Updated Progression-free Survival and Depth of Response in IKEMA, a Randomized Phase 3 Trial of Isatuximab, Carfilzomib and Dexamethasone (Isa-Kd) vs Kd in Relapsed Multiple Myeloma

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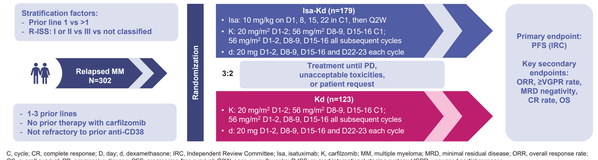
INTRODUCTION

- CD38 functions as a receptor and an ectoenzyme, uniformly expressed on multiple myeloma (MM) cells[1-5]
- Isatuximab (Isa), an IgG1 monoclonal antibody targeting a specific epitope of the CD38 transmembrane glycoprotein in MM, has multiple mechanisms of action,[6] including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis; direct apoptosis; immunomodulation; and inhibition of ectoenzyme activity
- Isa in combination with carfilzomib (K) and dexamethasone (d), is approved in various countries for patients with relapsed and/or refractory MM after ≥1 prior therapy, based on results of the IKEMA study[7]
- Preplanned interim analysis (IA) of IKEMA, assessing addition of Isa to Kd for the treatment of patients with relapsed MM, demonstrated:[8]
  - A significant improvement in progression-free survival (PFS) vs Kd, as per the Independent Review Committee (hazards ratio [HR], 0.53; 99% confidence interval [CI], 0.32–0.89; one-sided p=0.0007)
  - Improved rates of very good partial response or better (≥VGPR; 72.6% vs 56.1%), minimal residual disease negativity (MRD-; 29.6% vs 13.0%), and complete response (CR; 39.7% vs 27.6%), in the intent to treat (ITT) population
  - A manageable safety profile
- This prespecified analysis evaluated longer term outcomes for PFS, PFS2 (defined as the time from randomization to disease progression on next-line treatment or death, whichever occurred first), MRD- rate, CR rate, MRD- and CR rate in all randomized patients, and safety

METHODS

- Adult patients with relapsed MM, who had received 1–3 prior lines of therapy, were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123). The study design and dosing schedules are shown in **Figure 1**[9]
- Isa 10 mg/kg was given intravenously (IV) weekly for 4 weeks and then every 2 weeks; Kd (20/56 mg/m²) was administered in both arms

Figure 1. IKEMA (NCT03275285) study design



C, cycle; CR, complete response; D, day; d, dexamethasone; IRC, Independent Review Committee; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q2W, once every 2 weeks; R-ISS, revised international staging system; VGPR, very good partial response

RESULTS

Patient demographics and baseline characteristics

- Patient demographic and baseline characteristics were balanced between the treatment arms **(Table 1)**

Table 1. Key patient demographics and baseline characteristics

ITT population	Isa-Kd (n=179)	Kd (n=123)
Age in years, median (range)	65.0 (37–86)	63.0 (33–90)
Age in years, by category, n (%)		
<65	88 (49.2)	66 (53.7)
65 – <75	74 (41.3)	47 (38.2)
≥75	17 (9.5)	10 (8.1)
CrCl <60 mL/min/1.73 m² (MDRD)*, n (%)	43 (26.1)	18 (16.2)
ISS stage at baseline, n (%)		
Stage I	89 (49.7)	71 (57.7)
Stage II	63 (35.2)	31 (25.2)
Stage III	26 (14.5)	20 (16.3)
Cytogenetic risk at baseline†, %		
High	42 (23.5)	31 (25.2)
Standard	114 (63.7)	78 (63.4)
Missing	23 (12.8)	14 (11.4)
1q21+, n (%)†	75 (41.9)	52 (42.3)

ITT population	Isa-Kd (n=179)	Kd (n=123)
Prior lines of therapy, median (range)‡	2 (1–4)	2 (1–4)
1, n (%)	79 (44.1)	55 (44.7)
2, n (%)	64 (35.8)	36 (29.3)
3, n (%)	33 (18.4)	30 (24.4)
Prior proteasome inhibitors	166 (92.7)	105 (85.4)
Prior IMiDs	136 (76.0)	100 (81.3)
Patients refractory to, n (%)		
IMID	78 (43.6)	58 (47.2)
Lenalidomide	57 (31.8)	42 (34.1)
PI	56 (31.3)	44 (35.8)
Last regimen	89 (49.7)	73 (59.3)

*Incidence calculated on patients with race reported in CRF: 165 patients in Isa-Kd arm, 111 patients in Kd arm
†Cytogenetics by central lab – cytogenetic risk defined with cut-off 50% for del17p, 30% for t(4;14) and t(14;16); did not include 1q21+
**By central lab (cut-off 30%): 1q21+ included gain 1q21 (3 copies) and amplification 1q21 (4 or more copies)
‡3 patients (1.7%) and 2 patients (1.6%) had >3 prior lines in Isa-Kd and Kd arms, respectively
CrCl, creatinine clearance; d, dexamethasone; CRF, case report form; IMID, immunomodulatory drug; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; MDRD, modification of diet in renal disease; ISS, international staging system; PI, proteasome inhibitor

Patient disposition

- At cut-off, Jan 14, 2022, with a median follow-up of 44 months, 27.4% (n=49) of patients in Isa-Kd and 8.9% (n=11) of patients in Kd arms continued on treatment **(Figure 2)**

Figure 2. Patient disposition

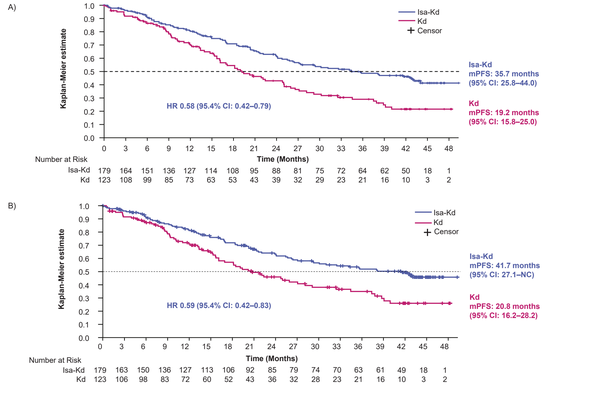


AE, adverse event; d, dexamethasone; Isa, isatuximab; K, carfilzomib; PD, progressive disease; PFS, progression-free survival

Efficacy

- Updated PFS was consistent with the IA results[8] and demonstrated significant benefit in favor of Isa-Kd (vs Kd): HR 0.58 (95.4% CI 0.42–0.79) with median PFS 35.7 vs 19.2 months in Isa-Kd vs Kd **(Figure 3A)**
- PFS as per FDA request/sensitivity for other countries (censoring occurring >8 weeks after last valid assessment) was 41.7 vs 20.8 months (HR 0.59, 95.4% CI 0.42-0.83), consistent with the interim analysis **(Figure 3B)**
- A consistent benefit was noted for Isa-Kd vs Kd in PFS subgroup analyses including poor prognosis patients, such as elderly by age ≥65 years, impaired renal function (<60 mL/min/1.73 m²), high-risk cytogenetics, 1q21+ status and refractory to lenalidomide **(Figure 4)**
- With additional follow up and using the Hydrashift 2/4 isatuximab immunofixation assay to rule out potential Isa interference in CR determination, final CR rate (Isa-Kd vs Kd) was 44.1% vs 28.5% (odds ratio [OR] 2.09, 95% CI 1.26–3.48)
- Deeper responses were seen with Isa-Kd vs Kd in the ITT population; for Isa-Kd, MRD- rate was 33.5% (29.6% at IA), and MRD- and CR rate was 26.3% (20.1% at IA) **(Figure 5)**
- Addition of Isa to Kd delayed the time to next treatment (44.9 vs 25.0 months) and the fewer patients received further anti-myeloma treatment (44.1% vs 64.2%) **(Figure 6)**
- Benefit of Isa-Kd over Kd was maintained late through PFS2; PFS2 was 47.2 vs 35.6 months in Isa-Kd vs Kd, with HR 0.68 (95% CI 0.50–0.94) **(Figure 7)**
- A trend in OS was observed in favor of Isa-Kd vs Kd patients, with HR 0.78 (95% CI: 0.54 to 1.12), and survival probability of 68.7% vs 62.9% at 36 months and 66.3% vs 54.5% at 42 months **(Figure 8)**; final OS is planned 3 years after interim PFS analysis
  - Death events in Isa-Kd vs Kd were reported in 35.8% and 43.9% patients, respectively

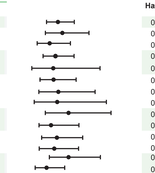
Figure 3. Updated PFS as per the IRC assessment : A) ITT population; B) By FDA censoring rules*



*Primary PFS analysis as per FDA *post-hoc* request and prior initial filing. CI, confidence interval; d, dexamethasone; FDA, Food and Drug Administration; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; m, median; MM, multiple myeloma; PFS, progression-free survival; PI, proteasome inhibitor

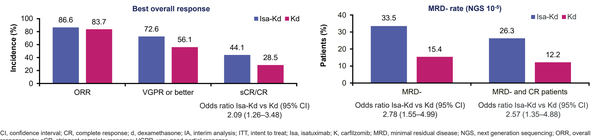
Figure 4. PFS subgroup analyses

Subgroup	Isa-Kd Events/total	Kd Events/total	Hazard ratio (95% CI)
All patients	86/179	77/123	0.576 (0.418–0.792)
Age			
<65 years	43/88	38/66	0.637 (0.410–0.990)
≥65 years	43/91	39/57	0.497 (0.321–0.771)
Baseline eGFR (MDRD)			
≥60 mL/min/1.73 m²	55/122	60/93	0.553 (0.382–0.801)
<60 mL/min/1.73 m²	23/43	10/18	0.562 (0.266–1.189)
ISS staging at study entry			
I	39/89	43/71	0.541 (0.350–0.837)
II	34/63	17/31	0.608 (0.336–1.099)
III	13/26	16/20	0.607 (0.290–1.268)
High-risk cytogenetic status			
Yes	26/42	21/31	0.724 (0.406–1.290)
No	50/114	48/77	0.508 (0.341–0.758)
1q21+			
Yes	39/75	35/52	0.582 (0.368–0.923)
No	39/84	33/55	0.546 (0.342–0.873)
Number of prior lines of therapy (as per IRT)			
1	41/80	31/55	0.712 (0.445–1.138)
>1	45/99	46/68	0.460 (0.302–0.698)
Prior PI treatment*			
Yes	43/81	26/47	0.824 (0.506–1.343)
No	43/98	51/76	0.434 (0.286–0.657)
Prior IMiD treatment*			
Yes	37/81	37/62	0.562 (0.355–0.892)
No	49/98	40/61	0.560 (0.367–0.854)
Refractory to lenalidomide			
Yes	31/57	30/42	0.586 (0.353–0.972)
No	55/122	47/81	0.560 (0.378–0.829)



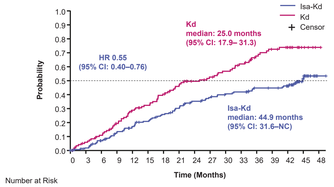
*163 patients in Isa-Kd and 102 in Kd had received prior bortezomib treatment; 8 patients in each arm prior ixazomib. 72 patients in Isa-Kd and 59 in Kd had received prior lenalidomide treatment; 91 patients in Isa-Kd and 67 in Kd prior thalidomide, 7 patients in Isa-Kd and 4 in Kd prior pomalidomide
CI, confidence interval; d, dexamethasone; eGFR, estimated glomerular filtration rate; IMID, immunomodulatory drug; Isa, isatuximab; IRT, Interactive response technology; ISS, International Staging System; K, carfilzomib; MDRD, modification of diet in renal disease equation; PFS, progression-free survival; PI, proteasome inhibitor

Figure 5. Depth of response



CI, confidence interval; CR, complete response; d, dexamethasone; IA, interim analysis; ITT, intent to treat; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; NGS, next generation sequencing; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response

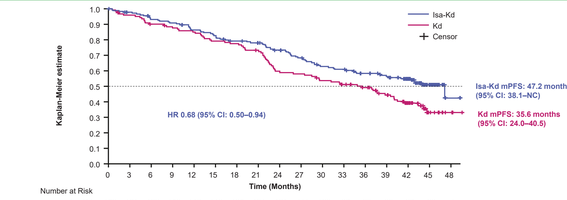
Figure 6. Time to next treatment (ITT population)



ITT population	Isa-Kd (n=179)	Kd (n=123)
Patients with further anti-myeloma treatment, n (%)	79 (44.1)	79 (64.2)
Main treatments, n (%)		
Alkylating agents	41 (51.9)	42 (53.2)
Proteasome inhibitors	36 (45.6)	26 (32.9)
Bortezomib	22 (27.8)	18 (22.8)
Carfilzomib	6 (7.6)	5 (6.3)
Ixazomib	14 (17.7)	6 (7.6)
Immunomodulatory drugs	64 (81.0)	61 (77.2)
Lenalidomide	34 (43.0)	34 (43.0)
Pomalidomide	38 (48.1)	35 (44.3)
Thalidomide	6 (7.6)	6 (7.6)
Anti-CD38 agents	20 (25.3)	48 (60.8)
Daratumumab	20 (25.3)	43 (54.4)
Isatuximab	1 (1.3)	9 (11.4)
Further transplant	12 (15.2)	14 (17.7)

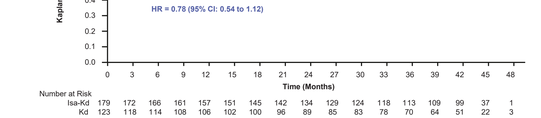
CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; m, median; NC, not calculable

Figure 7. PFS2 (ITT population)



PFS2 was defined as the time from randomization to disease progression on next-line treatment or death, whichever occurred first
CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; m, median; NC, not calculable; PFS, progression-free survival

Figure 8. Overall Survival (ITT population)



CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; m, median; OS, overall survival; PFS, progression-free survival

Treatment duration and relative dose intensity

- Longer treatment duration in the Isa-Kd arm did not have an impact on backbone dose intensities **(Table 2)**

Table 2. Treatment duration and relative dose intensity

	Isa-Kd (n=177)	Kd (n=122)
Median treatment duration, weeks (range)	94.0 (1–215)	61.9 (1 - 208)
Relative dose intensity (%), median (range)		
Isatuximab	93.2 (66.7–108.2)	-
Carfilzomib	89.5 (18.2–108.7)	90.8 (41.5–108.6)
Dexamethasone	82.6 (19.3–101.1)	88.1 (23.1–101.6)
Total number of cycles	4405	2181
Cycle delayed, n (%)	510 (11.6)	235 (10.8)
Between 4 and 7 days	265 (6.0)	133 (6.1)
More than 7 days	245 (5.6)	102 (4.7)

d, dexamethasone; Isa, isatuximab; K, carfilzomib

Safety

- Safety findings were consistent with prior IA results
- In Isa-Kd vs Kd, Grade ≥3 TEAEs were observed in 83.6% vs 73.0% patients, serious TEAEs in 70.1% vs 59.8% patients; TEAEs leading to definitive discontinuation in 12.4% vs 18.0% patients; and fatal TEAEs during study treatment in 5.6% vs 4.9% patients **(Table 3)**
- Considering the duration of exposure (event rate per year, **Table 4**), the increase in Grade ≥3 TEAEs in Isa-Kd vs Kd was lower in final analysis than in IA; it did not lead to a higher rate of serious TEAEs
- The most common, any-grade non-hematologic TEAEs in Isa-Kd were infusion reactions (45.8%; mostly grade 1-2, at first infusion), diarrhea (39.5%), hypertension (37.9%) and upper respiratory tract infection (37.3%); incidence of cardiac failure events was similar in both study arms **(Table 5)**

Table 3. Safety overview

TEAE overview, n (%)	Isa-Kd (n=177)	Kd (n=122)
Any TEAE	175 (98.9)	119 (97.5)
Grade ≥3 TEAEs	148 (83.6)	89 (73.0)
Drug-related grade ≥3 TEAEs	97 (54.8)	63 (51.6)
Serious TEAEs	124 (70.1)	73 (59.8)
Serious drug-related TEAEs	49 (27.7)	34 (27.9)
Any TEAE leading to definitive discontinuation	22 (12.4)	22 (18.0)
Any TEAE leading to premature discontinuation		
Isatuximab	1 (0.6)	-
Carfilzomib	31 (17.5)	1 (0.8)
Dexamethasone	23 (13.0)	7 (5.7)
Fatal TEAEs during study treatment	10 (5.6)	6 (4.9)

d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse event

Table 4. Safety overview - Event rate per patient year

	Interim Analysis		Final Analysis	
TEAE overview, %	**Isa-Kd (n=177)**	**Kd (n=122)**	**Isa-Kd (n=177)**	**Kd (n=122)**
Any TEAE	10.94	9.41	9.01	7.78
Grade ≥3 TEAEs	1.26	1.05	1.08	0.97
Grade ≥ 5 TEAEs	0.03	0.03	0.03	0.03
Serious TEAEs	0.70	0.72	0.58	0.62
Any TEAE leading to definitive discontinuation	0.07	0.13	0.06	0.12

d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse event

Table 5. Treatment-emergent adverse events

	Isa-Kd (n=177)		Kd (n=122)	
Selected TEAEs Preferred term, n (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Infusion reaction	81 (45.8)	1 (0.6)	4 (3.3)	0
Diarrhea	70 (39.5)	5 (2.8)	39 (32.0)	3 (2.5)
Hypertension	67 (37.9)	40 (22.6)	43 (35.2)	28 (23.0)
Upper respiratory tract infection	66 (37.3)	6 (3.4)	33 (27.0)	2 (1.6)
Fatigue	56 (31.6)	10 (5.6)	25 (20.5)	1 (0.8)
Dyspnea	54 (30.5)	10 (5.6)	27 (22.1)	1 (0.8)
Pneumonia	48 (27.1)	33 (18.6)	26 (21.3)	15 (12.3)
Cardiac failure events				
Cardiac failure, any class*	15 (8.5)	8 (4.5)	9 (7.4)	5 (4.1)
Hematologic laboratory abnormalities				
Anemia	177 (100)	43 (24.3)	121 (99.2)	26 (21.3)
Neutropenia	100 (56.5)	36 (20.3)	55 (45.1)	9 (7.4)
Thrombocytopenia	168 (94.9)	53 (29.9)	109 (89.3)	29 (23.8)

*Grouping using MedDRA SMQ cardiac failure narrow terms
d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse events

CONCLUSIONS

- Results of this prespecified PFS updated analysis are consistent with the IA and demonstrate improvement in PFS with addition of Isa to Kd (HR: 0.58 [95.4% CI: 0.42–0.79] vs Kd), with unprecedented median PFS of 3 years, the longest PFS on a PI backbone in the relapsed MM setting
- Consistent PFS benefit was observed across patients subgroups, including patients with poor prognosis
- The impressive CR rate and MRD- CR rate in ITT of 44.1% and 26.3% in Isa-Kd vs 28.5% and 12.2% in Kd, are the highest rates reported in a PI-based regimen in relapsed MM
- PFS2 in favor of Isa-Kd vs Kd (HR: 0.68 [95% CI: 0.496–0.941]) supports sustained treatment effect through subsequent therapies
- With 2 additional years of follow-up and despite the COVID-19 pandemic, the safety profile remains similar to the IA results
- At median follow up of ~44 months, mPFS of nearly 3 years and MRD negativity in 1/3 of patients further support Isa-Kd as a standard of care for relapsed MM

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