Isatuximab plus carfilzomib and dexamethasone in patients with early *versus* late relapsed multiple myeloma: IKEMA subgroup analysis

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Abstract

Patients with multiple myeloma (MM) who experience early relapse within 12 months of therapy initiation are considered functional high-risk and represent an unmet need, needing better therapies to improve outcomes. The final IKEMA (*clinicaltrials gov. identifier: NCT03275285*) progression-free survival (PFS) analysis confirmed the significant PFS improvement reported at interim analysis with isatuximab (Isa) plus carfilzomib and dexamethasone (Kd; Isa-Kd) *versus* Kd in patients with relapsed MM (updated median PFS: 35.7 *vs.* 19.2 months; hazard ratio [HR] =0.58, 95% confidence interval [CI]: 0.42-0.79). This IKEMA subgroup analysis examined efficacy and safety of Isa-Kd *versus* Kd in patients who experienced early (n=61 [Isa-Kd], n=46 [Kd]) *vs.* late relapse (n=104 [Isa-Kd], n=72 [Kd]). As expected, more aggressive features in baseline characteristics were observed in early relapse patients. Consistent with IKEMA overall population results, median PFS (early relapse: 24.7 *vs.* 17.2 months, HR=0.662, 95% CI: 0.407-1.077; late relapse: 42.7 *vs.* 21.9 months, HR=0.542, 95% CI: 0.355-0.826), minimal residual disease negativity (MRD^-) (early relapse: 24.6% *vs.* 15.2%; late relapse: 37.5% *vs.* 16.7%), and MRD^- complete response (≥CR) rates (early relapse: 18.0% *vs.* 10.9%; late relapse: 30.8% *vs.* 13.9%) were higher with Isa-Kd *versus* Kd, respectively, in both early and late relapse patients. Grade ≥3, serious treatment-emergent adverse events, and death rates were higher in the late relapse Isa-Kd arm. However, the numbers of deaths were low and treatment exposure was significantly longer in Isa-Kd *versus* Kd late relapse patients. These results support the addition of Isa to Kd as standard-of-care therapy for relapsed and/or refractory MM regardless of relapse timing.

Introduction

The availability of novel treatment options, such as immunomodulatory drugs (e.g., lenalidomide, pomalidomide, thalidomide), proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), targeted monoclonal antibodies (e.g., isatuximab, daratumumab, elotuzumab), and combination regimens, has improved treatment outcomes for patients with multiple myeloma (MM); however, MM is still associated with a significant patient burden.[1-3] Patients with MM frequently relapse and experience shorter duration of response with each successive regimen.[4] Those who experience early relapse within 1 year of initiating therapy with novel agents have worse prognosis, with significantly reduced median overall survival (21.0 months [early relapse] *vs.* not reached [late relapse]), and are classified as functional high-risk patients.[5,6] The survival disadvantage in early relapse patients is observed regardless of depth of response to initial therapy.[5] Furthermore, poor survival outcomes have been reported among patients who experienced early relapse within 12 months of autologous stem cell transplantation (ASCT), even in the era of novel agents.[5,7,8] Thus, more ef-

fective agents and combinations are needed for the early relapse subgroup of patients who are at higher risk of more aggressive disease.

Anti-CD38 monoclonal antibodies have demonstrated synergistic antitumor effects in combination with backbone therapies that include immunomodulatory drugs and proteasome inhibitors and are being increasingly used in the MM treatment continuum to improve patient outcomes.[9,10] Isatuximab (Isa), an anti-CD38 monoclonal antibody that targets a specific CD38 epitope, induces myeloma cell death via multiple mechanisms of action including antibody-dependent cellular-mediated cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, direct apoptosis without crosslinking, and direct inhibition of CD38 ectoenzyme activity.[11-13] Based on the results of the phase III ICARIA-MM study (*clinicaltrials gov. Identifier: NCT02990338*), Isa is approved in a number of countries in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory MM who have received ≥2 prior therapies, including lenalidomide and a proteasome inhibitor.[11,14,15] The phase III IKEMA study (*clinicaltrials gov. Identifier: NCT03275285*) compared Isa in combination with carfilzomib (K) and dexamethasone (d) (Isa-Kd) *versus* Kd in patients with relapsed MM.[16,17] Based on the primary interim analysis results of IKEMA, Isa-Kd is approved in the United States for the treatment of adult patients with relapsed or refractory MM who have received 1-3 prior lines of therapy, in the European Union and other countries for the treatment of adult patients with relapsed MM who have received ≥1 prior therapy, and in Japan for the treatment of adult patients with relapsed or refractory MM who have received one prior treatment.[11,14,17,18]

The final progression-free survival (PFS) analysis of the IKEMA study, performed 2 years after the prespecified interim analysis, at a median follow-up of 44 months, was recently published.[19] The results of this analysis confirmed the significant improvement in PFS reported at the time of the interim analysis with Isa-Kd *versus* Kd in patients with relapsed MM (updated median PFS 35.7 [Isa-Kd] *vs.* 19.2 months [Kd]; hazard ratio [HR] =0.58, 95% confidence interval [CI]: 0.42-0.79), with a clinically meaningful increase in minimal residual disease negativity (MRD^-) (33.5% *vs.* 15.4%) and complete response (CR) (44.1% *vs.* 28.5%) rates in the intent-to-treat population, and a manageable safety profile.[19] This subgroup analysis of IKEMA examined updated efficacy and safety of Isa-Kd *versus* Kd in patients with functional high-risk MM as defined by early relapse from the most recent prior line of therapy *versus* those who experienced late relapse.

Methods

Study design and participants

IKEMA was a prospective, multinational, randomized, open-label, phase III study.[16,17] The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study protocol was approved by an institutional ethics committee or independent review board at all participating centers. All patients provided written informed consent.

The IKEMA study design and dosing schedule of the study drugs were previously described in detail[16,17] and are summarized in the *Online Supplementary Appendix*. Briefly, 302 eligible patients with relapsed and/or refractory MM who had received one to three prior lines of therapy, were randomized 3:2 to receive Isa-Kd or Kd. Patients were classified into early or late relapse subgroups based on previously established definitions.[20,21] Early relapse was defined as relapse that occurred <12 months from initiation of the most recent line of therapy for patients with ≥2 prior lines of therapy, <18 months for patients with one prior line of therapy, or <12 months following frontline ASCT. Late relapse subgroup included patients who relapsed ≥12 months from initiation of the most recent line of therapy for those with ≥2 prior lines of therapy and ≥18 months for patients with one prior line of therapy. A few patients (n=14 [Isa-Kd], n=5 [Kd]) from the IKEMA overall population were not categorized into either early or late relapse because dates of relapse/progression and latest prior line or ASCT initiation were either not available or incomplete (only year reported) for these patients, and these patients have, therefore, been omitted from the current analysis.

MRD was assessed by next-generation sequencing at a central laboratory using the ClonoSEQ Assay (Adaptive Biotechnologies, Seattle, WA, USA) with a sensitivity of 10^{-5}. Adverse events (AE) and laboratory abnormalities were graded according to the National Cancer Information Center Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

Outcomes

The primary endpoint was PFS, defined using the International Myeloma Working Group criteria for progression and disease response evaluation.[22] Key secondary endpoints included overall response rate (ORR), rates of very good partial response or better (≥VGPR), MRD^-, and CR, and safety. PFS was assessed by a blinded independent review committee based on central laboratory M-protein quantification, local bone marrow aspiration when needed, and central radiologic review. In order to determine the CR rate, the Hydrashift 2/4 Isa immunofixation assay (Sebia, Lisses Evry Cedex, France)[23] was used to correct for M-protein interference, when needed.

Statistical analysis

A prespecified final PFS analysis was conducted on the IKEMA intent-to-treat population (n=179 [Isa-Kd], n=123 [Kd]) and utilized for this *post hoc* subgroup analysis. The median PFS and CI were calculated by the Kaplan-Meier method.

Non-stratified Cox proportional hazards models including treatment as a covariate were used to estimate HR.[24,25] The safety population included all treated patients (n=177 [Isa-Kd], n=122 [Kd]) and analyses of the safety variables were descriptive.

Results

Patient characteristics

Baseline characteristics for early (n=107) and late relapse (n=176) patients are shown in Table 1. Some imbalances in these characteristics were observed between treatment arms as well as between early and late relapse patients. Imbalances between early and late relapse patients were noted in International Staging System (ISS) stage at study entry and high-risk cytogenetics, with more aggressive features observed in early relapse patients. Additional imbalances were noted in prior lines of treatment and refractoriness. Patients with early relapse had more prior lines, fewer prior ASCT, and were more frequently refractory than those classified as late relapse.

Early relapse

In total, 61 of 179 (34.1%) patients in the Isa-Kd arm and 46 of 123 (37.4%) patients in the Kd arm were classified as early relapse. The Isa-Kd arm had a higher proportion of patients who had renal impairment (31.0% *vs.* 15.4%), prior ASCT (49.2% *vs.* 30.4%), or prior proteasome inhibitors (93.4% *vs.* 82.6%), and a lower proportion of patients aged ≥75 years old (11.5% *vs.* 17.4%), patients with ISS stage I at study entry (31.1% *vs.* 54.3%), or with chromosomal abnormality 1q21+ (41.0% *vs.* 56.5%) *versus* Kd arm, respectively. The median number of prior lines of therapy was two for both treatment arms; 32.8% of patients had one prior line of therapy with Isa-Kd *versus* 41.3% with Kd.

Late relapse

A total of 104 of 179 (58.1%) patients in the Isa-Kd arm and 72 of 123 (58.5%) patients in the Kd arm were classified as late relapse. The median number of prior lines of therapy was one in the Isa-Kd arm and two in the Kd arm; 55.8% of patients had one prior line of therapy with Isa-Kd *versus* 48.6% of patients with Kd. More patients were aged ≥75 years (8.7% *vs.* 2.8%), had renal impairment (21.7% *vs.* 16.7%), 1q21+ (44.2% *vs.* 33.3%), or two cytogenetic abnormalities (11.5% *vs.* 6.9%), and fewer patients were relapsed and refractory (52.9% *vs.* 68.1%) with Isa-Kd *versus* Kd, respectively.

Treatment exposure

At data cutoff (January 14, 2022), the median follow-up was 44 months. The duration of study treatment was longer in patients who received Isa-Kd *versus* Kd, regardless of early (median [min–max]: 79.0 [2–209] weeks [Isa-Kd]; 52.6 [4–208] weeks [Kd]) or late relapse (median [min–max]: 102.6 [6–206] weeks [Isa-Kd]; 64.9 [2–194] weeks [Kd]) (*Online Supplementary Table S1*). In addition, treatment duration was longer in late relapse patients compared with that in early relapse patients across both treatment arms. Notably, exposure to Isa-Kd was significantly longer in late relapse patients than that observed in early relapse patients.

Among early relapse patients, 16.4% of patients in the Isa-Kd arm and 6.5% of patients in the Kd arm were still on treatment at data cutoff. The median (min–max) number of cycles was 19.0 (1-49) cycles with Isa-Kd *versus* 13.5 (1-42) cycles with Kd. The median relative dose intensity (RDI) for Isa was 94.1%. The median RDI for carflizomib was similar in both arms (93.1%, Isa-Kd *vs.* 91.3%, Kd). The median RDI for dexamethasone was 83.1% in the Isa-Kd arm *versus* 87.2% in the Kd arm.

In late relapse patients, 32.7% of patients in the Isa-Kd arm and 11.1% of patients in the Kd arm were still on treatment at data cutoff. The median (min–max) number of cycles was 24.0 (2-50) cycles with Isa-Kd *versus* 16.0 (1-47) cycles with Kd. The median RDI for Isa was 91.9%. The median RDI for carfilzomib was 86.5% with Isa-Kd *versus* 90.5% with Kd. The median RDI for dexamethasone was 77.4% in the Isa-Kd arm *versus* 88.0% in the Kd arm.

Efficacy

Progression-free survival

At data cutoff, the PFS was longer for patients treated with Isa-Kd *versus* Kd, respectively, in both early relapse (median 24.7 *vs.* 17.2 months; HR=0.662, 95% CI: 0.407-1.077) and late relapse patients (median 42.7 *vs.* 21.9 months; HR=0.542, 95% CI: 0.355-0.826) (Figure 1). Among patients refractory to the last regimen, there was a similar treatment effect favoring Isa-Kd over Kd in early (HR=0.544, 95% CI: 0.313-0.944) and late relapse (HR=0.552, 95% CI: 0.279-1.093) patients (Figure 2). Similar treatment effect was also observed in early (median 21.5 *vs.* 14.8 months; HR=0.620, 95% CI: 0.359-1.069) and in late relapse (median PFS 42.7 *vs.* 16.2 months; HR=0.634, 95% CI: 0.334-1.202) patients who were refractory to an immunomodulatory agent or a proteasome inhibitor.

Depth of response

The ORR were 82.0% *versus* 82.6% in early relapse patients, and 90.4% *versus* 86.1% in late relapse patients with Isa-Kd *versus* Kd, respectively (Figure 3). We assessed depth of response by rates of ≥VGPR, ≥CR, MRD^-, MRD^- ≥VGPR, and MRD^- ≥CR. More patients achieved ≥VGPR (early relapse: 67.2% *vs.* 52.2%; late relapse: 76.0% *vs.* 58.3%), ≥CR (early relapse: 31.1% *vs.* 23.9%; late relapse: 52.9% *vs.* 30.6%), MRD^- (early relapse: 24.6% *vs.* 15.2%; late relapse: 37.5% *vs.* 16.7%), MRD^- ≥VGPR (early relapse: 24.6% *vs.* 13.0%; late relapse: 37.5% *vs.* 15.3%), MRD^- ≥CR rates (early relapse: 18.0% *vs.* 10.9%; late relapse: 30.8% *vs.* 13.9%) with Isa-Kd *versus* Kd, respectively, regardless of early or late relapse.

Table 1. Key patient demographics and baseline characteristics in IKEMA early relapse and late relapse patients (intent-to-treat population).

	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)
Sex, female, N (%)	30 (49.2)	21 (45.7)	46 (44.2)	33 (45.8)
CrCl <60 mL/min/1.73 m^2, MDRD[a], N (%)	18/58 (31.0)	6/39 (15.4)	20/92 (21.7)	11/66 (16.7)
β2 microglobulin in mg/L, by category, N (%)				
<3.5	21 (34.4)	29 (63.0)	74 (71.2)	48 (66.7)
≥3.5 to <5.5	26 (42.6)	8 (17.4)	21 (20.2)	15 (20.8)
≥5.5	14 (23.0)	9 (19.6)	9 (8.7)	9 (12.5)
Albumin g/L, by category, N (%)				
<35	17 (27.9)	9 (19.6)	18 (17.3)	10 (13.9)
≥35	43 (70.5)	37 (80.4)	84 (80.8)	60 (83.3)
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)
Unknown	0	0	1 (1.0)	1 (1.4)
Cytogenetics at study entry[b,c], 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)
Missing	7 (11.5)	2 (4.3)	14 (13.5)	11 (15.3)
del(17p)	10 (16.4)	8 (17.4)	6 (5.8)	8 (11.1)
t(4;14)	7 (11.5)	11 (23.9)	14 (13.5)	7 (9.7)
t(14;16)	5 (8.2)	0	1 (1.0)	0
1q21+	25 (41.0)	26 (56.5)	46 (44.2)	24 (33.3)
Gain 1q21	15 (27.8)	18 (41.9)	26 (28.0)	18 (30.0)
1 cytogenetic abnormality	26 (42.6)	19 (41.3)	34 (32.7)	20 (27.8)
2 cytogenetic abnormalities	9 (14.8)	8 (17.4)	12 (11.5)	5 (6.9)
Bone marrow plasma cells % at baseline, by category, N (%)				
0	0	2 (4.3)	1 (1.0)	0
>0 to <5	13 (21.3)	7 (15.2)	19 (18.3)	11 (15.3)
≥5 to <20	14 (23.0)	15 (32.6)	35 (33.7)	22 (30.6)
≥20 to <50	20 (32.8)	12 (26.1)	29 (27.9)	28 (38.9)
≥50	13 (21.3)	9 (19.6)	18 (17.3)	9 (12.5)
Missing	1 (1.6)	1 (2.2)	2 (1.9)	2 (2.8)
Prior lines of therapy, median (min-max)	2.0 (1-4)	2.0 (1-4)	1.0 (1-4)	2.0 (1-4)
1	20 (32.8)	19 (41.3)	58 (55.8)	35 (48.6)
2	24 (39.3)	12 (26.1)	34 (32.7)	22 (30.6)
3	16 (26.2)	14 (30.4)	11 (10.6)	14 (19.4)
>3	1 (1.6)	1 (2.2)	1 (1.0)	1 (1.4)
Prior ASCT, N (%)	30 (49.2)	14 (30.4)	81 (77.9)	53 (73.6)
Prior proteasome inhibitors, N (%)	57 (93.4)	38 (82.6)	96 (92.3)	63 (87.5)
Refractory status, N (%)				
Relapsed and refractory	54 (88.5)	41 (89.1)	55 (52.9)	49 (68.1)
Relapsed	7 (11.5)	5 (10.9)	49 (47.1)	23 (31.9)
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)

[a]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. [b]High risk was defined as the presence of del(17p), or t(4;14), or translocation t(14;16) by fluorescence *in situ* hybridization. [c]Cytogenetics was performed by a central laboratory with cutoffs of 50% for del(17p), 30% for t(4;14), t(14;16), and 1q21+. ASCT: autologous stem cell transplantation; CrCl: creatinine clearance; d: dexamethasone; IMiD: immunomodulatory drug; Isa: isatuximab; ISS: International Staging System; ITT: intent-to-treat; Kd: carfilzomib and dexamethasone; MDRD: modification of diet in renal disease; PI: proteasome inhibitor.

Depth of response in patients who were refractory to the last regimen was also in favor of Isa-Kd in both early and late relapse patients (Figure 4). Consistent with these results, depth of response was improved with Isa-Kd *versus* Kd after one or ≥2 prior lines of therapy, or after prior ASCT in both early and late relapse patients (Figure 5). Notably, for patients with one prior line of therapy, MRD$^-$ ≥CR rate with Isa-Kd was similar between early (30.0%) and late relapse (34.5%). Depth of response benefit with Isa-Kd *versus* Kd, regardless of relapse timing, was also consistent in patients who were refractory to an immunomodulatory agent or a proteasome inhibitor (*Online Supplementary Figure S1*).

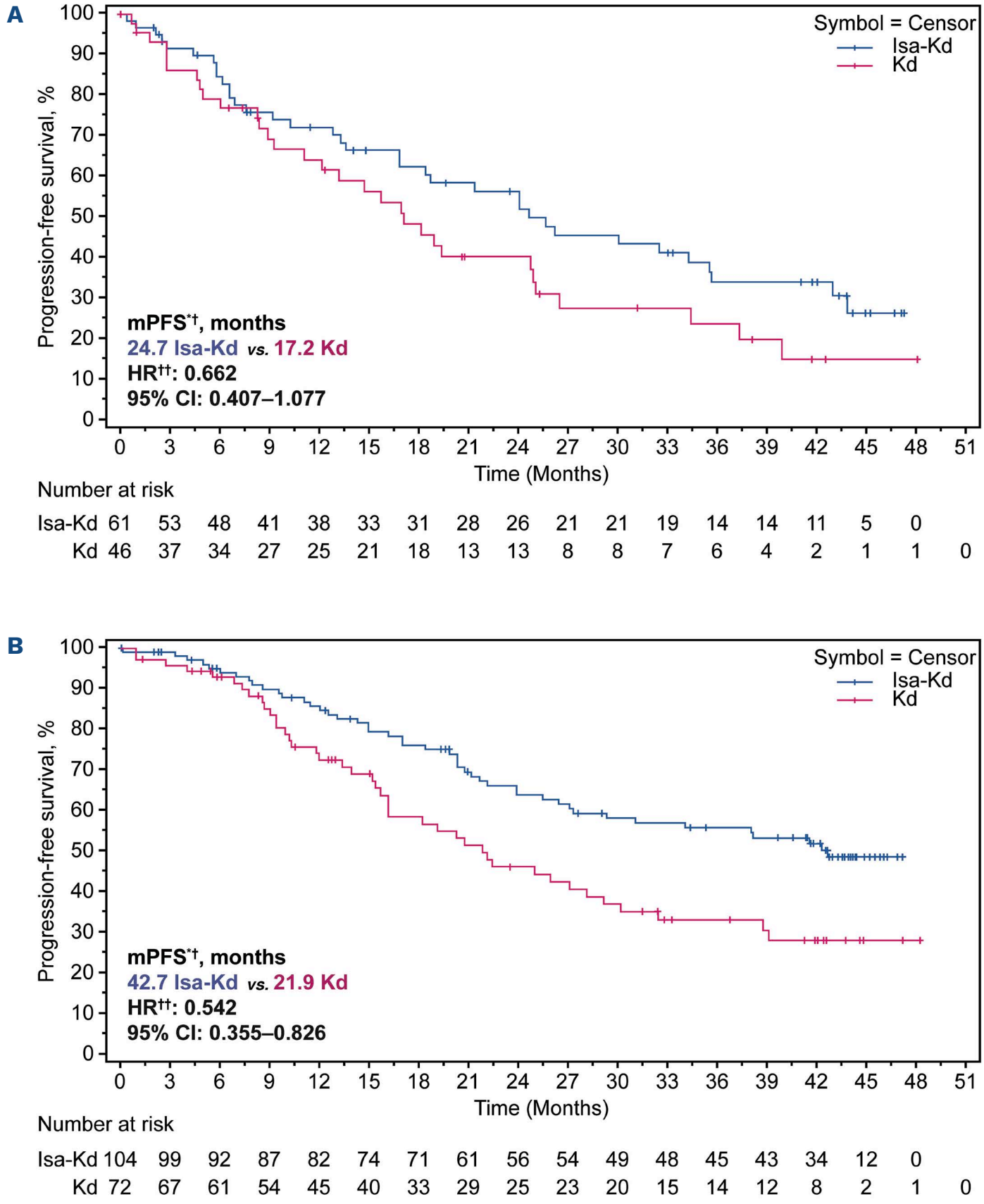
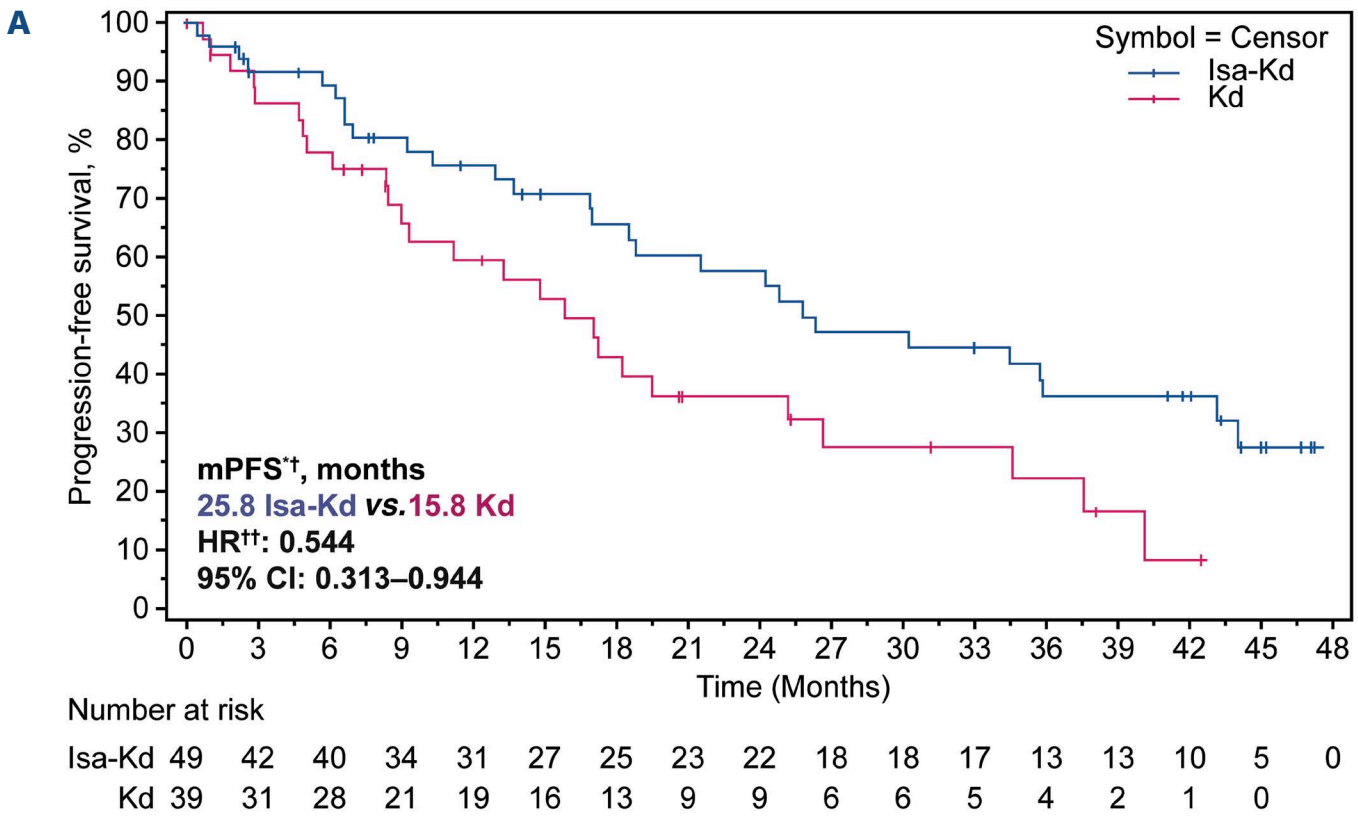


Figure 1. Median progression-free survival of early and late relapse patients in the IKEMA intent-to-treat population. (A) Median progression-free survival (mPFS) of early relapse patients. (B) mPFS of late relapse patients. Cut-off date: January 14, 2022. Median follow-up time: 44 months. *As per Independent Review Committee. †mPFS and 95% confidence interval (CI) were calculated by the Kaplan-Meier method. †† Non-stratified Cox proportional hazards models using treatment as a covariate were used to estimate hazard ratios (HR). For adjusted HR estimates, the confounding factors - age, renal impairment, International Staging System (ISS) stage at study entry, 1q21+, and number of prior lines - were used as adjustment covariates. When adjusted for confounding factors, the PFS HR was similar between early (0.577) and late relapse (0.527) patients and in favor of the isatuximab plus carfilzomib and dexamethasone (Isa-Kd) arm.



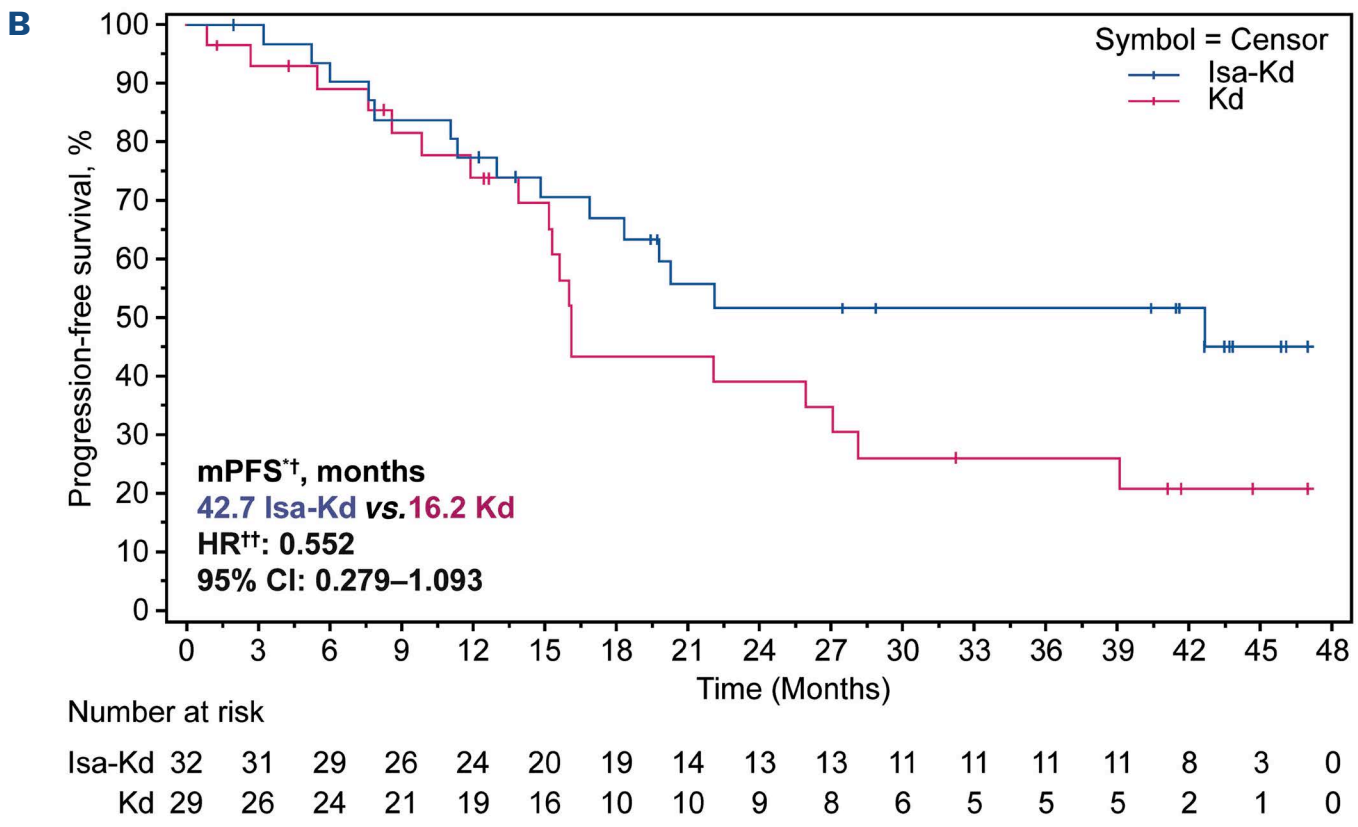


Figure 2. Median progression-free survival of early and late relapse patients refractory to the last regimen. (A) Median progression-free survival (mPFS) of early relapse patients refractory to the last regimen. (B) mPFS of late relapse patients refractory to the last regimen. Cut-off date: January 14, 2022. Median follow-up time: 44 months. *As per Independent Review Committee. †mPFS and 95% confidence interval (CI) were calculated by the Kaplan-Meier method. ††Non-stratified Cox proportional hazards models using treatment as a covariate were used to estimate hazard ratios (HR). Isa: isatuximab; Kd: carfilzomib and dexamethasone.

Safety

Among early relapse patients, rates of all-grade (98.4% [Isa-Kd], 97.8% [Kd]), grade ≥3 (83.6% [Isa-Kd], 80.4% [Kd]), and serious (68.9% [Isa-Kd], 65.2% [Kd]) treatment-emergent adverse events (TEAE) were similar between treatment arms (Table 2). In late relapse patients, rates of all-grade TEAE (99.0% [Isa-Kd], 97.2% [Kd]) were similar between treatment arms, but rates of grade ≥3 (82.4% [Isa-Kd], 70.4% [Kd]) and serious TEAE (66.7% [Isa-Kd], 54.9% [Kd]) were higher in the Isa-Kd arm. Rates of TEAE leading to definitive treatment discontinuation (early relapse: 11.5% [Isa-Kd] *vs.* 13.0% [Kd]; late relapse: 13.7% [Isa-Kd] *vs.* 19.7% [Kd]) were similar in both treatment arms across both early and late relapse patients. The rates of death were 4.9% [Isa-Kd] *versus* 6.5%

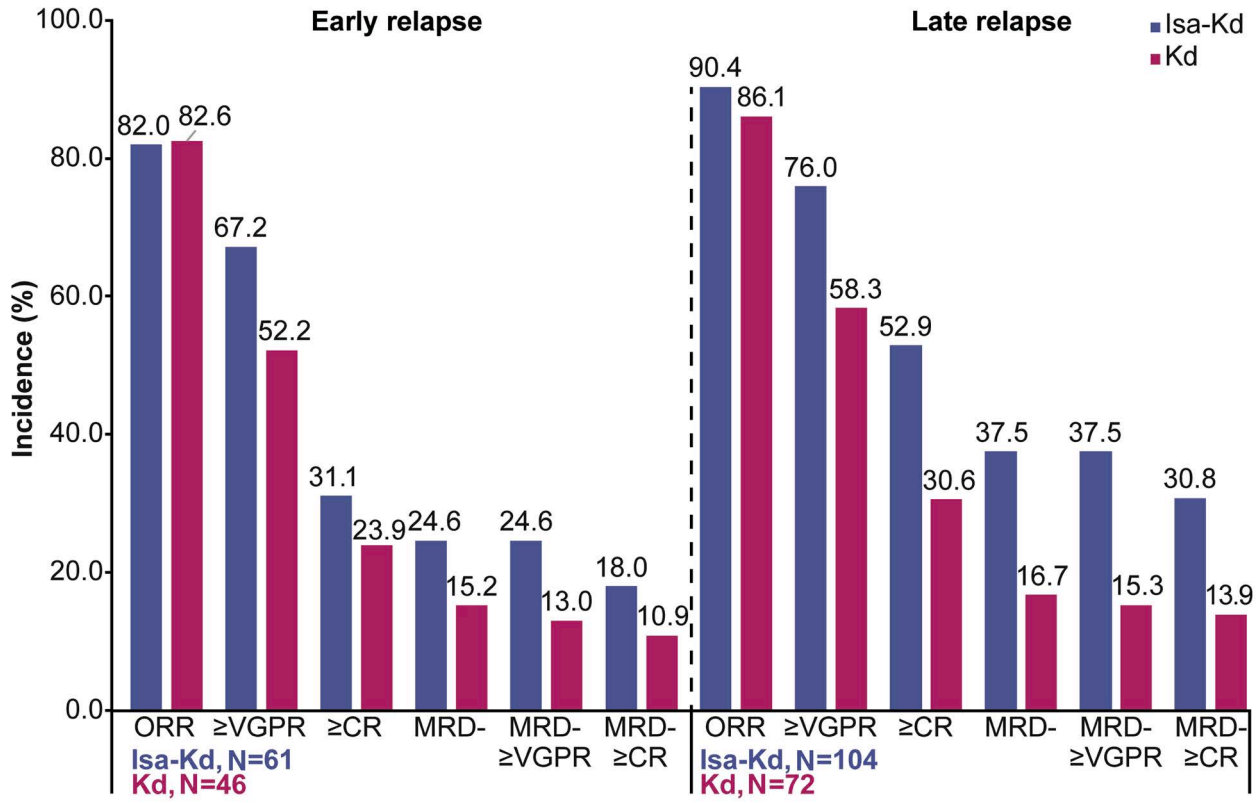


Figure 3. Depth of response of early and late relapse patients in the IKEMA intent-to-treat population. Cut-off date: January 14, 2022. Median follow-up time: 44 months. Minimal residual disease negativity (MRD⁻) was assessed by next-generation sequencing Adaptive ClonoSEQ Assay (Adaptive Biotechnologies) at 10^{-5} sensitivity. For analysis purpose, subjects in the intent-to-treat population but without MRD assessment were considered as having positive MRD. ≥Complete response (≥CR) rate is the proportion of patients who achieved stringent complete response (sCR) or CR as the best overall response according to the International Myeloma Working Group response criteria. Isa: isatuximab; Kd: carfilzomib and dexamethasone; ORR: overall response rate; VGPR: very good partial response.

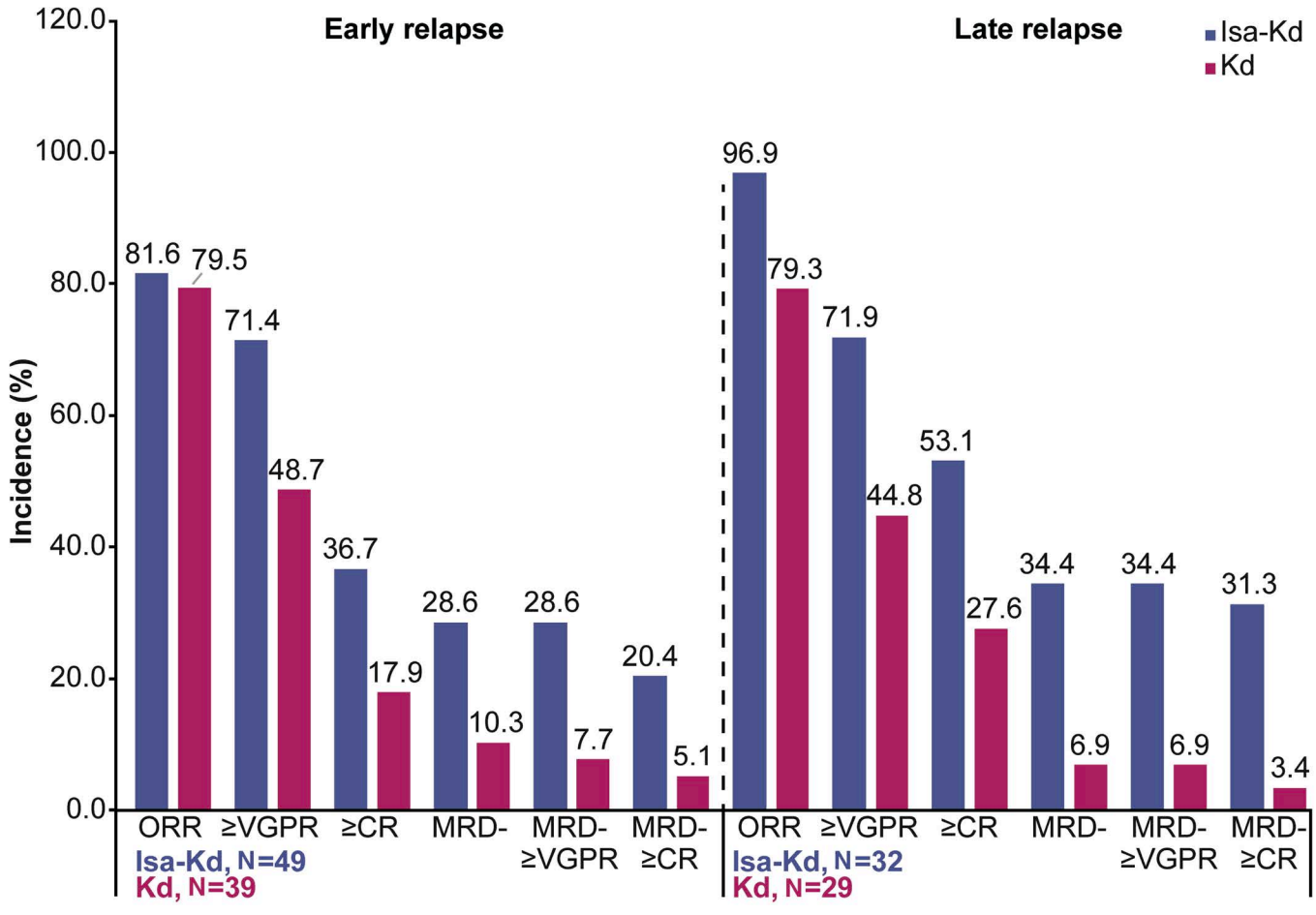
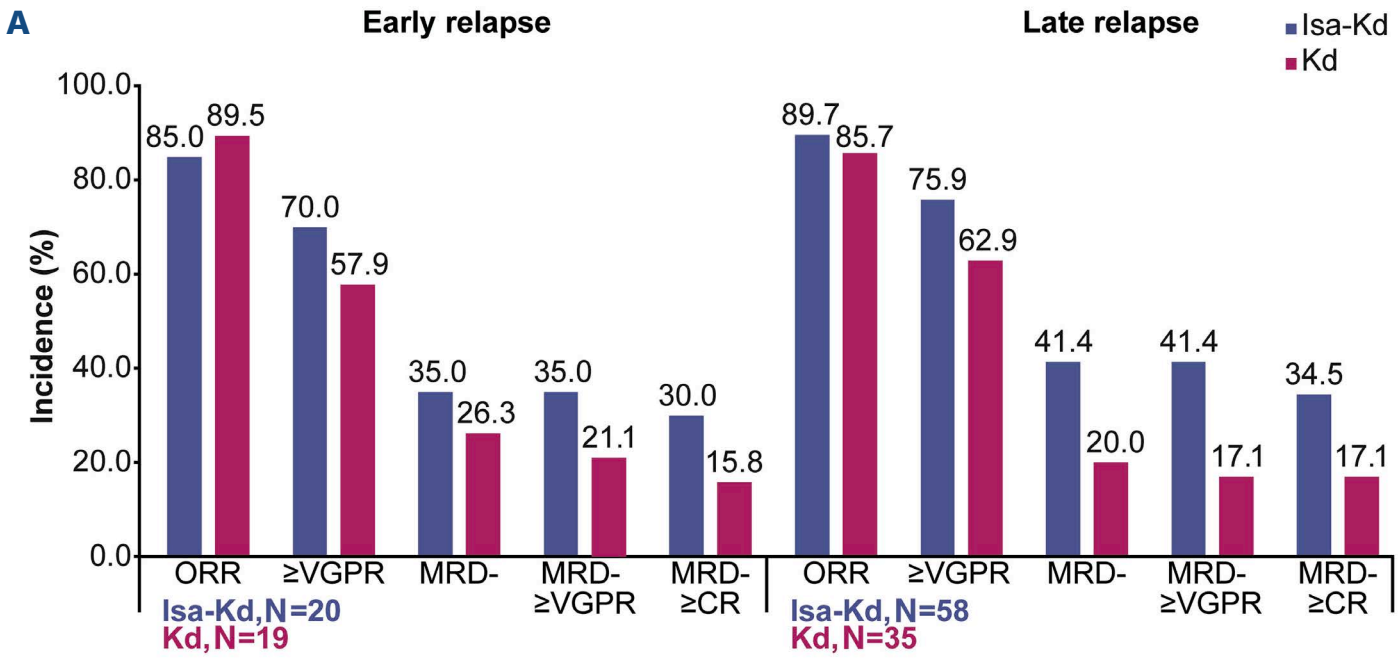
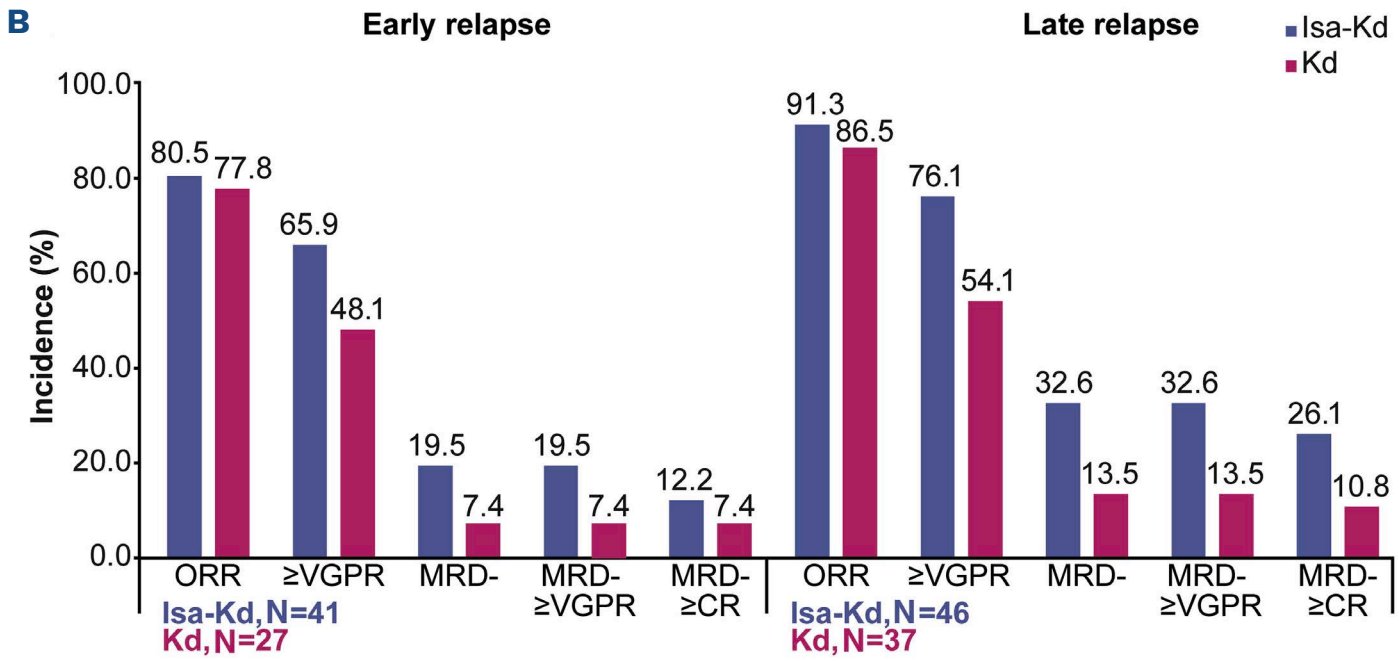


Figure 4. Depth of response of early and late relapse patients refractory to the last regimen. Cut-off date: January 14, 2022. Median follow-up time: 44 months. Minimal residual disease negativity (MRD⁻) was assessed by next-generation sequencing Adaptive ClonoSEQ Assay (Adaptive Biotechnologies) at 10^{-5} sensitivity. For analysis purpose, subjects in the intent-to-treat population but without MRD assessment were considered as having positive MRD. ≥Complete response (≥CR) is the proportion of patients who achieved stringent complete response (sCR) or CR as the best overall response according to the International Myeloma Working Group response criteria. Isa: isatuximab; Kd: carfilzomib and dexamethasone; ORR: overall response rate; VGPR: very good partial response.





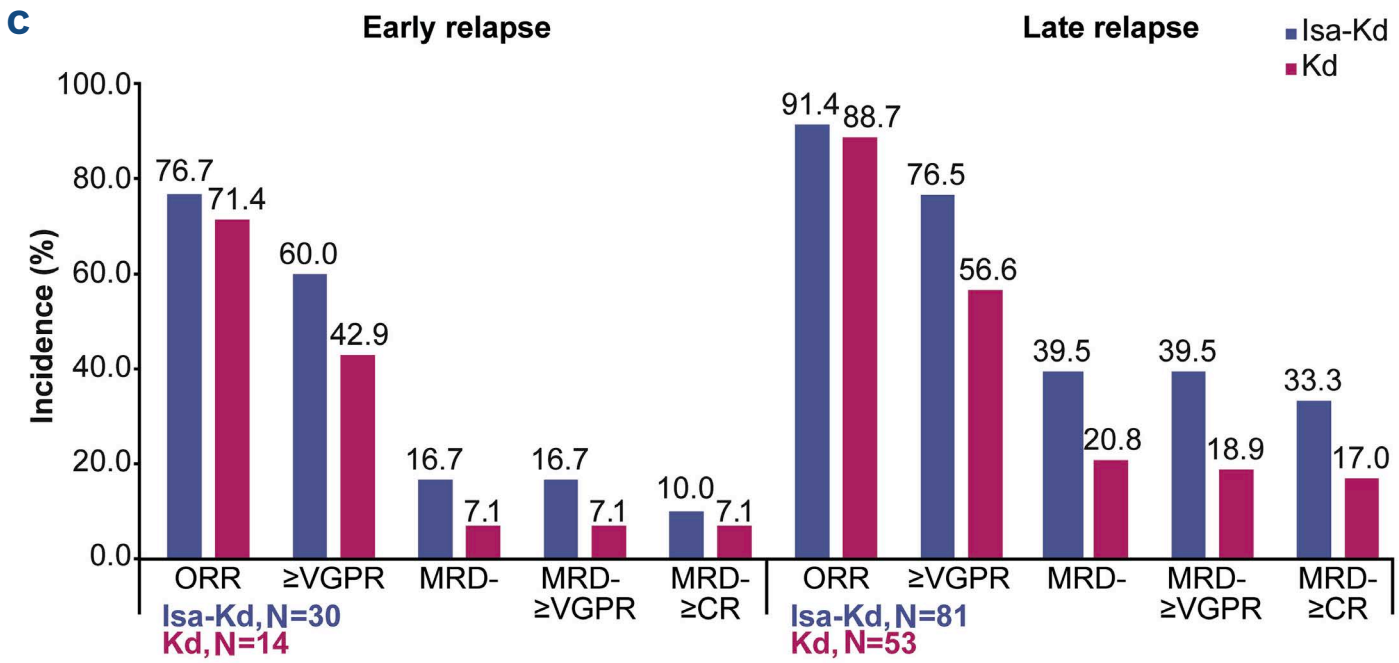


Figure 5. Depth of response of early and late relapse patients according to the number of prior lines of treatment or prior transplant. Depth of response after (A) 1 prior line of treament (LOT), or (B) ≥2 prior LOT, or (C) prior autologous stem cell transplant. Cut-off date: January 14, 2022. Median follow-up time: 44 months. Minimal residual disease negativity (MRD^-) was assessed by next-generation sequencing Adaptive ClonoSEQ Assay (Adaptive Biotechnologies) at 10^{-5} sensitivity. For analysis purpose, subjects in the intent-to-treat population but without MRD assessment were considered as having positive MRD. ≥Complete response (≥CR) is the proportion of patients who achieved stringent complete response (sCR) or CR as the best overall response according to the International Myeloma Working Group response criteria. Isa: isatuximab; Kd: carfilzomib and dexamethasone; ORR: overall response rate; VGPR: very good partial response.

[Kd] in early relapse patients and 5.9% [Isa-Kd] *versus* 2.8% [Kd] in late relapse patients. Significantly longer treatment duration in the Isa-Kd arm than in the Kd arm in late relapse patients may have contributed to the increased frequency of grade ≥3, serious TEAE, and deaths in this subgroup.

The most common all-grade TEAE were infusion reactions, and less than 10% of patients had all-grade cardiac failure across early (3.3% [Isa-Kd]; 8.7% [Kd]) and late relapse (4.9% [Isa-Kd]; 4.2% [Kd]) patients (Table 3). All-grade TEAE reported more frequently with Isa-Kd (≥10% difference *vs.* Kd) included infusion reactions in early relapse (41.0% *vs.* 6.5%) and late relapse patients (50.0% *vs.* 1.4%), and upper respiratory tract infection (38.2% *vs.* 26.8%), fatigue (32.4% *vs.* 19.7%), dyspnea (36.3% *vs.* 22.5%), bronchitis (30.4% *vs.* 12.7%), cough (23.5% *vs.* 11.3%), and gastroenteritis (14.7% *vs.* 4.2%) in late relapse patients.

Grade ≥3 TEAE with different incidences between treatment arms included hypertension in early relapse (19.7% [Isa-Kd] *vs.* 28.3% [Kd]) and pneumonia in late relapse (18.6% [Isa-Kd] *vs.* 9.9% [Kd]) (Table 3). Fatal (grade 5) TEAE during study treatment period in early relapse patients included cardiac failure in one (1.6%) patient, disease progression in one (1.6%) patient, and pneumonia and multiple non-site-specific injuries in one (1.6%) patient in the Isa-Kd arm; and acute myocardial infarction in one (2.2%) patient, disease progression in one (2.2%) patient, and COVID-19 in one (2.2%) patient in the Kd arm. Fatal TEAE during study treatment period in late relapse patients included pneumonia in one (1.0%) patient, atypical pneumonia in one (1.0%) patient, asthma in one (1.0%) patient, cardiac failure and acute kidney injury in one (1.0%) patient, and COVID-19 infections in two (2.0%) patients in the Isa-Kd arm; and cardiac failure and acute kidney injury in one (1.4%) patient, and sudden death in one (1.4%) patient in the Kd arm.

Hematologic laboratory abnormalities reported more frequently in the Isa-Kd arm included grade 3 anemia (42.6% *vs.* 30.4%) in early relapse patients and grade 3 neutropenia in early (18.0% *vs.* 4.3%) and late relapse (13.7% *vs.* 8.5%) patients, and thrombocytopenia in early relapse patients (21.3% *vs.* 15.2%) with Isa-Kd *versus* Kd, respectively (Table 3).

Discussion

Patients with MM frequently relapse, requiring successive lines of therapy; those who experience early relapse within 12 months of therapy initiation have worse outcomes and are considered functional high-risk patients.[5-8] In this *post hoc* subgroup analysis of IKEMA, the addition of Isa to Kd resulted in clinically meaningful improvement in PFS (early relapse: HR=0.662, 95% CI: 0.407-1.077; late relapse: HR=0.542, 95% CI: 0.355-0.826) and depth of response, with a manageable safety profile in both early and late relapse patients, consistent with the benefit observed in the overall IKEMA study population.[17,19] The benefit with Isa-Kd *versus* Kd was also observed in early and late relapse patients who were refractory to the last regimen. Similar to the observations in the IKEMA intent-to-treat population, the ORR in the current analysis were comparable between treatment arms, but deeper responses were seen with Isa-Kd *versus* Kd regardless of the timing of relapse, favoring Isa-Kd over Kd.[17,19] Notably, the depth of response (≥VGPR, ≥CR, MRD^-, MRD^- ≥VGPR, and MRD^- ≥CR rates) benefit with Isa-Kd *versus* Kd in early and late relapse patients was consistent across different subpopulations regardless of prior lines of therapy or prior transplant. Among patients who had received only one prior line of therapy, MRD^- ≥CR rates with Isa-Kd were similar regardless of early (30.0%) or late (34.5%) relapse, suggesting Isa-Kd as an effective treatment regimen for salvage in these patients and may lead to deep responses

Table 2. Safety overview with Isa-Kd *versus* Kd in IKEMA early and late relapse patients (safety population).

TEAE[a], 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 TEAE	51 (83.6)	37 (80.4)	84 (82.4)	50 (70.4)
Serious TEAE	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)
Fatal TEAE during study treatment	3 (4.9)	3 (6.5)	6 (5.9)	2 (2.8)

[a]Treatment-emergent adverse events (TEAE) were assessed according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.03. Isa: isatuximab; Kd: carfilzomib and dexamethasone.

despite patients' functional high-risk status. The depth of response results in the current study are consistent with our observations reported at IKEMA prespecified interim subgroup analysis, where deeper responses were observed with Isa-Kd *versus* Kd, regardless of number of prior lines of therapy or refractory status.[26] Clinically meaningful higher ≥VGPR (1 prior line: 75.0% *vs.* 61.8%; >1 prior line: 70.7% *vs.* 51.5%) and MRD$^-$ (1 prior line: 33.8% *vs.* 18.2%; >1 prior line: 26.3% *vs.* 8.8%) rates were observed with Isa-Kd *versus* Kd, regardless of number of prior lines of therapy. Deeper responses with Isa-Kd *versus* Kd were also reported for patients who were refractory to lenalidomide (≥VGPR: 66.7% *vs.* 35.7%; MRD$^-$: 24.6% *vs.* 9.5%), refractory to lenalidomide at last regimen (≥VGPR: 72.2% *vs.* 38.7%; MRD$^-$: 27.8% *vs.* 9.7%), refractory to bortezomib (≥VGPR: 55.8% *vs.* 51.3%; MRD$^-$: 17.3% *vs.* 10.3%), or refractory to bortezomib at last regimen (≥VGPR: 62.5% *vs.* 47.8%; MRD$^-$: 25.0% *vs.* 8.7%). Grade ≥3, serious TEAE, and deaths were higher in the Isa-Kd arm in late relapse patients. TEAE leading to definitive treatment discontinuation were similar between treatment

Table 3. Most common treatment-emergent adverse events, selected treatment-emergent adverse events, and hematologic laboratory abnormalities with Isa-Kd *versus* Kd in IKEMA early and late relapse patients (safety population).

Selected TEAE 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, N (%)								
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, N (%)	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
Lymphopenia	18 (29.5)	2 (3.3)	0	16 (34.8)	3 (6.5)	1 (2.2)	25 (24.5)	2 (2.0)	1 (1.0)	15 (21.1)	1 (1.4)	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)

Isa: isatuximab; Kd: carfilzomib and dexamethasone; TEAE: treatment-emergent adverse event; URTI: upper respiratory tract infection.

arms across early and late relapse patients. Significantly longer exposure to Isa-Kd in late relapse patients may also explain the increased frequency of grade ≥3, serious TEAE, and deaths in this subgroup. The numbers of deaths were low, so differences may be due to chance.

Other subgroup analyses with triplet regimens containing an anti-CD38 antibody in a similar patient subpopulation also showed efficacy benefit *versus* doublet control regimen. The definitions used to classify early and late relapse patients in the current study were the same as those used in the phase III CANDOR, CASTOR, and POLLUX subgroup analyses that evaluated triplet regimens based on another anti-CD38 monoclonal antibody, daratumumab.[20,27] *Post hoc* subgroup analyses of the CANDOR (daratumumab plus Kd *vs.* Kd), CASTOR (daratumumab plus bortezomib and dexamethasone [D-Vd] *vs.* Vd), and POLLUX (daratumumab plus lenalidomide and dexamethasone [D-Rd] *vs.* Rd) studies reported PFS HR=0.4-0.7, and ≥CR rates of 16.0-53.0% *versus* 0-17.0% in early relapse patients who had received daratumumab-based regimens *versus* control regimens, respectively.[20,27] MRD^{-} (10^{-5}) rates for early relapse patients were 13-30% with D-Vd /D-Rd *versus* 0-4% with Vd/Rd in CASTOR/POLLUX and were not reported for CANDOR.

Consistent with observations in the IKEMA overall population, the efficacy outcomes of patients in the Kd arm in the current subgroup analysis were favorable, indicating that the benefit observed with the addition of Isa is not due to suboptimal outcomes in the control group.[17,19] Our results align with a previous *post hoc* subgroup analysis of the phase III ASPIRE (carfilzomib, lenalidomide, and dexamethasone [KRd] *vs.* Rd) and ENDEAVOR (Kd *vs.* Vd) studies, which demonstrated improved PFS and ORR in patients receiving carfilzomib-based treatment compared with control arm, regardless of early (relapse ≤1 year after initiating most recent prior line of therapy) or late relapse (relapse after >1 year following initiation of most recent prior line of therapy).[28] A prospective observational study across Europe and Israel reported similar ORR benefit with KRd regardless of early relapse (83.3%; included patients who relapsed ≤12 months [≤18 months with 1 prior line of therapy] from start of most recent prior line of therapy) or late relapse (77.1%; included patients who relapsed >12 months [>18 months with 1 prior line of therapy] from start of most recent prior line of therapy), but ≥CR rates were lower in early relapse (16.7%) than in late relapse patients (22.9%).[21]

A common theme that is evident across all studies summarized above is that the outcomes in early relapse patients are generally worse than in late relapse patients. Consistent with these reports, the PFS and depth of response in the current study were lower in early relapse patients than in late relapse patients across both treatment arms, in the intent-to-treat population as well as in patients refractory to the last regimen, confirming the unmet need in the early relapse subgroup of patients. The only exception was the depth of response with one prior line of therapy, which was similar between early and late relapse patients in the Isa-Kd arm. Nevertheless, the PFS and the depth of response were in favor of Isa-Kd over Kd in both early and late relapse patients. Importantly, the median PFS of 24.7 months in the Isa-Kd arm of early relapse patients compares favorably to data recently reported for early relapse patients who had progression <18 months after frontline ASCT in the KarMMa-2 phase II trial of the BCMA-directed chimeric antigen receptor T-cell therapy, idecabtagene vicleucel (median PFS 11.4 months at a median follow-up of 21.5 months).[29] However, cross-trial comparisons should be interpreted with caution given the inherent differences between the study populations, and differences in follow-up duration, outcomes within the control arms, definitions used to classify early and late relapse patients, as well as limitations within each study.

A limitation of the current study includes small numbers of patients in the subgroup analyses. However, the PFS, depth of response, and safety profile of Isa-Kd *versus* Kd observed in the overall IKEMA population were consistent across early and late relapse patients, and in subgroups that were refractory to last regimen as well as those who received one or ≥2 prior lines of therapy or prior ASCT, favoring Isa-Kd over Kd. These results showed improved median PFS and depth of response with Isa in combination with Kd and support the use of Isa-Kd as a standard of care in patients with relapsed MM regardless of early or late relapse.

Disclosures

PM has received honoraria from and is part of the advisory board of AbbVie, Amgen, Celgene, GlaxoSmithKline, Janssen and Sanofi. RB has received grants from AbbVie, Acerta Pharma, Alexion, Amgen, Bayer, Biegene, BMS, Boehringer Ingelheim, Celgene, CSL Behring, Daiichi Sankyo, Jansen-Cilag, MorphoSys, Pfizer, Pharmaxis, Portola, Rigel Pharmaceuticals, Roche, Sanofi, Takeda and Technoclone; has received honoraria from Bayer, Cardinal Health, BMS, Jansen-Cilag and Roche; is part of the advisory board of Pharmaxis, Janssen-Cilag and Roche. MM has received grants from Janssen and Sanofi; consults for Adaptive Biotechnologies, Janssen, Oncopeptides and Sanofi; has received honoraria from Amgen, Astellas, BMS, Gilead, GlaxoSmithKline, Janssen, Novartis, Pfizer, Sanofi and Takeda; discloses other board/society/committee leadership at EBMT, IACH and IFM. LK has received honoraria from Amgen, Celgene, Sanofi, AbbVie, Takeda and Janssen; discloses other board/society/committee leadership at Amgen, Celgene, GlaxoSmithKline, Janssen and Takeda. TM has received research funding from Sanofi. NMA, CT, SS, and M-LR are employed by Sanofi; may hold stock and/or stock options in the company. All other authors have no conflicts of interest to disclose.

Contributions

TF, PM, RB, LP, C-KM, XL, MM, LK and TM were investigators in the study and contributed to data acquisition and analysis. CT, M-LR, NMA and SS contributed to study design, data

analysis, and interpretation. All authors revised the work for important intellectual content and assume responsibility for data integrity and the decision to submit this manuscript for publication, had full access to the study data, edited and reviewed manuscript drafts, and approved the final version for submission.

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Data-sharing statement

Qualified researchers can request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access are at: https://www.vivli.org.

References

1. Jagannath S, Abonour R, Durie BGM, et al. Heterogeneity of second-line treatment for patients with multiple myeloma in the Connect MM Registry (2010-2016). Clin Lymphoma Myeloma Leuk. 2018;18(7):480-485.
2. Raab MS, Fink L, Schoen P, et al. Evolution of multiple myeloma treatment practices in Europe from 2014 to 2016. Br J Haematol. 2019;185(5):981-984.
3. Song X, Cong Z, Wilson K. Real-world treatment patterns, comorbidities, and disease-related complications in patients with multiple myeloma in the United States. Curr Med Res Opin. 2016;32(1):95-103.
4. Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc. 2004;79(7):867-874.
5. Majithia N, Rajkumar SV, Lacy MQ, et al. Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. Leukemia. 2016;30(11):2208-2213.
6. Soekojo CY, Chung TH, Furqan MS, Chng WJ. Genomic characterization of functional high-risk multiple myeloma patients. Blood Cancer J. 2022;12(1):24.
7. Kumar S, Mahmood ST, Lacy MQ, et al. Impact of early relapse after auto-SCT for multiple myeloma. Bone Marrow Transplant. 2008;42(6):413-420.
8. Jimenez-Zepeda VH, Reece DE, Trudel S, Chen C, Tiedemann R, Kukreti V. Early relapse after single auto-SCT for multiple myeloma is a major predictor of survival in the era of novel agents. Bone Marrow Transplant. 2015;50(2):204-208.
9. Martin TG, Corzo K, Chiron M, et al. Therapeutic opportunities with pharmacological inhibition of CD38 with isatuximab. Cells. 2019;8(12):1522.
10. Leleu X, Martin T, Weisel K, et al. Anti-CD38 antibody therapy for patients with relapsed/refractory multiple myeloma: differential mechanisms of action and recent clinical trial outcomes. Ann Hematol. 2022;101(10):2123-2137.
11. Sanofi. Sarclisa (isatuximab-irfc) [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2021. http://products.sanofi.us/Sarclisa/sarclisa.pdf. Accessed August 3, 2023.
12. Jiang H, Acharya C, An G, et al. SAR650984 directly induces multiple myeloma cell death via lysosomal-associated and apoptotic pathways, which is further enhanced by pomalidomide. Leukemia. 2016;30(2):399-408.
13. Tai YT, Anderson KC. Targeting CD38 alleviates tumor-induced immunosuppression. Oncotarget. 2017;8(68):112166-112167.
14. Sanofi. Sarclisa (isatuximab) [summary of product characteristics]. Paris, France: Sanofi-Aventis; 2021. https://www.ema.europa.eu/en/documents/product-information/sarclisa-epar-product-information_en.pdf. Accessed August 3, 2023.
15. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019;394(10214):2096-2107.
16. Moreau P, Dimopoulos MA, Yong K, et al. Isatuximab plus carfilzomib/dexamethasone versus carfilzomib/dexamethasone in patients with relapsed/refractory multiple myeloma: IKEMA Phase III study design. Future Oncol. 2020;16(2):4347-4358.
17. Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021;397(10292):2361-2371.
18. Sanofi. Sarclisa (isatuximab) [Prescribing Information]. Nishi Shinjuku, Tokyo: Sanofi-Aventis; 2021. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/780069_4291454A1021_1_02. Accessed August 3, 2023.
19. Moreau P, Dimopoulos MA, Mikhael J, et al. Updated progression-free survival (PFS) and depth of response in IKEMA, a randomized phase III trial of isatuximab, carfilzomib and dexamethasone (Isa-Kd) vs Kd in relapsed multiple myeloma (MM). Ann Oncol. 2022;33(6):P664-665.
20. Weisel K, Geils G, Karlin L, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone in relapsed or refractory multiple myeloma: subgroup analysis of the phase 3 CANDOR study in patients with early or late relapse. Blood. 2020;136;(Suppl 1):S37-38.
21. Terpos E, Caers J, Gamberi B, et al. Response to carfilzomib

regimens among patients with early or late relapse following prior multiple myeloma therapy: a subgroup analysis from a prospective observational study across Europe and Israel. In: European Hematology Association; 2020 Virtual. p. Abstract EP1010.
22. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.
23. Finn F, Macé, S, Chu, R, et al. Development of a Hydrashift 2/4 isatuximab assay to mitigate interference with monoclonal protein detection on immunofixation electrophoresis in vitro diagnostic tests in multiple myeloma. Blood. 2020;136;(Suppl 1):S15.
24. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;282(53):457-481.
25. Cox D. Regression models and life-tables. J R Stat Soc Series B Stat Methodol. 1972;34(2):187-202.
26. Dimopoulos MA, Moreau P, Augustson B, et al. Isatuximab plus carfilzomib and dexamethasone in patients with relapsed multiple myeloma based on prior lines of treatment and refractory status: IKEMA subgroup analysis. Am J Hematol. 2023;98(1):E15-E19.
27. Spencer A, Moreau P, Mateos MV, et al. Daratumumab (DARA) in combination with bortezomib plus dexamethasone (D-Vd) or lenalidomide plus dexamethasone (D-Rd) in relapsed or refractory multiple myeloma (RRMM): subgroup analysis of the phase 3 CASTOR and POLLUX studies in patients (pts) with early or late relapse after initial therapy. J Clin Oncol. 2022;40;(Suppl 16):S8052.
28. Mateos MV, Goldschmidt H, San-Miguel J, et al. Carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy: A subgroup analysis of the randomized phase 3 ASPIRE and ENDEAVOR trials. Hematol Oncol. 2018;36(2):463-470.
29. Usmani S, Patel K, Kari P, et al. KarMMa-2 Cohort 2a: Efficacy and safety of idecabtagene vicleucel in clinical high-risk multiple myeloma patients with early relapse after frontline autologous stem cell transplantation. Blood. 2022;140;(Suppl 1):S875-877.