Long-Term Outcomes With Isatuximab-Carfilzomib-Dexamethasone (Isa-Kd) in Relapsed Multiple Myeloma Patients With 1q21+ Status: Updated Results From the Phase 3 IKEMA Study

Thierry Facon[1], Philippe Moreau[2], Ivan Špička[3], Kenshi Suzuki[4], Kwee Yong[5], Joseph Mikhael[6], Taro Fukao[7], Kamlesh Bisht[7], Nicole Armstrong[8], Sandrine Macé[9], Marie-Laure Risse[10], Thomas Martin[11]

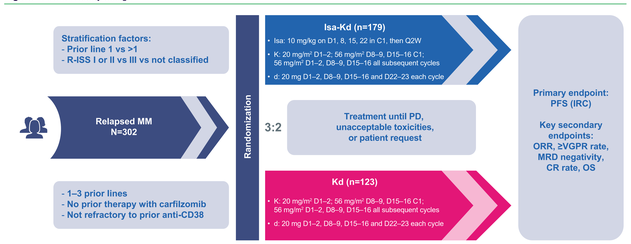
[1]Department of Hematology, Lille University Hospital, Lille, France; [2]Department of Hematology, University Hospital Hôtel-Dieu, Nantes, France; [3]Department of Hematology, 1st Faculty of Medicine, Charles University and General Hospital, Prague, Czech Republic; [4]Myeloma/Amyloidosis Center, Japanese Red Cross Medical Center, Tokyo, Japan; [5]Department of Haematology, University College Hospital, London, UK; [6]Translational Genomics Research Institute, City of Hope Cancer Center, Phoenix, AZ, USA; [7]Sanofi, Global Oncology, Cambridge, MA, USA; [8]Sanofi, Global Medical Affairs, Cambridge, MA, USA; [9]Sanofi, Research and Development, Chilly-Mazarin, France; [10]Sanofi, Research and Development, Vitry-sur-Seine, France; [11]University of California San Francisco Medical Center, San Francisco, CA, USA

INTRODUCTION

- Gain or amplification of 1q21 (1q21+, ≥3 copies) is a chromosomal abnormality frequently observed in multiple myeloma (MM), with a negative impact on prognosis, due to its potential involvement in resistance to anti-myeloma therapy and disease progression[1-3]
- Isatuximab (Isa) is an anti-CD38 antibody that mediates anti-myeloma activity through multiple mechanisms of action, including antibody-dependent cell-mediated cytotoxicity and direct induction of apoptosis[4]
- In the prespecified, interim analysis of the Phase 3 IKEMA trial in patients with relapsed MM, addition of Isa to carfilzomib-dexamethasone (Isa-Kd) showed significant improvement in progression-free survival (PFS) vs Kd (hazard ratio [HR] 0.538; 99% CI 0.318–0.889, one sided *P* value=0.0007) confirmed at the time of the long-term PFS analysis in which median PFS was reached for Isa-Kd (35.65 months with Isa-Kd vs 19.15 months with Kd) and with a meaningful increase in depth of response (complete response or better [≥CR] 44.1% vs 28.5%; minimal residual disease [MRD] negativity 33.5% vs 15.4%; MRD negativity ≥CR 26.3% vs 12.2%), as well as a manageable safety profile[5]
- Isa is approved with pomalidomide-dexamethasone (Pd) for relapsed/refractory MM (RRMM) patients with ≥2 prior therapies, based on the Phase 3 ICARIA-MM study, and with carfilzomib-dexamethasone for RRMM patients with 1–3 prior lines of therapy, based on interim PFS analysis of IKEMA[6,7]
- Results from prior subgroup analyses have shown benefit from adding Isa to Kd (IKEMA, interim analysis, 20.7 months follow-up) or to Pd (ICARIA-MM) in 1q21+ patients and 1q21+ subgroups[8]
- In this updated subgroup analysis of IKEMA, we evaluated PFS and depth of response with Isa-Kd vs Kd in relapsed MM patients with 1q21+ status (with or without high-risk chromosomal abnormalities [HRCA]) and in related patient subgroups, at long-term follow-up (44.2 months):
  - 1q21+ (≥3 copies, with or without HRCA)
  - Isolated 1q21+ (≥3 copies, without HRCA)
  - Gain(1q21) (3 copies, with or without HRCA)
  - Amp(1q21) (≥4 copies, with or without HRCA)

METHODS

Figure 1. IKEMA study design



C, cycle; 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; PD, progressive disease; PFS, progression-free survival; Q2W, once every 2 weeks; R-ISS, revised International Staging System; VGPR, very good partial response

- In IKEMA, MM patients with 1–3 prior lines of therapy were randomized 3:2 to Isa-Kd or Kd (**Figure 1**)
- The primary study endpoint was PFS, defined as the time from randomization to first documentation of progressive disease or death from any cause, whichever occurred first
- PFS was centrally assessed and determined by an independent response committee (IRC), based on central laboratory data for M-protein and central review of local imaging and local bone marrow aspirate results
- Estimates of median PFS and corresponding CIs were calculated by the Kaplan-Meier method. HR estimates were determined using an unstratified Cox regression model
- Best overall responses were evaluated according to the International Myeloma Working Group criteria
- Assessment of 1q21+ status (by fluorescence in situ hybridization, at 30% cutoff) was specified as ≥3 copies, gain(1q21) as 3 copies, and amp(1q21) as ≥4 copies
- MRD negativity rates were centrally determined by next-generation sequencing at 10^{-5} sensitivity

RESULTS

Patients

- Among patients randomized 3:2 to Isa-Kd (n=179) or Kd (n=123), 75 (41.9%) in Isa-Kd and 52 (42.3%) in Kd had 1q21+ status (**Table 1**)
- At the time of this updated analysis, more patients were still on treatment with Isa-Kd than Kd (17.3% vs 3.8% in the 1q21+ group and 34.5% vs 16.4% in patients without 1q21+) (**Table 1**)
- Although most patient characteristics were comparable between study arms, a few imbalances were observed (**Table 2**):
  - A lower proportion of 1q21+ patients in Isa-Kd than in Kd had revised International Staging System (R-ISS) stage I (18.7% vs 26.9%)
  - More 1q21+ patients in Isa-Kd than Kd had serum lactate dehydrogenase levels higher than upper limit of normal (26.7% vs 13.5%)
  - 36.0% of 1q21+ patients in Isa-Kd were refractory to lenalidomide vs 42.3% in Kd
  - Among patients without 1q21+, 28.2% in Isa-Kd (n=78) had an estimated glomerular filtration rate <60 mL/min/1.73 m^2 vs 16.7% in Kd (n=48)
- In the Isa-Kd and Kd arms, 41.9% and 42.3% of patients had 1q21+ status, 26.3% and 25.2% had isolated 1q21+, 24.0% and 30.1% had gain(1q21), 17.9% and 12.2% had amp(1q21), respectively (**Table 3**)

Table 1. Patient disposition

	With 1q21+		Without 1q21+	
n (%)	Isa-Kd (n=75)	Kd (n=52)	Isa-Kd (n=84)	Kd (n=55)
Randomized and treated	73 (97.3)	51 (98.1)	84 (100)	55 (100)
Patients still on treatment	13 (17.3)	2 (3.8)	29 (34.5)	9 (16.4)
Patients with definitive treatment discontinuation	60 (80.0)	49 (94.2)	55 (65.5)	46 (83.6)
Reason for definitive treatment discontinuation				
Adverse event	8 (10.7)	6 (11.5)	11 (13.1)	13 (23.6)
Progressive disease	39 (52.0)	33 (63.5)	32 (38.1)	22 (40.0)
Poor compliance with protocol	0	0	0	0
Withdrawal by patient	8 (10.7)	7 (13.5)	7 (8.3)	7 (12.7)
Other	5 (6.7)	3 (5.8)	5 (6.0)	4 (7.3)

d, dexamethasone; Isa, isatuximab; K, carfilzomib

Table 2. Patient demographics and baseline characteristics

	With 1q21+		Without 1q21+	
	Isa-Kd (n=75)	Kd (n=52)	Isa-Kd (n=84)	Kd (n=55)
Age in years, median (range)	63.0 (37–83)	66.5 (38–90)	65.0 (38–86)	63.0 (33–80)
<65, n (%)	40 (53.3)	23 (44.2)	40 (47.6)	34 (61.8)
65–74, n (%)	29 (38.7)	22 (42.3)	35 (41.7)	18 (32.7)
≥75, n (%)	6 (8.0)	7 (13.5)	9 (10.7)	3 (5.5)
R-ISS stage at study entry, n (%)				
I	14 (18.7)	14 (26.9)	30 (35.7)	16 (29.1)
II	51 (68.0)	33 (63.5)	47 (56.0)	32 (58.2)
III	9 (12.0)	4 (7.7)	6 (7.1)	4 (7.3)
Not classified	1 (1.3)	1 (1.9)	1 (1.2)	3 (5.5)
Prior lines of therapy, median (range)	2 (1–4)	2 (1–4)	2 (1–3)	2 (1–4)
Patients refractory to, n (%)				
Lenalidomide	27 (36.0)	22 (42.3)	22 (26.2)	16 (29.1)
PI	24 (32.0)	19 (36.5)	24 (28.6)	19 (34.5)
IMiD and PI	14 (18.7)	13 (25.0)	16 (19.0)	10 (18.2)
Serum LDH >ULN, n (%)	20 (26.7)	7 (13.5)	19 (22.6)	9 (16.4)
eGFR <60 mL/min/1.73 m^2, n (%)	16/69 (23.2)	10/48 (20.8)	22/78 (28.2)	8/48 (16.7)

d, dexamethasone; eGFR, estimated glomerular filtration rate (MDRD equation); IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; LDH, lactate dehydrogenase; MDRD, Modification of Diet in Renal Disease; PI, proteasome inhibitor; R-ISS, revised International Staging System; ULN, upper limit of normal

Table 3. Incidence of 1q21+ chromosomal abnormality among patients in IKEMA

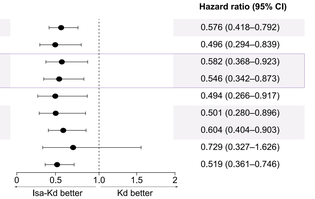
	Standard risk*		1q21+		Isolated 1q21+† (w/o HRCA)		Gain(1q21)		Amp(1q21)	
	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd
n (%)	65 (36.3)	43 (35.0)	75 (41.9)	52 (42.3)	47 (26.3)	31 (25.2)	43 (24.0)	37 (30.1)	32 (17.9)	15 (12.2)

*Standard risk: absence of the chromosomal abnormalities del(17p), t(4;14), t(4;16), and 1q21+.
†Isolated 1q21+: presence of 1q21+ without HRCA [absence of del(17p), t(4;14), t(4;16)].
Amp, amplification; d, dexamethasone; HRCA, high-risk chromosomal abnormality; Isa, isatuximab; K, carfilzomib

Efficacy: PFS

- PFS benefit was achieved with Isa-Kd vs Kd in patients with 1q21+ status (with or without HRCA; HR 0.58; 95% CI 0.37–0.92), with isolated 1q21+ (without HRCA; HR 0.50; 95% CI 0.27–0.92), with gain(1q21) (HR 0.50, 95% CI 0.28–0.90), or with amp(1q21) (HR 0.73; 95% CI 0.33–1.63) (**Figure 2**)
- Kaplan-Meier curves for PFS of Isa-Kd vs Kd are presented for the 1q21+ subgroups in **Figure 3**. The median PFS were:
  - 38.2 months (95% CI 18.8–not calculable [NC]) vs 16.2 months (95% CI 10.2–25.1) in patients with isolated 1q21+
  - 30.2 months (95% CI 20.8–NC) vs 18.2 months (95% CI 10.2–25.0) in patients with gain(1q21)
  - 18.4 months (95% CI 13.1–NC) vs 14.5 months (95% CI 2.8–NC) in patients with amp(1q21)
- Kaplan-Meier curves by treatment arm, in **Figure 4**, show the impact of 1q21+, gain(1q21), and amp(1q21) on PFS, thus underscoring the prognostic importance of this chromosomal abnormality
  - PFS benefit was observed with Isa-Kd vs Kd in all subgroups evaluated, although to a greater extent in patients with gain(1q21) than amp(1q21)

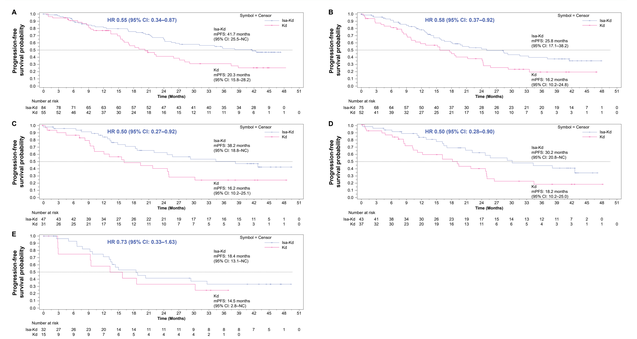
Figure 2. PFS subgroup analyses by 1q21+ chromosomal abnormality (per IRC assessment, ITT)



Subgroup		Isa-Kd Events/total	Kd Events/total	Hazard ratio (95% CI)
All patients		86/179	77/123	0.576 (0.418–0.792)
Standard risk*		29/65	28/43	0.496 (0.294–0.839)
1q21+	Present	39/75	35/52	0.582 (0.368–0.923)
	Absent	39/84	33/55	0.546 (0.342–0.873)
Isolated 1q21+	Present	21/47	20/31	0.494 (0.266–0.917)
Gain(1q21)	Present	21/43	26/37	0.501 (0.280–0.896)
	Absent	57/116	42/70	0.604 (0.404–0.903)
Amp(1q21)	Present	18/32	9/15	0.729 (0.327–1.626)
	Absent	60/127	59/92	0.519 (0.361–0.746)

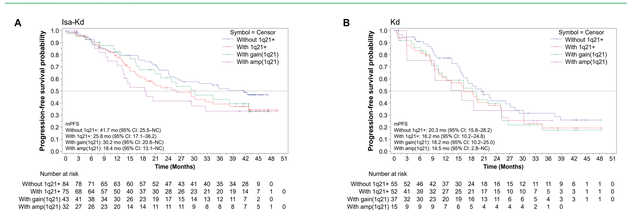
*Standard risk: absence of the chromosomal abnormalities del(17p), t(4;14), t(4;16), and 1q21+. Isolated 1q21+: presence of 1q21+ without high-risk chromosomal abnormalities [absence of del(17p), t(4;14), t(4;16)].
Amp, amplification; CI, confidence interval; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; PFS, progression-free survival

Figure 3. PFS with Isa-Kd vs Kd in patients without 1q21+ (A), with 1q21+ (B), with isolated 1q21+* (C), with gain(1q21) (D), and with amp(1q21) (E) (per IRC assessment, ITT)



*Isolated 1q21+: presence of 1q21+ without high-risk chromosomal abnormalities [absence of del(17p), t(4;14), t(4;16)].
Amp, amplification; CI, confidence interval; d, dexamethasone; HR, hazard ratio; IRC, Independent Response Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; m, median; NC, not calculable; PFS, progression-free survival

Figure 4. PFS in patients with and without 1q21+, with gain(1q21) (3 copies), and with amp(1q21) (≥4 copies) in the Isa-Kd (A) and Kd (B) treatment arms (per IRC assessment, ITT)

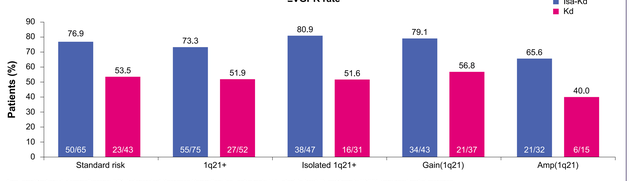


Amp, amplification; CI, confidence interval; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; m, median; NC, not calculable; PFS, progression-free survival

Efficacy: depth of response

- Clinically meaningful increases in very good partial response or better (≥VGPR), MRD negativity, and MRD negativity ≥CR rates were observed with addition of Isa to Kd across all 1q21+ subgroups (**Figures 5** and **6**)
- The MRD negativity and MRD negativity ≥CR rates were at least double with Isa-Kd vs Kd in most subgroups, except for amp(1q21) in which benefit was less pronounced, but remained meaningful
- In the Isa-Kd and Kd arms, the MRD negativity and ≥CR rate was 29.3% vs 15.4% in patients with 1q21+ status, 36.2% vs 12.9% in patients with isolated 1q21+, 27.9% vs 13.5% in patients with gain(1q21), and 31.3% vs 20.0% in patients with amp(1q21), respectively (**Figure 6**)

Figure 5. Rates of ≥VGPR with Isa-Kd vs Kd by 1q21+ chromosomal abnormality (per IRC assessment, ITT)



Amp, amplification; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; VGPR, very good partial response

Figure 6. Rates of MRD negativity and of MRD negativity and ≥CR with Isa-Kd vs Kd by 1q21+ chromosomal abnormality (per IRC assessment, ITT)*



*MRD negativity rates were assessed by next-generation sequencing (NGS) at 10^{-5} sensitivity.
Amp, amplification; CR, complete response; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; MRD, minimal residual disease

CONCLUSIONS

- The presence of 1q21+ chromosomal abnormalities (gain or amplification) is associated with a higher risk of progression and worse prognosis in patients with MM
  - Patients with isolated 1q21+, gain(1q21) with or without HRCA, and particularly amp(1q21) with or without HRCA, had shorter PFS compared with patients without 1q21+, in the control arm of IKEMA, suggesting a copy number-related dose effect in addition to the impact of HRCA
- At long-term follow-up (44.2 months), results from the IKEMA study continue to show PFS benefit with Isa-Kd compared with Kd in 1q21+ patients with relapsed MM, consistent with the overall population and the previous 1q21+ subgroup interim analyses
- PFS benefit was achieved with Isa-Kd therapy across all subgroups: in patients with isolated 1q21+ or combined with HRCA as well as in patients with gain(1q21) and patients with amp(1q21) who have a particularly poor prognosis
- Deeper responses – higher ≥VGPR rates, MRD negativity rates, and MRD negativity ≥CR rates – were reached with Isa-Kd vs Kd in 1q21+ patients (with or without HRCA), isolated 1q21+, gain(1q21), or amp(1q21)
- These long-term findings support Isa-Kd as an effective treatment option for patients with relapsed MM, including 1q21+ patients who have a higher risk of progression

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DISCLOSURES:
TF: participation on a data safety monitoring board or advisory board for Amgen, Bristol Myers Squibb, Janssen, Karyopharm, Oncopeptides, Roche, and Sanofi; speakers' bureau for Bristol Myers Squibb and Janssen. **PM**: honoraria and consulting/advisory role for AbbVie, Amgen, Celgene, Janssen, Oncopeptides, Roche, and Sanofi. **IŠ**: research funding, honoraria, and participation on a data safety monitoring board or advisory board for Amgen, Bristol Myers Squibb, Celgene, Janssen-Cilag, Novartis, PharmaMar, Sanofi, and Takeda. **KS**: honoraria from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Novartis, Ono Pharmaceutical, Sanofi, and Takeda. **KY**: nothing to disclose. **JM**: honoraria from Amgen, Celgene, GlaxoSmithKline, Janssen, Karyopharm, Sanofi, and Takeda. **TF, NA, SM, M-LR**: employed by Sanofi; may hold stock and/or stock options. **TM**: research funding (to institution) from Sanofi; participation on a steering committee for Sanofi.

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