



The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALY AVAILABLE THERAPIES

Idecabtagene Vicleucel (ide-cel) Versus Standard (std) Regimens in Patients (pts) with Triple-Class-Exposed (TCE) Relapsed and Refractory Multiple Myeloma (RRMM): Updated Analysis from KarMMa-3

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Introduction

A single ide-cel infusion showed significantly longer median progression-free survival (PFS) vs std regimens (13.3 vs 4.4 months [mo], HR 0.49, 95% CI 0.38–0.65, $P < 0.001$) with deep, durable responses in heavily pretreated TCE RRMM at an interim analysis

(IA) of KarMMa-3 (NCT03651128); safety data were consistent with prior studies (Rodríguez-Otero et al. *NEJM* 2023). Ide-cel benefits were consistent across pts in high-risk subgroups and across 2-4 prior lines of therapy (Tx). Results of the preplanned final PFS analysis of KarMMa-3 with 12.3 mo additional follow-up are reported.

Methods

In the phase 3 KarMMa-3 trial, pts with RRMM who received 2-4 prior regimens, including an immunomodulatory agent, proteasome inhibitor, and daratumumab, and were refractory to last regimen were randomized 2:1 to ide-cel or a std regimen (DPd, DVd, IRd, Kd, or EPd). In the ide-cel arm, pts could receive ≤ 1 cycle of optional bridging Tx for disease control. Pts in the std regimens arm could receive ide-cel after confirmed disease progression (PD). The primary endpoint was IRC-assessed PFS in the ITT population; final PFS was planned to be analyzed with ~ 289 events. Key secondary endpoints were IRC-assessed overall response rate (ORR) and overall survival (OS); other secondary endpoints included complete response rate (CRR), duration of response (DOR), minimal residual disease (MRD) status, time to next anti-myeloma Tx (TTNT; time from randomization to next anti-myeloma Tx [MTx]), event-free survival (EFS; time from randomization to first PD, next MTx or any-cause death, whichever is first), PFS2 (time from randomization to second objective PD or any-cause death, whichever is first), safety, and health-related quality of life (QOL).

Results

Of 386 randomized pts (ide-cel, $n = 254$; std regimens, $n = 132$), 225 received ide-cel and 126 received a std regimen. Baseline characteristics were generally balanced. Median follow-up from randomization to data cutoff (April 28, 2023) was 30.9 mo (range 12.7-47.8). Ide-cel significantly improved median PFS (95% CI) vs std regimens (13.8 [11.8-16.1] vs 4.4 [3.4-5.8] mo), representing a 51% reduced risk of PD or death (HR 0.49, 95% CI 0.38-0.63; **Figure**); 18 mo PFS rates were 41% vs 19%, respectively. Ide-cel significantly improved ORR vs std regimens (71% vs 42%) with deeper (CRR 44% vs 5%; \geq CR and MRD negative status [sensitivity level 10^{-5}], 22% vs 1%), more durable responses (median DOR 16.6 vs 9.7 mo; **Table**). PFS and ORR benefits of ide-cel vs std regimens were consistent with the IA. Interim OS will be included in the presentation. In pts who received ide-cel ($n = 225$) or a std regimen ($n = 126$), median PFS (95% CI) was 15.7 (12.5-18.9) vs 4.4 (3.4-5.8) mo, respectively. In the ITT population, median TTNT, EFS, and PFS2 were numerically longer with ide-cel vs std regimens. Median (range) TTNT was 20.9 (16.6-24.2) vs 7.0 (5.3-8.5) mo. Median (95% CI) EFS was 13.3 (11.3-15.7) vs 3.9 (3.0-5.3) mo. Median PFS2 (95% CI) was 23.5 (18.4-27.9) vs 16.7 (12.2-20.3) mo; ide-cel was next MTx in 70 (53%) pts in the std regimens arm. In the treated population, grade (gr) 3/4 infections occurred in 66/249 (27%) pts in the ide-cel arm vs 25/126 (20%) in the std regimens arm. In the ide-cel safety population, any gr cytokine release syndrome occurred in 197/225 (88%) pts, gr ≥ 3 in 11 (5%); median time to first onset was 1 d (1-14), median duration was 4 d (1-51). Any gr investigator-identified neurotoxicity occurred in 34/225 (15%) pts, gr ≥ 3 in 7 (3%); median time to onset was 3 d (range 1-317); median duration was 2.5 d (range 1-252). Ide-cel continued to demonstrate durable, clinically meaningful improvements in pt-reported outcomes, including symptoms, functioning, and QOL vs std regimens.

Conclusions

In this final PFS analysis of KarMMa-3, significantly longer PFS was maintained with ide-cel; PD or death risk reduced by 51%; responses were deeper and more durable vs std regimens. CRR with ide-cel increased since the IA, indicating a deepening response, but were unchanged with std regimens. A single ide-cel infusion vs continuous treatment with std regimens resulted in longer median TTNT and PFS2, indicating improved long-term disease control. The ide-cel safety profile was consistent with previous reports, with no parkinsonism or Guillain-Barré syndrome reported. These data continue to support use of ide-cel in pts with TCE RRMM.

Study support

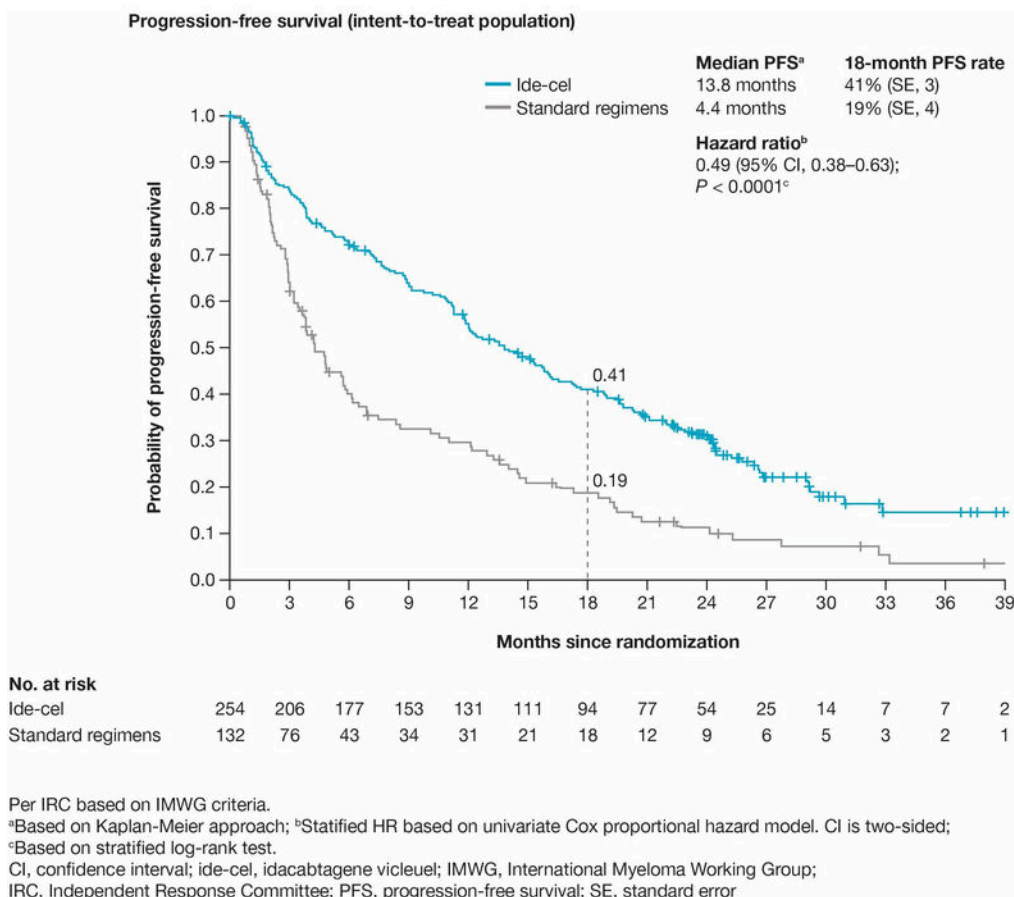
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OffLabel Disclosure: In the US, ide-cel is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The current abstract presents data from the phase 3 KarMMa-3 trial of ide-cel vs standard regimens in patients with RRMM who had received two to four prior regimens and were refractory to the last regimen.

Figure: Kaplan–Meier curve of progression-free survival (intent-to-treat population)**Table. Efficacy outcomes**

	Ide-cel (n = 254)	Standard regimens (n = 132)
ORR, ^a % (95% CI)	71.3 (65.7–76.8)	42.4 (34.0–50.9)
OR (95% CI) ^b		3.4 (2.2–5.2)
CR rate, ^c % (95% CI)	43.7 (37.6–49.8)	5.3 (1.5–9.1)
Median DOR, months (95% CI) ^{d,e}	16.6 (12.1–19.6)	9.7 (5.5–16.1)
DOR rate at 18 months, % (SE) ^f	46.1 (3.8)	27.6 (6.4)
MRD negativity in patients with ≥ CR, n/N (%) ^g	57/254 (22.4)	1/132 (0.8)
95% CI	(17.3–27.6)	(0.0–2.2)
Median TTNT, months (range) ^{d,h}	20.9 (16.6–24.2)	7.0 (5.3–8.5)
Median EFS, months (95% CI) ^d	13.3 (11.3–15.7)	3.9 (3.0–5.3)
Median PFS2, months (95% CI) ^d	23.5 (18.4–27.9)	16.7 (12.2–20.3) ⁱ

^aPatients with PR or better; ^bUnstratified OR. Calculated based on the observed response rate with 2-sided Wald CI; ^cPatients with CR or sCR; ^dBased on Kaplan–Meier estimation per IRC based on IMWG criteria; ^eIn patients with a response; ^fBased on Greenwood formula; ^gDefined as ≥ 1 negative MRD value within 3 months prior to achieving ≥ CR until PD or death. MRD was assessed by next-generation sequencing at a sensitivity of 10⁻⁵ per IMWG Uniform Response Criteria and as specified by the protocol. 95% CI was calculated using 2-sided Wald interval; ^hTime from randomization to first subsequent anti-myeloma therapy; ⁱIncludes 70 (53%) patients from the standard regimens arm who received ide-cel as subsequent therapy after experiencing confirmed disease progression.
 CR, complete response; DOR, duration of response; EFS, event-free survival; IMWG, International Myeloma Working Group; IRC, Independent Response Committee; ITT, intent-to-treat; MRD, minimal residual disease; OR, odds ratio; ORR, overall response rate; PD, progressive disease; PFS2, progression-free survival 2; PR, partial response; sCR, stringent complete response; SE, standard error; TTNT, time to next anti-myeloma therapy.

Figure 1

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