaneous tissue disorders	1 (<1)	1 (<1)	0	0
Decubitus ulcer	1 (<1)	1 (<1)	0	0

	Isa-Pd (*n* = 152)		Pd (*n* = 149)	
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
General disorders and administration site conditions	4 (3)	4 (3)	2 (1)	2 (1)
Death	2 (1)	2 (1)	1 (<1)	1 (<1)
General physical health deterioration	1 (<1)	1 (<1)	0	0
Multiple organ dysfunction syndrome	1 (<1)	1 (<1)	0	0
Sudden death	0	0	1 (<1)	1 (<1)

COVID-19 coronavirus disease 2019, *Isa-Pd* isatuximab–pomalidomide–dexamethasone, *Pd* pomalidomide–dexamethasone, *TEAE* treatment-emergent adverse event.
Data are *n* (%) of patients.

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