IKEMA Depth of Response and Response Kinetics of Isatuximab plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: IKEMA Interim Analysis

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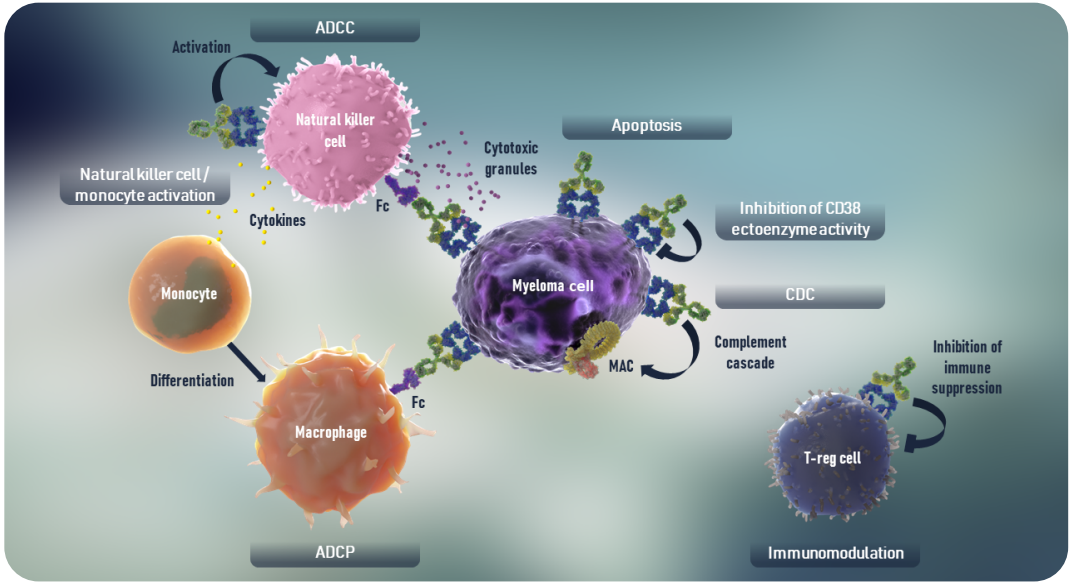
Isatuximab: Targets a specific epitope on CD38



Isatuximab, in combination with pomalidomide and dexamethasone, is approved in the US, EU, Canada, Australia, Switzerland, Japan, and Russia in RRMM after ≥2 prior therapies, including lenalidomide and a PI[7]

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

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

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

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. Leuk 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 2020.

ADCC, antibody dependent cellular cytotoxicity; ADCP, antibody dependent cellular phagocytosis; CD, cluster of differentiation; CDC, complement dependent cytotoxicity; EU, European Union; Fc, fragment crystallizable; Ig, immunoglobulin; MAC, membrane attack complex; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; Treg, regulatory T cells; US, United States.

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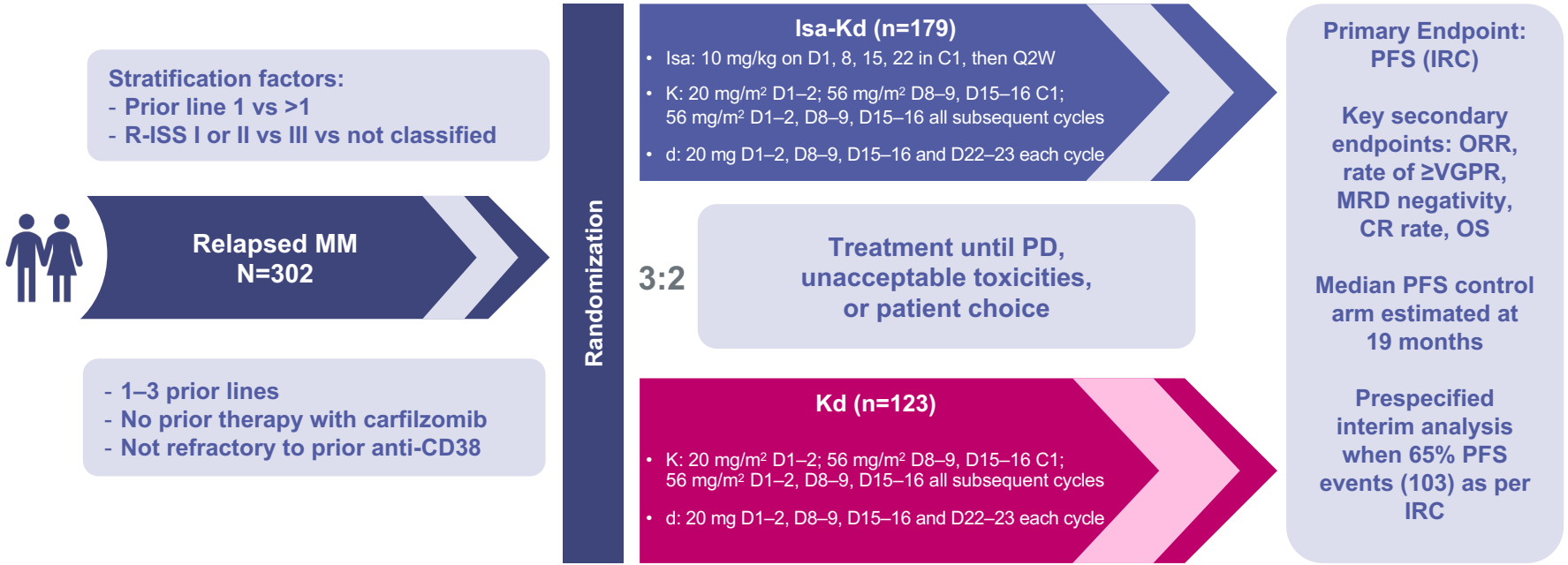
Study design: Isa-Kd vs Kd in relapsed multiple myeloma



Sample size calculation: ~300 patients and 159 PFS events to detect 41% risk reduction in hazard rate for PFS with 90% power and one-sided 0.025 significance level

Moreau P, et al. Future Oncol. 2020;16:4347–4358.

IKEMA study: NCT03275285
C, cycle; CD, cluster of differentiation; CR, complete response; D, day; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q2W, once every 2 weeks; R-ISS, Revised International Staging System; VGPR, very good partial response.

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Depth of response analysis

- Depth and kinetics of response were analyzed for each treatment arm
- Response was assessed by an Independent Response Committee based on central laboratory data for M-protein and central review of local imaging according to IMWG criteria[1] and bone marrow for plasma cell infiltration
- Minimal residual disease was assessed by the central laboratory in bone marrow aspirate samples from patients who achieved ≥VGPR by NGS at 10^{-5} sensitivity level

1. Kumar S, et al. Lancet Oncol. 2016;17:e328-e346.

CR, complete response; d, dexamethasone; IMWG, International Myeloma Working Group; Isa, isatuximab; K, carfilzomib; NGS, next generation sequencing; VGPR, very good partial response.

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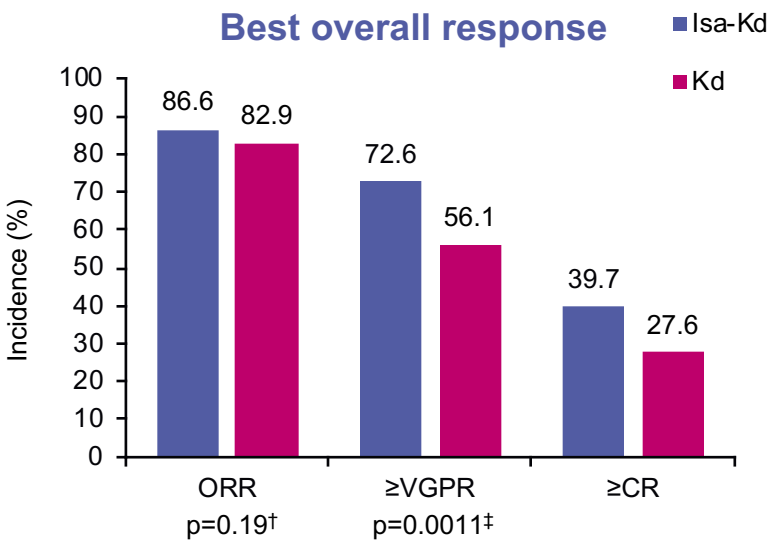
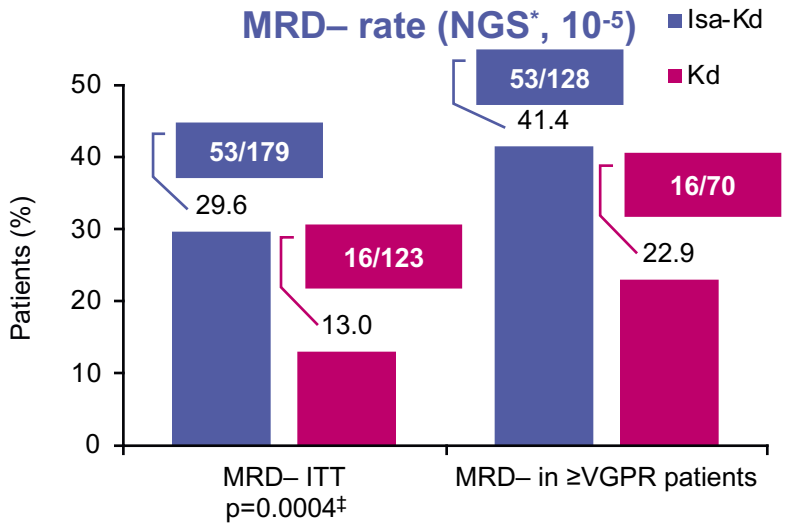
Depth of response





The MRD– rate more than doubled in patients receiving Isa-Kd and was approximately 30% in the ITT population

*Adaptive Biotechnologies NGS, MRD testing performed at time of VGPR or CR. †Stratified Cochran-Mantel-Haenszel test. One-sided significance level is 0.025. ‡Provided for descriptive purposes only.
CR, complete response; d, dexamethasone; ITT, intent-to-treat; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; neg, negative; NGS, next generation sequencing; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response.

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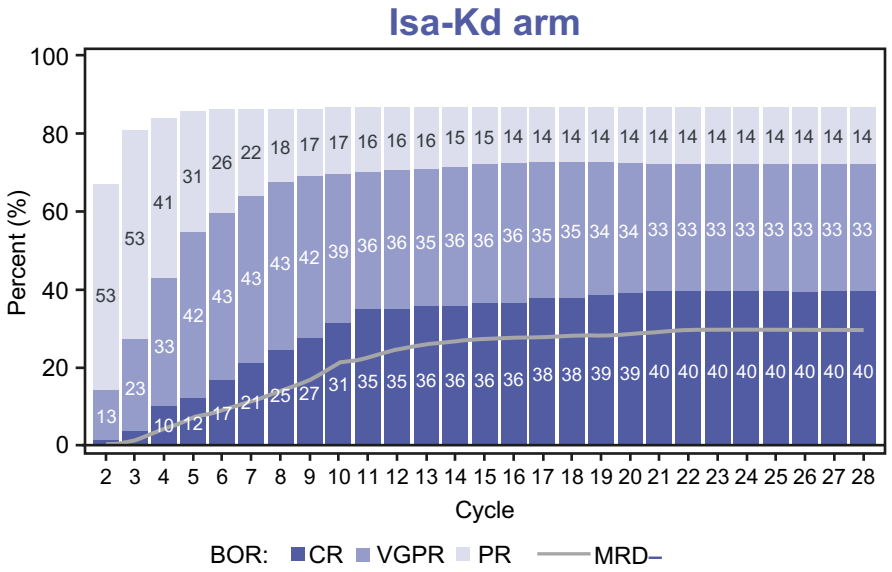
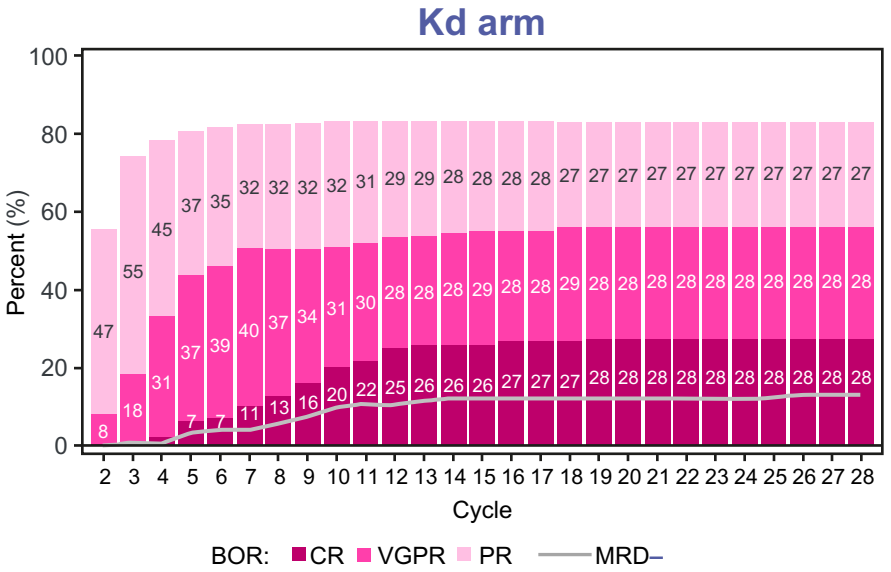
Isa-Kd leads to deeper responses





Depth and quality of response favors Isa-Kd with higher rates of ≥PR, VGPR, CR, and MRD– vs Kd and time to first complete response occurred earlier with Isa-Kd

BOR, best overall response; CR, complete response; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response.

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Key patient demographics and baseline characteristics by MRD status

Randomized population	MRD– (n=69)		MRD+ (n=233)	
	Isa-Kd (n=53)	Kd (n=16)	Isa-Kd (n=126)	Kd (n=107)
Age in years, median (range)	64.0 (37–83)	65.5 (33–78)	65.0 (38–86)	63.0 (38–90)
eGFR <60 mL/min/1.73 m² (MDRD)*, %	26.5	13.3	25.9	16.7
ISS stage at diagnosis, %				
Stage I	18.9	50.0	23.8	23.4
Stage II	24.5	37.5	31.7	39.3
Stage III	32.1	12.5	27.8	21.5
Unknown	24.5	0	16.7	15.9
Prior lines of therapy at study entry, median (range)	1.0 (1–4)	1.0 (1–3)	2.0 (1–4)	2.0 (1–4)
1, %	52.8	62.5	40.5	42.1
2, %	24.5	25.0	40.5	29.9
≥3, %	22.7	12.5	19.1	28.1
Patients refractory to, %				
Lenalidomide	26.4	25.0	34.1	35.5
IMiD and PI	11.3	12.5	23.0	23.4
Refractory to last regimen, %	47.2	31.3	50.8	63.6
Lenalidomide	18.9	18.8	20.6	26.2
Bortezomib	15.1	12.5	19.0	19.6
Cytogenetic risk at baseline†, % High risk	17.0	43.8	26.2	22.4
Gain(1q21) ††, % Present	45.3	43.8	40.5	42.1

Potential to reach MRD– with Isa-Kd is independent of adverse prognostic characteristics, such as:

- **Renal impairment**
- **ISS stage III at diagnosis**
- **≥3 prior lines**
- **Gain(1q21)**

*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).
†† Gain(1q21) is defined as the presence of at least 3 copies with a cut-off of 30%. CRF, case report form; d, dexamethasone; eGFR, estimated glomerular filtration rate; IMiD, immunomodulatory drug; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MDRD, modification of diet in renal disease; MRD, minimal residual disease; PI, proteasome inhibitor.

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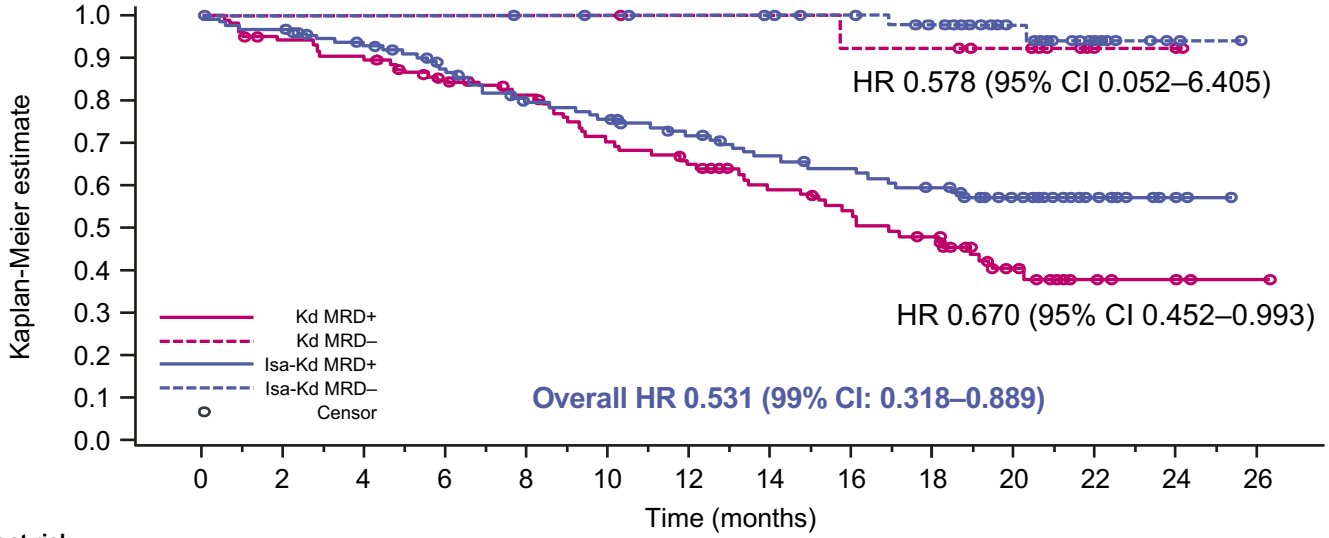
Progression-free survival according to MRD status



Number at risk

Kd - MRD+	107	83	58	38	4
Kd - MRD−	16	16	14	12	2
Isa-Kd - MRD+	126	98	73	57	3
Isa-Kd - MRD−	53	53	51	43	2

A more pronounced PFS benefit was seen in MRD– patients
PFS HR in favor of Isa-Kd for both MRD– and MRD+ patients and consistent with the primary PFS HR

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

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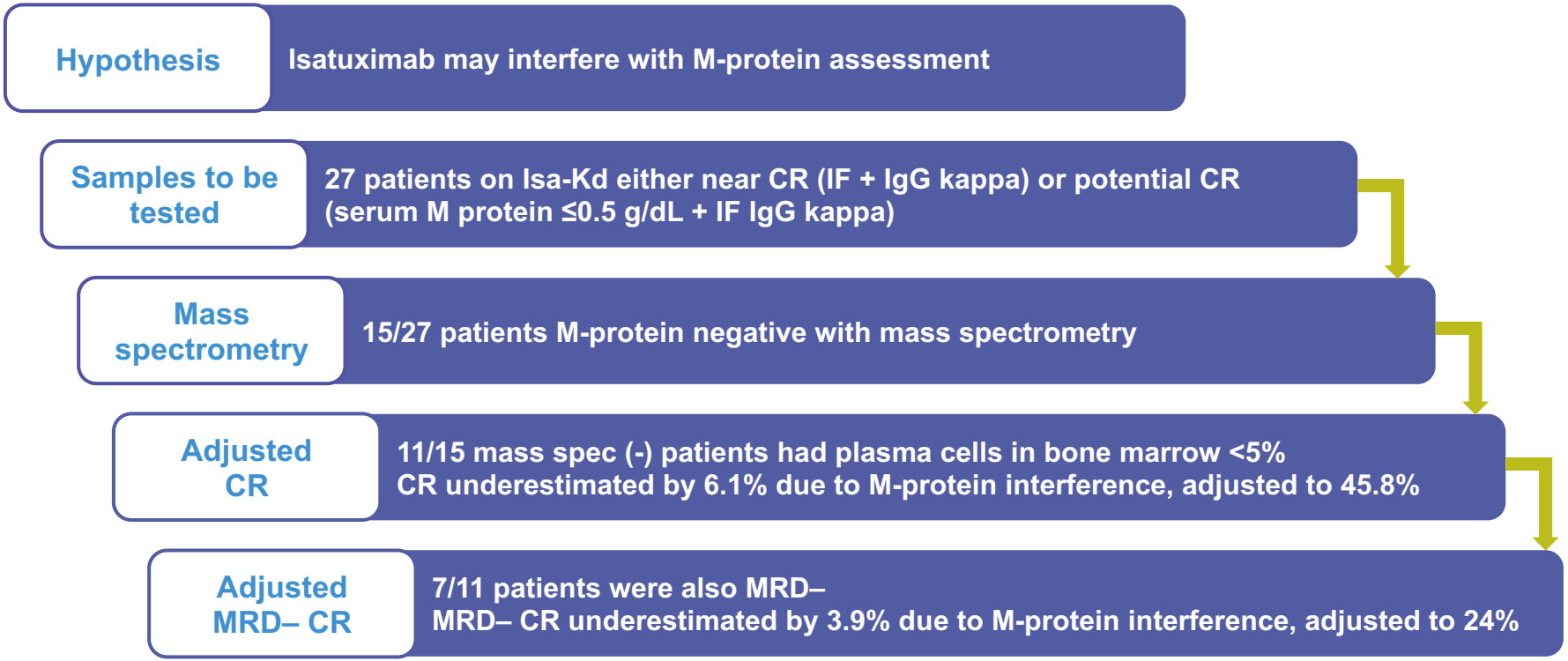
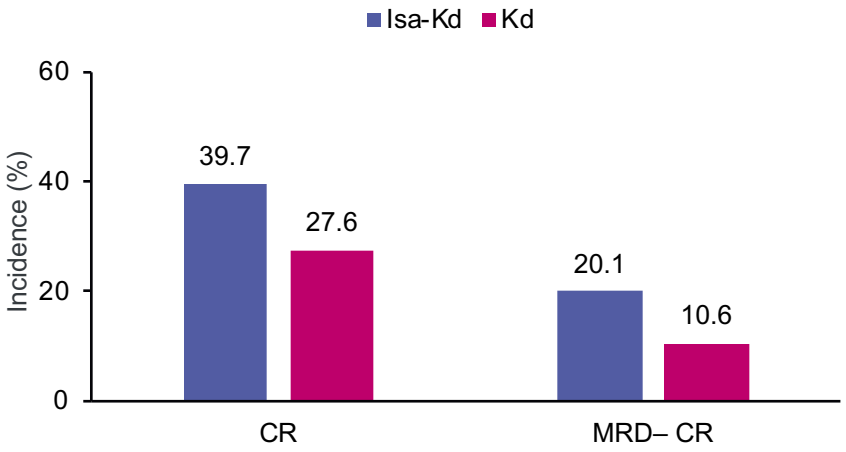
Use of mass spectrometry to assess isatuximab interference



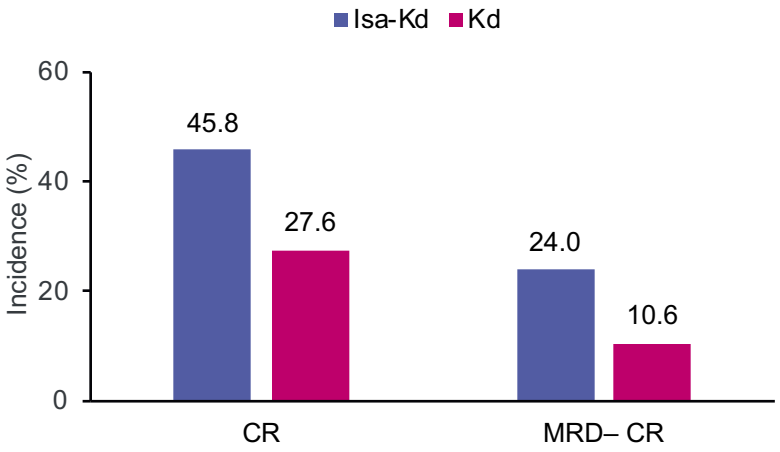
CR, complete response; d, dexamethasone; HR, hazard ratio; IFE, immunofixation electrophoresis; Isa, isatuximab; K, carfilzomib; SPEP, serum protein electrophoresis; VGPR, very good partial response.

Impact of M-protein interference on CR and MRD– rates

No adjustment for M-protein interference



With Mass Spec adjustment for M-protein



With adjustment for isatuximab interference in M-protein assessment, the rate of patients with both MRD– and CR increased to 24% in the Isa-Kd arm

MRD testing performed at time of VGPR or CR.
CR, complete response; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; Mass Spec, mass spectrometry; VGPR, very good partial response.

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Summary

- Isa-Kd leads to deeper responses with a clinically meaningful improvement in the complete response rate vs Kd
- Longer progression-free survival is seen in both MRD– and MRD+ patients and more patients in the Isa-Kd vs the Kd arm reached MRD– status (30% vs 13%).
- PFS was in favor of Isa-Kd in both MRD– and MRD+ patients (HR 0.578 and 0.670, respectively)
- Potential to reach MRD– with Isa-Kd is independent of adverse prognostic characteristics, such as, renal impairment, ISS stage III, ≥3 prior lines and gain(1q21)
- Mass spectrometry supports underestimation of complete response and MRD– complete response patients which could reach the unprecedented rate of 45.8% and 24.0%, respectively

Isa-Kd represents a potential new standard of care for patients with relapsed MM

CR, complete response; d, dexamethasone; Isa, isatuximab; ISS, International Staging System; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; PFS, progression-free survival.

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Disclosures

TM: Research funding – Amgen, Sanofi, Seattle Genetics, JNJ, and Janssen;
Consultancy fees – Legend Biotech

JM: Honoraria – Celgene, Takeda, BMS, Janssen, and Amgen;
Consulting or advisory role – Amgen, Bristol-Myers Squibb, Celgene, Janssen-Cilag, and Takeda

RH: Personal fees – AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Pharma Mar, Novartis, and Takeda; Grants – Novartis and Takeda

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HQ: Research funding – Amgen, Sanofi, Celgene, Karyopharm, and GSK; Board of directors or advisory committee – Amgen, Celgene, Karyopharm, Janssen, and Sanofi; Consultancy – GSK, Karyopharm, Amgen, Celgene, and Janssen; Honoraria – GSK, Karyopharm, Amgen, Celgene, and Janssen

CH, MG, HSi, AG, TK: Had nothing to disclose

M-LR, GA, SM, HvdV: Are employees of Sanofi and may hold shares and/or stock options in the company

PM: Honoraria – Amgen, Celgene, Janssen, Novartis, and Takeda; Consulting or advisory role – Amgen, Celgene, Janssen, Novartis, and Takeda

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