Isatuximab in Relapsed Multiple Myeloma Patients With Ultra-High-Risk Cytogenetics: ICARIA-MM and IKEMA Subgroup Analysis

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INTRODUCTION

- Although survival outcomes for multiple myeloma (MM) have improved significantly in recent years, patients with high-risk features such as cytogenetic abnormalities continue to have poorer outcomes[1]
- In the Revised International Staging System (R-ISS), the definition of high-risk MM includes the presence of at least one of the mutations related with poor prognosis — del(17p), t(4;14), and t(14;16).[2] Chromosomal abnormality 1q21+ has also recently been recognized as related to poor prognosis, and has been incorporated into the second revision of R-ISS (R2-ISS)[3,4]
- Isatuximab (Isa) is an approved monoclonal antibody that binds to a specific epitope of the CD38 receptor, inducing the death of MM cells through multiple mechanisms of action[5]
- Isa was investigated for the treatment of relapsed/refractory MM in the ICARIA-MM and IKEMA trials, in combination with pomalidomide and dexamethasone (Pd), and carfilzomib and dexamethasone (Kd), respectively[6,7]
- This post hoc analysis of ICARIA-MM and IKEMA data investigates the impact of Isa-Pd and Isa-Kd on progression-free survival (PFS), overall survival (OS), and depth of response in patients with ultra-high-risk and extended high-risk (including 1q21+) MM

METHODS

- The analyses excluded patients with one or more missing high-risk chromosomal abnormality (CA) information
- Standard risk was defined by the absence of the following high-risk CAs – del(17p), t(4;14), t(14;16), and 1q21+, which included both gain(1q21) and amp(1q21)
- Extended high-risk was defined as the presence of only one of these high-risk CAs
- Ultra-high-risk was defined as the presence of ≥2 high-risk CAs
- Assessment of cytogenetics in both trials used CD138-selected fluorescence in situ hybridisation with a cut-off of 50% for del(17p), and 30% for t(4;14), t(14;16) and 1q21+[6,7]

RESULTS

Baseline characteristics

- A total of 194 patients from ICARIA-MM were included for analysis – 101 Isa-Pd and 93 Pd
- A total of 257 patients from IKEMA were included for analysis – 154 Isa-Kd and 103 Kd
- The distribution of patients in both trials into standard risk, extended high-risk, and ultra-high-risk cytogenetics can be seen in **Table 1**
  - Of note, the percentage of patients with ultra-high-risk CA was lower in the Isa-Pd arm than in the Pd arm in the ICARIA-MM trial. Due to the low collection of 1q21+ data, there were few patients in the standard risk and ultra-high-risk categories
  - All ultra-high-risk patients in both trials had 1q21+, and t(4;14) was the second most frequent CA, followed by del(17p) and t(14;16) (**Table 2**)

Table 1. Summary of cytogenetic status in the ICARIA-MM and IKEMA trials

	ICARIA-MM			IKEMA		
Risk category, n (%)	**Isa-Pd (n=101)**	**Pd (n=93)**	**All (N=194)**	**Isa-Kd (n=154)**	**Kd (n=103)**	**All (N=257)**
Standard risk	29 (28.7)	35 (37.6)	64 (33.0)	65 (42.2)	43 (41.7)	108 (42.0)
Extended high-risk	61 (60.4)	38 (40.9)	99 (51.0)	64 (41.6)	41 (39.8)	105 (40.9)
Ultra-high-risk	11 (10.9)	20 (21.5)	31 (16.0)	25 (16.2)	19 (18.4)	44 (17.1)

d, dexamethasone; Isa, isatuximab; K, carfilzomib; P, pomalidomide

Table 2. Summary of CAs in ultra-high-risk patients in the ICARIA-MM and IKEMA trials

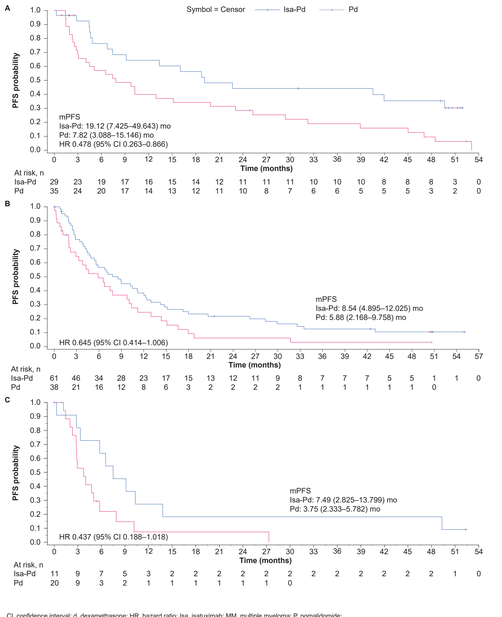
	ICARIA-MM		IKEMA	
N (%)	**Isa-Pd (n=11)**	**Pd (n=20)**	**Isa-Kd (n=25)**	**Kd (n=19)**
1q21+	11 (100.0)	20 (100.0)	25 (100.0)	19 (100.0)
t(4;14)	9 (81.8)	12 (60.0)	19 (76.0)	15 (78.9)
del(17p)	5 (45.5)	11 (55.0)	6 (24.0)	9 (47.4)
t(14;16)	0	1 (5.0)	4 (16.0)	0

CA, chromosomal abnormality; d, dexamethasone; Isa, isatuximab; K, carfilzomib; P, pomalidomide

PFS

- The Kaplan-Meier curves by cytogenetic risk for ICARIA-MM can be seen in **Figure 1**; those for IKEMA can be seen in **Figure 2**

Figure 1. Kaplan-Meier curves of PFS in ICARIA-MM for patients with (A) standard risk, (B) extended high-risk, and (C) ultra-high-risk MM

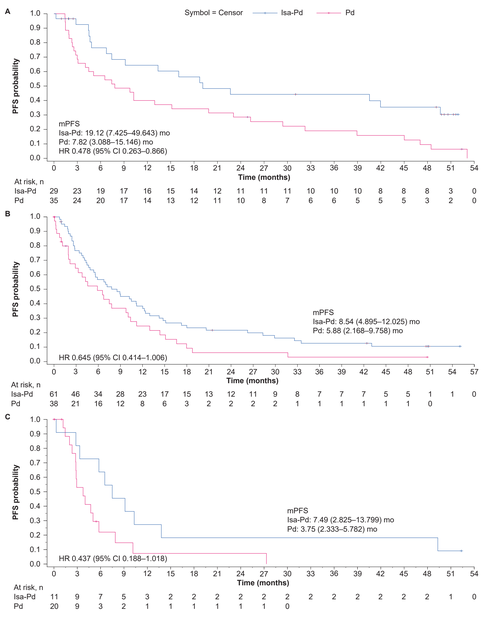


CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; MM, multiple myeloma; P, pomalidomide; mPFS, median PFS; PFS, progression-free survival

OS

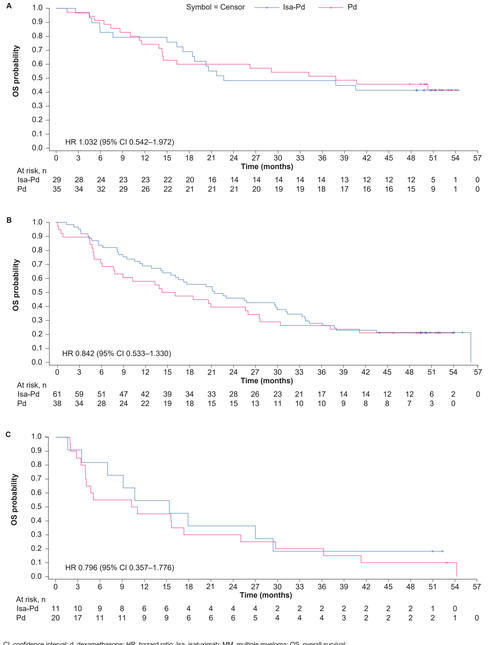
- In ICARIA-MM, hazard ratios for OS (Isa-Pd vs Pd) were 1.032 (95% CI 0.542–1.972), 0.842 (95% CI 0.533–1.330) and 0.796 (95% CI 0.357–1.776) for standard risk, extended high-risk, and ultra-high-risk patients, respectively (**Figure 3**)
  - The Kaplan-Meier curve for standard risk patients differed to that of the published ICARIA-MM results[6] due to the reclassification of 1q21+ as a high-risk CA, lowering the number of patients with standard risk CA
- The OS data for IKEMA were still immature at the time of the final PFS analysis

Figure 2. Kaplan-Meier curves of PFS in IKEMA for patients with (A) standard risk, (B) extended high-risk, and (C) ultra-high-risk MM



CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; mPFS, median PFS; PFS, progression-free survival

Figure 3. Kaplan-Meier curves of OS for patients with (A) standard risk, (B) extended high-risk, and (C) ultra-high-risk MM in ICARIA-MM



CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; MM, multiple myeloma; OS, overall survival; P, pomalidomide

Table 3. Safety summary in ICARIA-MM and IKEMA by risk category

	ICARIA-MM						IKEMA					
	Standard risk		Extended high-risk		Ultra-high-risk		Standard risk		Extended high-risk		Ultra-high-risk	
%	**Isa-Pd (n=29)**	**Pd (n=34)**	**Isa-Pd (n=60)**	**Pd (n=37)**	**Isa-Pd (n=11)**	**Pd (n=20)**	**Isa-Kd (n=65)**	**Kd (n=43)**	**Isa-Kd (n=63)**	**Kd (n=41)**	**Isa-Kd (n=25)**	**Kd (n=18)**
Patients with any TEAE	100	97.1	98.3	100	100	100	96.9	100	100	100	100	94.4
Patients with any Grade ≥3 TEAE	96.6	82.4	86.7	78.4	100	70.0	80.0	88.4	85.7	73.2	92.0	72.2
Patients with any Grade ≥5 TEAE*	6.9	2.9	5.0	10.8	27.3	10.0	6.2	9.3	6.3	2.4	0	0
Patients with any treatment emergent SAE	72.4	64.7	70.0	67.6	81.8	55.0	66.2	72.1	76.2	61.0	68.0	72.2
Patients with any TEAE leading to definitive discontinuation	27.6	2.9	3.3	13.5	9.1	25.0	12.3	23.3	15.9	22.0	0	0

*TEAE with fatal outcome during the treatment period
d, dexamethasone; Isa, isatuximab; K, carfilzomib; P, pomalidomide; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 4. Summary of select Grade ≥3 TEAEs and hematologic abnormalities occurring in ICARIA-MM and IKEMA

	ICARIA-MM						IKEMA					
	Standard risk		Extended high-risk		Ultra-high-risk		Standard risk		Extended high-risk		Ultra-high-risk	
%	**Isa-Pd (n=29)**	**Pd (n=34)**	**Isa-Pd (n=60)**	**Pd (n=37)**	**Isa-Pd (n=11)**	**Pd (n=20)**	**Isa-Kd (n=65)**	**Kd (n=43)**	**Isa-Kd (n=63)**	**Kd (n=41)**	**Isa-Kd (n=25)**	**Kd (n=18)**
Infections and infestations (SOC)												
Pneumonia	24.1	20.6	25.0	27.0	27.3	25.0	16.9	16.3	17.5	12.2	28.0	5.6
Upper respiratory tract infection	3.4	5.9	3.3	2.7	9.1	0	1.5	0	7.9	2.4	0	5.6
Others												
Infusion-related reaction	3.4	0	0	0	9.1	0	0	0	0	0	4.0	0
Hypertension	3.4	2.9	1.7	2.7	0	0	24.6	30.2	25.4	19.5	20.0	11.1
Cardiac failure	0	0	0	0	0	0	1.5	2.3	4.8	4.9	0	5.6
Hematologic abnormalities												
Anemia	27.6	14.7	31.7	33.3	36.4	45.0	16.9	23.3	33.3	19.5	28.0	33.3
Neutropenia	82.8	76.5	88.3	66.7	81.8	75.0	15.4	7.0	17.5	4.9	40.0	0
Thrombocytopenia	31.0	11.8	31.7	33.3	54.5	30.0	21.5	18.6	33.3	31.7	32.0	27.8

d, dexamethasone; Isa, isatuximab; K, carfilzomib; P, pomalidomide; SOC, system organ class; TEAE, treatment-emergent adverse event

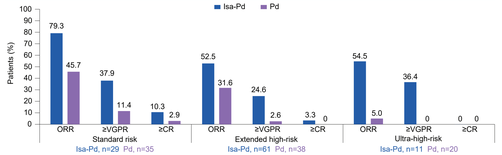
Response rates

- A summary of best overall responses in ICARIA-MM and IKEMA by cytogenetic risk are seen in **Figures 4** and **5**
  - Notably, the depth of response achieved by patients receiving Isa was better across all risk categories in both trials
  - In IKEMA, a large difference in very good partial response or better and complete response or better rates can be observed between Isa-Kd and Kd across all risk categories
  - The overall response rate in IKEMA was also consistent with that of the intention-to-treat analysis, but with increased depth of response in this post hoc analysis
- A summary of minimal residual disease negativity (MRD−) rates by risk status in IKEMA are shown in **Figure 6**, where higher rates of MRD− are observed with Isa

Safety

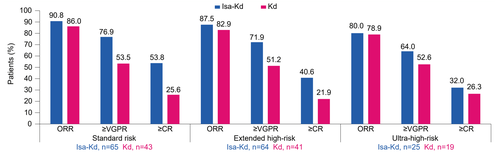
- Isa-containing regimens were well tolerated across all risk category subgroups in both the ICARIA-MM and IKEMA trials (**Table 3**)
- The incidence of Grade ≥3 treatment-emergent adverse events (TEAEs) was generally higher in the Isa-containing arm than control in both trials, regardless of risk category, with the exception of standard risk patients in IKEMA
- Despite higher exposure in the Isa arm across all subgroups in both trials, as evidenced by the total number of cycles, patients with any TEAE leading to treatment discontinuation were generally similar between arms across populations, with the exception of standard risk patients in ICARIA-MM
- A summary of selected Grade ≥3 TEAEs and hematologic abnormalities in both trials is seen in **Table 4**

Figure 4. Best overall responses in ICARIA-MM by risk category



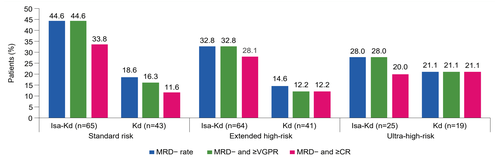
≥CR, complete response or better; d, dexamethasone; Isa, isatuximab; ORR, overall response rate; P, pomalidomide; ≥VGPR, very good partial response or better

Figure 5. Best overall responses in IKEMA by risk category



≥CR, complete response or better; d, dexamethasone; Isa, isatuximab; K, carfilzomib; ≥VGPR, very good partial response or better

Figure 6. MRD− rates by risk status in IKEMA



≥CR, complete response or better; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD−, minimal residual disease negativity; ≥VGPR, very good partial response or better

CONCLUSIONS

- The benefit of Isa on efficacy in the ultra-high-risk and extended high-risk subgroups was consistent with the primary results of each study
- Isa-containing regimens led to a benefit in PFS regardless of risk category
- Depth of response by patients receiving Isa-containing regimens was better than that of the control arm in both trials across all cytogenetic risk subgroups
- While few patients had ultra-high-risk cytogenetics in this post hoc analysis, there seemed to be an overall benefit in PFS and response rates with Isa-containing regimens vs control arms
- Ultra-high-risk patients are a population of unmet need as they have a less clear benefit compared with standard risk patients

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DISCLOSURES:
PNI: Participation on a Data Safety Monitoring Board or Advisory Board – AbbVie, Amgen, Celgene, Janssen, Sanofi, Takeda. **AP:** Honoraria – AbbVie, Amgen, BMS/Celgene, GSK, Janssen, Pfizer, Sanofi, and Takeda; Research funding – Takeda; Support for attending meetings and/or travel – Amgen, Janssen. **M-AD:** Honoraria – Amgen, Beigene, BMS, Janssen, Sanofi, Takeda. **TM:** Research funding – Sanofi. **TF:** Honoraria – BMS, Janssen. Participation on a Data Safety Monitoring Board or Advisory Board – Amgen, BMS, Janssen, Karyopharm, Oncopeptides, Roche, Sanofi. **MC:** Honoraria – BMS, Janssen, Sanofi; Support for attending meetings and/or travel – Janssen, Sanofi. **MB:** Honoraria – Janssen, Sanofi, Takeda; Participation on a Data Safety Monitoring Board or Advisory Board – Amgen, Menarini, Sanofi, Takeda. **NA, FD, SM, M-L R, CT,** and **ZK:** Employees of Sanofi and may hold stock and/or stock options. **PGR:** Research funding – Celgene/BMS, Karyopharm, Oncopeptides, Takeda; Consulting – AstraZeneca, Celgene/BMS, GSK, Janssen, Karyopharm, Oncopeptides, Sanofi, Secura Bio, Takeda.

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