IKEMA Isatuximab Plus Carfilzomib and Dexamethasone in Pts With Early Versus Late Relapsed Multiple Myeloma: IKEMA Subgroup Analysis

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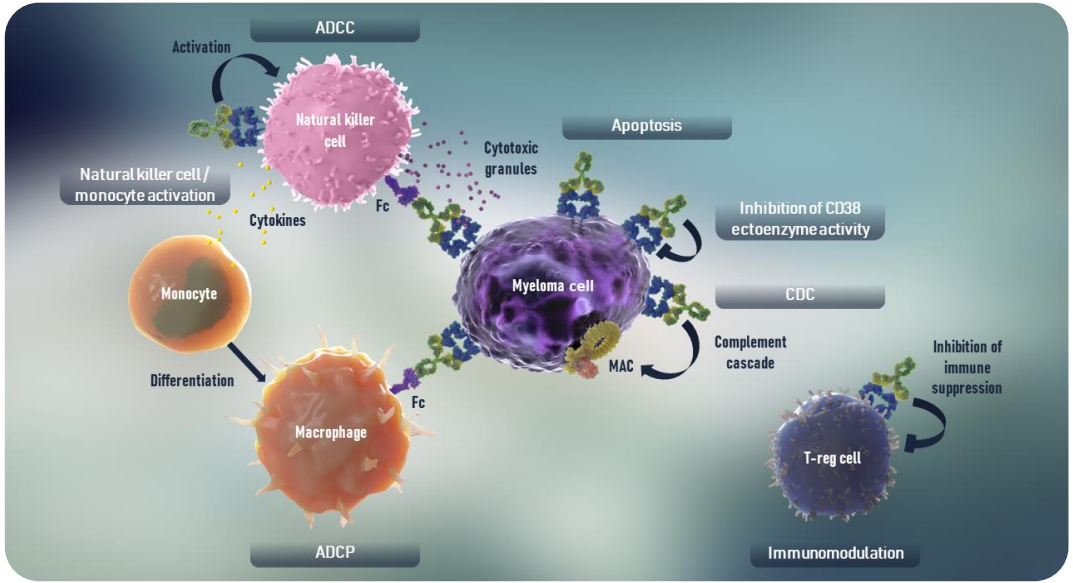
Isatuximab targets a specific epitope of CD38



CD38 functions as a receptor and an ectoenzyme, uniformly expressed on MM cells[1–5]

Isatuximab: IgG1 monoclonal antibody targeting a CD38 transmembrane glycoprotein in MM with multiple modes of action [6-8]:

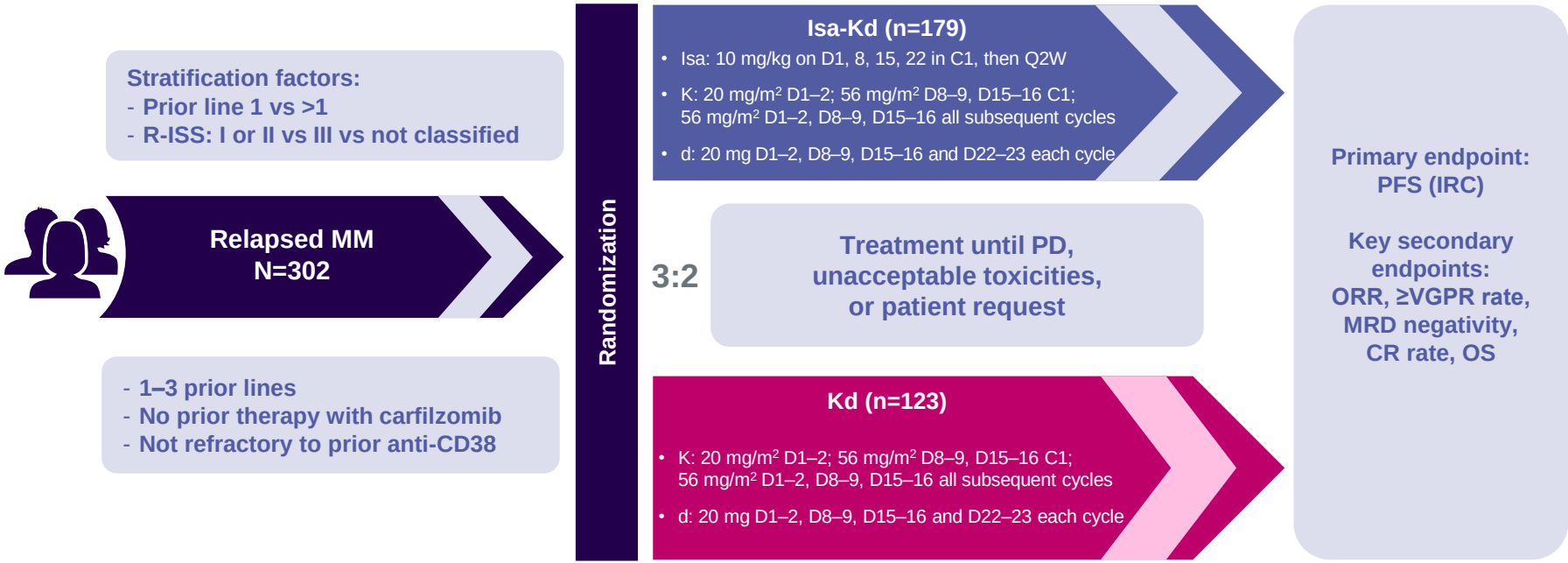
- **ADCC, ADCP, and CDC**
- **Direct apoptosis**
- **Immunomodulation**
- **Inhibition of ectoenzyme activity**

Isatuximab, in combination with carfilzomib and dexamethasone, 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]

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CD, cluster of differentiation; CDC, complement-dependent cytotoxicity; Fc, fragment crystallizable; Ig, immunoglobulin; MAC, membrane attack complex; MM, multiple myeloma; T-reg cell, T regulatory cell.

1. Lin P, et al. *Am J Clin Pathol*. 2004;121:482–488; 2. Angelopoulou MK, et al. *Eur J Haematol*. 2002;68:12–21; 3. Schwonzen M, et al. *Br J Haematol*. 1993;83:232–239;
4. Keyhani A, et al. *Leukemia Res*. 2000;24:153–159; 5. Domingo-Domènech E, et al. *Haematologica*. 2002;87:1021–1027; 6. Jiang H, et al. *Leukemia*. 2016;30:399–408;
7. Sanofi. SARCLISA [Package Insert]. Bridgewater, NJ, USA; 2021; 8. Tai YT, et al. *Oncotarget*. 2017;8:112166–112167.

Study design:[1,2] Isa-Kd vs Kd in relapsed multiple myeloma



IKEMA study: NCT03275285.
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.
1. Moreau P, et al. *Future Oncol*. 2020; 16(2):4347:4358; 2. Moreau P, et al. *Lancet* 2021;397:2361–2371.

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Background and objectives

- Patients with MM frequently relapse requiring successive lines of therapy; those who experience early relapse (within 12 months of therapy initiation) have worse outcomes[1]
- The final PFS analysis of IKEMA, performed 2 years after the prespecified interim analysis, at a median follow-up of 44 months, demonstrated:[2]
  - A significant improvement in PFS with Isa-Kd vs Kd, as per IRC (median PFS 35.7 [Isa-Kd] vs 19.2 months [Kd]; HR 0.58; 95.4% CI 0.42–0.79)
  - PFS analysis using FDA censoring rules* showed consistent results with the interim analysis (median PFS 41.7 [Isa-Kd] vs 20.8 months [Kd]; HR 0.59 (95.4% CI: 0.42–0.83)
  - A clinically meaningful increase in rates of MRD negativity (33.5% vs 15.4%) and CR (44.1% vs 28.5%), in the ITT population
  - A manageable safety profile as in the interim analysis results, with no new safety signals with longer follow-up
- This post hoc subgroup analysis is based on the prespecified final IKEMA PFS analysis
  - Examined updated efficacy and safety of Isa-Kd vs Kd in patients with relapsed MM who experienced early vs late relapse

*PFS primary analysis as per FDA request at time of initial filing/sensitivity for other countries: censoring event occurring >8 weeks after last valid assessment

CI, confidence interval; CR, complete response; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; PFS, progression-free survival.

1. Majithia N, et al. *Leukemia*. 2016;30:2208–2213; 2. Moreau P, et al. *Ann Oncol*. 2022;33:664–665.

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Early and late relapse – definitions

- Early relapse* (n = 107 [n = 61, Isa-Kd; n = 46, Kd])[1,2]
  - Relapsed <12 months from initiation of the most recent LOT for patients with ≥2 prior LOTs
  - Relapsed <18 months for patients with 1 prior LOT
  - Relapsed <12 months from ASCT
- Late relapse* (n = 176 [n = 104, Isa-Kd; n = 72, Kd])[1,2]
  - Relapsed ≥12 months from initiation of the most recent LOT for patients with ≥2 prior LOT
  - Relapsed ≥18 months for patients with 1 prior LOT

*Includes relapsed and refractory MM (excludes primary refractory).
ASCT, autologous stem cell transplantation; LOT, line of therapy; MM, multiple myeloma.
1. Weisel K, et al. *Blood*. 2020;136:37–38; 2. Terpos E, et al. EHA 2020. Abstract #EP1010.

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Key patient demographics and baseline characteristics

	Early relapse		Late relapse	
	Isa-Kd (n=61)	Kd (n=46)	Isa-Kd (n=104)	Kd (n=72)
Age in years, median (range)	65.0 (39–83)	66.0 (33–90)	64.5 (37–86)	63.0 (40–78)
Age in years, by category, n (%)				
<65	30 (49.2)	21 (45.7)	52 (50.0)	41 (56.9)
65–74	24 (39.3)	17 (37.0)	43 (41.3)	29 (40.3)
≥75	7 (11.5)	8 (17.4)	9 (8.7)	2 (2.8)
CrCl <60 mL/min/1.73 m² (MDRD)*, n (%)	18/58 (31.0)	6/39 (15.4)	20/92 (21.7)	11/66 (16.7)
ISS stage at study entry, n (%)				
Stage I	19 (31.1)	25 (54.3)	63 (60.6)	44 (61.1)
Stage II	28 (45.9)	12 (26.1)	31 (29.8)	18 (25.0)
Stage III	14 (23.0)	9 (19.6)	9 (8.7)	9 (12.5)
Cytogenetics at study entry†, ‡, n (%)				
High risk	21 (34.4)	16 (34.8)	19 (18.3)	13 (18.1)
Standard risk	33 (54.1)	28 (60.9)	71 (68.3)	48 (66.7)
1q21+, n (%)	25 (41.0)	26 (56.5)	46 (44.2)	24 (33.3)
Gain 1q21, n (%)	15 (27.8)	18 (41.9)	26 (28.0)	18 (30.0)
1 CA	26 (42.6)	19 (41.3)	34 (32.7)	20 (27.8)
2 CA	9 (14.8)	8 (17.4)	12 (11.5)	5 (6.9)

Some imbalances in baseline characteristics were observed between treatment arms and between early and late relapse patients. Imbalances in ISS Stage at study entry and high-risk cytogenetics were noted between early and late relapse patients, with more aggressive features observed in early relapse patients.

Cut-off date: January 14, 2022. Median follow-up time: 44 months.
*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 was defined as the presence of del(17p), or t(4;14), or translocation t(14;16) by fluorescence in-situ hybridization.
‡‡Cytogenetics was performed by a central laboratory with cut-offs of 50% for del(17p), 30% for t(4;14), t(14;16), and 1q21+.
CA, cytogenetic abnormality; CrCl, creatinine clearance; d, dexamethasone; Isa, isatuximab; ISS, International Staging System; ITT, intent-to-treat; K, carfilzomib; MDRD, Modification of Diet in Renal Disease.

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Key patient demographics and baseline characteristics – prior lines of therapy

	Early relapse		Late relapse	
	Isa-Kd (n=61)	Kd (n=46)	Isa-Kd (n=104)	Kd (n=72)
Prior lines of therapy, median (min–max)	2.0 (1–4)	2.0 (1–4)	1.0 (1–4)	2.0 (1–4)
1, n (%)	20 (32.8)	19 (41.3)	58 (55.8)	35 (48.6)
2, n (%)	24 (39.3)	12 (26.1)	34 (32.7)	22 (30.6)
3, n (%)	16 (26.2)	14 (30.4)	11 (10.6)	14 (19.4)
>3, n (%)	1 (1.6)	1 (2.2)	1 (1.0)	1 (1.4)
Prior ASCT	30 (49.2)	14 (30.4)	81 (77.9)	53 (73.6)
Refractory status, n (%)				
Relapsed and refractory	54 (88.5)	41 (89.1)	55 (52.9)	49 (68.1)
Refractory to IMiD agent	33 (54.1)	27 (58.7)	34 (32.7)	27 (37.5)
Refractory to PI	34 (55.7)	24 (52.2)	15 (14.4)	17 (23.6)
Refractory to IMiD agent and PI	21 (34.4)	14 (30.4)	8 (7.7)	11 (15.3)
Refractory to last regimen	49 (80.3)	39 (84.8)	32 (30.8)	29 (40.3)

Patients with early relapse had more prior lines, less prior ASCT, and were more frequently refractory than those classified as late relapse

Cut-off date: January 14, 2022. Median follow-up time: 44 months.
ASCT, autologous stem cell transplantation; d, dexamethasone; IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; PI, proteasome inhibitor.

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Treatment duration and relative dose intensity

	Early relapse		Late relapse	
	Isa-Kd (n=61)	Kd (n=46)	Isa-Kd (n=104)	Kd (n=72)
Median treatment duration, weeks (min–max)	79.0 (2–209)	52.6 (4–208)	102.6 (6–206)	64.9 (2–194)
Relative dose intensity (%), median				
Isatuximab	94.1	NA	91.9	NA
Carfilzomib	93.1	91.3	86.5	90.5
Dexamethasone	83.1	87.2	77.4	88.0
Median (min–max) number of cycles	19.0 (1–49)	13.5 (1–42)	24.0 (2–50)	16.0 (1–47)
Ongoing treatment, n (%)	10 (16.4)	3 (6.5)	34 (32.7)	8 (11.1)

While median duration of treatment was longer in patients with late relapse, relative dose intensity was slightly lower

Cut-off date: January 14, 2022. Median follow-up time: 44 months.
d, dexamethasone; Isa, isatuximab; K, carfilzomib; NA, not applicable.

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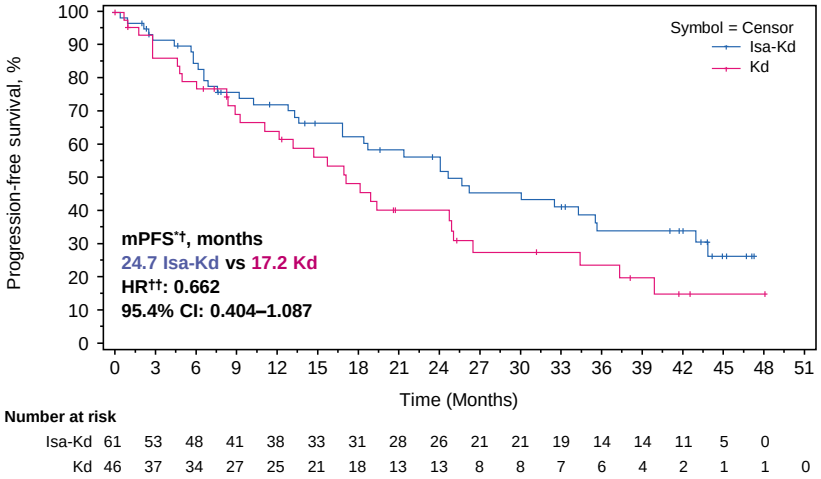
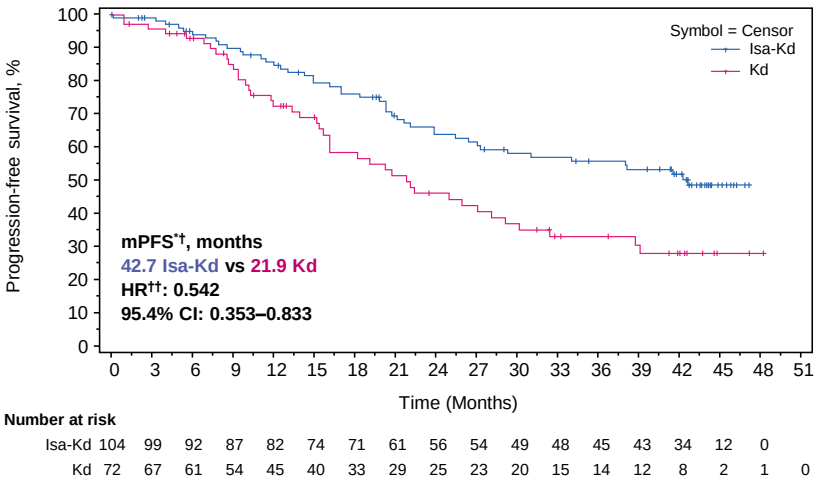
Median PFS in early and late relapse patients

Early relapse



Late relapse

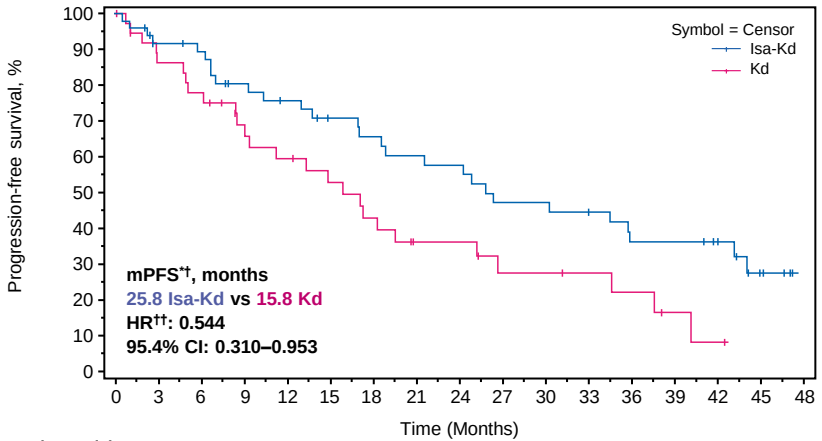


Median PFS was longer with Isa-Kd vs Kd in both early (HR=0.662) and late relapse (HR=0.542) patients

Cut-off date: January 14, 2022. Median follow-up time: 44 months.
*As per IRC.
†Median PFS and CIs were calculated by the Kaplan-Meier method.
†† Unstratified 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, renal impairment, ISS stage at study entry, 1q21+, and number of prior lines). When adjusted for confounding factors, the PFS HR was similar between early (0.577) and late relapse (0.527) patients.
CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; K, carfilzomib; mPFS, median progression-free survival; n/N, events/total.

Median PFS in early and late relapse patients refractory to the last regimen

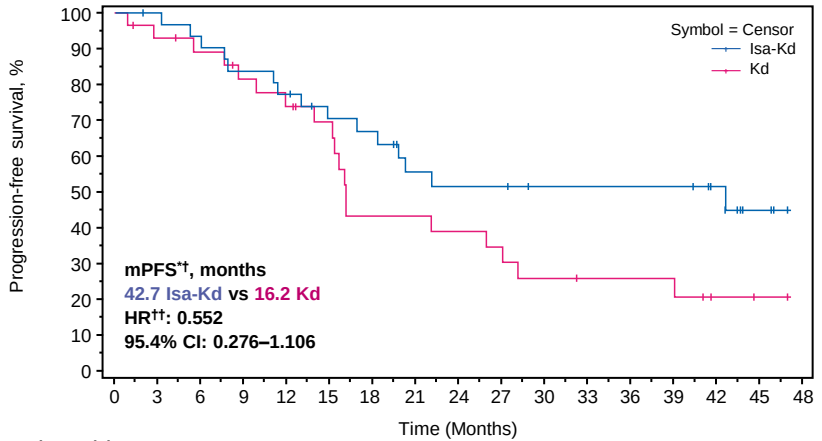
Early relapse and refractory to last regimen



Number at risk

Isa-Kd	49	42	40	34	31	27	25	23	22	18	18	17	13	13	10	5	0
Kd	39	31	28	21	19	16	13	9	9	6	6	5	4	2	1	0	

Late relapse and refractory to last regimen



Number at risk

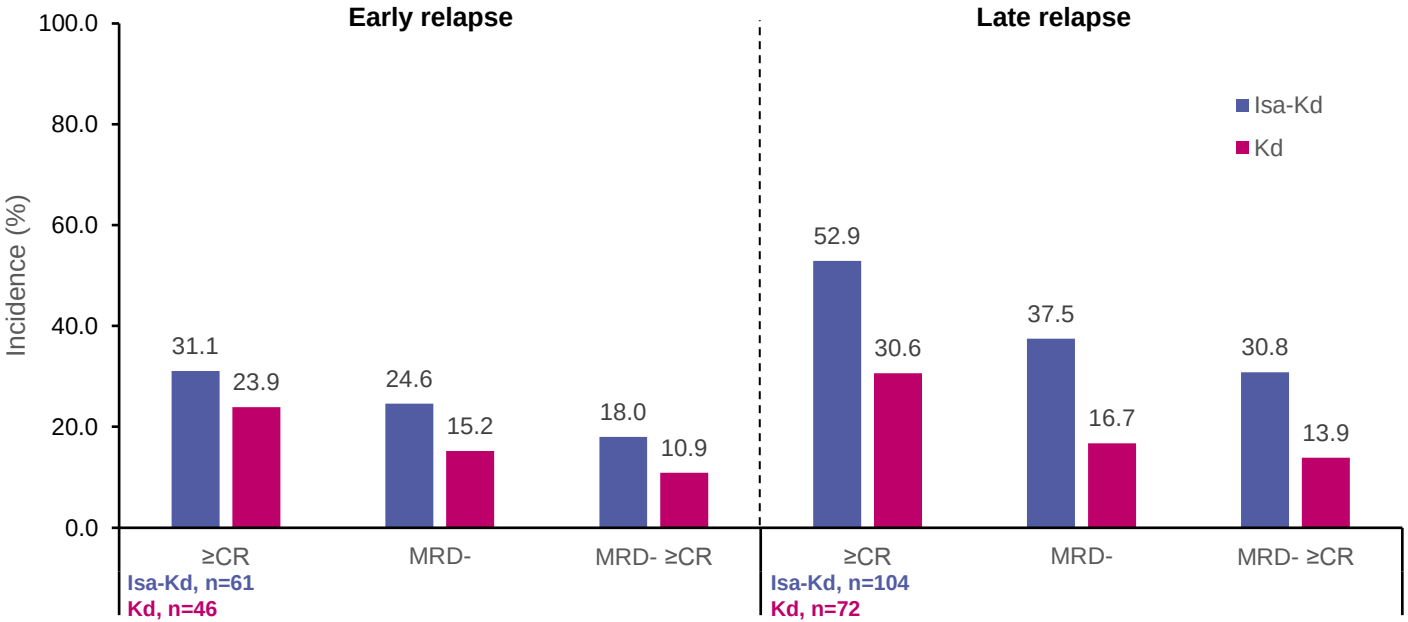
Isa-Kd	32	31	29	26	24	20	19	14	13	13	11	11	11	11	8	3	0
Kd	29	26	24	21	19	16	10	10	9	8	6	5	5	5	2	1	0

PFS in patients refractory to the last regimen was similar between early (HR=0.544) and late relapse (HR=0.552) patients, favoring Isa-Kd over Kd

Cut-off date: January 14, 2022. Median follow-up time: 44 months.
*As per IRC.
†Median PFS and CIs were calculated by the Kaplan-Meier method.
††Unstratified HR estimates were determined using the non-stratified Cox proportional hazard model using treatment as covariate.
CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; mPFS, median progression-free survival; PI, proteasome inhibitor.

Depth of response in early and late relapse patients

Response rates in early and late relapse patients

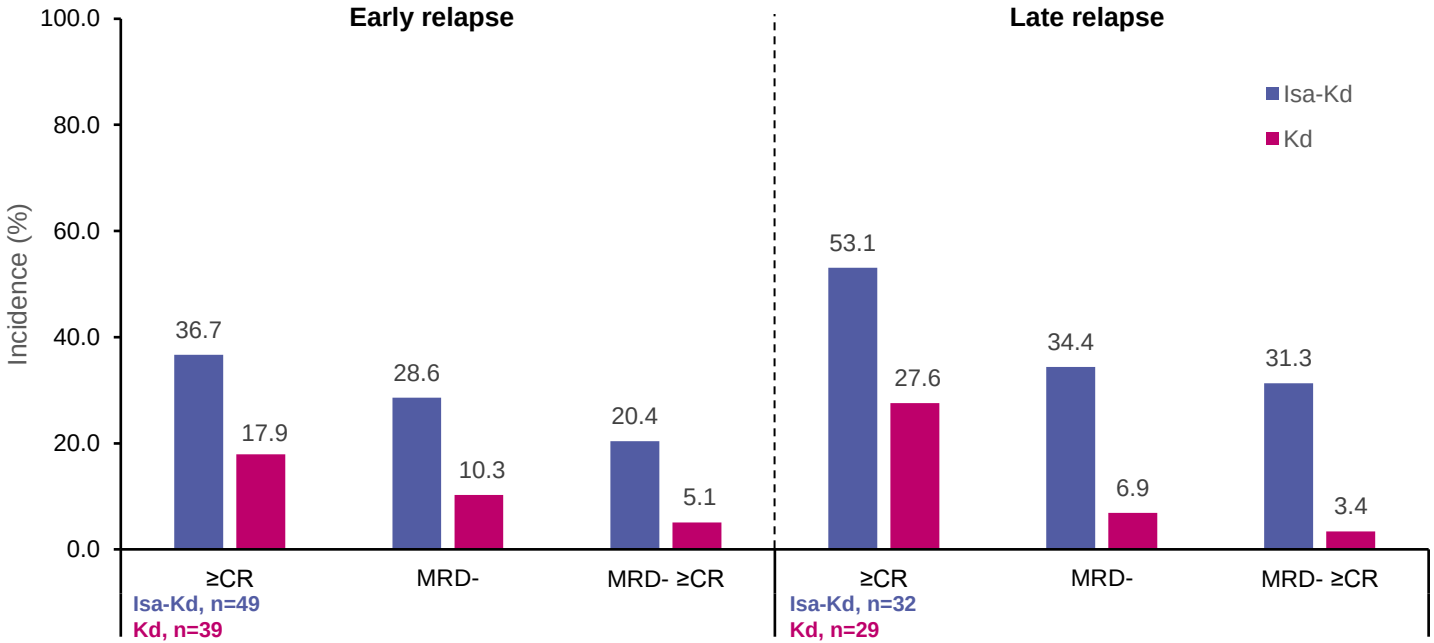


Depth of response was higher with Isa-Kd vs Kd in both early and late relapse patients

Cut-off date: January 14, 2022. Median follow-up time: 44 months. MRD- was assessed by next generation sequencing Adaptive clonoSEQ Assay (Adaptive Biotechnologies) at 10^{-5} sensitivity.
For analysis purpose, subjects in the ITT population but without MRD assessment were considered as having positive MRD.
CR, complete response; d, dexamethasone; Isa, Isatuximab; ITT, intent-to-treat; K, carfilzomib; MRD-, minimal residual disease negativity; VGPR, very good partial response.

Depth of response in early and late relapse patients refractory to the last regimen

Response rates in early and late relapse among patients refractory to last regimen



Depth of response in patients refractory to the last regimen was higher with Isa-Kd vs Kd in both early and late relapse patients

Cut-off date: January 14, 2022. Median follow-up time: 44 months. MRD- was assessed by next generation sequencing Adaptive clonoSEQ Assay (Adaptive Biotechnologies) at 10^{-5} sensitivity.
For analysis purpose, subjects in the ITT population but without MRD assessment were considered as having positive MRD.
CR, complete response; d, dexamethasone; IMiD, immunomodulatory drug; Isa, Isatuximab; ITT, intent-to-treat; K, carfilzomib; MRD-, minimal residual disease negativity; PI, proteasome inhibitor.

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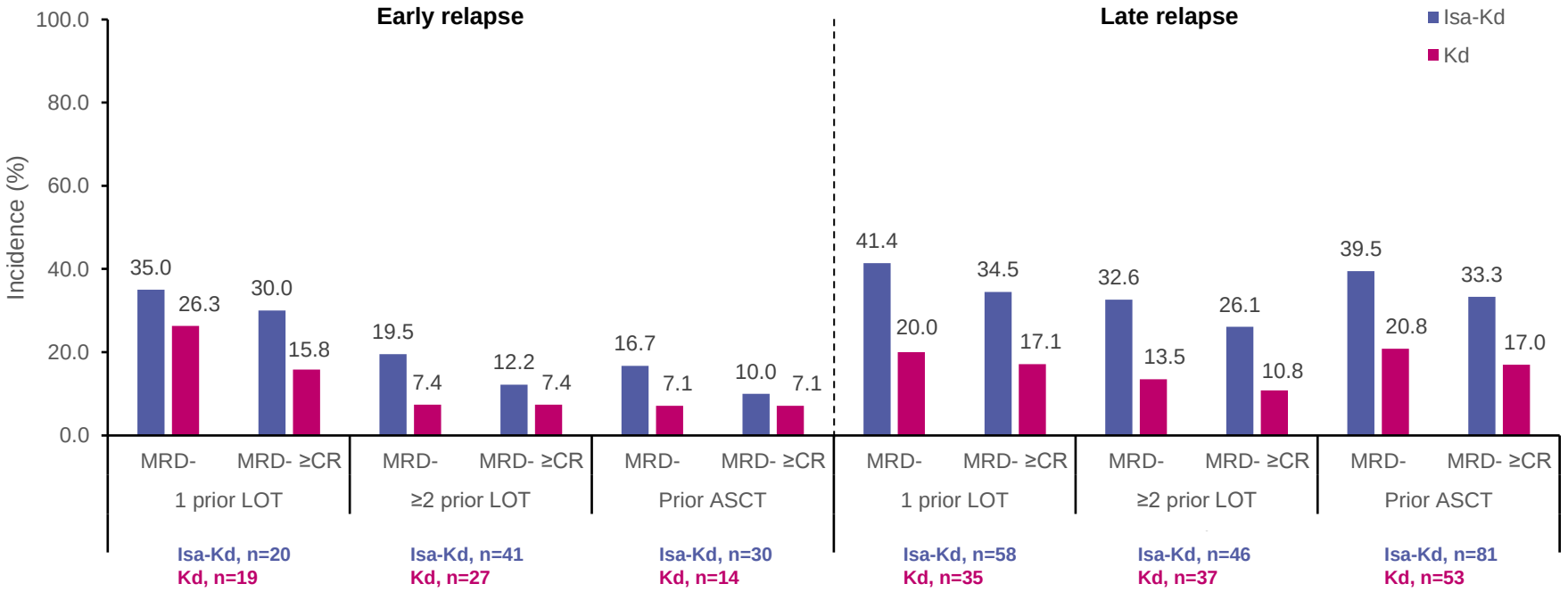
Depth of response after 1 or ≥2 prior LOT or prior ASCT in early and late relapse patients

Response rates in early and late relapse patients after 1 or ≥2 prior LOT or prior ASCT



Depth of response was improved with Isa-Kd vs Kd after 1 or ≥2 prior LOT or prior ASCT in both early and late relapse patients

Cut-off date: January 14, 2022. Median follow-up time: 44 months. MRD- was assessed by next generation sequencing Adaptive clonoSEQ Assay (Adaptive Biotechnologies) at 10^{-5} sensitivity. For analysis purpose, subjects in the ITT population but without MRD assessment were considered as having positive MRD.
ASCT, autologous stem cell transplant; CR, complete response; d, dexamethasone; Isa, Isatuximab; ITT, intent-to-treat; K, carfilzomib; LOT, line of treatment; MRD-, minimal residual disease negativity.

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Safety overview in early and late relapse patients

TEAE overview, n (%)	Early relapse		Late relapse	
	Isa-Kd (n=61)	Kd (n=46)	Isa-Kd (n=102)	Kd (n=71)
Any TEAE	60 (98.4)	45 (97.8)	101 (99.0)	69 (97.2)
Grade ≥3 TEAEs	51 (83.6)	37 (80.4)	84 (82.4)	50 (70.4)
Serious TEAEs	42 (68.9)	30 (65.2)	68 (66.7)	39 (54.9)
Any TEAE leading to definitive treatment discontinuation	7 (11.5)	6 (13.0)	14 (13.7)	14 (19.7)
Any TEAE leading to premature discontinuation				
Isatuximab	1 (1.6)	0	0	0
Carfilzomib	10 (16.4)	0	19 (18.6)	1 (1.4)
Dexamethasone	9 (14.8)	5 (10.9)	13 (12.7)	2 (2.8)
TEAEs fatal during study treatment*	3 (4.9)	3 (6.5)	6 (5.9)	2 (2.8)

Although frequency of Grade ≥3 and serious TEAEs was higher in the Isa-Kd arm in late relapse patients, TEAEs leading to definitive treatment discontinuation or death were similar between treatment arms across early and late relapse patients

*Fatal TEAEs in early relapse patients: Isa-Kd – cardiac failure and disease progression in 1 patient each, pneumonia and multiple non-site-specific injuries in 1 patient; Kd – acute myocardial infection, disease progression, and COVID-19 in 1 patient each. Fatal TEAEs in late relapse patients: Isa-Kd – pneumonia, atypical pneumonia, and asthma in 1 patient each, cardiac failure and acute kidney injury in 1 patient, COVID-19 infections in 2 patients; Kd – cardiac failure and acute kidney injury in 1 patient, sudden death in 1 patient.
d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse event.

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Most common TEAEs and hematologic laboratory abnormalities in early and late relapse patients

Selected TEAEs Preferred term, n (%)	Early relapse				Late relapse			
	Isa-Kd (n=61)		Kd (n=46)		Isa-Kd (n=102)		Kd (n=71)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Infusion reaction	25 (41.0)	0	3 (6.5)	0	51 (50.0)	1 (1.0)	1 (1.4)	0
Hypertension	23 (37.7)	12 (19.7)	17 (37.0)	13 (28.3)	37 (36.3)	22 (21.6)	25 (35.2)	15 (21.1)
Diarrhea	21 (34.4)	2 (3.3)	14 (30.4)	1 (2.2)	44 (43.1)	3 (2.9)	24 (33.8)	2 (2.8)
URTI	20 (32.8)	2 (3.3)	12 (26.1)	1 (2.2)	39 (38.2)	3 (2.9)	19 (26.8)	1 (1.4)
Fatigue	20 (32.8)	3 (4.9)	11 (23.9)	1 (2.2)	33 (32.4)	7 (6.9)	14 (19.7)	0
Dyspnea	14 (23.0)	2 (3.3)	9 (19.6)	0	37 (36.3)	8 (7.8)	16 (22.5)	1 (1.4)
Pneumonia	14 (23.0)	11 (18.0)	9 (19.6)	7 (15.2)	29 (28.4)	19 (18.6)	15 (21.1)	7 (9.9)
Cough	11 (18.0)	0	9 (19.6)	0	24 (23.5)	0	8 (11.3)	0
Bronchitis	10 (16.4)	0	5 (10.9)	0	31 (30.4)	3 (2.9)	9 (12.7)	1 (1.4)
Gastroenteritis	3 (4.9)	2 (3.3)	6 (13.0)	2 (4.3)	15 (14.7)	0	3 (4.2)	0
Cardiac failure events								
Cardiac failure, any class	2 (3.3)	2 (3.3)	4 (8.7)	3 (6.5)	5 (4.9)	2 (2.0)	3 (4.2)	1 (1.4)

Hematologic laboratory abnormalities	Early relapse						Late relapse					
	Isa-Kd (n=61)			Kd (n=46)			Isa-Kd (n=102)			Kd (n=71)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Anemia	61 (100)	26 (42.6)	0	45 (97.8)	14 (30.4)	0	102 (100)	14 (13.7)	0	71 (100)	10 (14.1)	0
Neutropenia	35 (57.4)	11 (18.0)	2 (3.3)	18 (39.1)	2 (4.3)	1 (2.2)	53 (52.0)	14 (13.7)	2 (2.0)	33 (46.5)	6 (8.5)	0
Thrombocytopenia	57 (93.4)	13 (21.3)	11 (18.0)	39 (84.8)	7 (15.2)	6 (13.0)	99 (97.1)	17 (16.7)	8 (7.8)	66 (93.0)	11 (15.5)	3 (4.2)

The most common all-grade TEAEs were infusion reactions. <10% of patients had all-grade cardiac failure events across early and late relapse patients.

d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse event, URTI, upper respiratory tract infection.

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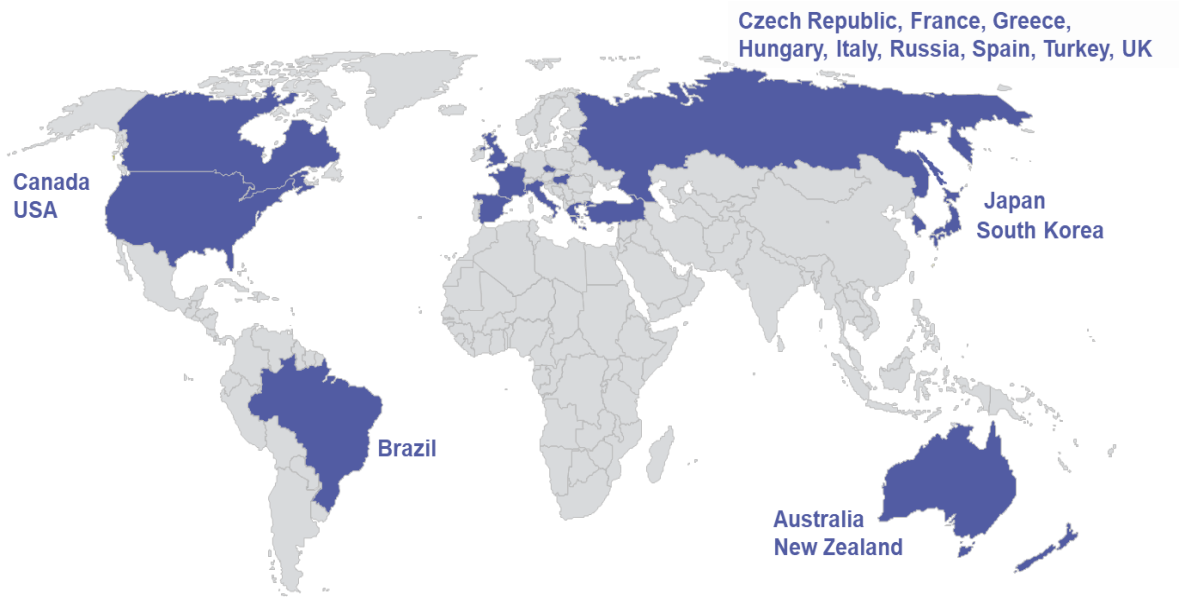
Summary

- The addition of Isa to Kd resulted in clinically meaningful improvement in PFS and depth of response (including MRD- and MRD- ≥CR rates), with a manageable safety profile in both early and late relapse patients, consistent with the benefit observed in the overall IKEMA study population
- Limitations in this post hoc subgroup analysis include small numbers of patients and some imbalances in baseline characteristics between treatment arms and between early and late relapse patients
- In early and late relapse patients who were refractory to the last regimen, PFS and depth of response (including MRD- and MRD- ≥CR rates) was higher with Isa-Kd vs Kd
- Grade ≥3 and serious TEAEs were higher in the Isa-Kd arm in late relapse patients, but TEAEs leading to definitive treatment discontinuation or death were similar between treatment arms across early and late relapse patients

Improved median PFS and depth of response with Isa in combination with Kd in patients with relapsed MM regardless of early or late relapse support Isa-Kd as a standard of care in these subgroups of patients

CR, complete response; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD-, minimal residual disease negativity; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Acknowledgements



16 countries participating in IKEMA I 69 study centers

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