Extended treatment-free hospitalization-free time and quality-of-life benefits with chimeric antigen receptor T-cell therapy in subgroups of patients with relapsed/refractory multiple myeloma: insights from the KarMMa-3 trial

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Background

- Numerous treatments for relapsed/refractory multiple myeloma (RRMM) require treat-to-progression, which can result in cumulative toxicities from repeated dosing
- Conversely, chimeric antigen receptor (CAR) T-cell therapies offer the potential for a treatment-free interval following a 1-time infusion[1]
- Using KarMMa-3 trial (NCT03651128) data,[2] this research investigated treatment-free hospitalization-free time (TFT) and compared quality of life (QoL)–adjusted event-free survival (EFS) in different patient subgroups (age, tumor burden, prior regimen number, refractory disease status) receiving idecabtagene vicleucel (ide-cel) vs standard regimens; findings in the overall trial population were previously published
- Hospitalizations owing to infusion, serious adverse events, and other factors were considered

Methods

- KarMMa-3 is an open-label, phase 3 trial where adults with RRMM who had received 2–4 previous regimens with disease refractory to last regimen were randomized (2:1) to ide-cel or a standard-of-care regimen[2]
  - Daratumumab, pomalidomide, and dexamethasone (DPd)
  - Daratumumab, bortezomib, and dexamethasone (DVd)
  - Ixazomib, lenalidomide, and dexamethasone (IRd)
  - Carfilzomib and dexamethasone (Kd)
  - Elotuzumab, pomalidomide, and dexamethasone (EPd)
- In total, 348 efficacy-evaluable patients were included in the analysis (ide-cel, n = 225; standard regimen, n = 123)
- EFS was defined as the time from randomization to disease progression, subsequent anti-myeloma therapy, or death, whichever occurred first, and was categorized into 4 health states based on study treatment and hospitalization status (**Table 1**)
  - Time under study treatment was measured as time from randomization to the last dose of study treatment

Table 1. EFS health states

Under study treatment?[a]	Hospitalized?	Health state
Yes	Yes	Study treatment (+) Hospitalized (+)
Yes	No	Study treatment (+) Hospitalized (−)
No	Yes	Study treatment (−) Hospitalized (+)
No	No	Study treatment (−) Hospitalized (−)[b]

[a]Time under study treatment was measured as time from randomization to the last dose of study treatment; [b]Health state represents TFT.

- A patient may have multiple episodes of the same health state
- Time spent in each health state was summarized using the restricted mean survival time (RMST)
- The average QoL in each health state was determined using the EQ-5D-5L (EuroQol 5 Dimension-5 Level) index[3]
  - 1 = perfect health and 0 = perceived as no better than death
- In this analysis, QoL-adjusted EFS was calculated as the sum of RMST in each state, weighted by the mean EQ-5D-5L index for each respective state
- Statistical significance of EFS and QoL-adjusted EFS was assessed using either a *t* test or Mann-Whitney U test, depending on data normality
- EFS, TFT, EQ-5D-5L index and QoL-adjusted EFS are reported as mean values

Results

EFS

- Mean EFS (95% CI) and TFT outcomes were favorable and consistently longer in the ide-cel arm compared with the standard regimen arm across all subgroups including age, tumor burden, number of prior regimens, and triple-class refractoriness (**Table 2**)
- Patients treated with ide-cel spent most of their EFS time in the TFT state in all subgroups
- In contrast, patients in all subgroups receiving standard regimens spent most of their EFS time under study treatment while being hospitalization-free
- EFS time spent in each health state was similar within and across subgroups among patients treated with ide-cel **(Figures 1A and 1B)** and standard regimen **(Figures 1C and 1D)**

Table 2. Mean time spent in each EFS health state calculated by RMST

Health state	Mean time in EFS (months, 95% CI)			
	Age ≥70 y		Age <70 y	
	Ide-cel (n = 47)	Standard regimen (n = 26)	Ide-cel (n = 178)	Standard regimen (n = 97)
Study treatment (+) Hospitalized (+)	0.16 (0.05-0.28)	0.18 (0.09-0.30)	0.13 (0.09-0.18)	0.12 (0.07-0.17)
Study treatment (+) Hospitalized (−)	1.85 (1.64-2.06)	9.22 (5.97-13.05)	1.83 (1.74-1.95)	8.37 (6.20-10.57)
Study treatment (−) Hospitalized (+)	0.16 (0.04-0.31)	0.00 (0.00-0.00)[b]	0.30 (0.16-0.48)	0.02 (0.00-0.06)
Study treatment (−) Hospitalized (−)[a]	15.76 (12.67-19.11)	0.17 (0.03-0.49)	16.05 (13.82-18.30)	0.17 (0.05-0.31)
Total	17.94 (14.79-21.09)	9.52 (5.94-13.10)	18.40 (16.17-20.62)	8.65 (6.54-10.75)

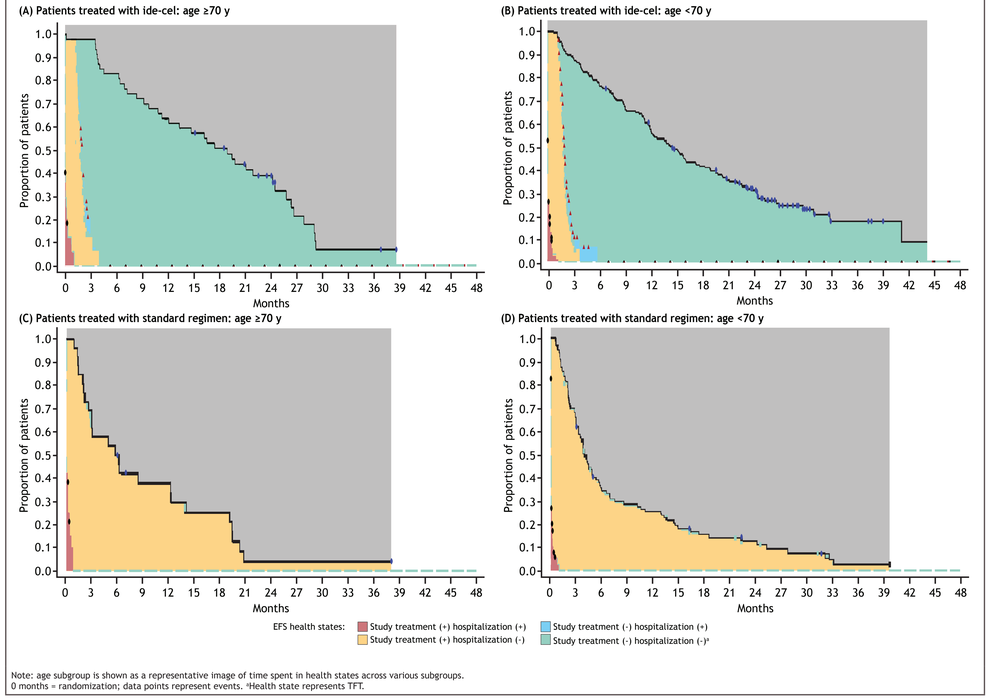
Health state	Mean time in EFS (months, 95% CI)			
	With high tumor burden		Without high tumor burden	
	Ide-cel (n = 56)	Standard regimen (n = 32)	Ide-cel (n = 161)	Standard regimen (n = 85)
Study treatment (+) Hospitalized (+)	0.19 (0.10-0.30)	0.07 (0.04-0.11)	0.10 (0.06-0.16)	0.15 (0.10-0.21)
Study treatment (+) Hospitalized (−)	1.92 (1.68-2.15)	8.11 (5.16-11.58)	1.81 (1.73-1.91)	8.95 (6.76-11.61)
Study treatment (−) Hospitalized (+)	0.21 (0.10-0.36)	0.00 (0.00-0.01)	0.25 (0.13-0.41)	0.02 (0.00-0.06)
Study treatment (−) Hospitalized (−)[a]	15.72 (12.50-19.34)	0.10 (0.02-0.20)	15.93 (13.59-18.36)	0.20 (0.08-0.35)
Total	18.10 (14.60-21.59)	8.35 (5.11-11.59)	18.40 (16.15-20.64)	9.36 (7.01-11.71)

Health state	Mean time in EFS (months, 95% CI)			
	2 prior regimens		3-4 prior regimens	
	Ide-cel (n = 71)	Standard regimen (n = 38)	Ide-cel (n = 154)	Standard regimen (n = 85)
Study treatment (+) Hospitalized (+)	0.17 (0.10-0.27)	0.19 (0.09-0.30)	0.12 (0.07-0.17)	0.10 (0.07-0.13)
Study treatment (+) Hospitalized (−)	1.85 (1.71-2.00)	10.55 (6.96-14.54)	1.82 (1.71-1.93)	7.53 (5.72-9.63)
Study treatment (−) Hospitalized (+)	0.15 (0.05-0.28)	0.03 (0.00-0.11)	0.29 (0.15-0.47)	0.02 (0.00-0.05)
Study treatment (−) Hospitalized (−)[a]	16.26 (13.75-18.83)	0.10 (0.02-0.27)	15.21 (13.07-17.40)	0.17 (0.00-0.35)
Total	18.48 (15.97-20.98)	10.91 (7.02-14.80)	17.52 (15.26-19.79)	7.83 (5.93-9.74)

Health state	Mean time in EFS (months, 95% CI)			
	With triple-class refractory disease		Without triple-class refractory disease	
	Ide-cel (n = 139)	Standard regimen (n = 83)	Ide-cel (n = 86)	Standard regimen (n = 40)
Study treatment (+) Hospitalized (+)	0.14 (0.09-0.20)	0.08 (0.06-0.11)	0.12 (0.05-0.24)	0.26 (0.13-0.40)
Study treatment (+) Hospitalized (−)	1.79 (1.67-1.90)	5.65 (4.28-7.10)	1.91 (1.79-2.05)	15.22 (10.48-20.11)
Study treatment (−) Hospitalized (+)	0.18 (0.11-0.25)	0.03 (0.00-0.06)	0.39 (0.15-0.69)	0.01 (0.00-0.01)
Study treatment (−) Hospitalized (−)[a]	14.19 (11.86-16.72)	0.18 (0.07-0.32)	18.52 (15.70-21.31)	0.05 (0.00-0.23)
Total	16.55 (14.12-18.97)	5.93 (4.55-7.31)	21.17 (18.34-24.00)	15.53 (11.04-20.03)

[a]Health state represents TFT. [b]Indicates there were 0 patients.

Figure 1. Reconstructed Kaplan-Meier curves of time spent in each health state of EFS in patients

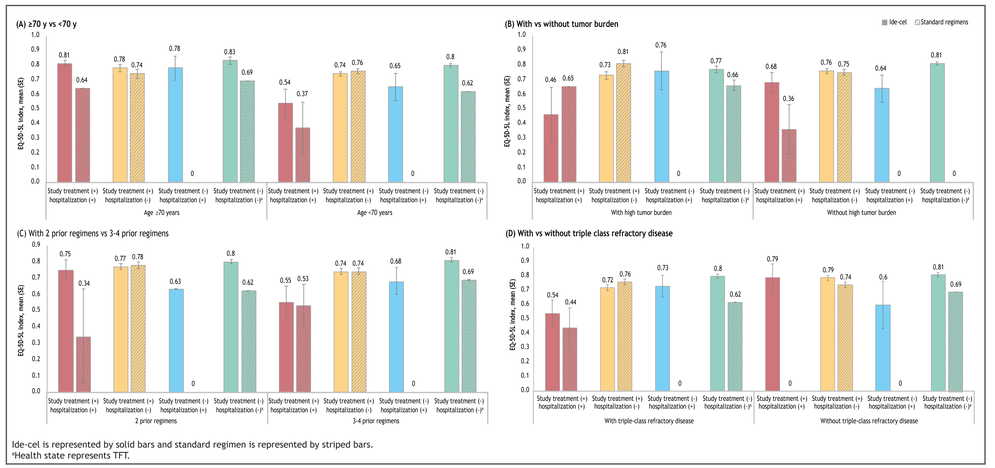


Note: age subgroup is shown as a representative image of time spent in health states across various subgroups. 0 months = randomization; data points represent events. [a]Health state represents TFT.

EQ-5D-5L

- Within the TFT state, all patient subgroups receiving ide-cel had a higher mean (SE) EQ-5D-5L index, which was comparable to that of the general population of the same age, than those who received standard regimens (**Figure 2**)

Figure 2. Mean (SE) EQ-5D-5L index in each health state of EFS in patients

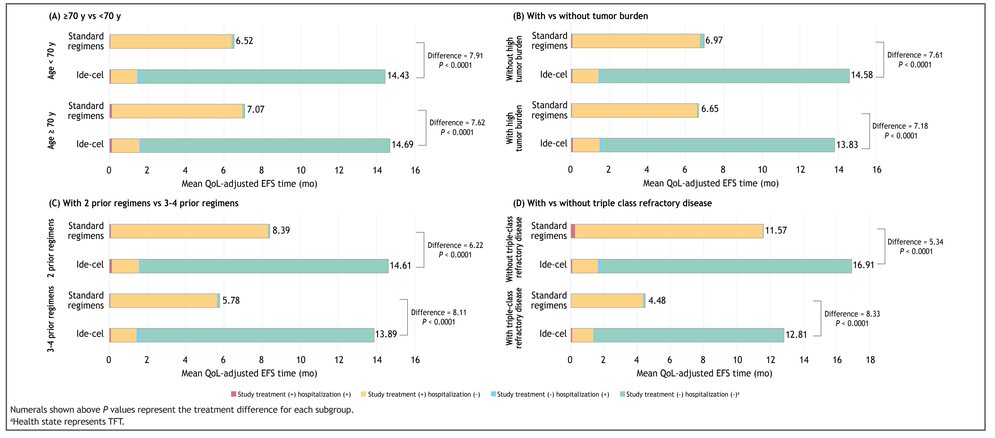


Ide-cel is represented by solid bars and standard regimen is represented by striped bars. [a]Health state represents TFT.

QoL-adjusted EFS

- Across all patient subgroups, the mean QoL-adjusted EFS (95% CI) was significantly greater in the ide-cel compared with the standard regimen arm (*P* < 0.0001; **Figure 3**)

Figure 3. Mean QoL-adjusted EFS overall and in each health state of EFS in patients



Numerals shown above *P* values represent the treatment difference for each subgroup. [a]Health state represents TFT.

Conclusions

- Irrespective of age, tumor burden, number of prior regimens, and triple-class refractoriness, patients receiving ide-cel demonstrated significantly longer EFS and QoL-adjusted EFS than those receiving standard regimens
- Patient improvement was primarily due to extended periods free from treatment and hospitalization, during which their QoL was comparable to that of the general population of the same age, even if patients were older (≥70 y), were heavily pretreated (3-4 prior regimens), or had triple-refractory disease
- A single infusion of ide-cel leads to improved survival and QoL compared with standard treat-to-progression regimens consistently across patient subpopulations

References

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