Depth of Response of Isatuximab Plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: IKEMA Updated Analysis

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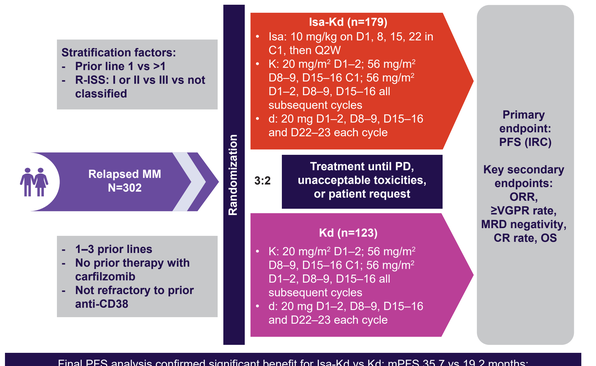
INTRODUCTION

- Isatuximab (Isa), an immunoglobulin (Ig) G1 monoclonal antibody targeting a specific epitope of the CD38 transmembrane glycoprotein in multiple myeloma (MM), has multiple mechanisms of action,[1] including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis; direct apoptosis; immunomodulation; and inhibition of ectoenzyme activity
  - CD38 functions as a receptor and an ectoenzyme, uniformly expressed on MM cells[2-6]
- Isatuximab, 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]
- Achievement of minimal residual disease negativity (MRD–) status in MM is associated with improved progression-free survival (PFS) and overall survival
- Here, we report updated, longer-term depth of response results from IKEMA, including MRD– status

METHODS

- This prespecified analysis evaluated PFS (primary endpoint) at 159 events and secondary endpoints of ≥complete response ([CR] + stringent CR), MRD–, and ≥CR + MRD– rates, as determined by Independent Response Committee (IRC) based on central laboratory data and IRC review of local radiology (**Figure 1**)
  - The HYDRASHIFT 2/4 isa immunofixation electrophoresis (IFE) test, which removes the interference of Isa in IFE assay, was used to update the ≥CR rate
- MRD was assessed by next-generation sequencing clonoSEQ assay in bone marrow aspirates from patients achieving ≥very good partial response (VGPR), and MRD status was reported at 10^{-5} sensitivity level
  - All randomized patients not reaching MRD– or without MRD assessment were considered as MRD+
- Secondary endpoints were compared between treatment arms using the Cochran-Mantel-Haenszel test. One-sided descriptive p-value is provided

Figure 1. IKEMA (NCT03275285) study design



Final PFS analysis confirmed significant benefit for Isa-Kd vs Kd: mPFS 35.7 vs 19.2 months; HR: 0.58 [95.4% CI: 0.42; 0.79] with a median follow-up of 44 months[8]

C, cycle; CD, cluster of differentiation; 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 treatment arms; at a median follow-up of 44 months (as of data cut off 14 Jan 2022), 27.4% of patients in the Isa-Kd arm continued on treatment

Table 1. Patient demographics and baseline characteristics: ITT population

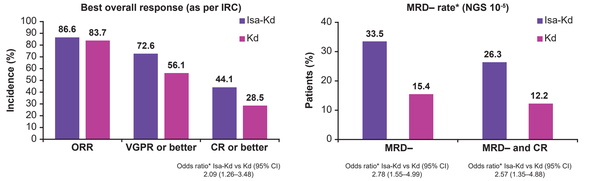
ITT population	Isa-Kd (n=179)	Kd (n=123)
Age in years, median (range)	65.0 (37–86)	63.0 (33–90)
Age in years, by category, n (%)		
<65	88 (49.2)	66 (53.7)
65 to <75	74 (41.3)	47 (38.2)
≥75	17 (9.5)	10 (8.1)
eGFR <60 mL/min/1.73 m² (MDRD)*, n (%)	43 (26.1)	18 (16.2)
ISS stage at study entry, n (%)		
Stage 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 study entry†, %		
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)
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 PIs	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. CRF, case report form; d, dexamethasone; eGFR, estimated glomerular filtration rate; IMiD, immunomodulatory drug; Isa, isatuximab; ISS, International Staging System; ITT, intent to treat; K, carfilzomib; MDRD, modification of diet in renal disease; PI, proteasome inhibitor.

Efficacy

- Deeper responses were seen with Isa-Kd vs Kd. The MRD– rate (NGS 10^{-5}) more than doubled in patients receiving Isa-Kd and deepened over time to 33.5% in the ITT population (vs 29.6% at time of interim analysis) (**Figure 2**)
- Depth and quality of response favored Isa-Kd, with higher rates of ≥PR, VGPR, CR, and MRD– vs Kd; time to first CR occurred earlier with Isa-Kd (**Figure 3**)
- MRD– rates with Isa-Kd were higher among patients with poor prognostic characteristics such as older age, renal impairment, higher ISS stage at diagnosis, 1q21+, more lines of prior therapy, and refractoriness to lenalidomide (**Figure 4**)
- More patients in the Isa-Kd arm achieved MRD–. In both arms, more patients achieving MRD– remained on treatment and a more pronounced PFS benefit was seen in MRD– patients (**Table 2** and **Figure 5**)

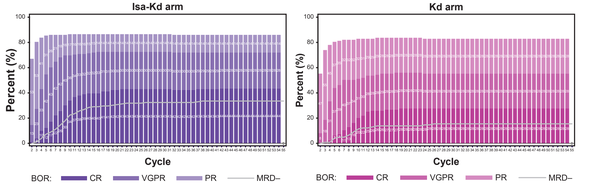
Figure 2. Depth of response: ITT population



*Stratified on randomization factors according to IRT.

CI, confidence interval; CR, complete response; d, dexamethasone; IRC, Independent Response Committee; IRT, interactive response technology; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; MRD, minimal residual disease; NGS, next generation sequencing; ORR, overall response rate; VGPR, very good partial response.

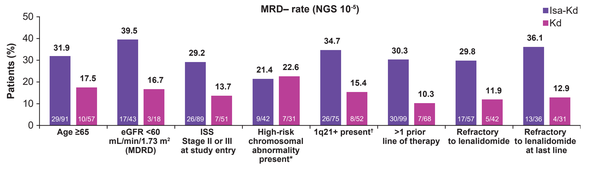
Figure 3. Depth of response over time*



*Cumulative best overall response based on Independent Response Committee by cycle.

BOR, best overall response; CR, complete response; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response.

Figure 4. MRD negativity rate among select subgroups



*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).

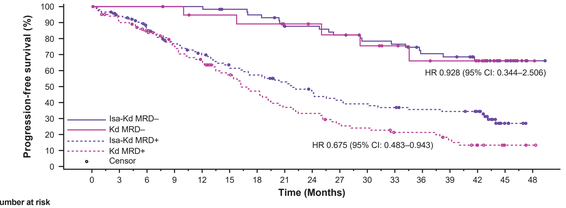
d, dexamethasone; eGFR, estimated glomerular filtration rate; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MDRD, modification of diet in renal disease; MRD, minimal residual disease; NGS, next generation sequencing.

Table 2. Patient disposition by MRD status

ITT population, n (%)	MRD– (n=79)		MRD+ (n=223)	
	Isa-Kd (n=60)	Kd (n=19)	Isa-Kd (n=119)	Kd (n=104)
Randomized and treated	60 (100)	19 (100)	117 (98.3)	103 (99.0)
Patients still on treatment	29 (48.3)	6 (31.6)	20 (16.8)	5 (4.8)
Patients with definitive treatment discontinuation	31 (51.7)	13 (68.4)	97 (81.5)	98 (94.2)

d, dexamethasone; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; MRD, minimal residual disease.

Figure 5. PFS by MRD status*



Number at risk

Isa-Kd MRD–	60	60	60	59	59	56	54	48	48	45	41	40	35	34	25	13	1
Kd MRD–	19	19	19	19	17	17	16	14	13	12	11	9	7	6	5	1	1
Isa-Kd MRD+	119	104	91	77	68	58	54	47	40	36	34	32	29	28	25	5	0
Kd MRD+	104	89	80	66	56	46	37	29	26	20	18	14	14	10	5	2	1

*HR was estimated using an unstratified Cox proportional hazards model with treatment group as factor.

CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; PFS, progression-free survival.

Safety

- Safety findings were consistent with overall population; addition of Isa to Kd did not increase fatal TEAEs or events leading to discontinuation (**Table 3**)

Table 3. Safety overview by MRD status

TEAE overview, n (%)	MRD– (n=79)		MRD+ (n=220)	
	Isa-Kd (n=60)	Kd (n=19)	Isa-Kd (n=117)	Kd (n=103)
Any TEAE	59 (98.3)	19 (100)	116 (99.1)	100 (97.1)
Grade ≥3 TEAEs	51 (85.0)	14 (73.7)	97 (82.9)	75 (72.8)
Drug-related Grade ≥3 TEAEs	37 (61.7)	10 (52.6)	60 (51.3)	53 (51.5)
Serious TEAEs	40 (66.7)	12 (63.2)	84 (71.8)	61 (59.2)
Serious drug-related TEAEs	16 (26.7)	7 (36.8)	33 (28.2)	27 (26.2)
Any TEAE leading to definitive discontinuation	2 (3.3)	2 (10.5)	20 (17.1)	20 (19.4)
Any TEAE leading to premature discontinuation				
Isatuximab	0 (0)	0 (0)	1 (0.9)	0 (0)
Carfilzomib	15 (25.0)	1 (5.3)	16 (13.7)	0 (0)
Dexamethasone	14 (23.3)	4 (21.1)	9 (7.7)	3 (2.9)
Fatal TEAEs during study treatment	1 (1.7)	0 (0)	9 (7.7)	6 (5.8)

d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- The impressive CR rate (44.1%) and MRD– and CR rate (26.3%) with Isa-Kd are the highest rates reported for a PI-based regimen in relapsed MM
- MRD– rates with Isa-Kd were higher among patients with poor prognostic characteristics, such as advanced age, renal impairment, higher ISS stage at diagnosis, 1q21+, more lines of prior therapy, and refractoriness to lenalidomide
- Achieving MRD– led to better PFS in both treatment arms, with Isa-Kd patients having a more than 2-fold higher likelihood of achieving both MRD– and MRD+ and CR
- The addition of isatuximab to Kd improved PFS even in patients that remained MRD+
- The observed clinically meaningful improvement in depth of response with Isa-Kd further supports its use as a standard-of-care therapy for relapsed MM

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