

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 outcomes¹
- 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 action⁵
- 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 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

Risk category, n (%)	ICARIA-MM			IKEMA		
	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)

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

N (%)	ICARIA-MM		IKEMA	
	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

PFS

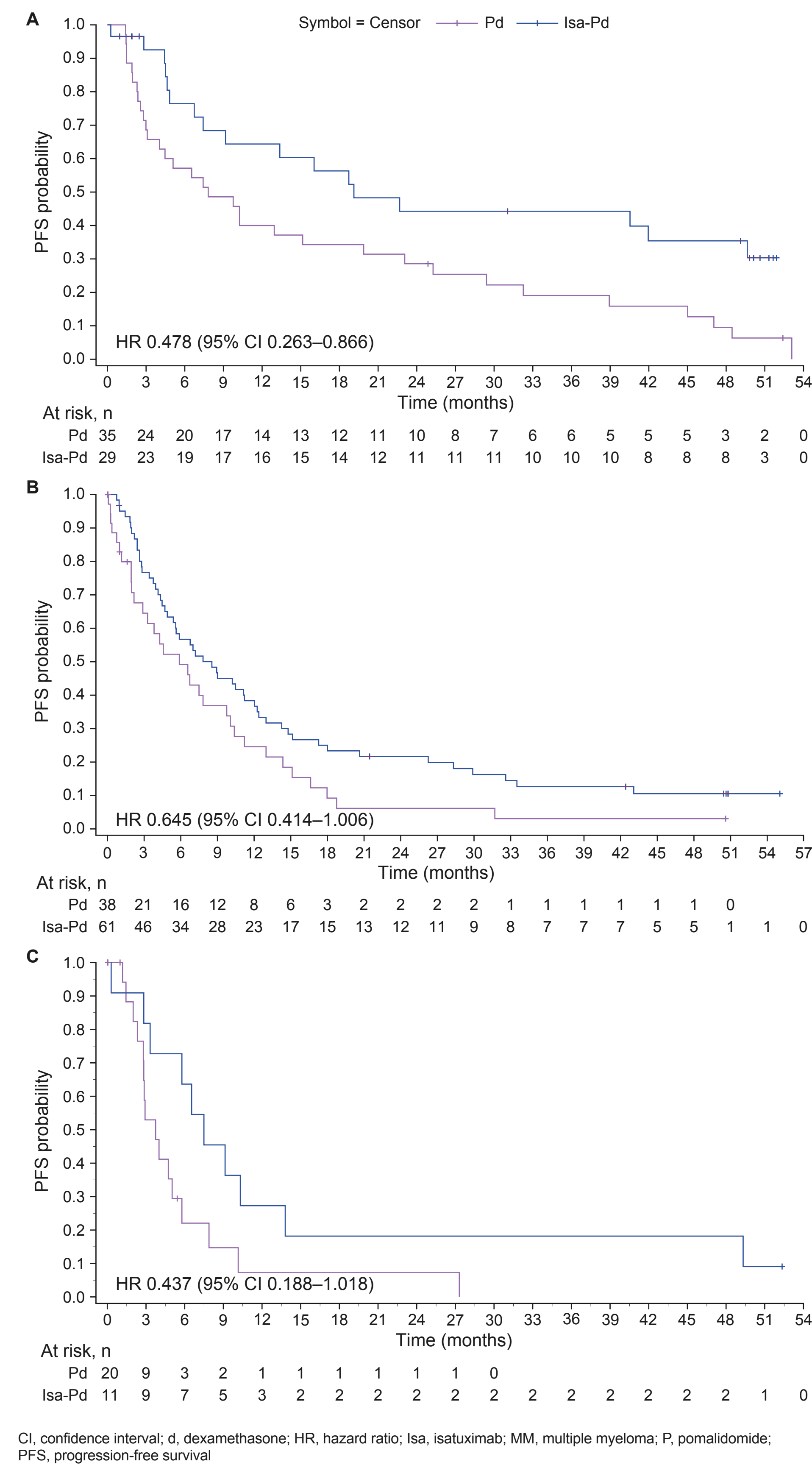
- In ICARIA-MM, the median PFS (95% confidence interval [CI]) values for each risk category were as follows:
 - Standard risk: 19.12 (7.425–49.643) months (mo) with Isa-Pd vs 7.82 (3.088–15.146) mo with Pd (**Figure 1A**)
 - Extended high-risk: 8.54 (4.895–12.025) mo with Isa-Pd vs 5.88 (2.168–9.758) mo with Pd (**Figure 1B**)
 - Ultra-high-risk: 7.49 (2.825–13.799) mo with Isa-Pd vs 3.75 (2.333–5.782) mo with Pd (**Figure 1C**)
- In IKEMA, median PFS (95% CI) values for each risk category were as follows:
 - Standard risk: 42.38 (26.283–not reached [NR]) mo with Isa-Kd vs 20.27 (15.244–28.189) mo with Kd (**Figure 2A**)
 - Extended high-risk: 31.11 (22.144–NR) mo with Isa-Kd vs 18.99 (10.283–25.035) mo with Kd (**Figure 2B**)
 - Ultra-high-risk: 17.08 (11.433–30.160) mo with Isa-Kd vs 16.16 (4.008–24.969) mo with Kd (**Figure 2C**)

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

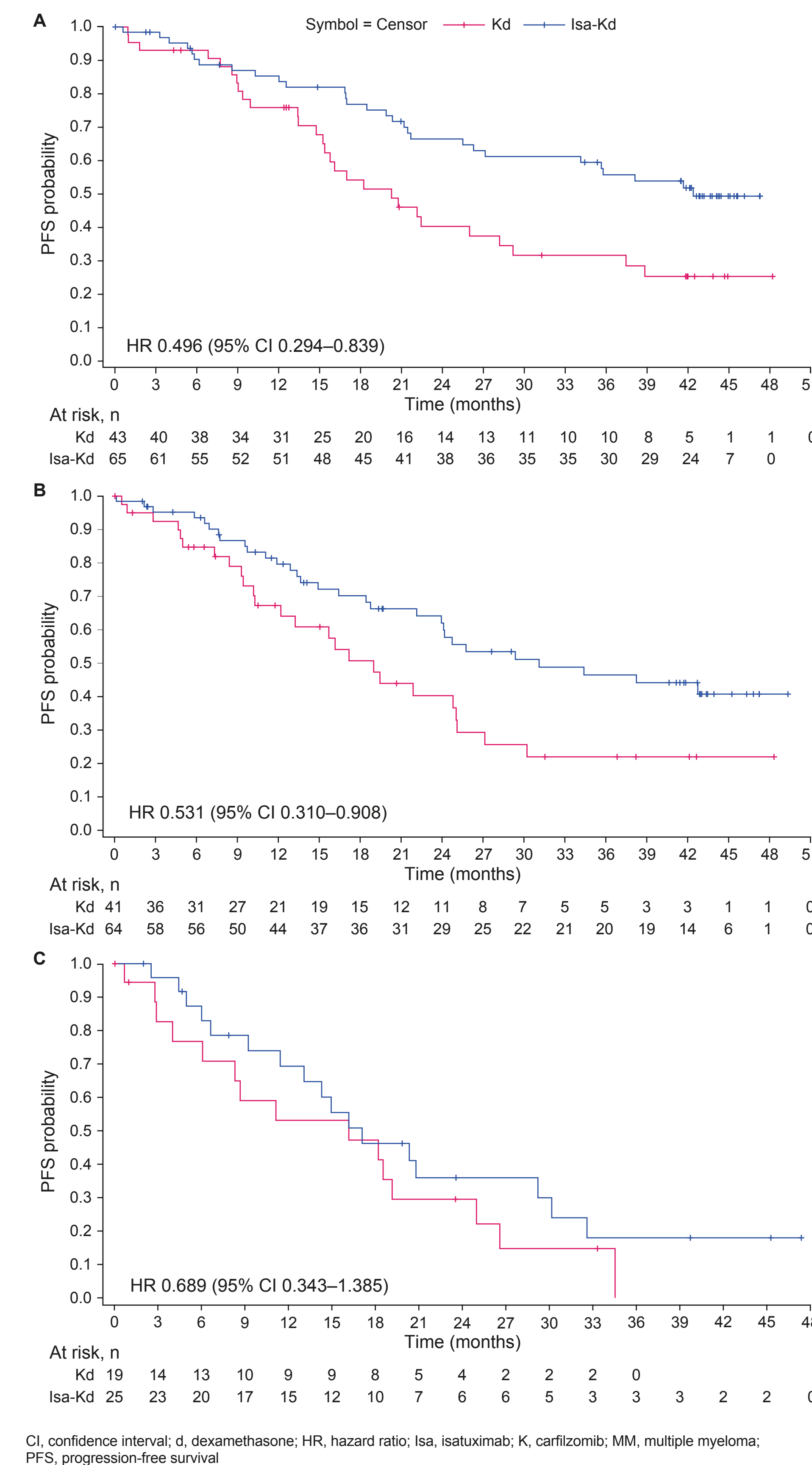
Figure 1. Kaplan-Meier curves of PFS in ICARIA-MM for patients with (A) standard risk, (B) extended high-risk, and (C) ultra-high-risk MM



OS

- In ICARIA-MM, hazard ratios for OS 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 results⁶ 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 are still immature
- Response rates**
- A summary of best overall responses in ICARIA-MM and IKEMA by cytogenetic risk are seen in **Figures 4** and **5**

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



Safety

- 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 (VGPR) or better and complete response (CR) or better rates can be observed between Isa-Kd and Kd across all risk categories
- The overall response rate (ORR) 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

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

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

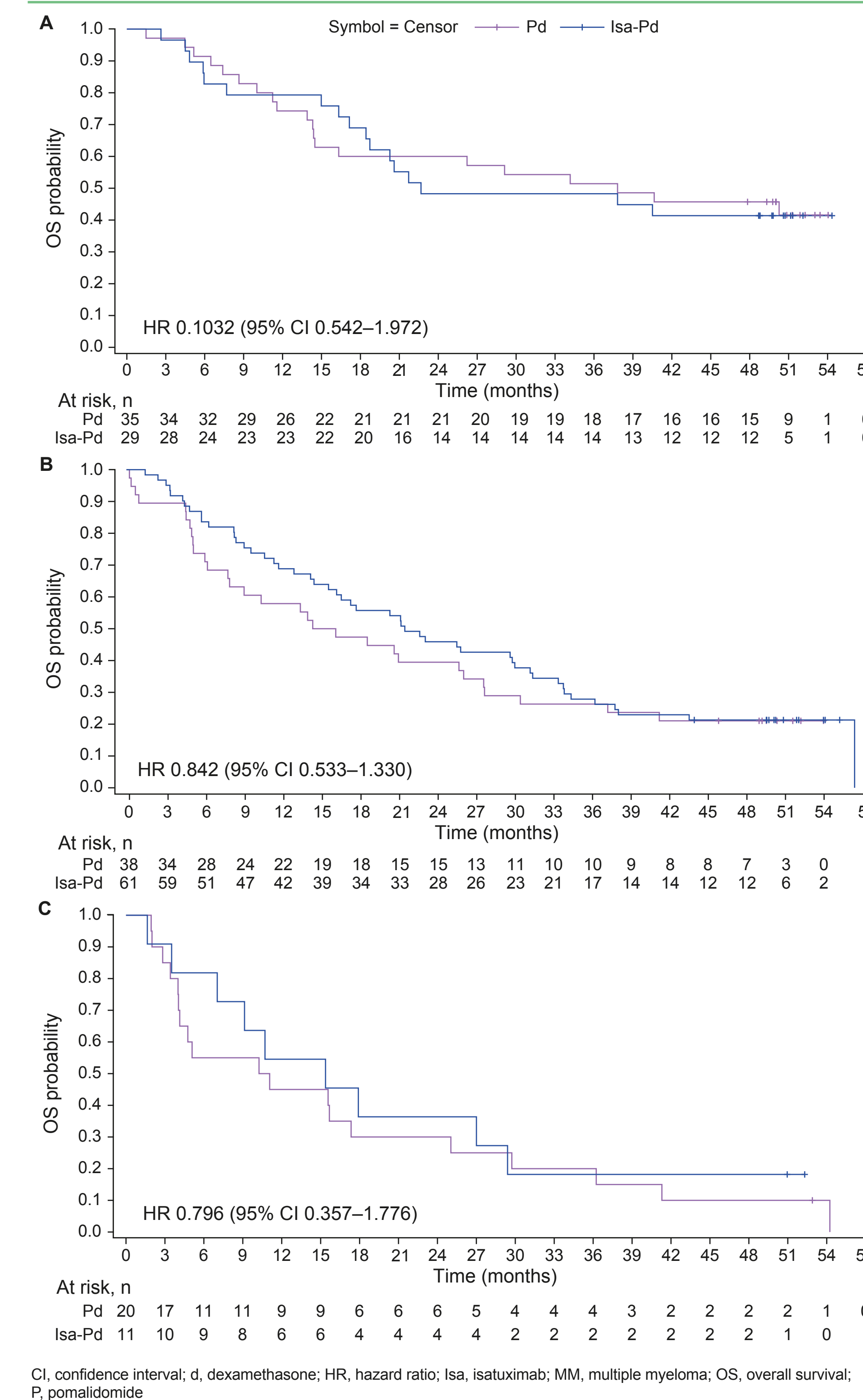


Figure 4. Best overall responses in ICARIA-MM by risk category

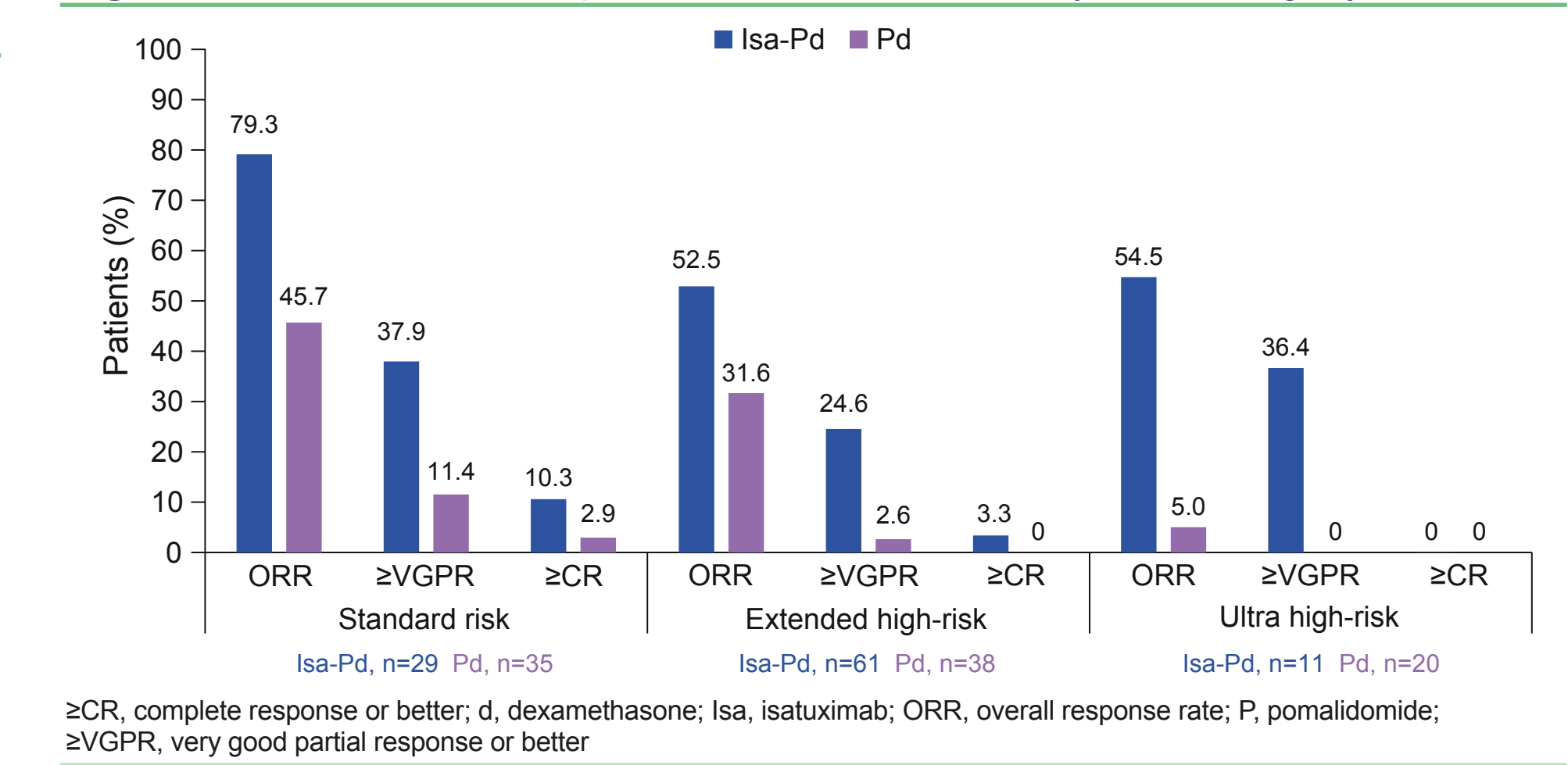


Figure 5. Best overall responses in IKEMA by risk category

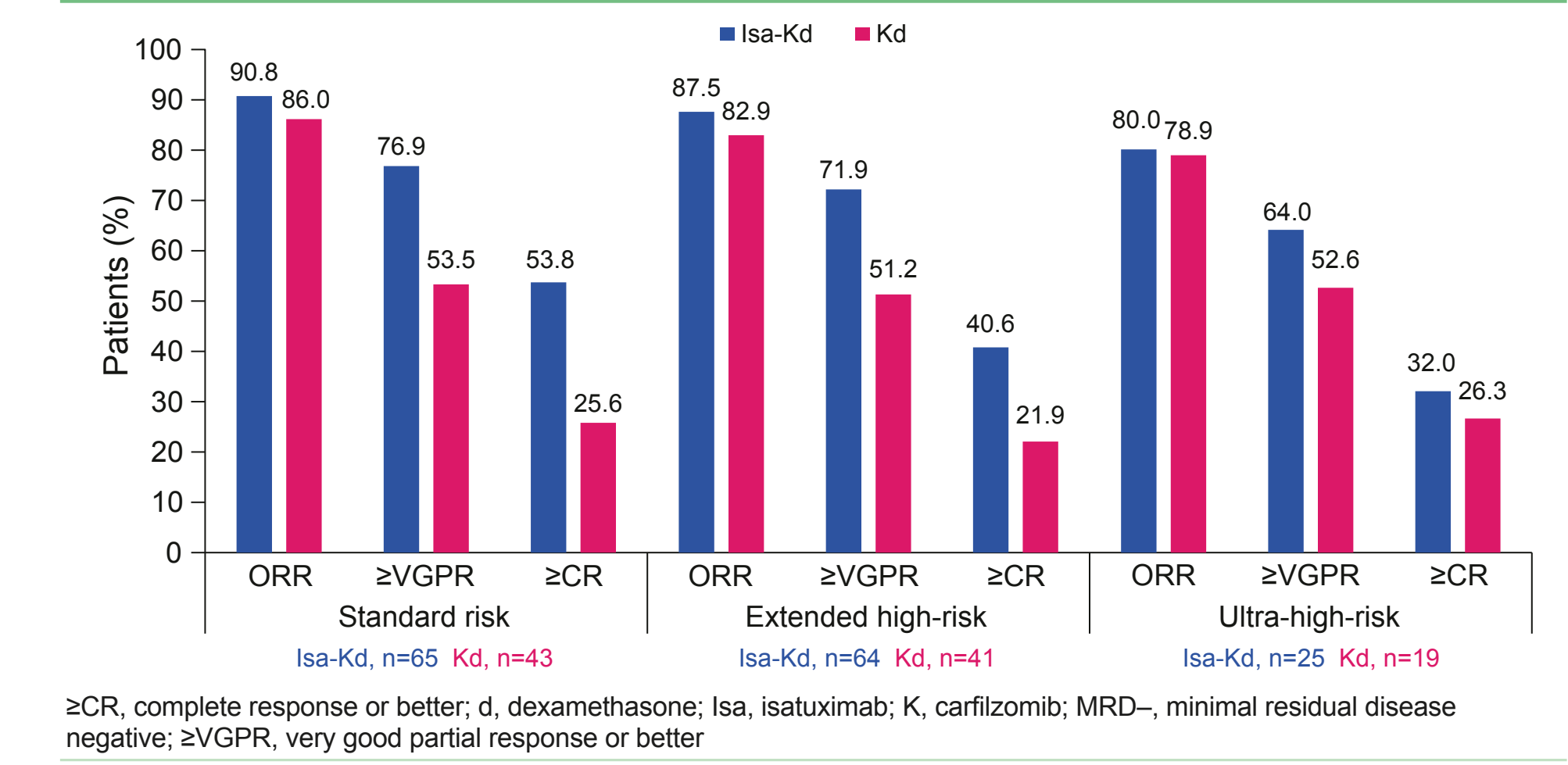
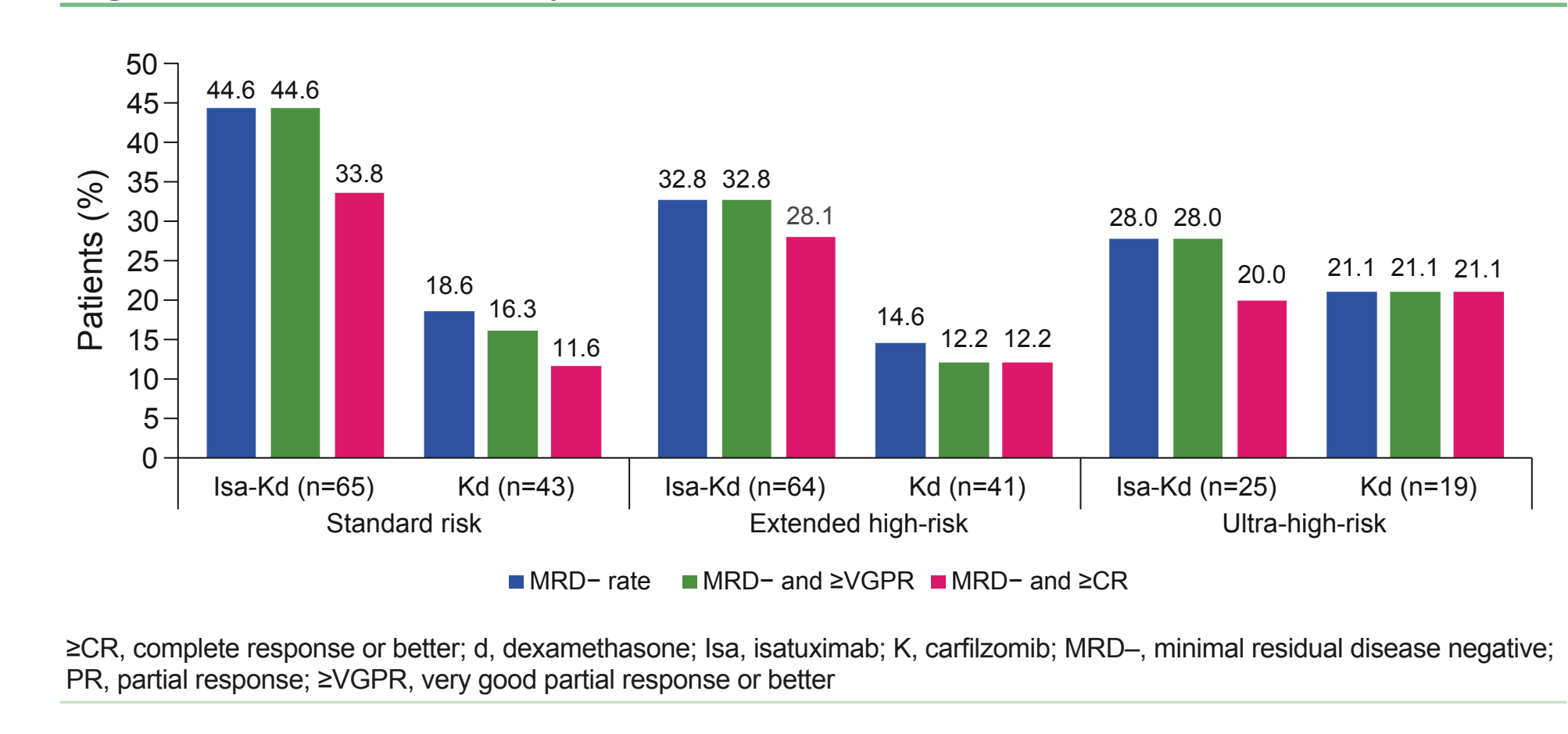


Figure 6. MRD- rates by risk status in IKEMA



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

ACKNOWLEDGMENTS: The ICARIA-MM and IKEMA studies were sponsored by Sanofi. The authors thank the participating patients and their families, and the study centers and investigators, for their contributions to the study. Coordination of the development of this poster, facilitation of author discussion, and critical review was provided by Aude Ayala Camargo, PhD, SOI Corinna Director at Sanofi. Medical writing support was provided by Kelly Lee, MPH of Envivo Pharma Group, funded by Sanofi.

DISCLOSURES: PM: 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&D, Honoraria — Amgen, BMS, Janssen, Sanofi, Takeda. TM: Research funding — Sanofi. TF: Honoraria — BMS, Janssen, Karyopharm, Oncocept, 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. SM, ML, R, CT, and ZK: Employees of Sanofi and may hold stock and/or stock options. PGR: Research funding — Celgene/BMS, Karyopharm, Oncocept, Takeda, Consulting — AstraZeneca, Celgene/BMS, GSK, Janssen, Karyopharm, Oncocept, Sanofi, Secura Bio, Takeda.

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