

Isatuximab Plus Carfilzomib and Dexamethasone Versus Carfilzomib and Dexamethasone in Elderly Patients With Relapsed Multiple Myeloma: IKEMA Subgroup Analysis

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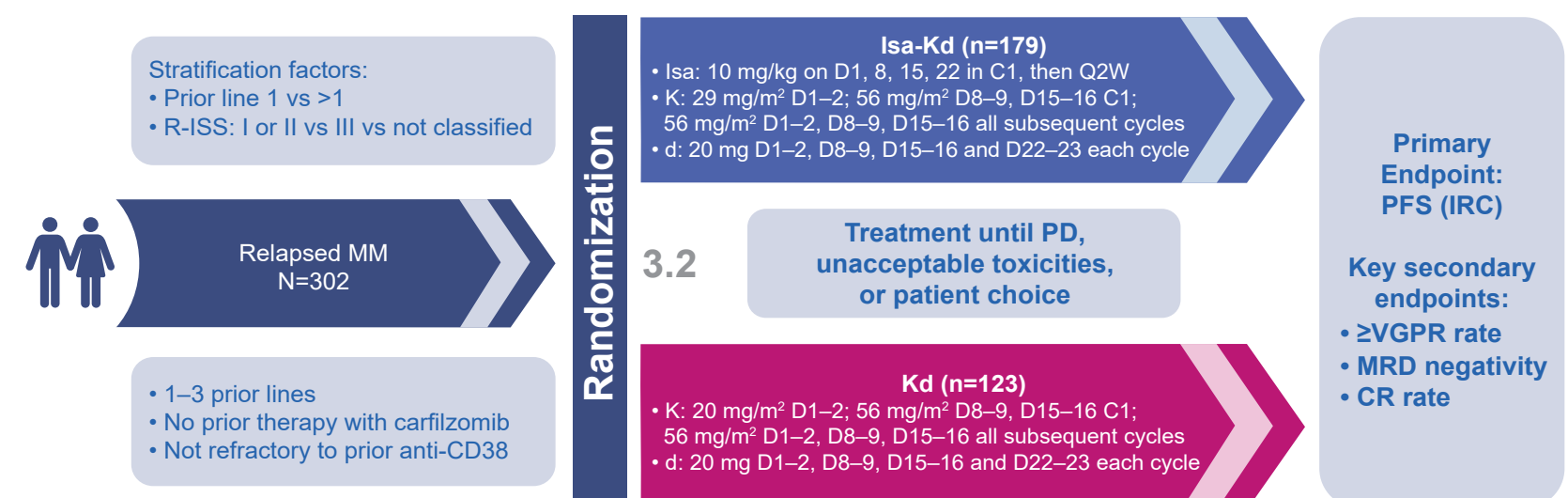
INTRODUCTION

- Multiple myeloma (MM) typically affects elderly patients, and is most frequently diagnosed in people aged 65–74 years, with a median age at diagnosis of 69 years^{1,2}.
- Elderly patients comprise a heterogeneous population with the potential for comorbidities, reduced functional status, and increased risk of frailty^{1,2}.
- Based on the Phase 3 ICARIA-MM study, the anti-CD38 monoclonal antibody isatuximab (Isa) is approved in a number of countries in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed/refractory MM (RRMM) who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor.³ Based on the Phase 3 IKEMA study, Isa in combination with carfilzomib (K) and dexamethasone (d) (Isa-Kd) is approved in the United States for the treatment of adult patients with RRMM who have received 1–3 prior lines of therapy, and in the European Union for the treatment of adult patients with relapsed MM who have received at least 1 prior therapy^{3–6}.
- IKEMA (NCT03275285) was a randomized, open-label, active-controlled, multicenter, Phase 3 study that compared treatment with Isa in combination with Kd vs Kd in relapsed MM patients with 1–3 prior lines of therapy. The study showed improvement in progression-free survival (PFS) for Isa-Kd vs Kd (hazard ratio [HR] 0.53; 99% confidence interval [CI] 0.32–0.89; one-sided $p=0.0007$), with clinically meaningful increases in minimal residual disease negativity (MRD–, 29.6% vs 13.0%) and complete response ([CR], 39.7% vs 27.6%) rates in the intent-to-treat (ITT) population, as well as a manageable safety profile^{5,6}.
- This subgroup analysis of IKEMA evaluated the efficacy and safety of treatment with Isa-Kd vs Kd in patients aged ≥ 70 and < 70 years

METHODS

- Adult patients with relapsed MM, who had received 1–3 prior lines of therapy, were randomized 3:2 to receive Isa-Kd ($n=179$) or Kd ($n=123$). The study design and dosing schedules are shown in **Figure 1**⁵.
- The primary study endpoint was PFS, as assessed by an independent response committee (IRC). Key secondary endpoints included very good partial response or better ($\geq$ VGPR), MRD–, and CR rates⁹.
- We compared efficacy and safety of treatment with Isa-Kd vs Kd in patients ≥ 70 and < 70 years of age; division into different or additional age groups resulted in smaller sample sizes.
- Median PFS and corresponding CIs were calculated by the Kaplan-Meier method. HR estimates were determined using the stratified Cox proportional hazard model⁹.
- Adverse events (AEs) were graded per the National Cancer Information Center Common Terminology Criteria for AEs (NCI-CTCAE) version 4.03⁵.

Figure 1. IKEMA study design: Isa-Kd vs Kd in patients with relapsed MM⁵



C, cycle; CR, complete response; D, day; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; K, carfilzomib; MM, multiple myeloma; MRD, minimal residual disease; PD, progressive disease; PFS, progression-free survival; Q2W, once every 2 weeks; R-ISS, Revised International Staging System; VGPR, very good partial response

RESULTS

Patient age at baseline

- Age at baseline was balanced between the treatment arms (**Table 1**)
 - Among the 302 randomized patients, 28.5% were ≥ 70 years of age (29.1% in Isa-Kd, 27.6% in Kd) and 71.5% were < 70 years of age (70.9% in Isa-Kd, 72.4% in Kd). Age ranged from 33 to 90 years across treatment arms

Table 1. Age at baseline

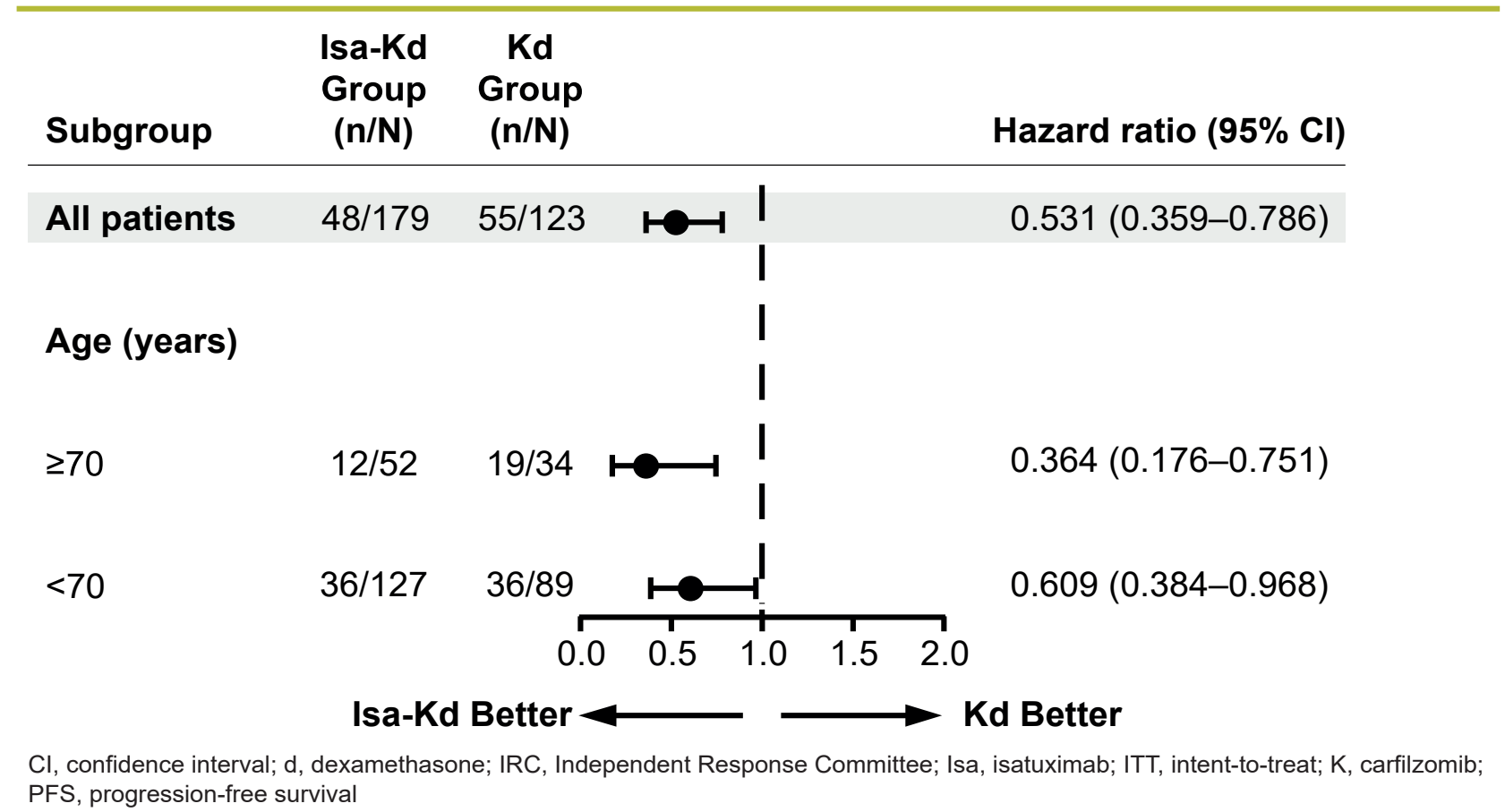
Randomized population	Isa-Kd (n=179)	Kd (n=123)	All (N=302)
Age in years, median (range)	65 (37–86)	63 (33–90)	64 (33–90)
Age group (years), n (%)			
≥ 70	52 (29.1)	34 (27.6)	86 (28.5)
< 70	127 (70.9)	89 (72.4)	216 (71.5)

d, dexamethasone; Isa, isatuximab; K, carfilzomib

Efficacy: PFS

- The addition of Isa to Kd resulted in improved PFS independently of age, with a HR of 0.36 (95% CI 0.18–0.75) in patients ≥ 70 years of age and of 0.61 (95% CI 0.38–0.97) in patients < 70 years of age, consistent with the significant prolongation of PFS observed in the overall IKEMA population (**Figures 2 and 3**)
- At the time of the analysis, median PFS with Isa-Kd in patients ≥ 70 years of age was not reached (NR) (95% CI NR–NR), while it was reached in Kd patients with 16.2 months (95% CI 10.3–NR). Median PFS was not reached in either study arm in patients < 70 years of age (95% CI 15.8–NR in Kd)

Figure 2. PFS by IRC by age group: ≥ 70 and < 70 years, ITT population



CI, confidence interval; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; PFS, progression-free survival

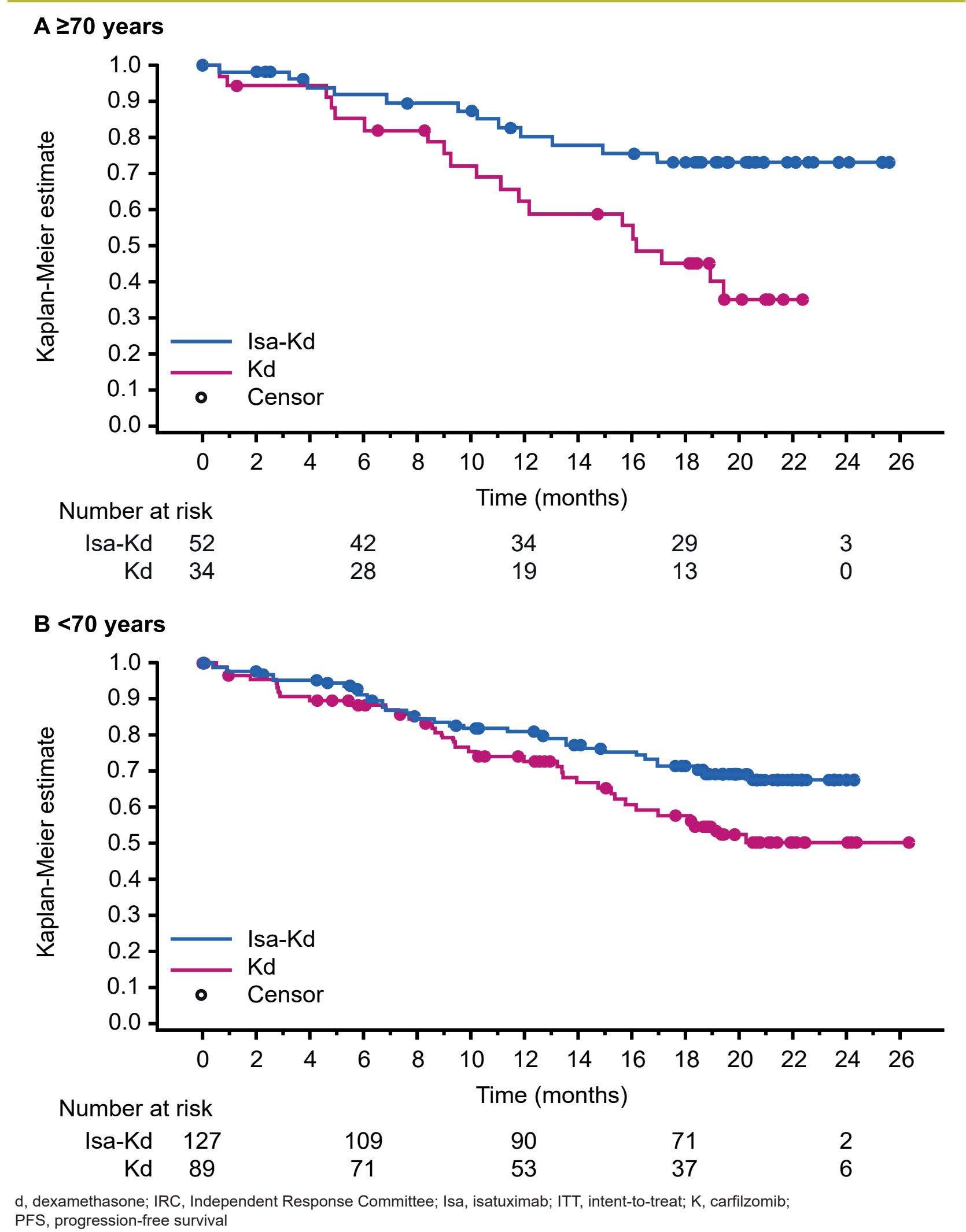
Efficacy: Depth of response

- The addition of Isa to Kd improved depth of response, with the rates of CR, $\geq$ VGPR, and MRD– being higher with Isa-Kd vs Kd. Within the Isa-Kd arm, CR and $\geq$ VGPR rates were similar in elderly and younger patients (**Figure 4**)
- MRD negativity with Isa-Kd was observed in 23.1% of patients ≥ 70 years of age (vs 11.8% with Kd) and 32.3% of patients < 70 years of age (vs 13.5% with Kd)

Safety

- In both study arms, Grade ≥ 3 and serious treatment-emergent AEs (TEAEs) were more frequently reported in the elderly than in the younger patients (**Table 2**)
- For both age groups, the incidence of Grade ≥ 3 TEAEs was higher, whereas the incidence of serious TEAEs was similar between Isa-Kd and Kd

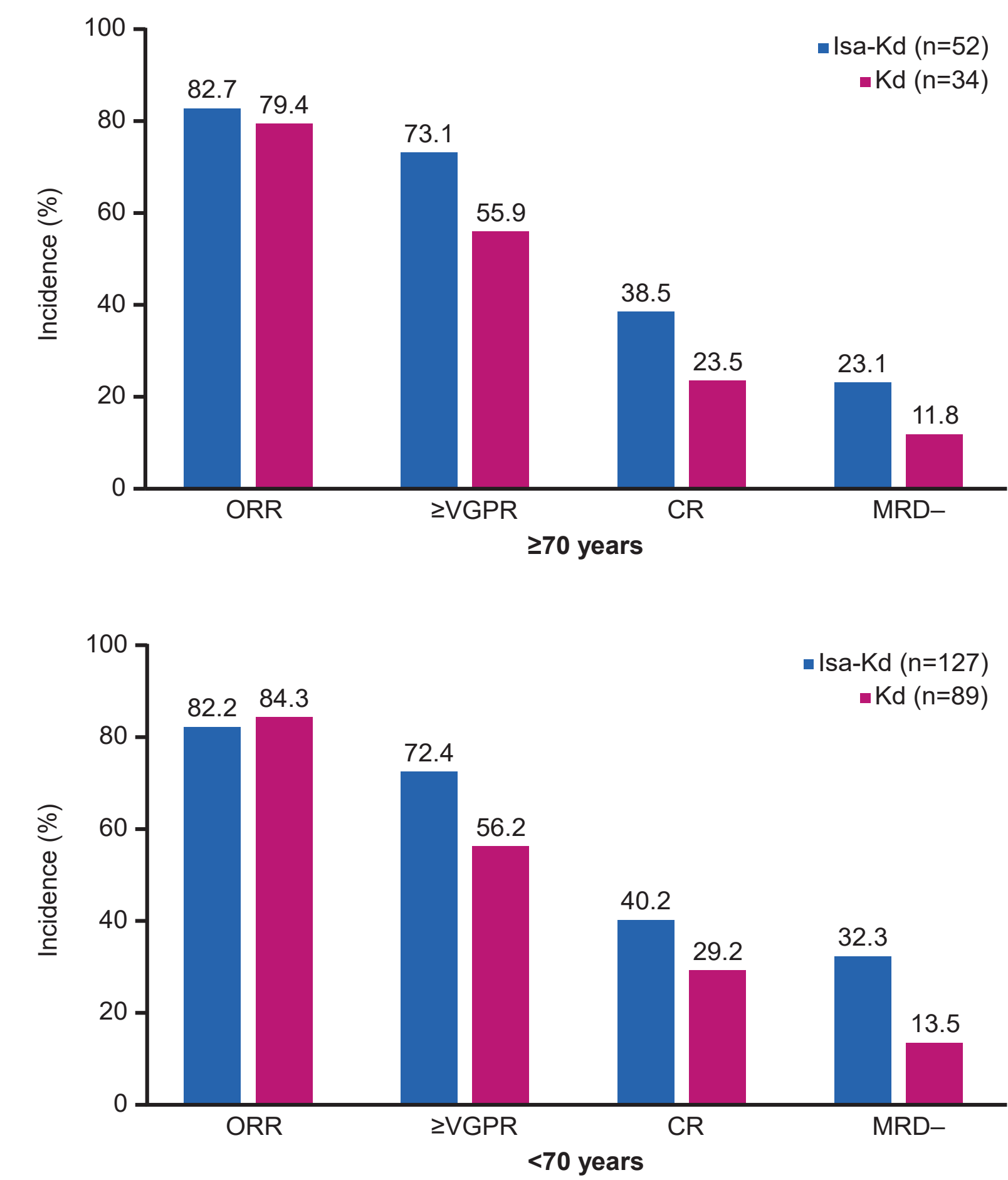
Figure 3. PFS by IRC – Kaplan-Meier estimates by age group (≥ 70 and < 70 years), ITT population



d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; ITT, intent-to-treat; K, carfilzomib; PFS, progression-free survival

- In the elderly subgroup, 3 (5.9%) patients receiving Isa-Kd and 1 (2.9%) receiving Kd had TEAEs with fatal outcome during study treatment (Isa-Kd: pneumonia, Kd: general health deterioration due to progressive disease)
- In both age groups, fewer patients definitively discontinued treatment due to a TEAE in the Isa-Kd than in the Kd arm (11.8% vs 23.5% ≥ 70 years] and 7.1% vs 10.2% [< 70 years]) (**Table 2**)
- Any-grade TEAEs reported in $\geq 20\%$ of patients with Isa-Kd are presented in **Table 3** by age group, vs the respective Kd arm. In patients ≥ 70 years of age, the most common TEAEs were diarrhea (43.1% vs 29.4%), dyspnea (43.1% vs 26.5%), upper respiratory infection (39.2% vs 23.5%), fatigue (39.2% vs 23.5%), and hypertension (37.3% vs 29.4%); in patients < 70 years of age, they were hypertension (36.5% vs 31.8%), upper respiratory infection (34.9% vs 23.9%), and diarrhea (33.3% vs 28.4%). Infusion reactions occurred in 37.3% vs 5.9% of patients ≥ 70 years of age and in 47.6% vs 2.3% of patients < 70 years of age
- The most common Grade ≥ 3 TEAEs in patients ≥ 70 and < 70 years of age treated with Isa-Kd vs Kd were hypertension (25.5% vs 26.5% ≥ 70 years] and 18.3% vs 17.0% [< 70 years]) and pneumonia (21.6% vs 20.6% ≥ 70 years] and 14.3% vs 9.1% [< 70 years])

Figure 4. Response rates based on IRC assessment by age group: ≥ 70 and < 70 years



CR, complete response; d, dexamethasone; IRC, Independent Response Committee; Isa, isatuximab; K, carfilzomib; MRD–, minimal residual disease negativity; ORR, overall response rate; VGPR, very good partial response

Table 2. Safety summary by age group: ≥ 70 and < 70 years, safety population

n (%)	≥ 70 years (n=85)				< 70 years (n=214)			
	Isa-Kd (n=51)	Kd (n=34)	Isa-Kd (n=126)	Kd (n=88)	Isa-Kd (n=51)	Kd (n=34)	Isa-Kd (n=126)	Kd (n=88)
Any Grade ≥ 3 TEAE	46 (90.2)	26 (76.5)	90 (71.4)	56 (63.6)	46 (90.2)	26 (76.5)	90 (71.4)	56 (63.6)
Any serious TEAE*	37 (72.5)	24 (70.6)	68 (54.0)	46 (52.3)	37 (72.5)	24 (70.6)	68 (54.0)	46 (52.3)
Any Grade 5 TEAE†	3 (5.9)	1 (2.9)	3 (2.4)	3 (3.4)	3 (5.9)	1 (2.9)	3 (2.4)	3 (3.4)
Any TEAE leading to definitive discontinuation	6 (11.8)	8 (23.5)	9 (7.1)	9 (10.2)	6 (11.8)	8 (23.5)	9 (7.1)	9 (10.2)
Any TEAE leading to premature discontinuation of isatuximab	1 (2.0)	NA	0	NA	1 (2.0)	NA	0	NA
Any TEAE leading to premature discontinuation of carfilzomib	8 (15.7)	0	18 (14.3)	1 (1.1)	8 (15.7)	0	18 (14.3)	1 (1.1)
Any TEAE leading to premature discontinuation of dexamethasone	3 (5.9)	1 (2.9)	8 (6.3)	3 (3.4)	3 (5.9)	1 (2.9)	8 (6.3)	3 (3.4)

*TEAEs with a start date before the cut-off date and becoming serious after the cut-off date were not counted as serious TEAE in this analysis
†TEAE with fatal outcome during the treatment period
d, dexamethasone; Isa, isatuximab; K, carfilzomib; NA, not applicable; TEAE, treatment-emergent adverse event

Table 3. Any-grade TEAEs by age group: ≥ 70 and < 70 years, safety population

Any grade TEAEs Preferred term, n (%)	≥ 70 years (n=85)		< 70 years (n=214)	
	Isa-Kd (n=51)	Kd (n=34)	Isa-Kd (n=126)	Kd (n=88)
Most common in $\geq 20\%$ of patients ≥ 70 years				
Diarrhea	22 (43.1)	10 (29.4)	42 (33.3)	25 (28.4)
Dyspnea	22 (43.1)	9 (26.5)	27 (21.4)	17 (19.3)
Upper respiratory tract infection	20 (39.2)	8 (23.5)	44 (34.9)	21 (23.9)
Fatigue	20 (39.2)	8 (23.5)	30 (23.8)	15 (17.0)
Infusion-related reaction	19 (37.3)	2 (5.9)	60 (47.6)	2 (2.3)
Hypertension	19 (37.3)	10 (29.4)	46 (36.5)	28 (31.8)
Bronchitis	16 (31.4)	2 (5.9)	24 (19.0)	13 (14.8)
Pneumonia	15 (29.4)	9 (26.5)	27 (21.4)	15 (17.0)
Edema, peripheral	13 (25.5)	10 (29.4)	10 (7.9)	11 (12.5)
Insomnia	10 (19.6)	10 (29.4)	32 (25.4)	18 (20.5)
Asthenia	9 (17.6)	10 (29.4)	23 (18.3)	10 (11.3)
Pyrexia	3 (5.9)	9 (26.5)	13 (10.3)	9 (10.2)
Selected TEAEs				
Respiratory infection*	47 (92.2)	25 (73.5)	100 (79.4)	65 (73.9)
Thromboembolic events†	9 (17.6)	3 (8.8)	18 (14.3)	17 (19.3)
Cardiac failure‡	7 (13.7)	5 (14.7)	6 (4.8)	3 (3.4)
Ischemic heart disease‡	3 (5.9)	3 (8.8)	5 (4.0)	2 (2.3)
Renal failure	2 (3.9)	1 (2.9)	1 (0.8)	1 (1.1)
Second primary malignancy*	8 (15.7)	4 (11.8)	5 (4.0)	2 (2.3)
Solid skin malignancy	7 (13.7)	3 (8.8)	2 (1.6)	0
Solid non-skin malignancy	2 (3.9)	2 (5.9)	3 (2.4)	2 (2.3)

*Customized MedDRA query. †MedDRA SMO (narrow term)
d, dexamethasone; Isa, isatuximab; K, carfilzomib; TEAE, treatment-emergent adverse event

Table 4. Hematologic laboratory abnormalities by age group: ≥ 70 and < 70 years, safety population

Laboratory parameter, n (%)	≥ 70 years (n=85)				< 70 years (n=214)			
	Any grade	Grade 3	Grade 4	Grade 5	Any grade	Grade 3	Grade 4	Grade 5
Anemia	51 (100)	9 (17.6)	0	0	33 (97.1)	7 (20.6)	0	0
Thrombocytopenia	48 (94.1)	11 (21.6)	0	0	28 (82.4)	7 (20.6)	1 (2.9)	0
Neutropenia	28 (54.9)	8 (15.7)	0	0	5 (14.7)	1 (2.9)	0	0

d, dexamethasone; Isa, isatuximab; K, carfilzomib

CONCLUSIONS

- Consistent with the overall IKEMA study population, a strong PFS benefit (HR 0.36; 95% CI 0.18–0.75) was observed in elderly MM patients with Isa-Kd vs Kd
- $\geq$ VGPR, CR, and MRD– rates were higher with Isa-Kd vs Kd in elderly patients as well as in younger patients
- Isa-Kd had a manageable safety profile in elderly MM patients, with a similar proportion of serious TEAEs in both treatment arms. Fewer patients had TEAEs leading to definitive treatment discontinuations with Isa-Kd vs Kd
- Isa-Kd provides a consistent benefit vs Kd in elderly patients and is a new treatment option for relapsed MM

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DISCLOSURES:

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