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Idecabtagene Vicleucel (ide-cel, bb2121) in Relapsed and Refractory Multiple Myeloma: KarMMa High-Risk Subgroup Analyses

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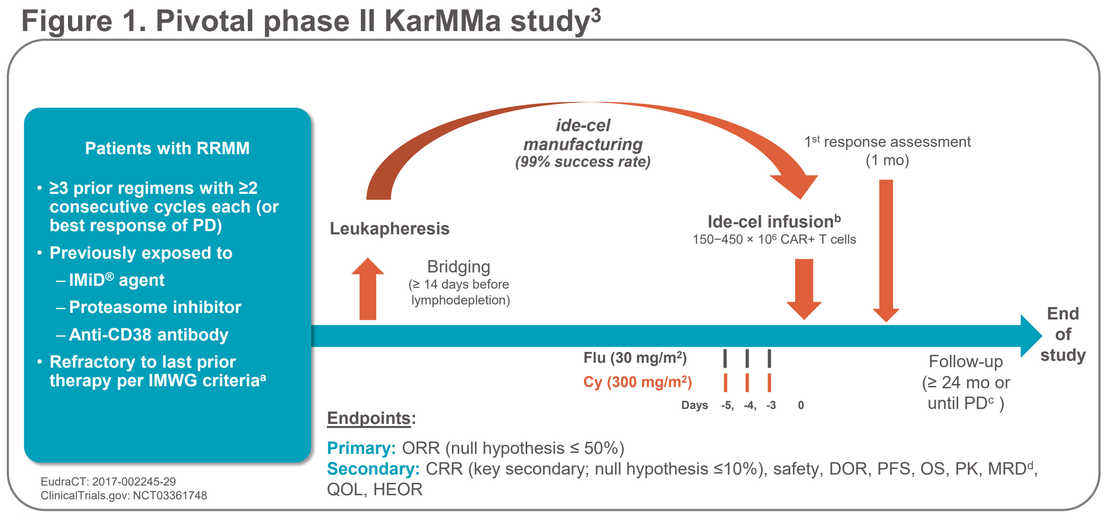
INTRODUCTION

- Outcomes remain poor in patients with high-risk RRMM receiving conventional treatments, including IMiD® agents, PIs, and anti-CD38 antibodies[1,2]
- Ide-cel, a BCMA-directed CAR T cell therapy, showed deep and durable responses in the pivotal phase II KarMMa study of patients with triple-class−exposed RRMM[3]
- **Objective**: To report safety and efficacy of ide-cel in historically difficult-to-treat patient subgroups from the KarMMa study

Figure 1. Pivotal phase II KarMMa study[3]



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP, gene expression profiling; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life; RRMM, relapsed and refractory multiple myeloma. [a] Defined as documented PD during or within 60 days from last dose of prior antimyeloma regimen. [b] Patients were required to be hospitalized for 14 days postinfusion. Ide-cel retreatment was allowed at PD for best response of at least stable disease. [c] Patients were followed for ≥ 24 months or until PD, whichever was longer. Upon study discontinuation, all patients who received ide-cel were asked to participate in a separate long-term follow-up study. [d] By next-generation sequencing.

1. Gandhi UH, et al. Leukemia. 2019;33:2266-2275. 2. Nijhof IS, et al. Drugs. 2018;78:19-37. 3Munshi et al. NEJM. 2021;384:705-16.

RESULTS

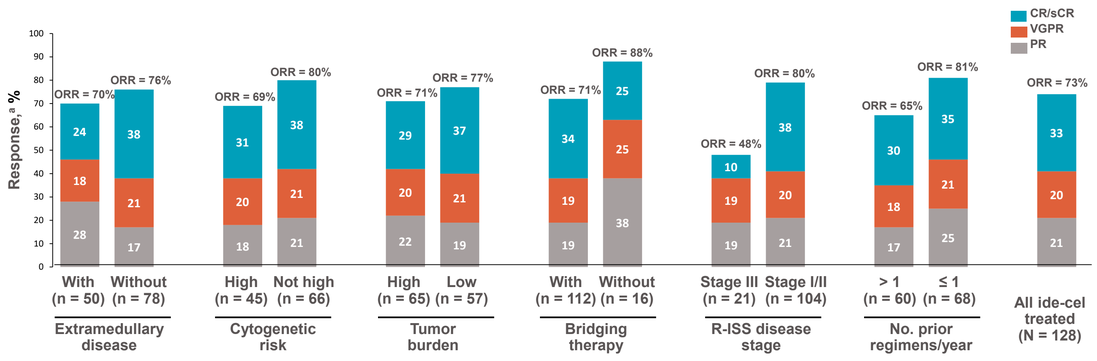
Table 1. Baseline demographics and clinical characteristics

Characteristic	Ide-cel treated (N = 128)
Age, median (range), y	61 (33-78)
Male, %	59
ECOG performance status, %	
0	45
1	53
2	2
Tumor BCMA expression (≥ 50% BCMA+),[a] %	85
Time since initial diagnosis, median (range), y	6 (1-18)
No. of prior antimyeloma regimens, median (range)	6 (3-16)
Prior autologous SCT, %	
≥ 1	94
> 1	34
Refractory status, %	
IMiD agent-refractory	98
PI-refractory	91
Anti-CD38 antibody-refractory	94
Triple-refractory	84
Extramedullary disease, %	39
High-risk cytogenetics [del(17p), t(4;14), t(14;16)],[b] %	35
High tumor burden (≥ 50% BMPCs), %	51
Any bridging therapies for multiple myeloma, %	88
R-ISS disease stage,[c] %	
I	11
II	70
III	16
No. of prior antimyeloma regimens per year, %	
≤ 1	53
> 1	47

- More than one third of patients had high-risk cytogenetics and extramedullary disease (35% and 39%, respectively), and approximately half (51%) had high tumor burden
- Most patients (88%) received bridging therapy during CAR T cell manufacturing
- Most patients (70%) had R-ISS disease stage II, with 16% having stage III
- Patients were heavily pretreated, with 47% having received > 1 prior antimyeloma regimen per year

Data cutoff date: 14 Jan 2020. BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; ECOG PS, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; PI, proteasome inhibitor; R-ISS, revised International Staging System; SCT, stem cell transplantation.
a No minimum tumor BCMA expression required for study entry. b Baseline cytogenetics not evaluable/missing for 17 patients; 45 patients (35%) had 1q amp abnormality. c R-ISS stage was assessed at enrollment; unknown for 3 patients.

Figure 2. Response rate by subgroup

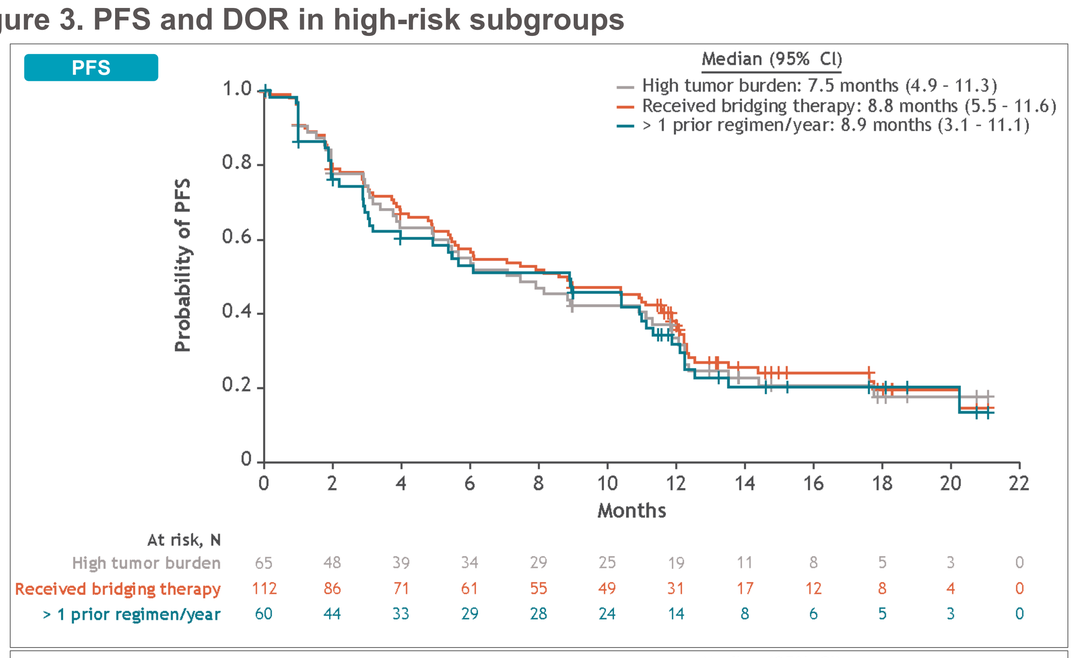


Data cutoff date: 14 Jan 2020. CR, complete response; ORR, overall response rate; PR, partial response; R-ISS, revised International Staging System; sCR, stringent CR; VGPR, very good PR. a Sum of CR/sCR, VGPR, and PR rates may differ from the ORR rate due to rounding.

- ORR was ≥ 65% and CR rate was ≥ 20% across all high-risk subgroups except R-ISS disease stage III
- Presence of extramedullary disease and baseline tumor burden did not substantially affect ORR
- Among high-risk subgroups treated with the highest target dose of 450 × 10^6 CAR+ T cells, ORR and CR rate were ≥ 75% and ≥ 19%, respectively, across all subgroups except R-ISS disease stage III

RESULTS

Figure 3. PFS and DOR in high-risk subgroups



DOR, duration of response; PFS, progression-free survival; NE, not estimable; R-ISS, revised International Staging System.

- Median PFS was ≥ 7.5 months in patients who had high tumor burden, bridging therapy, and > 1 prior regimen per year
- Median DOR was ≥ 9.2 months in all high-risk subgroups examined, except patients with R-ISS stage III
- Among patients treated with the target dose of 450 × 10^6 CAR+ T cells, median PFS was ≥ 8.9 months and median DOR was ≥ 10.3 months in all high-risk subgroups except R-ISS stage III

Table 2. Summary of adverse events in high-risk subgroups

n (%)	Extramedullary disease (n = 50)	High-risk cytogenetics (n = 45)	High tumor burden (n = 65)	Received bridging therapy (n = 112)	R-ISS disease stage III (n = 21)	> 1 prior regimens/year (n = 60)	All ide-cel treated (N = 128)
Any-grade TEAE	50 (100)	45 (100)	65 (100)	112 (100)	21 (100)	60 (100)	128 (100)
Grade 3/4 TEAE	50 (100)	45 (100)	64 (99)	111 (99)	21 (100)	60 (100)	127 (99)
SAE	36 (72)	32 (71)	50 (77)	78 (70)	15 (71)	41 (68)	86 (67)
≥ 1 CRS event	41 (82)	41 (91)	57 (88)	94 (84)	16 (76)	49 (82)	107 (84)
Max. grade (Lee criteria),[a,b]							
1	24 (48)	21 (47)	31 (48)	55 (49)	8 (38)	27 (45)	61 (48)
2	14 (28)	18 (40)	23 (35)	32 (29)	7 (33)	20 (33)	39 (31)
≥ 3	3 (6)	2 (4)	3 (5)	7 (6)	1 (5)	2 (3)	7 (5)

- No new safety signals were identified in the subgroups examined
- Across all high-risk subgroups, the incidence of CRS was comparable with that of the overall ide-cel treated population
- Median time to onset of CRS was 1 day in all subgroups and in the overall ide-cel treated population; median duration of CRS ranged from 5 to 7 days

CRS, cytokine release syndrome; R-ISS, revised International Staging System; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Sum of percentages may differ from the total due to rounding. [b]CRS graded according to Lee criteria (Lee DW, et al. Blood. 2014;124:188-195).

CONCLUSIONS

- In the KarMMa study, ide-cel demonstrated deep and durable responses in most subgroups examined, including those with the highest risk, such as extramedullary disease, high-risk cytogenetics, and high tumor burden
- No new safety signals were observed in evaluated high-risk subgroups
- The ongoing phase II KarMMa-2 study (NCT03601078) is assessing ide-cel in patients with RRMM and high-riska MM; the phase I KarMMa-4 study is evaluating ide-cel in patients with high-riskb NDMM (Usmani et al, ASH 2020, Abstract 1418)
- These results further support the favorable benefit−risk profile of ide-cel and suggest that ide-cel represents a promising treatment option for patients with RRMM, including historically difficult-to-treat patient subsets

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