Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, for the treatment of patients with relapsed and refractory multiple myeloma: updated results from KarMMa

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Introduction

- Patients with RRMM previously exposed to immunomodulatory agents, PIs, and anti-CD38 antibodies have poor outcomes with subsequent therapy using previously approved regimens[1,2]
  - Deep and durable responses are uncommon
  - ORR, 26%–31%; median PFS, 2–4 months; median OS, < 9 months
- Ide-cel, a BCMA-directed CAR T cell therapy, demonstrated favorable tolerability and deep, durable responses in heavily pretreated patients with RRMM[3,4]
- Ide-cel was recently approved by the FDA for patients with RRMM after ≥ 4 prior lines of therapy, including an immunomodulatory agent, a PI, and an anti-CD38 antibody, based on results of the pivotal phase 2 KarMMa trial[4,5]
- Here we present longer-term efficacy and safety results from the KarMMa trial, overall and by number of prior lines of therapy

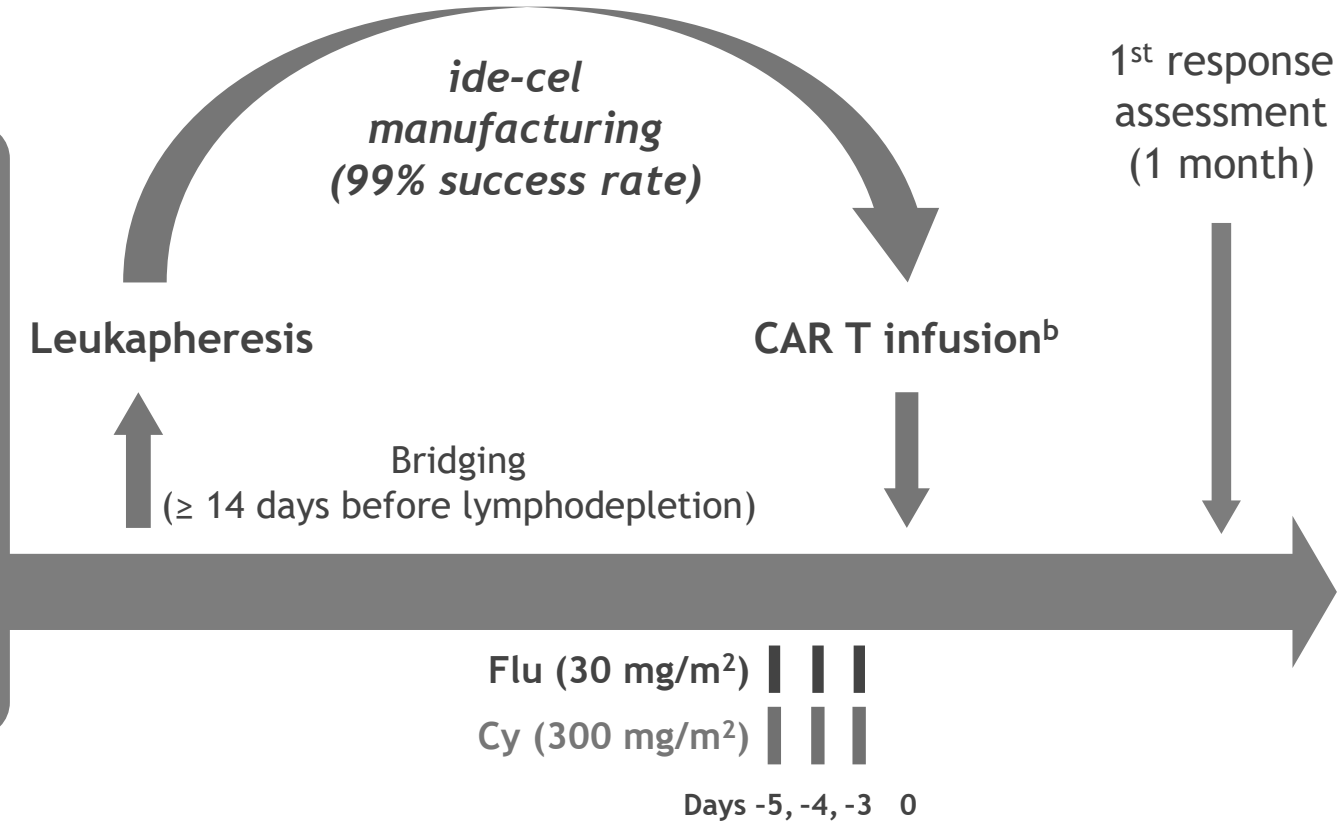
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

1. Chari A, et al. *N Engl J Med* 2019;381:727–738; 2. Lonial S, et al. *Lancet Oncol* 2019;2045:1–15; 3. Raje N, et al. *N Engl J Med* 2019;380:1726–1737; 4. Munshi NC, et al. *N Engl J Med* 2021;384:705–716; 5. ABECMA® (idecabtagene vicleucel) [package insert]. Summit, NJ: Celgene, a Bristol-Myers Squibb Company and bluebird bio; March 2021.

Study design

KarMMa™

- RRMM
- ≥ 3 prior regimens with ≥ 2 consecutive cycles each (or best response of PD)
- Previously exposed to:
  - Immunomodulatory agent
  - PI
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG[a]



- Primary endpoint: ORR
- Secondary endpoints: CRR (key secondary), safety, DOR, PFS, OS, PK, MRD,[c] QOL, HEOR

EudraCT: 2017-002245-29; ClinicalTrials.gov: NCT03361748

[a]Defined as documented disease progression during or within 60 days from last dose of prior antimyeloma regimen; [b]Patients were required to be hospitalized for 14 days post-infusion. Ide-cel re-treatment was allowed at disease progression for best response of at least stable disease; [c]By next-generation sequencing.

CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; HEOR, health economics and outcomes research; IMWG, International Myeloma Working Group; MRD, minimal residual disease; PD, progressive disease; PK, pharmacokinetics; QOL, quality of life.

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Baseline demographics and clinical characteristics

Characteristics	Prior line of therapy		All ide-cel treated (N = 128)
	3 (n = 15[a])	≥ 4 (n = 113)	
Age, median (range), years	58 (38–74)	61 (33–78)	61 (33–78)
Male sex, %	80	57	59
ECOG PS (0 / 1 / 2), %	40 / 60 / 0	45 / 52 / 3	45 / 53 / 2
R-ISS Stage (I / II / III), %	7 / 87 / 7	12 / 68 / 18	11 / 70 / 16
High risk cytogenetics,[b] %	47	34	35
High tumor burden,[c] %	47	51	51
Tumor BCMA expression ≥ 50%,[d] %	87	85	85
Extramedullary disease, %	47	38	39
Time since initial diagnosis, median (range), years	4 (2–7)	7 (1–18)	6 (1–18)
Prior anti-myeloma regimens, median (range)	3 (3–3)	6 (4–16)	6 (3–16)
Prior autologous SCT (any / > 1), %	87 / 0	95 / 39	94 / 34
Any bridging therapies for multiple myeloma, %	87	88	88
Refractory status, %			
Anti-CD38 antibody-refractory	100	93	94
Triple-refractory[e]	93	83	84
Penta-refractory[f]	27	26	26

[a]Eight patients received the target dose of 300 × 10^6 CAR+ T cells and 7 patients received the target dose of 450 × 10^6 CAR+ T cells; [b]Included del(17p), t(4;14), and t(14;16); [c]Defined as ≥ 50% CD138+ plasma cells in bone marrow; [d]No minimum tumor BCMA expression required for study entry; [e]Refractory to an immunomodulatory agent, a PI, and an anti-CD38 monoclonal antibody; [f]Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.

PS, performance status; R-ISS, revised International Staging System; SCT, stem cell transplantation.

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Summary of efficacy by CAR+ T cell target dose range and in all patients

	Dose, × 10^6 CAR+ T cells				All ide-cel treated (N = 128)
	150 (n = 4)	300 (n = 70)	450 (n = 54)	300-450 (n = 124)[c]	
ORR, n (%)	2 (50)	48 (69)	44 (81)	92 (74)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	41 (33)	42 (33)
Median DOR, mo[a,b]	—	9.9	11.3	10.9	10.9
Median PFS, mo[a,b]	—	5.8	12.2	8.8	8.6
Median OS, mo[a,b]	—	20.4	24.8	24.8	24.8

- At data cutoff (Dec 21, 2020), median follow-up among surviving patients was 24.8 months (range, 1.7–33.6 months)
- Median time to first response was 1.0 month (range, 0.5–8.8 months); median time to CR was 2.8 months (range, 1.0–15.8 months)
- ORR, CRR, and median PFS with the highest target dose (450 × 10^6 CAR+ T cells) were 81%, 39%, and 12.2 months, respectively

[a]Kaplan–Meier estimate; [b]150 × 10^6 CAR+ T cell dose not reported due to small sample size; [c]FDA censoring was used for the data in this presentation. Using EMA censoring, median DOR was 10.6 months and median PFS was 8.6 months.

CR, complete response; EMA, European Medicines Agency; sCR, stringent complete response.

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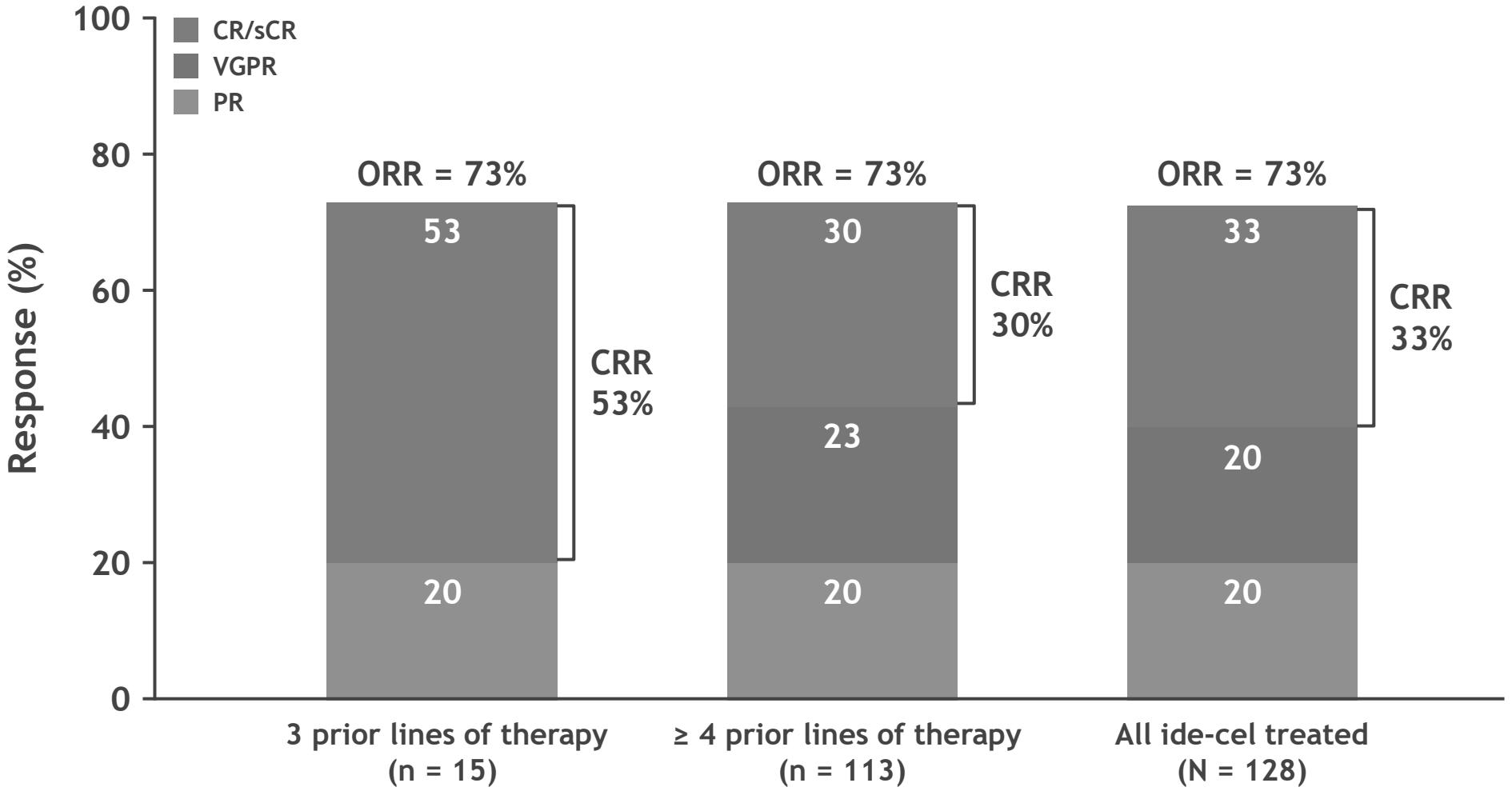
Best overall response by prior line of therapy



- ORR did not vary by number of prior lines of therapy (3 vs ≥ 4)

PR, partial response; VGPR, very good partial response.

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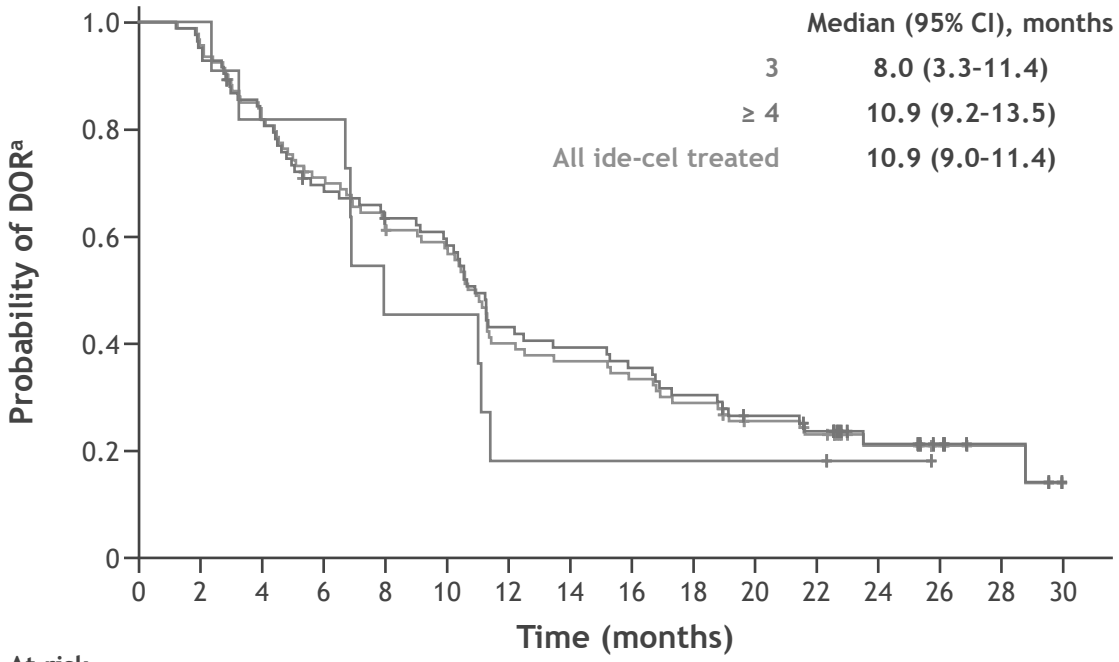
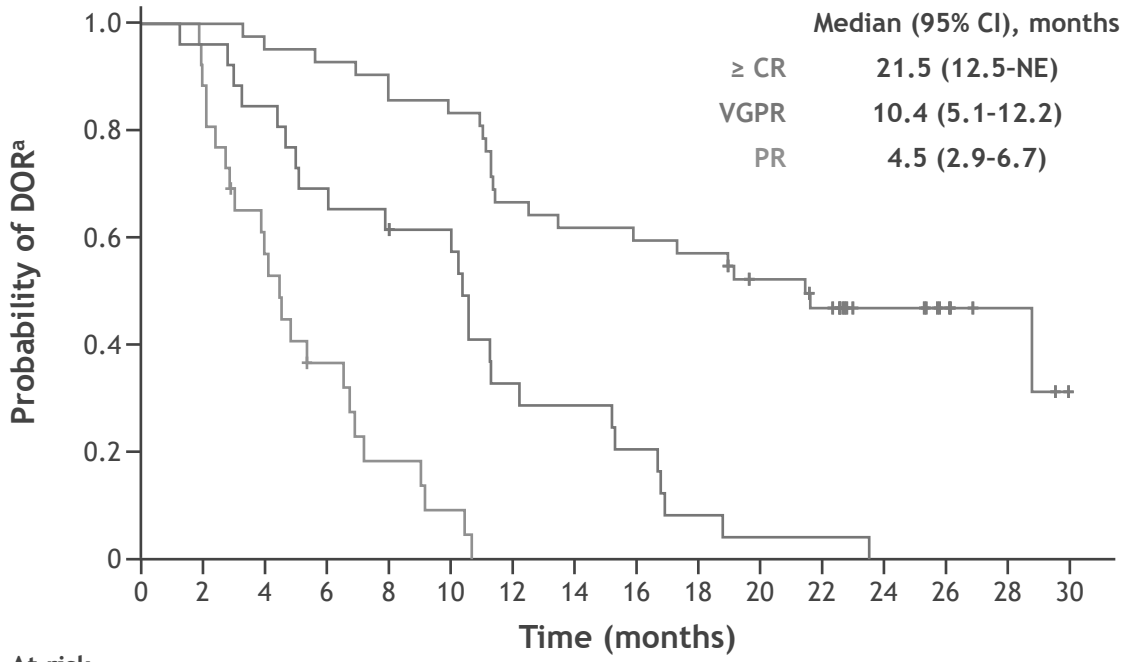
Duration of response

DOR by number of prior lines of therapy and in all ide-cel treated patients



At risk																
3	11	11	9	9	5	5	2	2	2	2	2	2	1	0	0	0
≥ 4	83	79	67	56	51	47	34	31	28	24	19	16	9	6	3	0
All ide-cel treated	94	90	76	65	56	52	36	33	30	26	21	18	10	6	3	0

DOR by response



At risk																
≥ CR	42	42	40	39	36	35	28	26	25	24	20	17	10	6	3	0
VGPR	26	25	22	18	16	15	8	7	5	2	1	1	0	0	0	0
PR	26	23	14	8	4	2	0	0	0	0	0	0	0	0	0	0

- Median DOR was 10.9 months among all ide-cel treated patients and increased with depth of response
- Rate of event-free 24-month DOR was similar in patients who received 3 vs ≥ 4 prior lines of therapy (18.2% vs 21.3%)

[a]DOR was measured from the start of first PR or better and is only applicable for patients with PR or better.

NE, not estimable.

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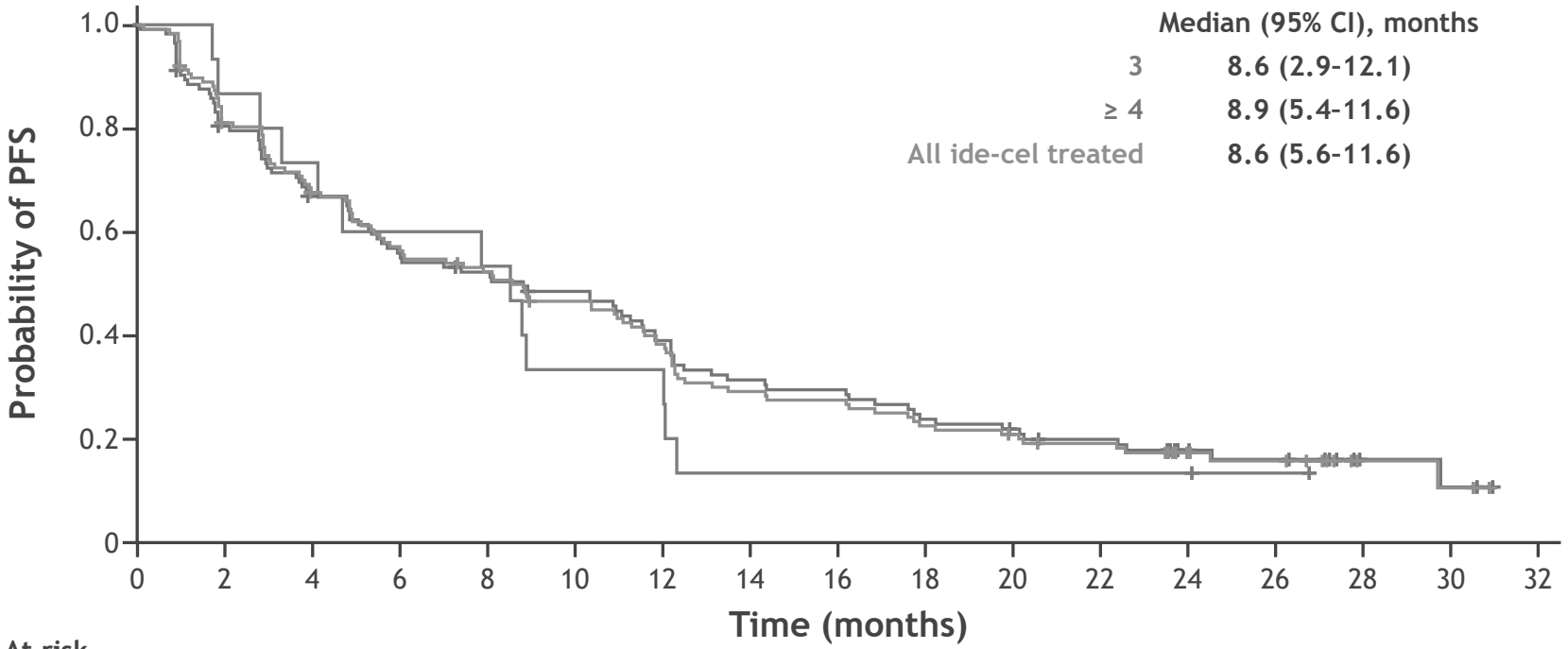
PFS by number of prior lines of therapy and in all ide-cel treated patients



At risk

3	15	13	11	9	8	5	5	2	2	2	2	2	2	1	0	0	0
≥ 4	113	89	73	62	56	51	41	33	31	25	22	19	10	9	3	2	0
All ide-cel treated	128	102	84	71	64	56	46	35	33	27	24	21	12	10	3	2	0

- Median PFS was 8.6 months in all ide-cel treated patients and was similar in patients with 3 and ≥ 4 prior lines of therapy

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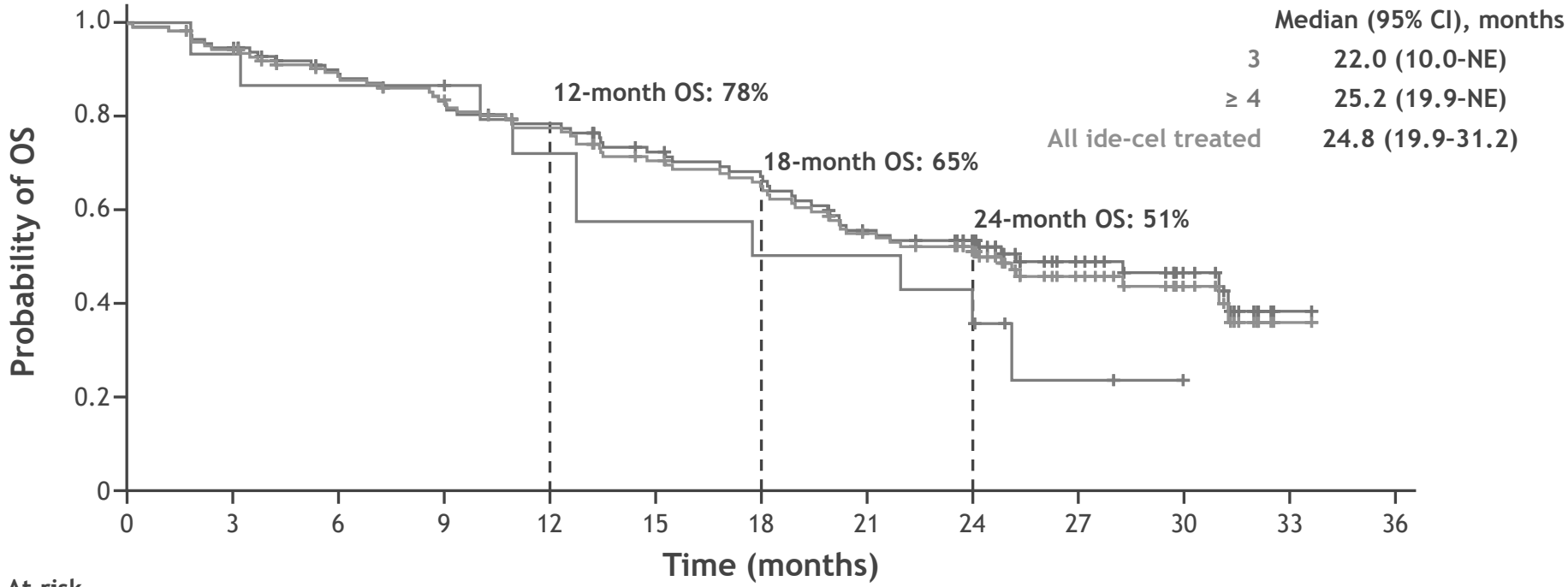
OS by number of prior lines of therapy and in all ide-cel treated patients



At risk

3	15	14	13	13	10	8	7	7	5	2	0	0	0
≥ 4	113	106	94	87	80	71	65	52	43	24	14	1	0
All ide-cel treated	128	120	107	100	90	79	72	59	48	26	14	1	0

- Median OS was 24.8 months among all ide-cel treated patients
- Median OS was 22.0 and 25.2 months in patients with 3 and ≥ 4 prior lines of therapy, respectively

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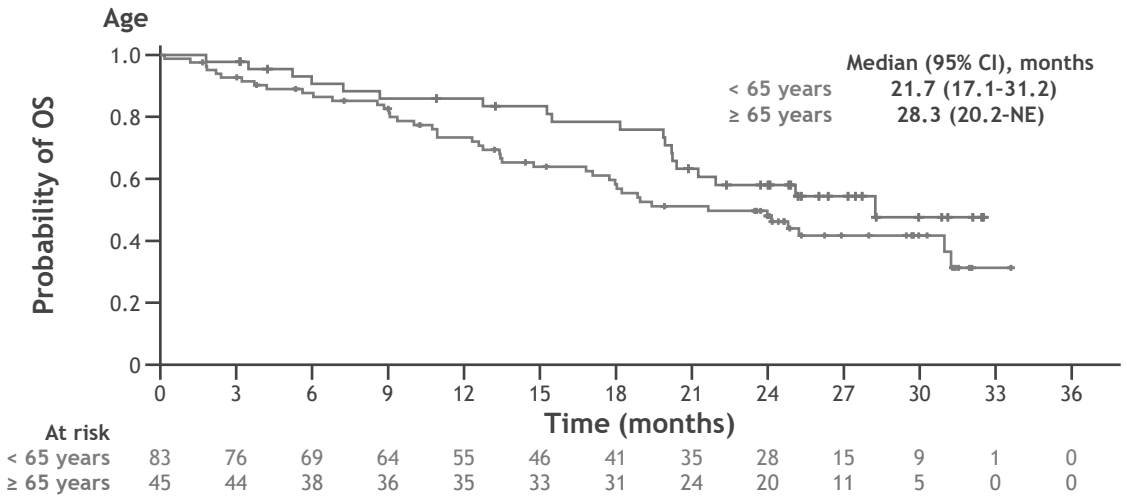
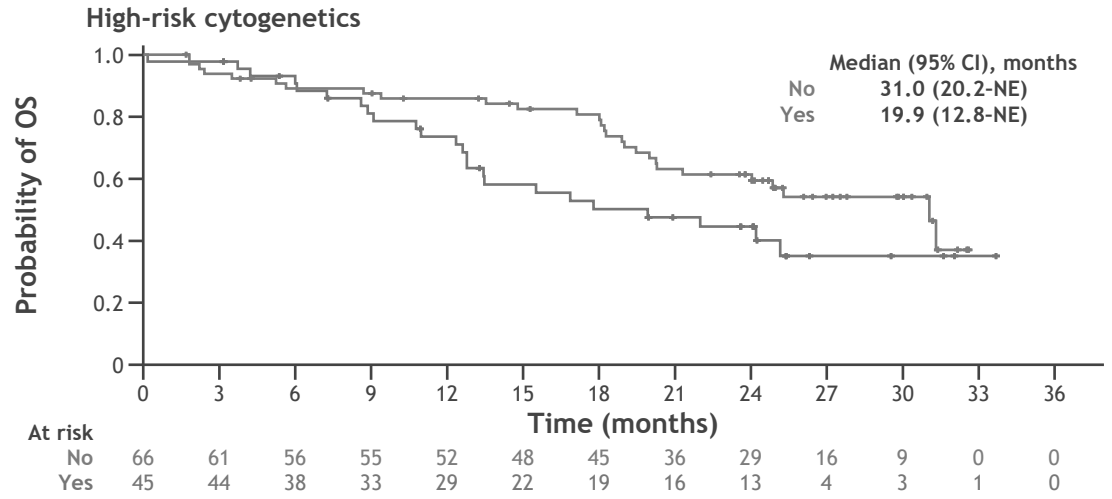
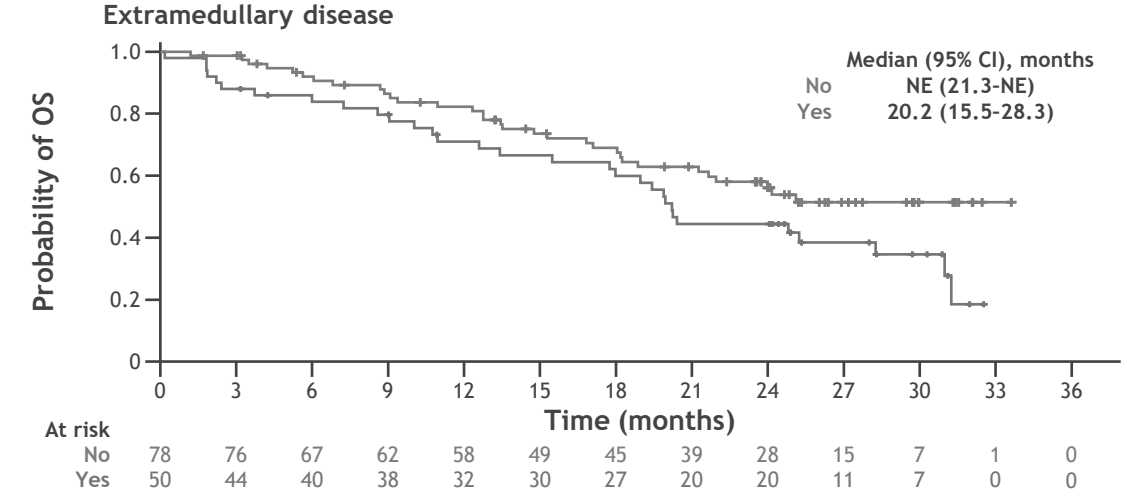
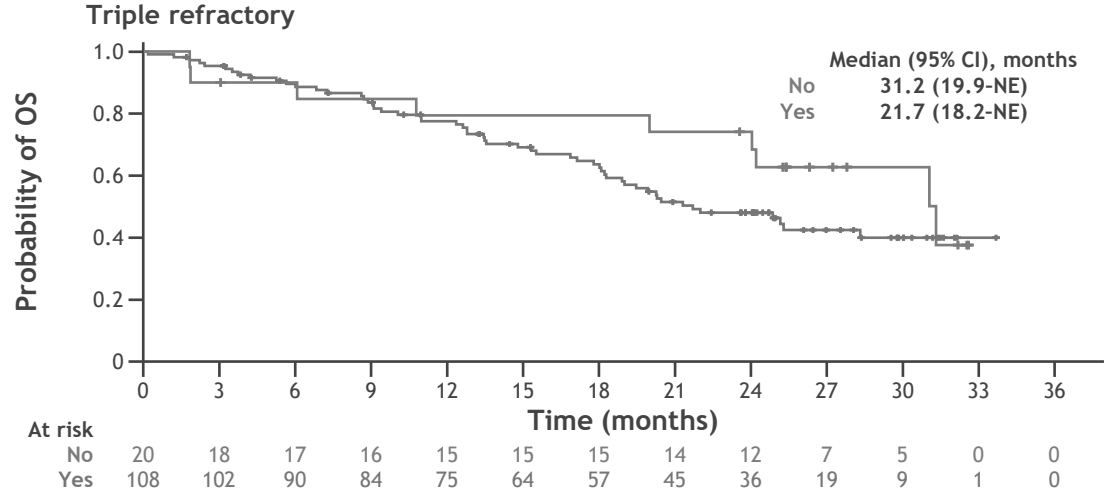
Overall survival in high-risk patient subgroups









- Median OS was > 20 months in several key high-risk subgroups, including age (≥ 65 years), extramedullary disease, and triple-refractory status

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Incidence of CRS and neurotoxicity

	Prior line of therapy		All ide-cel treated (N = 128)
	3 (n = 15)	≥ 4 (n = 113)	
≥ 1 CRS event, n (%)	13 (87)	94 (83)	107 (84)
Maximum grade,[a] n (%)			
1/2	12 (80)	88 (78)	100 (78)
3	1 (7)	4 (4)	5 (4)
4	0	1 (< 1)	1 (< 1)
5	0	1 (< 1)	1 (< 1)
Median onset (range), days	1 (1–2)	1 (1–12)	1 (1–12)
Median duration (range), days	4 (1–63)	6 (2–28)	5 (1–63)
≥ 1 NT event, n (%)	2 (13)	21 (19)	23 (18)
Maximum grade,[b] n (%)			
1	1 (7)	10 (9)	11 (9)
2	0	7 (6)	7 (5)
3	1 (7)	4 (4)	5 (4)[c]
Median onset (range), days	3 (1–5)	2 (1–10)	2 (1–10)
Median duration (range), days	3 (2–5)	3 (1–26)	3 (1–26)

- Incidences of CRS and NT were similar in patients who received 3 or ≥ 4 prior lines of therapy and were mostly low grade

[a]CRS graded according to Lee criteria[1]; [b]NT events were graded according to the NCI CTCAE v4.03; [c]One patient previously graded as maximum grade 1 NT has been changed to grade 3 to align with underlying sign of grade 3 encephalopathy.

CRS, cytokine release syndrome; NT, neurotoxicity. 1. Lee DW, et al. *Blood* 2014;124:188–195.

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Adverse events of interest

Adverse events of interest, n (%)	Prior line of therapy				All ide-cel treated (N = 128)	
	3 (n = 15)		≥ 4 (n = 113)			
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Hematologic						
Neutropenia	14 (93)	13 (87)	103 (91)	101 (89)	117 (91)	114 (89)
Anemia	10 (67)	5 (33)	80 (71)	73 (65)	90 (70)	78 (61)
Thrombocytopenia	11 (73)	8 (53)	71 (63)	59 (52)	82 (64)	67 (52)
Leukopenia	7 (47)	6 (40)	47 (42)	44 (39)	54 (42)	50 (39)
Lymphopenia	7 (47)	7 (47)	29 (26)	28 (25)	36 (28)	35 (27)
Nonhematologic						
Infections	12 (80)	2 (13)	78 (69)	32 (28)	90 (70)	34 (27)
SPM[a]	0	0	9 (8)	3 (3)	9 (7)	3 (2)
HLH/MAS	1 (7)	1 (7)	3 (3)	1 (1)	4 (3)	2 (2)

- With longer follow-up, similar rates of infections and SPMs, as well as no unexpected gene therapy-related toxicities were observed
- Median time to recovery of grade ≥ 3 neutropenia and thrombocytopenia was 2 months for 3 and ≥ 4 prior lines of therapy subgroups and in all treated patients

[a]SPM included basal cell carcinoma (n = 5), anal cancer, lung adenocarcinoma, myelodysplastic syndromes, and squamous cell carcinoma (n = 1, each). Basal cell carcinoma (n = 1) and lung adenocarcinoma (n = 1) were new events observed since the earlier data cutoff date of January 14, 2020.

HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; SPM, second primary malignancy.

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Conclusions

- Long term results from the KarMMa trial continue to demonstrate frequent, deep, and durable responses in heavily pretreated patients with RRMM
  - ORR, CRR, DOR, and PFS were consistent with previous reports[1,2] and patients received similar benefit regardless of number of prior lines of therapy
  - With longer follow-up, efficacy remains greatest with the highest target dose (450 × 10^6 CAR+ T cells)
  - Median OS was 24.8 months in all ide-cel treated patients and > 20 months in several high-risk subgroups
- The safety profile of ide-cel was consistent with previous reports across all groups
  - The frequencies of CRS and NT remain consistent with previous reports[1,2]
  - Similar rates of infections and SPMs, and no unexpected gene therapy-related toxicities were observed with longer follow-up
- The favorable benefit-risk profile of ide-cel regardless of the number of prior lines of therapy supports its role as a treatment option for heavily pretreated RRMM

Ide-cel is being explored in ongoing clinical trials: KarMMa-2 KarMMa-4 KarMMa-3 KarMMa-7

1. Munshi NC, et al. *N Engl J Med* 2021;384:705–716; 2. Munshi NC, et al. Poster presentation at the 2020 ASCO Annual Meeting; May 29-31, 2020; Virtual. Abstract 8503.

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