Isatuximab Plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: IKEMA Subgroup Analysis by Number of Prior Lines of Treatment

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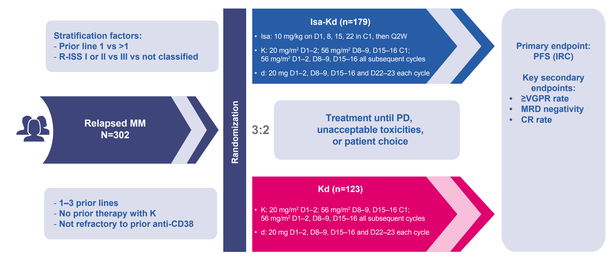
INTRODUCTION

- Recently, there have been significant advances in the number of therapies available for patients with multiple myeloma (MM). However, patients continue to experience several relapses and/or become refractory to treatments[1,2]
- There is limited guidance from the treatment guidelines on the sequencing of therapies. The number of previous lines of therapy and the types of agents that a patient has received are important considerations when determining treatment sequencing in the relapsed/refractory MM (RRMM) setting[3]
- Based on the Phase 3 ICARIA-MM study, the anti-CD38 monoclonal antibody isatuximab (Isa) is approved in several countries in combination with pomalidomide and dexamethasone (d) for the treatment of adult patients with RRMM who have received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor[4,5]
- Based on the Phase 3 IKEMA study (NCT03275285), Isa is approved in combination with carfilzomib (K) and d, in the United States for RRMM patients after 1–3 prior lines of therapy, in the European Union and other countries for patients with relapsed MM who have received ≥1 prior therapy, and in Japan for patients with RRMM[4–6]
- The final IKEMA progression-free survival (PFS) analysis, performed 2 years after the prespecified interim analysis, confirmed that Isa-Kd significantly improved PFS vs Kd in patients with relapsed MM (hazard ratio [HR] 0.58; 95.4% confidence interval [CI] 0.42–0.79), with clinically meaningful increases in minimal residual disease negativity (MRD−; 33.5% vs 15.4%) and complete response (CR; 44.1% vs 28.5%) rates in the intent-to-treat population, and a manageable safety profile[7]
- In this post hoc subgroup analysis of IKEMA, we evaluated the efficacy and safety of Isa-Kd by the observed number of prior lines of therapy (1 vs >1)

METHODS

- A total of 302 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 schedule are shown in **Figure 1**
- The primary study endpoint was PFS, assessed by independent response committee using the International Myeloma Working Group criteria, based on central lab M-protein quantification and central radiological evaluation
  - These updated, longer-term data are based on a prespecified final PFS analysis of IKEMA at 159 PFS events
- Key secondary endpoints included overall response rate (ORR), very good partial response or better (≥VGPR), MRD−, and CR rates
  - MRD− was assessed by next-generation sequencing using Adaptive clonoSEQ Assay (Adaptive Biotechnologies) at 10^{-5} sensitivity
  - CR rate was updated using the Hydrashift 2/4 isatuximab immunofixation assay, which was used to remove Isa and to assess residual monoclonal M-protein
- Median PFS (mPFS) and corresponding CIs were calculated by the Kaplan–Meier method. HR estimates were determined using the unstratified Cox proportional hazard model
- Sensitivity analyses were done to adjust the Cox models for baseline covariates that were not balanced between the two arms
- Adverse events (AEs) were graded per the National Cancer Information Center Common Terminology Criteria for AEs (NCI-CTCAE) version 4.03

Figure 1. IKEMA study design: Isa-Kd vs Kd in patients with relapsed MM



C, cycle; CR, complete response; D, day; d, dexamethasone; IRC, independent response committee; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; 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 baseline characteristics

- At the median follow-up of 44 months of the 302 randomized patients, 134 (44.4%; 79 Isa-Kd, 55 Kd) had received 1 prior line of therapy, and 168 (55.6%; 100 Isa-Kd, 68 Kd) had received >1 prior line of therapy
- Baseline characteristics in each subgroup are shown in **Table 1**
  - In the 1 prior line subgroup, more Isa-Kd vs Kd patients were: aged ≥65 years (57.0% vs 40.0%), had β2-microglobulin at study entry >3.5 mg/L (34.2% vs 25.5%), had renal impairment (23.9% vs 9.8%), and had 1q21 amplification (21.6% vs 13.0%)
  - In the >1 prior line subgroup, a similar proportion of patients were International Staging System Stage III, standard-risk cytogenetic abnormalities, 1q21+, and refractory to last regimen in the Isa-Kd vs Kd subgroups. Patients in the Isa-Kd arm had shorter time from initial diagnosis to randomization (3.98 vs 5.27 years)

Table 1. Disease and patient baseline characteristics by number of prior lines of therapy

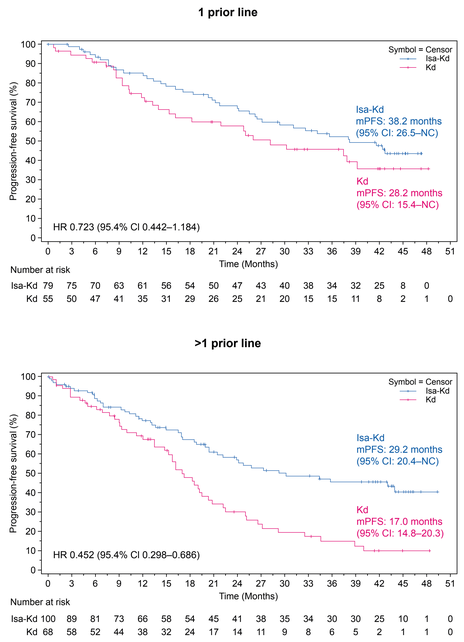
	1 prior line		>1 prior line	
	Isa-Kd (n=79)	Kd (n=55)	Isa-Kd (n=100)	Kd (n=68)
Time from initial diagnosis of MM to randomization in years, median (range)	2.72 (0.4–11.8)	2.68 (0.2–10.4)	3.98 (0.4–17.9)	5.27 (0.6–21.3)
Time since last ASCT to randomization in years, median (range)	2.5 (0.5–10.8)	2.6 (0.3–9.7)	3.2 (0.3–13.3)	2.9 (0.6–9.4)
Age in years, median (range)	66.0 (37–86)	63.0 (33–75)	64.0 (38–83)	65.0 (38–90)
Age in years, by category, n (%)				
<65	34 (43.0)	33 (60.0)	54 (54.0)	33 (48.5)
65 to <75	35 (44.3)	21 (38.2)	39 (39.0)	26 (38.2)
≥75	10 (12.7)	1 (1.8)	7 (7.0)	9 (13.2)
β2-microglobulin at study entry in mg/L, n (%)				
<3.5	52 (65.8)	41 (74.5)	51 (51.0)	38 (55.9)
≥3.5 to <5.5	20 (25.3)	9 (16.4)	30 (30.0)	15 (22.1)
≥5.5	7 (8.9)	5 (9.1)	19 (19.0)	15 (22.1)
CrCl <60 mL/min/1.73 m² (MDRD)*, n (%)	17/71 (23.9)	5/51 (9.8)	26/92 (28.3)	13/59 (22.0)
ISS stage at study entry, n (%)				
Stage I	47 (59.5)	37 (67.3)	42 (42.0)	34 (50.0)
Stage II	25 (31.6)	13 (23.6)	38 (38.0)	18 (26.5)
Stage III	7 (8.9)	5 (9.1)	19 (19.0)	15 (22.1)
Unknown	0	0	1 (1.0)	1 (1.5)
Cytogenetic risk at baseline, n (%)				
High-risk CA†	22 (27.8)	12 (21.8)	20 (20.0)	19 (27.9)
del(17p)	11 (13.9)	8 (14.5)	7 (7.0)	8 (11.8)
t(4;14)	8 (10.1)	6 (10.9)	14 (14.0)	14 (20.6)
t(14;16)	5 (6.3)	0	1 (1.0)	0
Standard-risk CA	51 (64.6)	35 (63.6)	63 (63.0)	43 (63.2)
Unknown or missing	6 (7.6)	8 (14.5)	17 (17.0)	6 (8.8)
1q21+, n (%)‡	33 (41.8)	26 (47.3)	42 (42.0)	26 (38.2)
1q21 amplification	16 (21.6)	6 (13.0)	16 (18.8)	9 (14.8)
Prior PI, n (%)	73 (92.4)	43 (78.2)	93 (93.0)	62 (91.2)
Prior IMiD agents, n (%)	44 (55.7)	38 (69.1)	92 (92.0)	62 (91.2)
Patients refractory to, n (%)				
IMiD agents	13 (16.5)	14 (25.5)	65 (65.0)	44 (64.7)
Lenalidomide	9 (11.4)	9 (16.4)	48 (48.0)	33 (48.5)
PI	11 (13.9)	11 (20.0)	45 (45.0)	33 (48.5)
IMiD agents and PI	3 (3.8)	4 (7.3)	32 (32.0)	23 (33.8)
Last regimen	23 (29.1)	27 (49.1)	66 (66.0)	46 (67.6)

*Incidence calculated in patients with race reported in case report form: 165 patients in Isa-Kd arm, 111 patients in Kd arm in the overall IKEMA ITT population.
†High-risk CA is defined as the presence of del(17p) (50% threshold) and/or translocation t(4;14) and/or translocation t(14;16) (30% threshold).
‡By central lab (30% threshold): 1q21+ included 1q21 gain (3 copies) and 1q21 amplification (≥4 copies).
ASCT, autologous stem cell transplant; CA, chromosomal abnormality; CrCl, creatinine clearance; d, dexamethasone; IMiD, immunomodulatory drug; Isa, isatuximab; ISS, International Staging System; ITT, intention-to-treat; K, carfilzomib; MDRD, Modification of Diet in Renal Disease; MM, multiple myeloma; PI, proteasome inhibitor

Efficacy

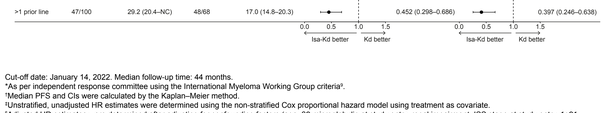
- The addition of Isa to Kd improved PFS regardless of number of prior lines of therapy (**Figure 2**)
  - In the 1 prior line subgroup, mPFS was 38.2 months for Isa-Kd vs 28.2 for Kd (10.0 months; HR 0.723; 95.4% CI 0.442–1.184)
  - In the >1 prior line subgroup, mPFS was 29.2 months for Isa-Kd vs 17.0 for Kd (12.2 months; HR 0.452; 95.4% CI 0.298–0.686)
- When the Cox model was adjusted for the following baseline confounding factors which were not balanced between arms: age, β2-microglobulin at study entry, renal impairment, ISS stage at study entry, 1q21 amplification (≥4 copies), and prior exposure to proteasome inhibitors (PI) or immunomodulatory drug (IMiD) agents, the estimated HR for the 1 prior line subgroup improved from 0.723 to 0.595 and for the >1 prior line subgroup improved from 0.452 to 0.397 (**Figure 3**)

Figure 2. Kaplan–Meier estimate of PFS* by number of prior lines of therapy in the intent-to-treat population



*Cut-off date: January 14, 2022. Median follow up time: 43.86 months 1 prior line and 44.06 months for >1 prior line.
CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; mPFS, median PFS; NC, not calculable; PFS, progression-free survival

Figure 3. PFS* with Isa-Kd vs Kd in IKEMA by number of prior lines of therapy, including adjusted HRs



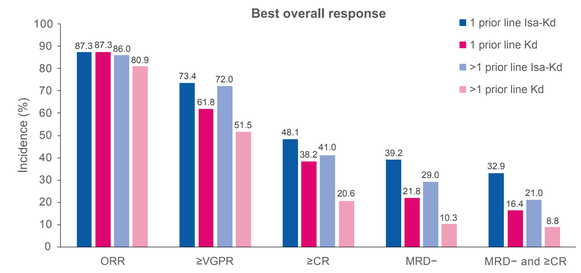
Cut-off date: January 14, 2022. Median follow-up time: 44 months.
*As per independent response committee using the International Myeloma Working Group criteria[3].
†Median PFS and CIs were calculated by the Kaplan–Meier method.
‡Unstratified, unadjusted HR estimates were determined using the non-stratified Cox proportional hazard model using treatment as covariate.
§Adjusted HR estimates were determined after adjusting for confounding factors (age, β2-microglobulin at study entry, renal impairment, ISS stage at study entry, 1q21 amplification, and prior exposure to PI or IMiD agents).
CI, confidence interval; d, dexamethasone; HR, hazard ratio; IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; mPFS, median progression-free survival; n/N, number of events/total number of patients; NC, not calculable; PI, proteasome inhibitor

- The addition of Isa to Kd improved depth of response (≥VGPR, MRD−, ≥CR, and MRD− and CR rates) both in patients who received 1 prior line as well as those who received >1 prior line (**Figure 4**)

Treatment exposure and safety

- The median treatment duration for Isa-Kd in the 1 prior line subgroup was 43 weeks longer vs Kd and for the >1 prior line subgroup was 25 weeks longer (**Table 2**)
  - The median relative dose intensity for all three drugs was comparable across arms and subgroups
- Isa-Kd had a manageable safety profile in patients regardless of number of prior lines of therapy and was consistent with the overall safety population (**Table 2**)
  - Serious treatment emergent AEs (TEAEs) occurred in 66.7% vs 51.9% of patients (1 prior line subgroup) and 72.7% vs 66.2% of patients (>1 prior line subgroup) with Isa-Kd vs Kd, respectively
  - TEAEs leading to definitive treatment discontinuations were lower in Isa-Kd than Kd regardless of number of prior lines: 9.0% vs 13.0% (1 prior line) and 15.2% vs 22.1% (>1 prior line)
  - TEAEs with fatal outcome during the treatment period occurred in 4 patients (5.1%) in the Isa-Kd arm in the 1 prior line of therapy subgroup vs none in the Kd arm, and in 6 patients (6.1%) in the Isa-Kd arm vs 6 patients (8.8%) in the Kd arm in the >1 prior line of therapy subgroup

Figure 4. Depth of response by the number of prior lines of therapy



CR, complete response; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD−, minimal residual disease negativity; ORR, overall response rate; VGPR, very good partial response

Table 2. Disease and patient baseline characteristics by number of prior lines of therapy

	1 prior line		>1 prior line	
	Isa-Kd (n=78)	Kd (n=54)	Isa-Kd (n=99)	Kd (n=68)
Treatment exposure				
Median treatment duration, weeks (range)	118.4 (11–209)	75.6 (4–208)	79.0 (1–215)	54.5 (1–193)
Number of cycles started per patient, median (range)	27.5 (3–50)	18.5 (1–46)	19.0 (1–50)	12.5 (1–47)
Total number of cycles	2140	1136	2265	1045
Median relative dose intensity, % (range)				
Isatuximab	92.4 (78.4–103.0)	–	93.8 (66.7–108.2)	–
Carfilzomib	89.8 (25.4–108.6)	87.5 (44.7–103.4)	89.4 (18.2–108.7)	91.7 (41.5–108.6)
Dexamethasone	81.9 (19.3–100.0)	87.4 (26.6–101.6)	83.1 (24.5–101.1)	88.9 (23.1–101.1)
Safety summary, n (%)				
Any TEAE	77 (98.7)	53 (98.1)	98 (99.0)	66 (97.1)
Grade ≥3 TEAEs	65 (83.3)	39 (72.2)	83 (83.8)	50 (73.5)
Serious TEAEs*	52 (66.7)	28 (51.9)	72 (72.7)	45 (66.2)
Any TEAE leading to definitive treatment discontinuation	7 (9.0)	7 (13.0)	15 (15.2)	15 (22.1)
Any TEAE leading to premature discontinuation				
Isatuximab	0	0	1 (1.0)	0
Carfilzomib	20 (25.6)	1 (1.9)	11 (11.1)	0
Dexamethasone	15 (19.2)	4 (7.4)	8 (8.1)	3 (4.4)
Fatal TEAEs during study treatment	4 (5.1)	0	6 (6.1)	6 (8.8)

*TEAE with a start date before the operational cut-off date and becoming serious after the operational cut-off date were not counted as serious TEAE in this analysis.
d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE; treatment emergent adverse event

CONCLUSIONS

- The addition of Isa to Kd improved PFS and depth of response in patients with relapsed MM with a manageable safety profile, regardless of the number of prior lines of therapy, including those with first relapse
- This post hoc subgroup analysis of IKEMA by number of prior lines has limitations, including small number of patients and imbalances between arms. In an attempt to correct for these imbalances, we created a Cox model which adjusted for unbalanced baseline confounding factors (age, β2-microglobulin at study entry, renal impairment, ISS stage at study entry, 1q21 amplification, and prior exposure to PI or IMiD agents). As a result, the estimated effect was maintained in favor of Isa-Kd vs Kd, and the HR improved from 0.723 to 0.595 for the 1 prior line subgroup and from 0.452 to 0.397 for the >1 prior line subgroup
- These results showed an overall meaningful treatment effect consistent with the benefit observed in the overall IKEMA study population and further support Isa-Kd as a standard-of-care treatment for patients with relapsed MM

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