KarMMa-3 subgroup analysis in older patients with relapsed/refractory multiple myeloma treated with idecabtagene vicleucel

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Background

- Chimeric antigen receptor (CAR) T-cell therapies are an effective treatment option for patients with relapsed/refractory multiple myeloma (RRMM)[1]
- Idecabtagene vicleucel (ide-cel) is a B-cell maturation antigen-targeted CAR T-cell therapy approved for patients with RRMM with ≥ 2 prior lines of therapy[2]
- Ide-cel has been associated with an increase in progression-free survival and improved response compared with standard regimens in patients with triple-class-exposed RRMM who had received 2-4 prior regimens[1]
- The median age of diagnosis for patients with RRMM is 71 years, and older individuals are the largest increasing population of patients with RRMM, though investigations within this patient subpopulation are limited[3]
- Developing a better understanding of the relationship between patient age and CAR T-cell therapy outcomes may help guide treatment and clinical practice[3]
- This analysis of data from the KarMMa-3 trial describes efficacy and safety outcomes in older and younger patients who received either ide-cel or standard therapy regimens

Methods

- KarMMa-3 (NCT03651128) is an open-label, phase 3 trial in patients with RRMM **(Figure 1)**[1,4]

Figure 1. Study design, key eligibility criteria, and study objectives

[a]DPd, DVd, EPd, IRd, or Kd. [b]Crossover to ide-cel was allowed after confirmed progressive disease. DPd, daratumumab, pomalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; ECOG, Eastern Cooperative Oncology Group; EPd, elotuzumab, pomalidomide, dexamethasone; Ird, ixazomib, lenalidomide, dexamethasone; Kd, carfilzomib, dexamethasone; LDC, lymphodepleting chemotherapy; R, randomization.

Results

Patients

- A total of 386 patients were randomized to ide-cel (n = 254) or standard regimens (n = 132**; Table 1**)
  - Of patients who were randomized to receive ide-cel, 19.3% (49/254) were ≥ 70 years of age
  - Of patients who were randomized to receive standard regimens, 20.5% (27/132) were ≥ 70 years of age
- Baseline characteristics are shown in **Table 1**
  - Among those in the ide-cel arm, 44.4% and 32.7% of patients who were < 70 years and ≥ 70 years of age, respectively, had high-risk cytogenetic abnormalities and 66.8% and 55.1%, respectively, had triple-class refractory disease
- The median time to progression from the last prior anti-myeloma treatment was longer for patients receiving ide-cel vs standard regimens in the ≥ 70 years age group (8.6 months vs 6.7 months, respectively) and similar for patients receiving ide-cel vs standard regimens in the < 70 years age group (6.5 months vs 6.9 months, respectively)

Table 1. Baseline characteristics

Characteristic	Age < 70 years		Age ≥ 70 years	
	Ide-cel (n = 205)	Standard regimens (n = 105)	Ide-cel (n = 49)	Standard regimens (n = 27)
Age, median (range), years	60 (30-69)	59 (42-69)	72 (70-81)	72 (70-83)
Sex, male, n (%)	124 (60.5)	62 (59.0)	32 (65.3)	17 (63.0)
Race, n (%)				
White	138 (67.3)	58 (55.2)	34 (69.4)	20 (74.1)
Black or African American	15 (7.3)	16 (15.2)	3 (6.1)	2 (7.4)
Asian	5 (2.4)	4 (3.8)	2 (4.1)	1 (3.7)
Unknown	44 (21.5)	23 (21.9)	10 (20.4)	4 (14.8)
Other	3 (1.5)	4 (3.9)	0	0
Extramedullary disease, n (%)	48 (23.4)	27 (25.7)	13 (26.5)	5 (18.5)
High-risk cytogenetics, n (%)				
Del(17p), t(4;14), and/or t(14;16)	91 (44.4)	46 (43.8)	16 (32.7)	15 (55.6)
Del(17p)	57 (27.8)	30 (28.6)	9 (18.4)	12 (44.4)
t(4;14)	34 (16.6)	15 (14.3)	9 (18.4)	3 (11.1)
t(14;16)	6 (2.9)	3 (2.9)	2 (4.1)	1 (3.7)
ECOG PS, n (%)				
0	101 (49.3)	57 (54.3)	19 (38.8)	9 (33.3)
1	103 (50.2)	45 (42.9)	30 (61.2)	17 (63.0)
≥ 2	1 (0.5)	3 (2.9)	0	1 (3.7)
Prior stem cell transplant, n (%)				
1 transplantation	139 (67.8)	74 (70.5)	28 (57.1)	13 (48.1)
> 1 transplantation	41 (20.0)	23 (21.9)	6 (12.2)	4 (14.8)
R-ISS stage III, n (%)	26 (12.7)	9 (8.6)	5 (10.2)	5 (18.5)
Triple-class refractory disease, n (%)	137 (66.8)	69 (65.7)	27 (55.1)	20 (74.1)

PS, performance status; R-ISS, Revised International Staging System.

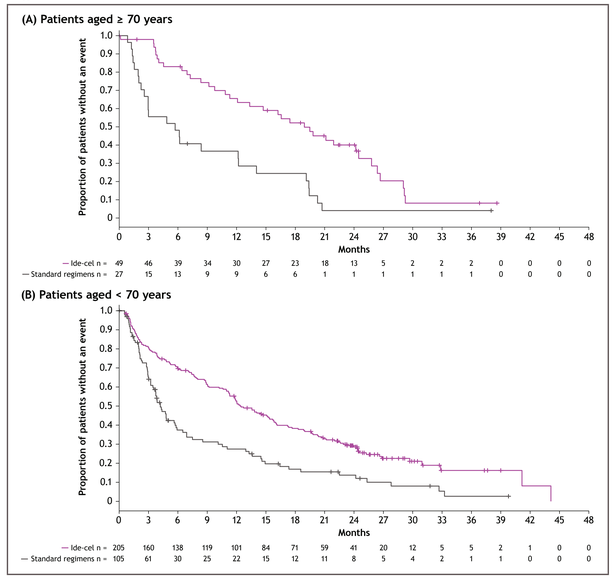
Efficacy

- ORR was higher among older (≥ 70 years of age) and younger (< 70 years of age) patients treated with ide-cel (ORR, 81.6% and 68.8%, respectively) when compared with older and younger patients treated with standard regimens (ORR, 48.1% and 41.0%, respectively) **(Table 2)**
- In older patients, median PFS was longer among those who received ide-cel as compared with standard regimens **(Figure 2A, Table 2)**
  - Similarly, in younger patients, median PFS was longer among those who received ide-cel as compared with standard regimens **(Figure 2B)**

Table 2. Response rates

Outcomes	Age < 70 years		Age ≥ 70 years	
	Ide-cel (n = 205)	Standard regimens (n = 105)	Ide-cel (n = 49)	Standard regimens (n = 27)
ORR, % (95% CI)	68.8 (62.4, 75.1)	41.0 (31.5, 50.4)	81.6 (70.8, 92.5)	48.1 (29.3, 67.0)
***P* value**	< 0.0001		0.0037	
PFS, median (95% CI)	12.5 (11.2-15.4)	4.2 (3.5-5.7)	18.9 (12.1-24.5)	5.7 (2.2-12.2)
***P* value**	< 0.0001		0.0012	

Figure 2. Kaplan-Meier PFS

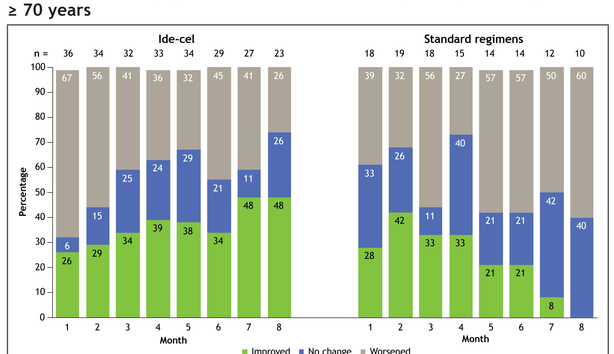


- Median OS may be confounded by the number of patients who crossed over from standard regimens to ide-cel: 67% (18/27) of patients ≥ 70 years of age and 53% (56/105) of patients < 70 years of age
  - Despite this, OS was clinically meaningful in older and younger patients who received ide-cel (median [95% CI], NR and 39.5 [27.8, NR] mo, respectively)

Patient-reported quality of life

- Generally, a consistently higher proportion of patients aged ≥ 70 years treated with ide-cel met the responder definition for improvement in global health status/QoL versus those who were treated with standard regimens **(Figure 3)**

Figure 3. EORTC QLQ-C30 Global Health Status/QoL for patients aged ≥ 70 years



Patient-reported outcomes were assessed using the EORTC QLQ-C30 Global Health Status/QoL questionnaire at monthly visits in patients aged ≥ 70 years, comparing ide-cel with standard regimens. Responders were defined by a change from baseline of ≥ +5 (improvement) or ≤ −5 (deterioration).

Safety

- No significant differences in safety profile were observed between the older and younger age groups among patients treated with ide-cel **(Table 3)**

Table 3. Treatment-emergent adverse events of special interest/select adverse events grade ≥3 (safety population)

AESI/Select AE, n (%)	Age < 70 years		Age ≥ 70 years	
	Ide-cel (n = 178)	Standard regimens (n = 99)	Ide-cel (n = 47)	Standard regimens (n = 27)
At least one AESI/Select AE[a]	70 (39.3)	29 (29.3)	14 (29.8)	13 (48.1)
CRS	8 (4.5)	-	3 (6.4)	-
Infections	48 (27.0)	20 (20.2)	12 (25.5)	6 (22.2)
iiNT	4 (2.2)	-	3 (6.4)	-

[a]Includes CRS, neurologic toxicity - Focused 2.0 FDA, and infections.
AE, adverse event; AESI, AE of special interest; CRS, cytokine release syndrome; iiNT, investigator identified neurotoxicity.

Conclusions

- Patients aged ≥ 70 years from the KarMMa-3 trial experienced benefit from ide-cel treatment, as evidenced by a longer median PFS and notable ORR compared with patients treated with standard regimens
- While efficacy and safety outcomes were consistent between the 2 age groups, patients aged ≥ 70 years were more likely to have favorable baseline characteristics and less aggressive, heavily pretreated disease at baseline
  - These differences may reflect selection bias towards enrolling older patients considered to be easier to treat in first CAR T trials for MM, although more contemporaneous real-world data from late-line settings suggest ide-cel treatment is based on less restrictive selection criteria
- No new safety signals were identified among older and younger patient subpopulations
- Older and younger patients treated with ide-cel exhibited similar OS, though OS data may be confounded by patients who crossed over from standard regimens to ide-cel treatment
- Ide-cel was associated with greater improvements in patient-reported global health status and QoL compared with standard regimens among patients aged ≥ 70 years
- These observations reinforce the potential for durable benefit with a single ide-cel infusion in a real-world context without additional adverse safety signals, supporting its use across age groups

References

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