Real-world Experience With Isatuximab in Patients With Relapsed and/or Refractory Multiple Myeloma (RRMM): IONA-MM Second Interim Analysis

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INTRODUCTION

- Isatuximab (Isa), an immunoglobulin G1 monoclonal antibody, targets a specific epitope of human CD38, inducing myeloma cell death via multiple mechanisms[1-3]
- Phase 3 trials have shown the benefits of adding Isa to standard backbone regimens, with the combination therapies isatuximab-pomalidomide-dexamethasone (Isa-Pd; in the ICARIA-MM trial)[4] and isatuximab-carfilzomib-dexamethasone (Isa-Kd; in the IKEMA trial)[5,6] being approved for the treatment of relapsed and/or refractory multiple myeloma (RRMM) in numerous geographic areas[2,7]
- Isa, in combination with bortezomib, lenalidomide, and dexamethasone (VRd), was recently approved by the Food and Drug Administration for treating adult patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant[2]; this approval was based on positive results from the IMROZ Phase 3 study, which demonstrated significantly improved progression-free survival (PFS) and deep, sustained responses with Isa-VRd compared with VRd alone in this population[8]
- The IMAGE study recently reported real-world effectiveness and safety of Isa-Pd in patients with RRMM in an early access program in France[9]
- We previously reported the results of the first interim analysis of the multinational IONA-MM registry study (NCT04458831) for patients with RRMM treated with Isa in the real-world setting (in combination with Pd or Kd or other), detailing baseline characteristics, treatment exposure, and safety[10]
- Here, we present updated results from the second interim analysis, planned based on enrollment, of IONA-MM, including updated baseline characteristics, efficacy, and safety data

METHODS

- IONA-MM is an ongoing, non-interventional, multinational, observational study of patients with RRMM treated with Isa in a real-world setting
- Patients aged ≥18 years who received ≥1 prior line of therapy were prospectively and retrospectively enrolled (if exposed to Isa for ≤3 months)
- Treating physicians determined Isa treatment before and independent of study enrollment
- The treatment observation period began at Isa initiation, and routine clinical assessments were collected at 4 weeks and every 3 months after treatment initiation up to 30 days after discontinuation
  - Upon discontinuation, patients were followed up for a maximum of 6 months
- Primary outcome measures included overall response rate (ORR), very good partial response or better (≥VGPR) rate, complete response or better (≥CR) rate, duration of response (DOR), time to first response, PFS, time to subsequent anti-MM therapy, quality of life, and adverse events (AEs)
- AEs and laboratory abnormalities were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0

RESULTS

- As of December 31, 2023, the patient inclusion cutoff, 429 patients (safety population) were enrolled and had received ≥1 dose of Isa in combination with Pd (n=239), or in combination with Kd (n=167), or other Isa-based regimens (n=23)
- Among them, 408 patients (Isa-Pd, 230; Isa-Kd, 156; other Isa-based regimens, 22) had ≥1 post-baseline assessment by March 31, 2024, the data cutoff for the enrolled patients
- Patients were enrolled from the United States, Japan, Germany, France, Italy, Spain, United Kingdom, Switzerland, Argentina, Austria, Belgium, Hong Kong, Netherlands, and United Arab Emirates
- Other Isa-based regimens received (n=23) included Isa-dexamethasone (n=10); Isa alone and Isa-lenalidomide-dexamethasone (n=3 each); Isa-carfilzomib-cyclophosphamide-dexamethasone (n=2); and Isa-pomalidomide, Isa-carfilzomib-methylprednisolone-dexamethasone, Isa-carfilzomib-pomalidomide-dexamethasone, Isa-ixazomib-pomalidomide-dexamethasone, and Isa-selinexor-carfilzomib-pomalidomide-dexamethasone (n=1 each)

Baseline Patient Characteristics

- Baseline patient characteristics are presented in **Table 1**
- 35.2% of Isa-Pd– and 19.9% of Isa-Kd–treated patients were aged ≥75 years (median age: 71 and 67 years, respectively)
  - A majority were frail (using a simplified frailty score)[11] in both cohorts (Isa-Pd, 77.8%; Isa-Kd, 62.1%)
- 15.9% (Isa-Pd) and 25.0% (Isa-Kd) of patients had high-risk cytogenetics, defined as the presence of del(17p), t(4;14), or t(14;16)
- 26.2% (Isa-Pd) and 28.8% (Isa-Kd) of patients had 1q21 gain/amplification
- Patients in both the Isa-Pd and Isa-Kd cohorts had a median of 2 prior lines of therapy, whereas those who received other Isa-based regimens had a median of 4 prior lines of therapy
- 60.4% of Isa-Pd– and 51.9% of Isa-Kd–treated patients were refractory to lenalidomide; 28.3% and 23.7%, respectively, were refractory to daratumumab

Table 1. Baseline patient characteristics

	Isa-Pd (n=230)	Isa-Kd (n=156)
Age group, n (%)		
<65 years	62 (27.0)	62 (39.7)
65–74 years	87 (37.8)	63 (40.4)
≥75 years	81 (35.2)	31 (19.9)
ISS stage, n (%)		
Stage I	40/97 (41.2)	27/78 (34.6)
Stage II	32/97 (33.0)	23/78 (29.5)
Stage III	25/97 (25.8)	28/78 (35.9)
High-risk cytogenetics,[a] n (%)		
Yes	23/145 (15.9)	26/104 (25.0)
No	112/145 (77.2)	76/104 (73.1)
Unknown	10/145 (6.9)	2/104 (1.9)
1q21 abnormalities, n (%)		
1q21 gain/amplification	38/145 (26.2)	30/104 (28.8)
Isolated 1q21 gain/amplification	7/145 (4.8)	7/104 (6.7)
Frailty status,[b] n (%)		
Fit	6/158 (3.8)	14/124 (11.3)
Intermediate	29/158 (18.4)	33/124 (26.6)
Frail	123/158 (77.8)	77/124 (62.1)
Median time from initial diagnosis (Q1–Q3), years	5.0 (2.6–7.6)	4.1 (2.1–6.3)
Median number of prior lines (Q1–Q3)	2.0 (2.0–4.0)	2.0 (1.0–3.0)
Number of prior lines, n (%)		
1	47/227 (20.6)	65/154 (42.2)
2	70/227 (30.7)	33/154 (21.4)
3	45/227 (19.7)	21/154 (13.6)
≥4	65/227 (28.5)	35/154 (22.7)
Main prior therapies, n (%)		
PI	212 (92.2)	134 (85.9)
Bortezomib	184 (80.0)	129 (82.7)
Carfilzomib	101 (43.9)	21 (13.5)
IMiD	193 (83.9)	137 (87.8)
Lenalidomide	189 (82.2)	129 (82.7)
Pomalidomide	41 (17.8)	34 (21.8)
Monoclonal antibodies	87 (37.8)	60 (38.5)
Daratumumab	77 (33.5)	53 (34.0)
Refractory to lenalidomide, n (%)	139 (60.4)	81 (51.9)
Refractory to lenalidomide at last prior line, n (%)	46 (20.0)	33 (21.2)
Refractory to PI, n (%)	136 (59.1)	62 (39.7)
Refractory to IMiD and PI, n (%)	32 (13.9)	14 (9.0)
Refractory to daratumumab, n (%)	65 (28.3)	37 (23.7)

[a]High-risk cytogenetics derived from FISH. Yes was defined as presence of del(17p), t(4;14), or t(14;16); No was defined as none of these abnormalities; Unknown was defined as missing or unknown information about these abnormalities: all 3 items were missing, or some were missing and the rest were normal.
[b]Patients were categorized using an algorithm based on the sum of age (score = 0 if <75 years; score = 1 if 75–≤80 years; score = 2 if >80 years), CCI score (score = 0 if CCI ≤1, score = 1 if CCI >1), and ECOG (score = 0 if ECOG = 0; score = 1 if ECOG = 1; score = 2 if ECOG ≥2).[11]
CCI, Charlson Comorbidity Index; d, dexamethasone; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; IMiD, immunomodulatory drug; Isa, isatuximab; ISS, international staging system; K, carfilzomib; P, pomalidomide; PI, proteasome inhibitor; Q, quartile.

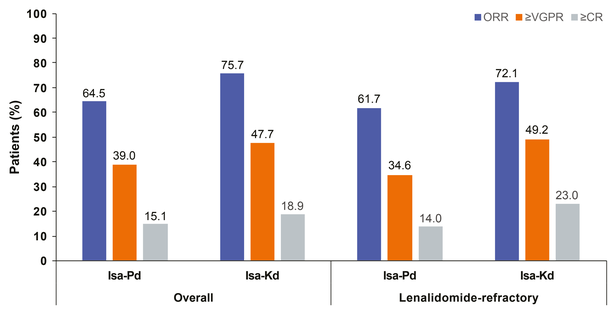
Treatment Exposure

- The median relative dose intensity of Isa in this real-world cohort was 78.3% and 76.1% in the Isa-Pd and Isa-Kd cohorts, respectively
- The median number of 28-day treatment cycles received was 14.0 in the Isa-Pd cohort and 12.0 in the Isa-Kd cohort

Response Rates

- Response rates in the Isa-Pd and Isa-Kd cohorts can be seen in **Figure 1**
- Overall, Isa-Pd patients had an ORR of 64.5%, ≥VGPR of 39.0%, and ≥CR of 15.1%; in the Isa-Kd cohort, the rates were 75.7%, 47.7%, and 18.9%, respectively
- Patients who were refractory to lenalidomide had an ORR of 61.7% and 72.1% in the Isa-Pd and Isa-Kd cohorts, respectively, consistent with the findings in the overall population
  - 34.6% and 49.2% of lenalidomide-refractory patients had ≥VGPR, and 14.0% and 23.0% had ≥CR
- Patients refractory to lenalidomide at last prior line had an ORR of 63.2% and 75.0% in the Isa-Pd and Isa-Kd cohorts, respectively
  - 28.9% and 54.2% of these patients, respectively, had ≥VGPR, while 10.5% and 25.0% had ≥CR
- ORR in patients refractory to daratumumab was 41.7% in the Isa-Pd cohort and 63.0% in the Isa-Kd cohort; among daratumumab-naive patients, the ORR was 73.7% in the Isa-Pd cohort and 82.2% in the Isa-Kd cohort
- The median DOR was 30.8 months in the Isa-Pd cohort and was not reached in the Isa-Kd cohort

Figure 1. Response rates

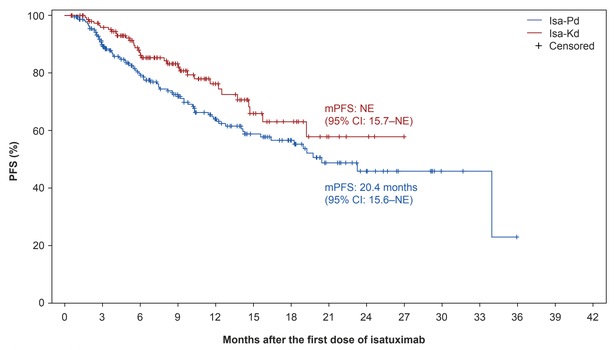


≥CR, complete response or better; d, dexamethasone; Isa, isatuximab; K, carfilzomib; ORR, overall response rate; P, pomalidomide; ≥VGPR, very good partial response or better.

PFS

- After a median time on study of 11.2 months (Isa-Pd) and 9.6 months (Isa-Kd) at the time of analysis, the median PFS (mPFS) was 20.4 months (95% CI: 15.6–not estimable [NE]) with Isa-Pd and was not reached (95% CI: 15.7–NE) with Isa-Kd (**Figure 2**)
- At month 30, 45.8% and 57.8% of patients in the Isa-Pd and Isa-Kd cohorts, respectively, had neither died nor experienced disease progression
- In the lenalidomide-refractory subgroup, the mPFS was 18.2 months (95% CI: 11.7–NE) with Isa-Pd and was not reached (95% CI: 14.6–NE) with Isa-Kd

Figure 2. Kaplan-Meier curves of progression-free survival



d, dexamethasone; Isa, isatuximab; K, carfilzomib; m, median; NE, not estimable; P, pomalidomide; PFS, progression-free survival.

Safety

- All-grade treatment-emergent AEs (TEAEs) occurred in 69.9% and 77.2% of Isa-Pd and Isa-Kd patients, respectively, and grade ≥3 TEAEs occurred in 49.8% (Isa-Pd) and 42.5% (Isa-Kd) of patients
- A safety summary is presented in **Table 2**
- **Table 3** presents the most common TEAEs, with an incidence ≥5% in either the Isa-Pd or Isa-Kd cohort, as well as selected cardiac disorders (Medical Dictionary for Regulatory Activities [MedDRA] high level group terms)
  - In both cohorts, the proportions of patients experiencing all-grade cardiac arrhythmias, heart failures, or coronary artery disorders were <5%
- Among TEAEs of special interest, all-grade neutropenia occurred in 34.3% of the Isa-Pd cohort and 11.4% of the Isa-Kd cohort (27.2% and 9.0% for neutropenia as a MedDRA preferred term), and all-grade infusion-associated reactions (IARs) occurred in 10.9% and 19.8% of patients, respectively (2.1% and 4.2% of patients experienced grade ≥3 IARs)
  - 2.1% of Isa-Pd and 3.0% of Isa-Kd patients experienced grade ≥3 IARs during the first cycle

Table 2. Safety summary

Patients, n (%)	Isa-Pd (n=239)	Isa-Kd (n=167)
Any TEAE	167 (69.9)	129 (77.2)
Grade ≥3 TEAE	119 (49.8)	71 (42.5)
TEAE leading to death[a]	15 (6.3)	10 (6.0)
Treatment-emergent SAE	91 (38.1)	50 (29.9)
TEAE leading to definitive Isa discontinuation	29 (12.1)	17 (10.2)
Treatment-related TEAE	145 (60.7)	107 (64.1)

[a]AEs leading to death were considered possibly related to Isa treatment in 2 patients each in the Isa-Pd and Isa-Kd cohorts. In the Isa-Pd cohort, the reasons for death were pneumoperitoneum and decreased neutrophil count. In the Isa-Kd cohort, reasons for death were disease progression and multiple organ dysfunction syndrome.
d, dexamethasone; Isa, isatuximab; K, carfilzomib; P, pomalidomide; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 3. Most common TEAEs[a] and incidences of selected cardiac disorders

Patients, n (%)	Isa-Pd (n=239)		Isa-Kd (n=167)	
MedDRA PT	All grades	Grade ≥3	All grades	Grade ≥3
Neutropenia	65 (27.2)	62 (25.9)	15 (9.0)	7 (4.2)
COVID-19	29 (12.1)	6 (2.5)	15 (9.0)	2 (1.2)
Pneumonia	26 (10.9)	18 (7.5)	11 (6.6)	8 (4.8)
Diarrhea	26 (10.9)	5 (2.1)	19 (11.4)	1 (0.6)
Neutrophil count decreased	20 (8.4)	17 (7.1)	4 (2.4)	3 (1.8)
Infusion-related reaction	19 (7.9)	2 (0.8)	26 (15.6)	4 (2.4)
Anemia	18 (7.5)	9 (3.8)	23 (13.8)	8 (4.8)
Fatigue	18 (7.5)	2 (0.8)	12 (7.2)	2 (1.2)
Constipation	17 (7.1)	0	3 (1.8)	0
Cough	17 (7.1)	0	11 (6.6)	0
Bronchitis	16 (6.7)	1 (0.4)	13 (7.8)	1 (0.6)
Asthenia	14 (5.9)	1 (0.4)	9 (5.4)	2 (1.2)
Nausea	14 (5.9)	0	18 (10.8)	1 (0.6)
Back pain	14 (5.9)	1 (0.4)	2 (1.2)	1 (0.6)
Dyspnea	14 (5.9)	3 (1.3)	11 (6.6)	0
Platelet count decreased	14 (5.9)	11 (4.6)	9 (5.4)	7 (4.2)
Thrombocytopenia	11 (4.6)	3 (1.3)	21 (12.6)	10 (6.0)
Pyrexia	7 (2.9)	0	21 (12.6)	2 (1.2)
Nasopharyngitis	6 (2.5)	0	12 (7.2)	0
Vomiting	2 (0.8)	0	13 (7.8)	1 (0.6)
Hypertension	1 (0.4)	0	20 (12.0)	5 (3.0)
Cardiac disorders MedDRA HLGT				
Cardiac arrhythmias	11 (4.6)	3 (1.3)	4 (2.4)	1 (0.6)
Heart failures	5 (2.1)	2 (0.8)	4 (2.4)	3 (1.8)
Coronary artery disorders	0	0	1 (0.6)	0

[a]MedDRA PT with incidence ≥5% in either the Isa-Pd or Isa-Kd cohort.
d, dexamethasone; HLGT, high level group term; Isa, isatuximab; K, carfilzomib; MedDRA, Medical Dictionary for Regulatory Activities; P, pomalidomide; PT, preferred term; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- The results of this second interim analysis of the IONA-MM study indicate that Isa-Kd has similar efficacy and safety in the real world to that observed in the IKEMA trial (mPFS not reached vs 35.7 months),[6] despite IONA-MM including a higher proportion of patients who were refractory to lenalidomide and daratumumab
- The mPFS with Isa-Pd was numerically longer in IONA-MM than in the ICARIA-MM trial (20.4 vs 11.5 months)[4]
  - However, patients in ICARIA-MM had a median 3 prior lines of therapy[4] (vs 2 in IONA-MM), and over 90% of patients were lenalidomide-refractory[4] (vs ~60% in IONA-MM)
- Results for lenalidomide-refractory patients were consistent with those in the overall patient population in IONA-MM
- Compared with the ORR in the overall Isa-Pd cohort (64.5%) and overall Isa-Kd cohort (75.7%), ORR was higher in the daratumumab-naive subgroup (73.7% and 82.2%) and lower for daratumumab-refractory patients (41.7% and 63.0%)
- The safety profile of Isa-Pd and Isa-Kd was manageable, consistent with previous observations, and in line with the pivotal ICARIA-MM and IKEMA studies[4-6]
  - Rates of TEAEs leading to discontinuation of Isa were low in both cohorts
- These data support the use of Isa in combination with Pd and Kd in RRMM outside of clinical trials and in wider populations that include elderly and lenalidomide-refractory patients
- The study closed for enrollment in August 2024; however, patients continue to be followed and data with longer follow-up will be reported in the future

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QUESTIONS:
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