IKEMA Isatuximab Plus Carfilzomib and Dexamethasone Versus Carfilzomib and Dexamethasone in Patients With Relapsed Multiple Myeloma (IKEMA): Overall Survival Analysis

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Disclosures

- **Kwee Yong:** *Research Support* – BMS, Janssen, Sanofi; *Honoraria* – Amgen, Sanofi, Takeda; *Advisory Role* – Janssen, Sanofi.
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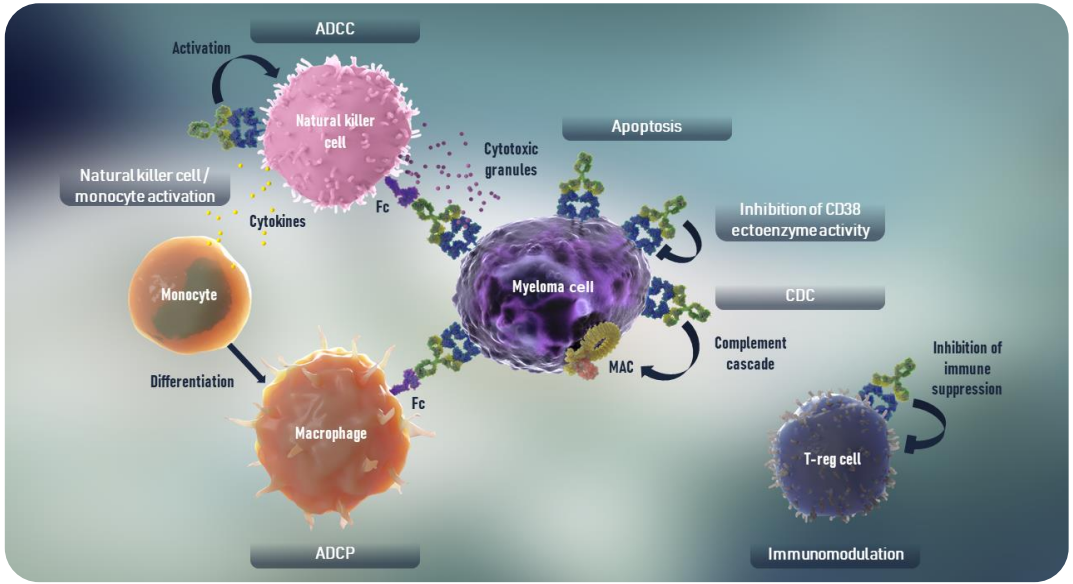
- **France Casca:** Employee of Sanofi and may hold stock and/or stock options.
- **Sandrine Mace:** Employee of Sanofi and may hold stock and/or stock options.
- **Marie-Laure Risse:** Employee of Sanofi and may hold stock and/or stock options.
- **Philippe Moreau:** *Advisory Role* – AbbVie, Amgen, Celgene, GlaxoSmithKline, Janssen, Sanofi.

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]:

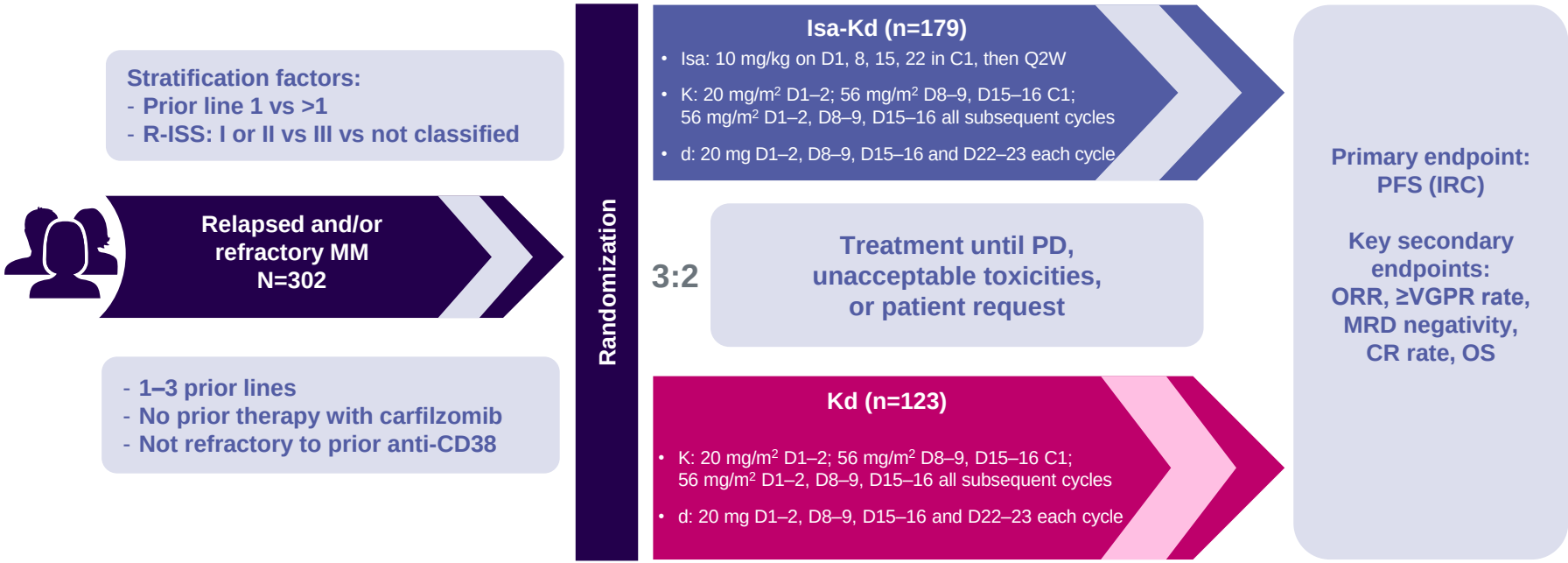
- ADCC, ADCP, and CDC
- Direct apoptosis
- Immunomodulation
- Inhibition of ectoenzyme activity

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 versus Kd in relapsed and/or refractory MM



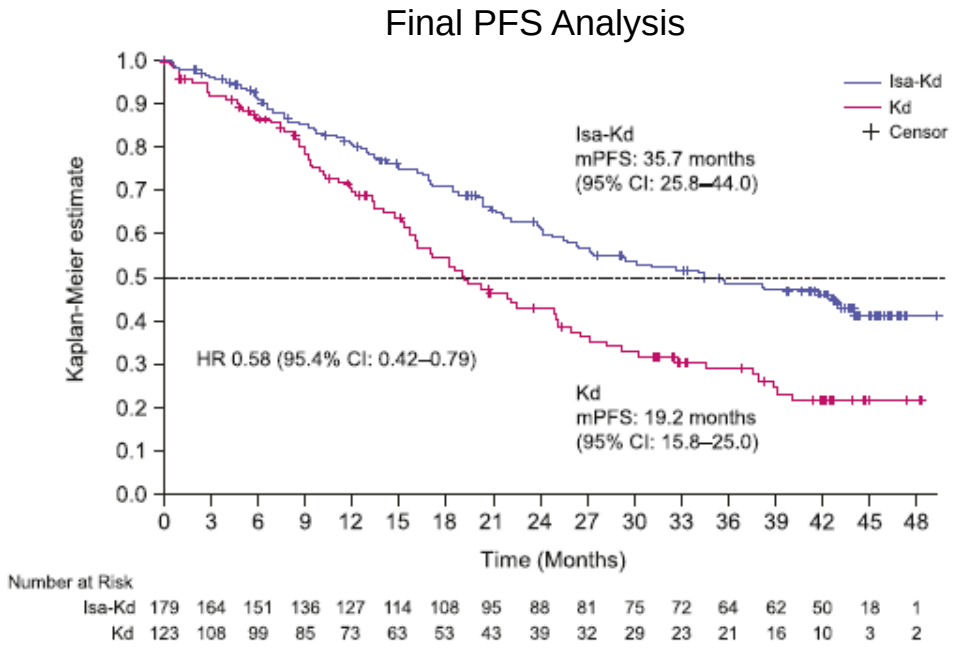
IKEMA study: NCT03275285.

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.

Background and objective

- The primary prespecified interim PFS analysis (median follow-up 20.73 months), demonstrated[1]:
  - A significant improvement in PFS with Isa-Kd versus Kd (HR 0.53; 99% CI 0.32–0.89; one-sided p=0.0007)
- The final PFS analysis (2 years after the prespecified interim analysis; median follow-up 43.96 months) confirmed the results[2]:
  - HR 0.58 (95.4% CI 0.42–0.79)
- **This analysis was planned to occur 3 years after the primary PFS analysis, regardless of the number of OS events, to summarize the OS in IKEMA**



CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; K, carfilzomib; PFS, progression-free survival; mPFS, median PFS.

1. Moreau P, et al. *Lancet*. 2021;397:P2361–P2371; 2. Martin T, et al. *Blood Cancer J*. 2023;13(1):72.

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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 to <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)

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 (any)	166 (92.7)	105 (85.4)
Prior IMiDs (any)	136 (76.0)	100 (81.3)
Patients refractory to, n (%)		
IMiD (any)	78 (43.6)	58 (47.2)
Lenalidomide	57 (31.8)	42 (34.1)
PI (any)	56 (31.3)	44 (35.8)
Last regimen	89 (49.7)	73 (59.3)

Patient characteristics were balanced in both arms

*Incidence calculated on patients with race reported in CRF:165 patients in Isa-Kd arm, 111 patients in Kd arm;
†Cytogenetics by central lab – cut-off 50% for del17p, 30% for t(4;14) and t(14;16);
‡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; ISS, International Staging System;
ITT, intent to treat; K, carfilzomib; MDRD, Modification of Diet in Renal Disease; PI, proteasome inhibitor.

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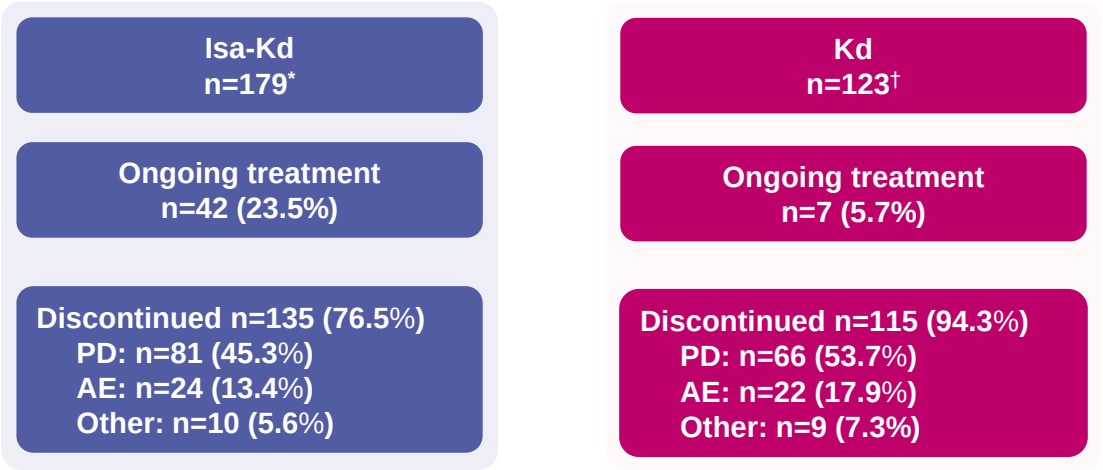
Patient disposition



Median duration of follow-up: 56.61 months (≈ 4 years and 8 months)

More patients are still on treatment in the Isa-Kd arm
Fewer patients discontinued due to PD and AE in Isa-Kd arm

*Randomized and treated, n=177;
†Randomized and treated, n=122.
AE, adverse event; CI, confidence interval; d, dexamethasone; Isa, isatuximab; K, carfilzomib; PD, progressive disease.

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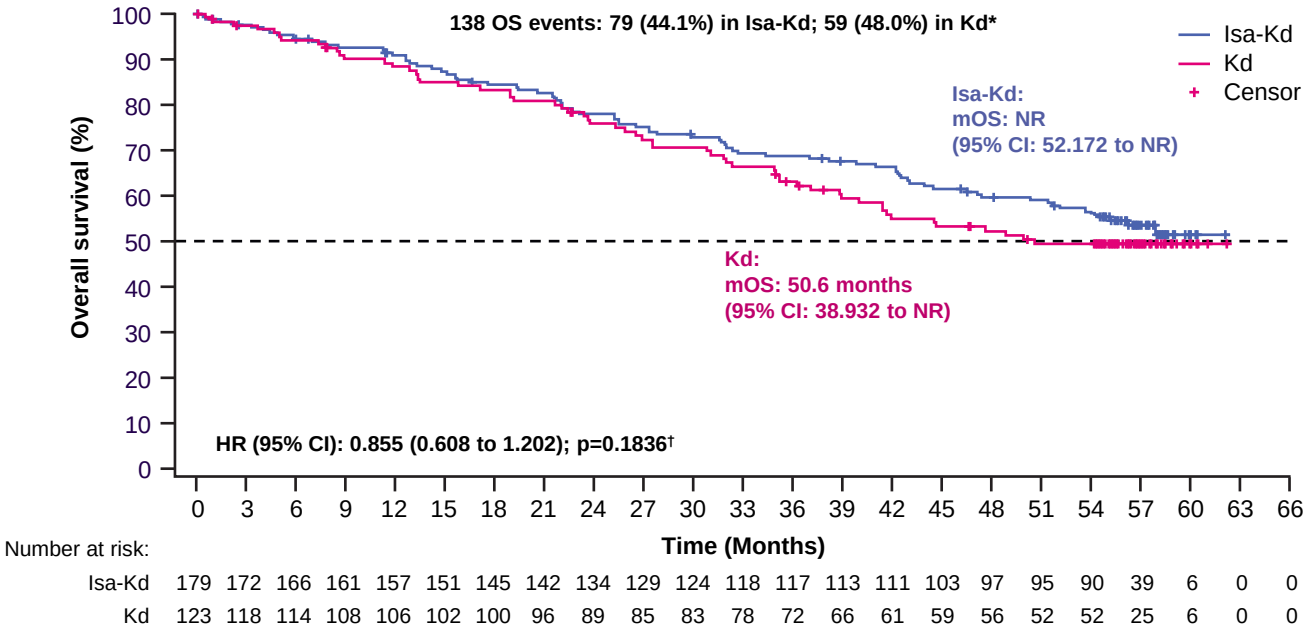
Exposure to study treatments

	Isa-Kd (n=177)	Kd (n=122)
Median treatment duration, weeks (range)	94.0 (1–268)	61.9 (1–265)
Median relative dose intensity, % (range)		
Isatuximab	92.95 (66.7–108.2)	NA
Carfilzomib	88.26 (18.2–108.7)	90.77 (41.5–108.6)
Dexamethasone	81.14 (17.1–101.1)	88.12 (18.5–101.6)
Total cycles	4964	2310
Delayed cycles, n (%)	584 (11.8)	259 (11.2)
Between 4 and 7 days	296 (6.0)	145 (6.3)
More than 7 days	288 (5.8)	114 (4.9)
Cycles delayed due to COVID-19	38 (0.8)	13 (0.6)
Partial cycles due to COVID-19*	189 (3.8)	53 (2.3)

In the Isa-Kd arm, treatment duration was 1.5 times as long, with a similar relative dose intensity of carfilzomib in both arms

*At least 1 dose omission due to COVID-19.
d, dexamethasone; Isa, isatuximab; K, carfilzomib; NA, not applicable.

OS analysis



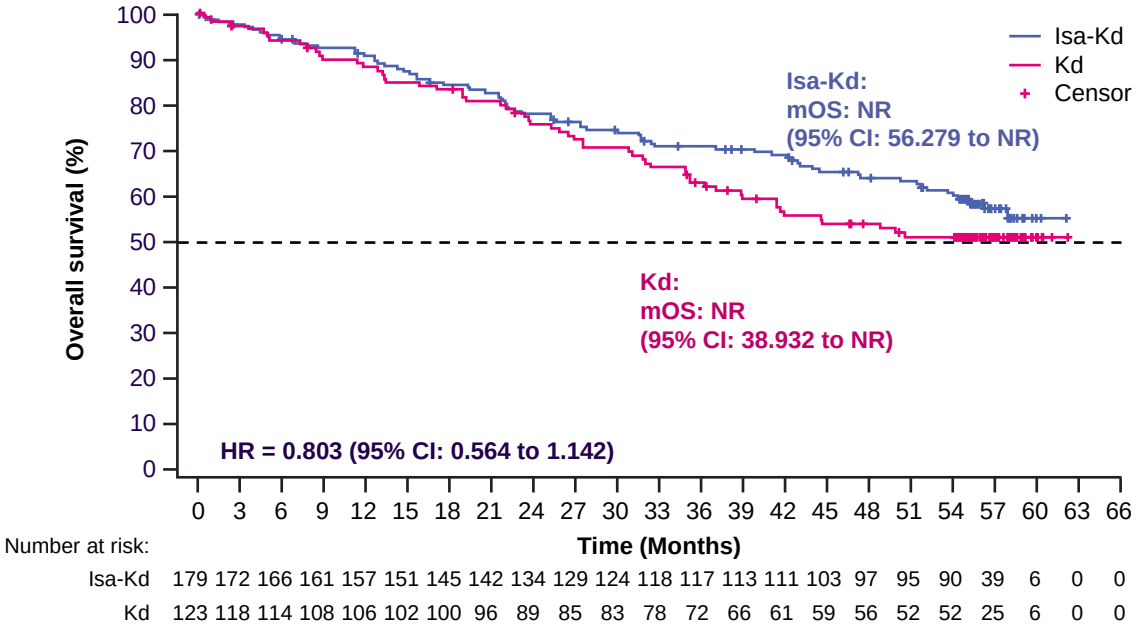
Extrapolating the current observed trend for an additional 12 months of follow-up, the mOS estimate for Isa-Kd arm is **63 months** (95% CI: 59–69)

This corresponds to an estimated 1-year difference in mOS

After a median follow-up of 56.6 months, mOS was not reached in the Isa-Kd arm. The extrapolated mOS estimate of 63 months for Isa-Kd corresponds to an estimated 1-year difference in mOS versus Kd

*Cutoff date for OS analysis: February 7, 2023.
†Nominal one-sided p-value.
CI, confidence interval; HR, hazard ratio; d, dexamethasone; Isa, isatuximab; K, carfilzomib; mOS, median OS; NR, not reached; OS, overall survival.

OS sensitivity analysis censoring deaths due to COVID-19



n (%)	Isa-Kd (n=179)	Kd (n=123)
COVID-19 infections (all grades)	34 (19.2)	5 (4.1)
Deaths due to COVID-19, n (%)	8* (4.5)	2† (1.6)
Deaths‡ included in the sensitivity analysis, n (%)	71 (39.7)	57 (46.3)

	HR (95% CI)
OS analysis (ITT)	0.855 (0.608–1.202)
Sensitivity analysis censoring death due to COVID-19	0.803 (0.564–1.142)

Results of the sensitivity analysis show that COVID-19 disproportionately impacted OS in the Isa-Kd arm

Cutoff date: February 7, 2023.

‡In the Isa-Kd arm, there were 12 deaths during study treatment (COVID-19, n=3; pneumonia, n=2; and 1 each due to cardiac failure, health deterioration due to progression of disease, large intestine perforation, severe asthma attack, cardiac decompensation, atypical lower lobe pneumonia, and polytrauma) and 66 during follow-up (progressive disease, n=43; adverse event of *Pneumocystis jirovecii* pneumonia, n=1; other, n=22). In the Kd arm, there were 6 deaths during study treatment (COVID-19, acute myocardial infarction, septic shock, unknown, cardiac failure, and health deterioration due to progression of disease) and 53 during follow-up (progressive disease, n=43; other, n=10).

CI, confidence interval; HR, hazard ratio; d, dexamethasone; Isa, isatuximab; ITT, intent to treat; K, carfilzomib; mOS, median OS; NR, not reached; OS, overall survival.

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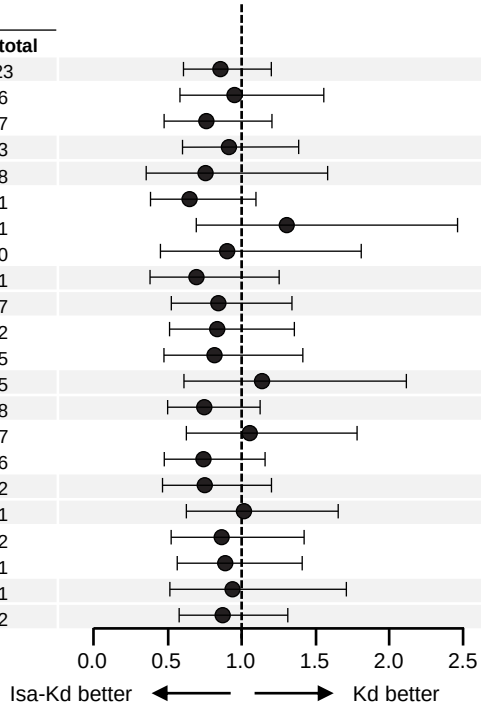
OS subgroup analysis

Subgroup		Isa-Kd Events/total	Kd Events/total	Hazard ratio (95% CI)
All patients		79/179	59/123	0.855 (0.608-1.202)
Age	<65	36/88	28/66	0.952 (0.581-1.560)
	>65	43/91	31/57	0.760 (0.478-1.207)
Baseline eGFR (MDRD)	>60 mL/min/1.73 m^2	49/122	41/93	0.914 (0.603-1.385)
	<60 mL/min/1.73 m^2	23/43	10/18	0.752 (0.358-1.583)
ISS staging at study entry	I	26/89	30/71	0.646 (0.382-1.094)
	II	36/63	13/31	1.305 (0.692-2.461)
	III	17/26	15/20	0.903 (0.451-1.809)
High-risk cytogenetic status	Yes	24/42	21/31	0.692 (0.381-1.254)
	No	41/114	31/77	0.841 (0.527-1.341)
1q21+	Yes	37/75	29/52	0.833 (0.512-1.355)
	No	30/84	22/55	0.816 (0.470-1.416)
Number of prior lines of therapy	1	27/80	16/55	1.139 (0.614-2.115)
	>1	52/99	43/68	0.749 (0.500-1.122)
Prior PI treatment	Yes	39/81	22/47	1.056 (0.626-1.781)
	No	40/98	37/76	0.742 (0.474-1.160)
Prior IMiD treatment	Yes	36/81	33/62	0.748 (0.466-1.200)
	No	43/98	26/61	1.016 (0.624-1.653)
Refractory to lenalidomide	Yes	35/57	28/42	0.864 (0.525-1.421)
	No	44/122	31/81	0.890 (0.562-1.410)
Refractory to lenalidomide at last prior regimen	Yes	23/36	20/31	0.936 (0.513-1.707)
	No	56/143	39/92	0.871 (0.578-1.311)

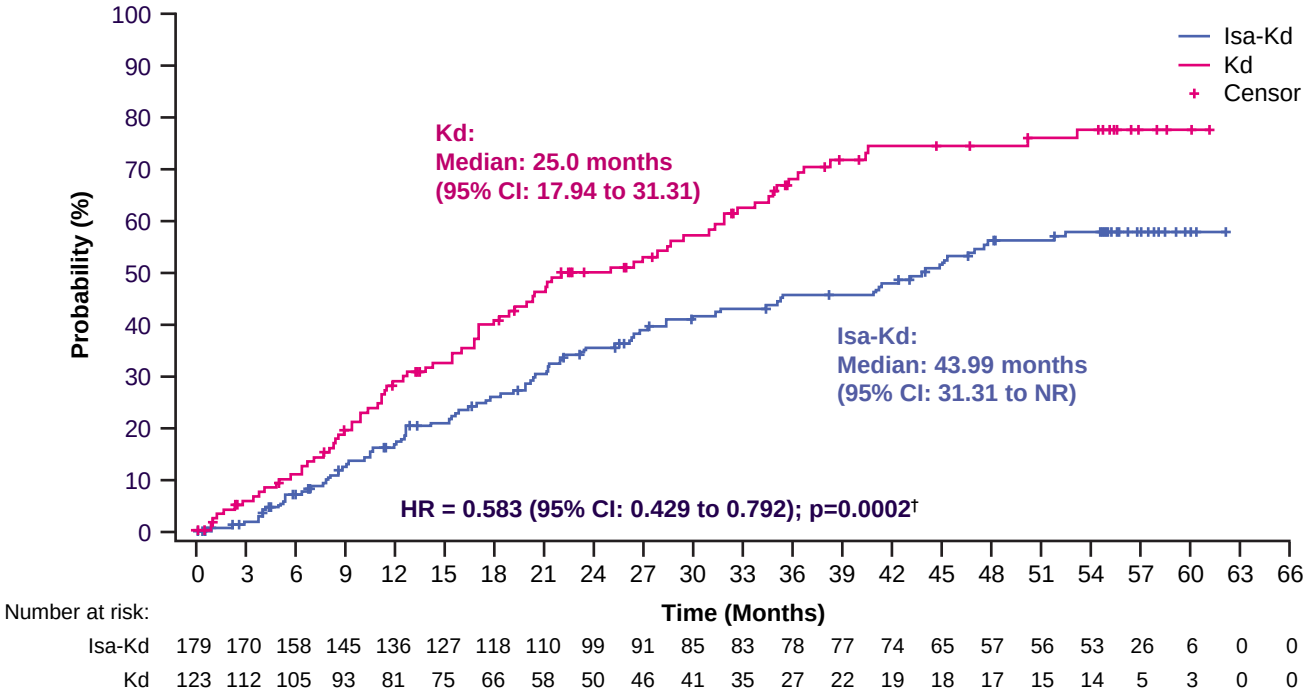


1 prior line:
COVID-19 deaths:
5 of 8 (Isa-Kd) vs
1 of 2 (Kd)

Subgroup analyses of OS show a consistent treatment effect for Isa-Kd in most subgroup comparisons

AEs, adverse events; CI, confidence interval; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; IMiD, immunomodulatory drug; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MDRD, Modification of Diet in Renal Disease; OS, overall survival; PI, proteasome inhibitor.

Time to next treatment*



Time to next treatment analysis showed a clinically meaningful delay in the Isa-Kd versus Kd arm

*Defined as the time between randomization and subsequent antimyeloma therapy;
†Nominal, one-sided p-value.

CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; K, carfilzomib; NR, not reached.

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Summary of subsequent antimyeloma treatments

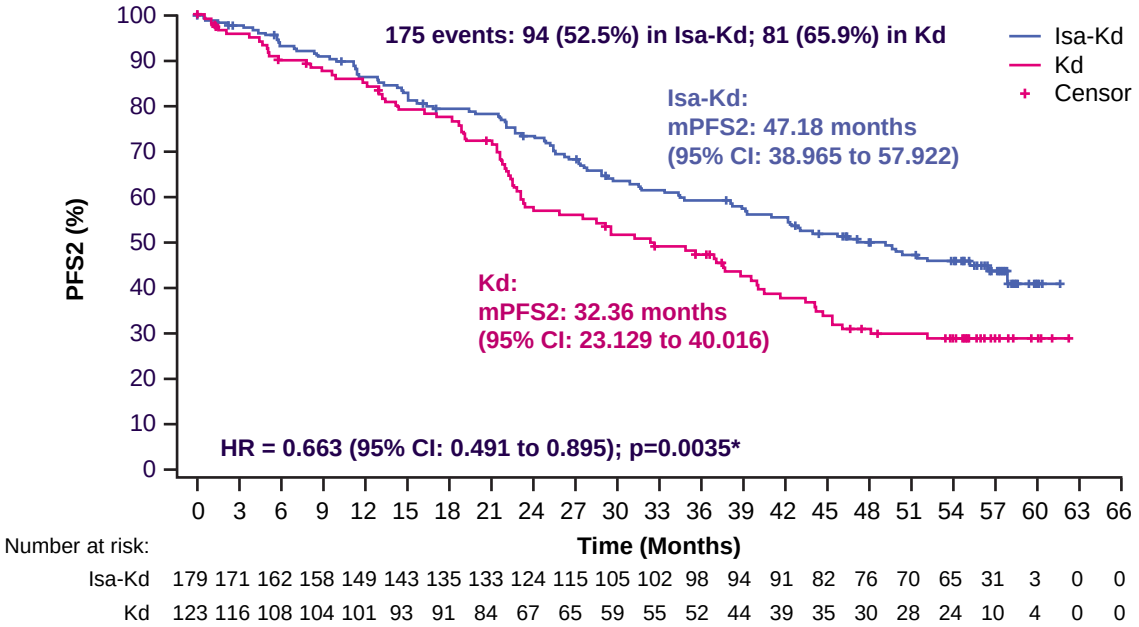
	Isa-Kd (n=179)	Kd (n=123)
Any subsequent antimyeloma treatment, n (%)	89 (49.7)	81 (65.9)
Number of subsequent regimens, median (range)	2.0 (1–8)	2.0 (1–13)
Number of subsequent regimens, n (%)		
1	44 (49.4)	25 (30.9)
2	19 (21.3)	30 (37.0)
≥3	26 (29.2)	26 (32.1)
Subsequent antimyeloma treatments, n (%)		
Corticosteroids	80 (89.9)	72 (88.9)
Immunomodulators	76 (85.4)	66 (81.5)
Alkylating agents	44 (49.4)	45 (55.6)
Proteasome inhibitors	42 (47.2)	33 (40.7)
Anti-CD38 agents	26 (29.2)	51 (63.0)
Daratumumab	26 (29.2)	44 (54.3)
Isatuximab	1 (1.1)	11 (13.6)
Other anti-CD38 agents	0	2 (2.5)

	Isa-Kd (n=179)	Kd (n=123)
Subsequent antimyeloma treatments, n (%) (cont)		
Anti-BCMA	18 (20.2)	5 (6.2)
Belantamab mafodotin	14 (15.7)	2 (2.5)
Elranatamab	3 (3.4)	1 (1.2)
Teclistamab	3 (3.4)	2 (2.5)
Further transplant	12 (13.5)	14 (17.3)
Anthracyclins	9 (10.1)	14 (17.3)
Topoisomerase inhibitors	7 (7.9)	6 (7.4)
Platinum compound	7 (7.9)	4 (4.9)
CAR T cell	2 (2.2)	4 (4.9)
Other	12 (13.5)	4 (4.9)
Selinexor	6 (6.7)	3 (3.7)

Among those receiving subsequent therapy, 63.0% of the patients randomized to the Kd arm received anti-CD38 therapy versus 29.2% in the Isa-Kd arm

BCMA, B-cell maturation antigen; CAR T, chimeric antigen receptor T cell; CD, cluster of differentiation; d, dexamethasone; HDAC, histone deacetylase; Isa, isatuximab; K, carfilzomib.

PFS2 (time from randomization to PD on subsequent therapy or death)



ITT population	PFS2 HR (95% CI)
At final PFS analysis Median follow-up: 43.96 months	0.683 (0.496–0.941)
At OS analysis Median follow-up: 56.6 months	0.663 (0.491–0.895)

The PFS benefit of Isa-Kd versus Kd is maintained after the first subsequent therapy

*Nominal, one-sided p-value.

CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intention-to-treat; K, carfilzomib; m, median; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, second PFS.

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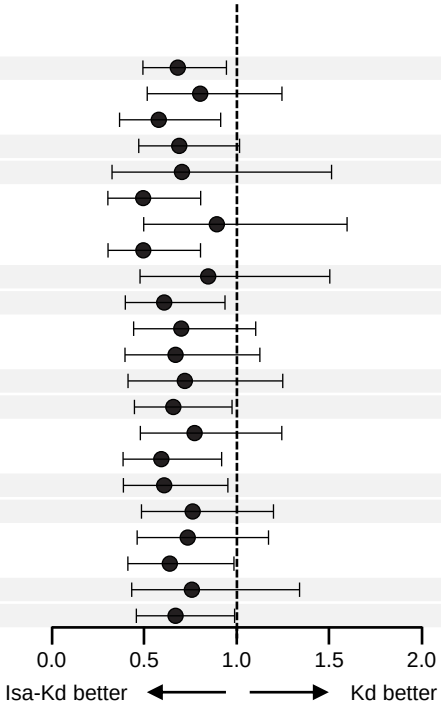
PFS2 subgroup analysis

Subgroup		Isa-Kd Events/total	Kd Events/total	Hazard ratio (95% CI)
All patients		80/179	73/123	0.683 (0.494-0.946)
Age	<65	42/88	37/66	0.802 (0.515-1.248)
	>65	38/91	36/57	0.579 (0.366-0.914)
Baseline eGFR (MDRD)	>60 mL/min/1.73 m^2	51/122	54/93	0.692 (0.471-1.016)
	<60 mL/min/1.73 m^2	21/43	10/183	0.706 (0.329-1.512)
ISS staging at study entry	I	28/89	39/71	0.496 (0.305-0.807)
	II	34/63	17/31	0.894 (0.499-1.601)
	III	18/26	16/20	0.852 (0.434-1.671)
High-risk cytogenetic status	Yes	26/42	22/31	0.850 (0.479-1.507)
	No	42/114	41/77	0.611 (0.397-0.940)
1q21+	Yes	40/75	35/52	0.702 (0.446-1.106)
	No	30/84	27/55	0.670 (0.398-1.128)
Number of prior lines of therapy	1	27/80	24/55	0.721 (0.415-1.252)
	>1	53/99	49/68	0.661 (0.448-0.975)
Prior PI treatment	Yes	40/81	29/47	0.774 (0.480-1.249)
	No	40/98	44/76	0.596 (0.388-0.917)
Prior IMiD treatment	Yes	37/81	40/62	0.610 (0.390-0.955)
	No	43/98	33/61	0.763 (0.485-1.202)
Refractory to lenalidomide	Yes	38/57	33/42	0.737 (0.462-1.176)
	No	40/81	42/122	0.639 (0.414-0.986)
Refractory to lenalidomide at last prior regimen	Yes	24/36	24/31	0.761 (0.432-1.342)
	No	56/143	49/92	0.674 (0.459-0.989)



Subgroup analyses of PFS2 show a consistent treatment effect for Isa-Kd across subgroups

CI, confidence interval; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MDRD, Modification of Diet in Renal Disease; PFS2, second PFS.

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Safety summary

TEAE overview, n (%)	Interim PFS analysis Median follow-up: 20.73 months		Final PFS analysis Median follow-up: 43.96 months		OS analysis Median follow-up: 56.6 months	
	Isa-Kd (n=177)	Kd (n=122)	Isa-Kd (n=177)	Kd (n=122)	Isa-Kd (n=177)	Kd (n=122)
Any TEAE	172 (97.2)	117 (95.9)	175 (98.9)	119 (97.5)	175 (98.9)	119 (97.5)
Grade ≥3 TEAEs	136 (76.8)	82 (67.2)	148 (83.6)	89 (73.0)	149 (84.2)	89 (73.0)
Grade 5 TEAE	6 (3.4)	4 (3.3)	10 (5.6)	6 (4.9)	12 (6.8)	6 (4.9)
Serious TEAEs	105 (59.3)	70 (57.4)	124 (70.1)	73 (59.8)	126 (71.2)	74 (60.7)
Any TEAE leading to definitive treatment discontinuation	15 (8.5)	17 (13.9)	22 (12.4)	22 (18.0)	24 (13.6)	22 (18.0)
Any TEAE leading to premature discontinuation						
Isatuximab	1 (0.6)	-	1 (0.6)	-	1 (0.6)	-
Carfilzomib	26 (14.7)	1 (0.8)	31 (17.5)	1 (0.8)	32 (18.1)	1 (0.8)
Dexamethasone	11 (6.2)	4 (3.3)	23 (13.0)	7 (5.7)	24 (13.6)	8 (6.6)

With an additional year of follow-up, the safety profile was similar at the OS analysis versus the final PFS analysis

d, dexamethasone; Isa, isatuximab; K, carfilzomib; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

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Safety summary – event rate per patient-year

TEAE overview	Interim PFS analysis Median follow-up: 20.73 months		Final PFS analysis Median follow-up: 43.96 months		OS analysis Median follow-up: 56.6 months	
	Isa-Kd (n=177)	Kd (n=122)	Isa-Kd (n=177)	Kd (n=122)	Isa-Kd (n=177)	Kd (n=122)
Any TEAE	10.94	9.41	9.01	7.78	8.56	7.78
Grade ≥3 TEAEs	1.26	1.05	1.08	0.97	1.01	0.96
Grade 5 TEAE	0.03	0.03	0.03	0.03	0.03	0.03
Serious TEAEs	0.70	0.72	0.58	0.62	0.54	0.62
Any TEAE leading to definitive treatment discontinuation	0.07	0.13	0.06	0.12	0.06	0.12

The exposure-adjusted event rates for Grade ≥3 TEAEs were similar between arms
The event rate for discontinuations did not increase with additional follow-up

d, dexamethasone; Isa, isatuximab; K, carfilzomib; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

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Safety – Incidence of cardiac failure

Preferred term (%)	Isa-Kd (n=177)		Kd (n=122)	
	All grades	Grade ≥3	All grades	Grade ≥3
Cardiac Failure SMQ*	**15 (8.5)**	**8 (4.5)**	**10 (8.2)**	**5 (4.1)**
Cardiac disorders	14 (7.9)	7 (4.0)	10 (8.2)	5 (4.1)
Cardiac failure	8 (4.5)	4 (2.3)	8 (6.6)	4 (3.3)
Cardiac failure congestive	4 (2.3)	1 (0.6)	1 (0.8)	0
Cardiac failure acute	1 (0.6)	1 (0.6)	0	0
Cardiac failure chronic	1 (0.6)	1 (0.6)	0	0
Left ventricular failure	0	0	1 (0.8)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	1 (0.6)	1 (0.8)	1 (0.8)
Pulmonary edema	1 (0.6)	1 (0.6)	1 (0.8)	1 (0.8)

There was a similar incidence of cardiac failure events in both arms

1 additional patient in Kd
*Grouping using MedDRA SMQ cardiac failure narrow terms.
d, dexamethasone; Isa, isatuximab; K, carfilzomib; SMQ, standardized MedDRA queries; TEAE, treatment-emergent adverse event.

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Summary – Efficacy

- At a median follow-up of 56.6 months, this time-defined OS analysis revealed a favorable OS benefit of Isa-Kd versus Kd (median OS not reached vs 50.6 months; HR 0.86; 95% CI: 0.61–1.20), representing the longest OS in a Phase 3 trial of a lenalidomide-free regimen in the relapsed setting
  - The extrapolated mOS estimate of 63 months for Isa-Kd corresponds to an estimated 1-year difference in mOS versus Kd
  - This was seen despite subsequent treatment with anti-CD38 agents, introduction of treatments with novel mechanisms of action among further therapies, and the COVID-19 pandemic
- Improvements in TTNT (44.0 months vs 25.0 months; HR: 0.58; 95% CI: 0.43–0.79) and PFS2 (47.2 vs 32.4 months; HR: 0.66; 95% CI: 0.49–0.90) were observed with Isa-Kd versus Kd, demonstrating sustained isatuximab benefit through the subsequent line of treatment

These findings support Isa-Kd as a standard of care in patients with relapsed and/or refractory MM

CD, cluster of differentiation; d, dexamethasone; Isa, isatuximab; K, carfilzomib; HR, hazard ratio; MM, multiple myeloma; mOS, median OS; OS, overall survival; PFS, progression-free survival; PFS2, second PFS; TTNT, time to next treatment.

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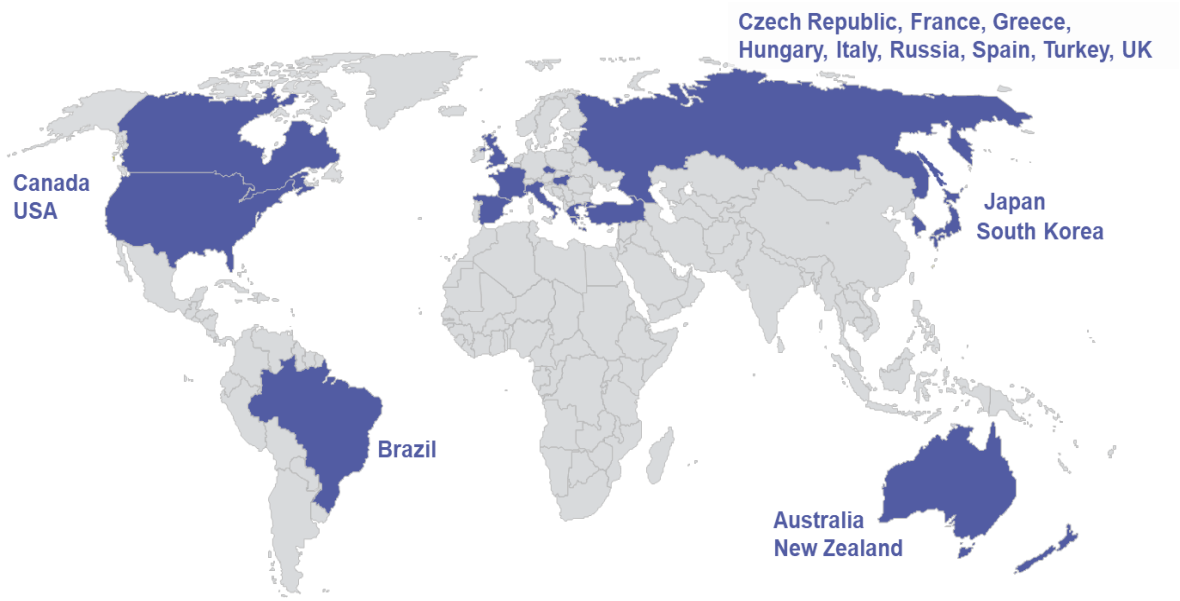
Summary – Safety

- The Isa-Kd safety profile was consistent with previous analyses
  - The proportion of TEAEs fatal during treatment and discontinuations due to TEAEs remained similar between arms, despite an additional 30 weeks of treatment exposure in the Isa-Kd arm
  - A comparable incidence of carfilzomib-associated events, such as cardiac failure and hypertension, was observed between arms, despite longer treatment exposure in the Isa-Kd arm

These findings support Isa-Kd as a standard of care in patients with relapsed and/or refractory MM

d, dexamethasone; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; TEAE, treatment-emergent adverse event.

Acknowledgments



16 countries participating in IKEMA I 69 study centers

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Thank you for your attention