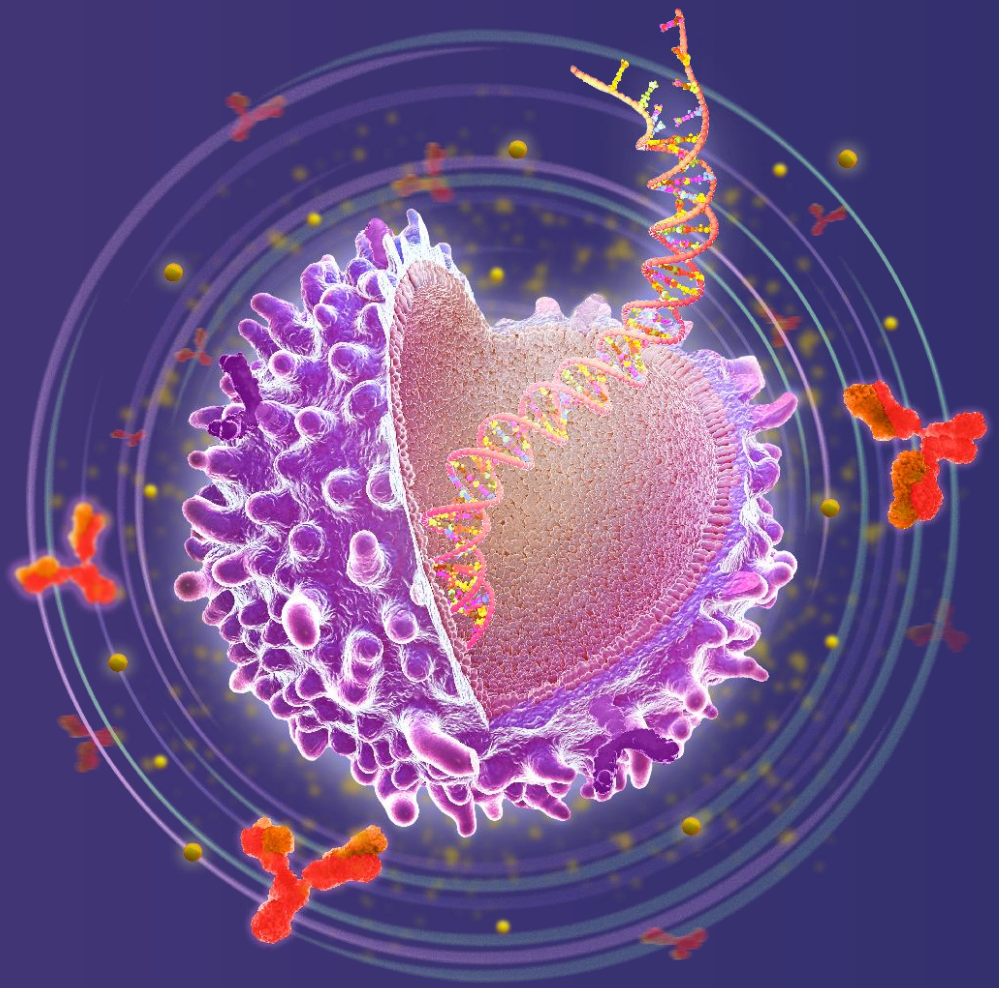
The ins and outs of CAR T cells in the real world

Biomarkers and patient eligibility for CAR T-cell therapies in multiple myeloma and DLBCL

Presented by: Shaji Kumar

Kieron Dunleavy



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Disclosures

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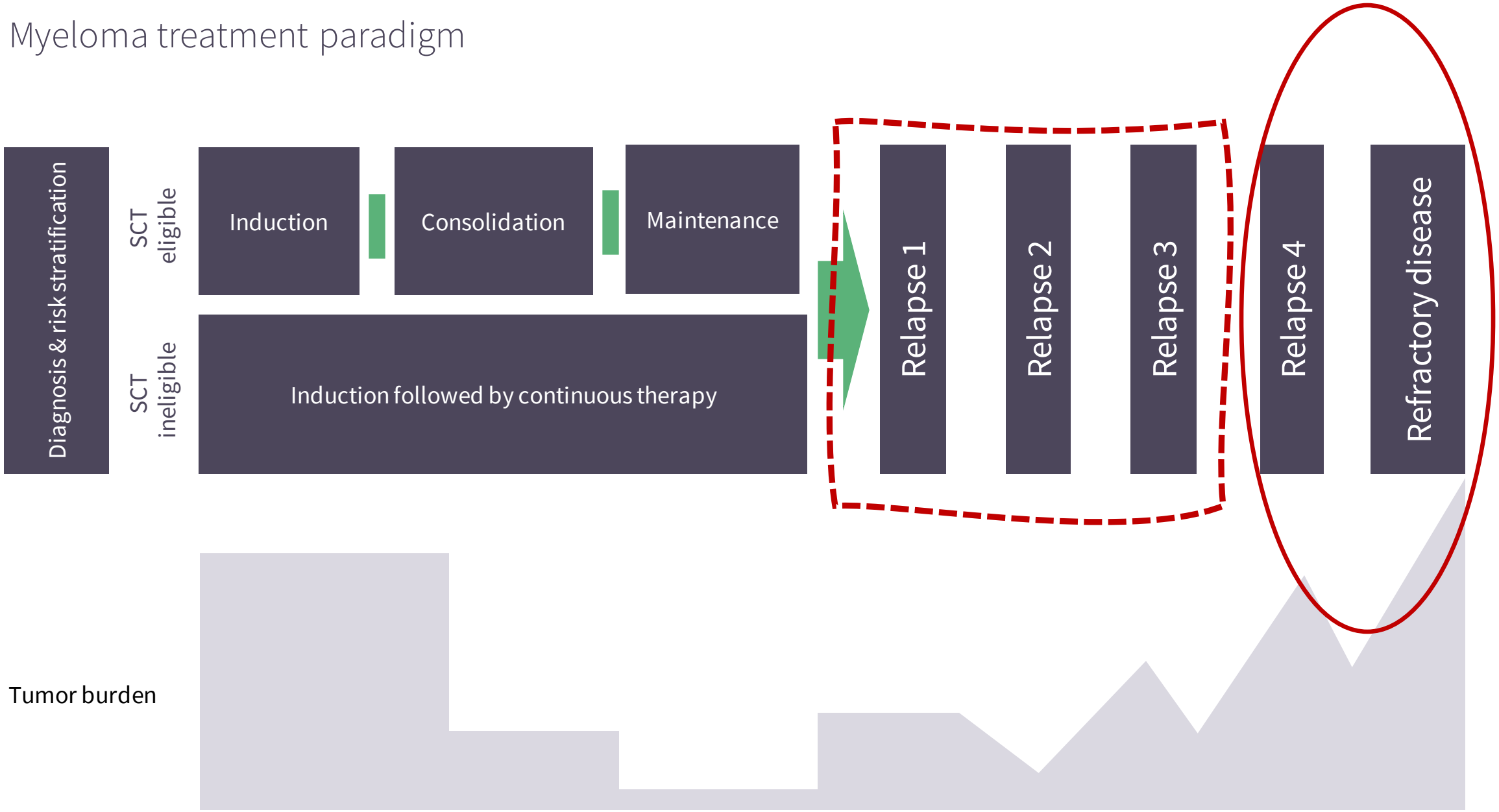
Which of the following features have not been associated with shortened duration of response with CAR-T in multiple myeloma?

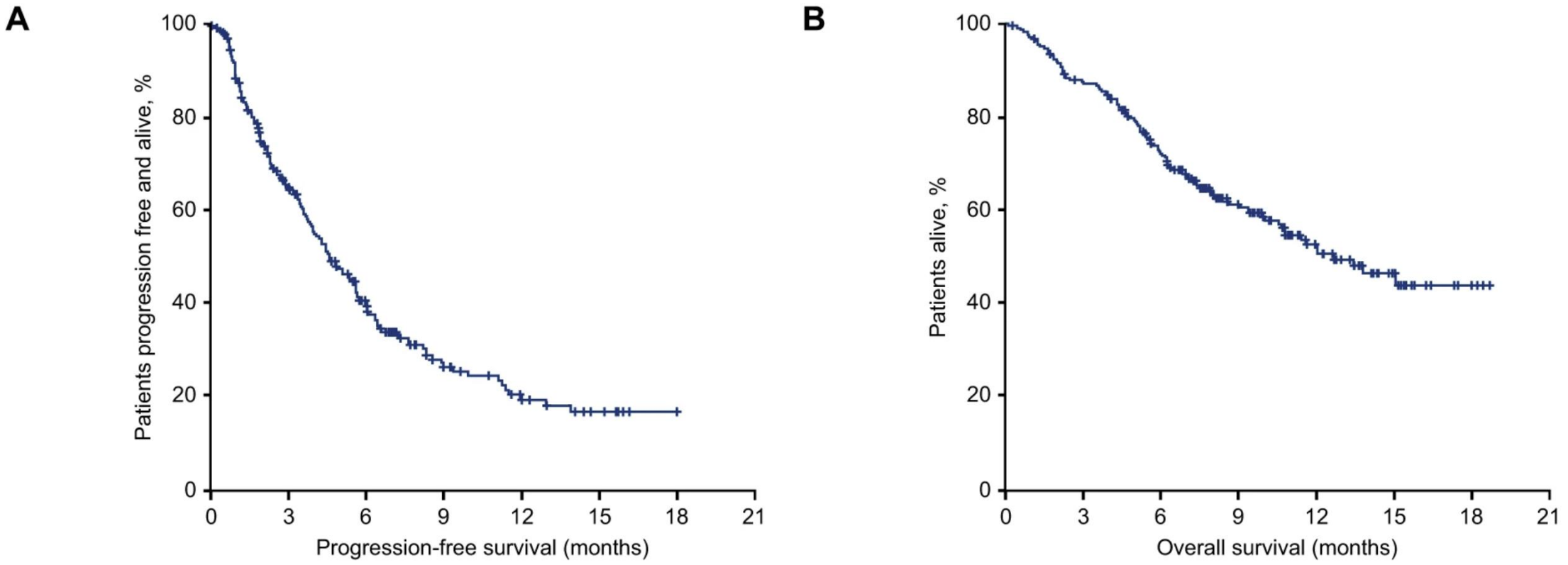
A. Age
B. Presence of extramedullary disease
C. High risk cytogenetics
D. Triple class refractory status

Myeloma treatment paradigm



SCT, stem cell transplant.
Shaji Kumar. Personal communication; Jun 9, 2023

Poor outcomes in triple class refractory patients – LocoMMotion[1]



1. Mateos MV, et al. Leukemia. 2022;36(5):1371-1376.

Approved CAR T-cell products for multiple myeloma[1]

Feature	Idecabtagene vicleucel	Ciltacabtagene autoleucel
Design	Second generation	
Ectodomain	One anti-BCMA	Two anti-BCMA
Endo-domain	CDζ,-4-1BB	
Pivotal study	**KarMMa** NCT03361748	**CARTITUDE-1** NCT03548207
FDA approval date	Mar 26, 2021	Feb 28, 2022
EMA approval date	Aug 18, 2021	May 25, 2022
Therapy class	BCMA-directed CAR T cell	
Indications	Triple-class exposed R/R MM	
Recommended dose	300–460 × 10^6 CAR^+ T cells/kg	0.5–1.0 × 10^6 CAR^+ T cells/kg

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; MM, multiple myeloma; R/R, relapsed/refractory.

1. Chekol Abebe E, et al. *Front Immunol.* 2022;13:991092.

Efficacy

Feature	KarMMa[1] NCT03361748 Idecabtagene vicleucel	CARTITUDE-1[2,3] NCT03548207 Ciltacabtagene autoleucel
Number of patients	127	97
ORR	73%	97.9%
≥CR	33.1%	82.5%
≥VGPR	57.9%	94.9%
MRD negativity at 10^{-5}	26%	58%
PFS	8.6 months	34.9 months
OS	24.8 months	NR (62.9% survival at 36 months)
DoR	10.9 months	33.9 months

CR, complete response; DoR, duration of response; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; VGPR, very good partial response.

1. Chekol Abebe E, et al. *Front Immunol*. 2022;13:991092. **2.** Martin T, et al. *J Clin* Oncol. 2023;41(6):1265-1274. **3.** Munshi N, et al. EHA2023. Oral abstract #S202.

Safety

Feature	KarMMa[1] NCT03361748 Idecabtagene vicleucel	CARTITUDE-1[2,3] NCT03548207 Ciltacabtagene autoleucel
Any grade CRS	84%	94.8%
Grade≥3 CRS	5%	5.1%
Any grade ICANS	18%	21.6%
Grade≥3 ICANS	3%	12.3%
Deaths	44 patients (34%) PD, 27 AE, 9 Other, 8	35 patients (36%) PD, 17 Related, 6 Unrelated, 12

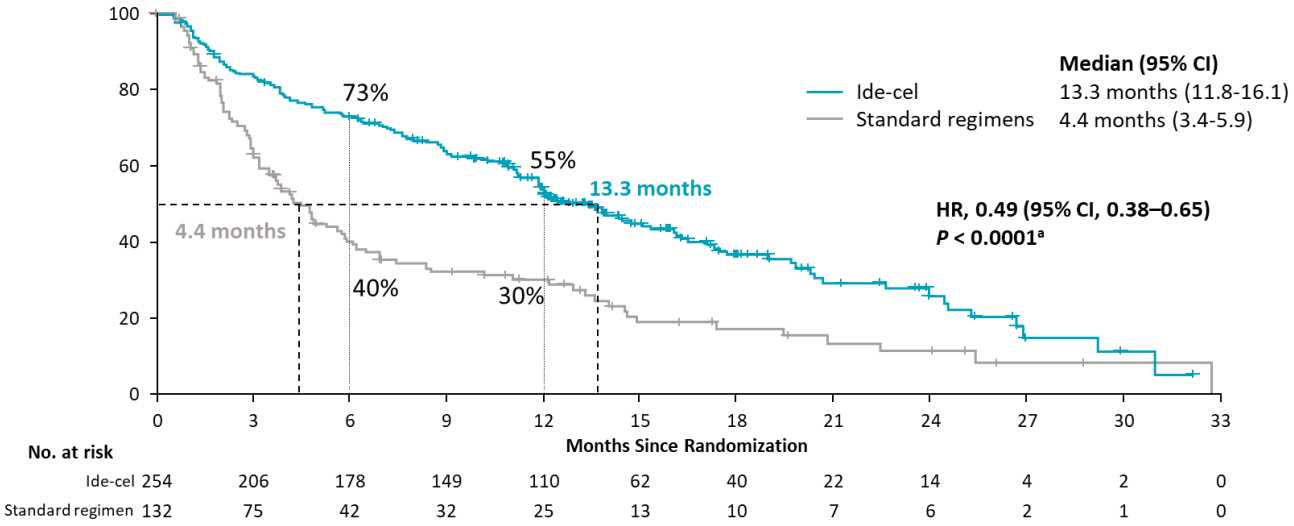
AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; PD, progressive disease.

1. Chekol Abebe E, et al. *Front Immunol.* 2022;13:991092. **2.** Martin T, et al. *J Clin* Oncol. 2023;41(6):1265-1274. **3.** Munshi N, et al. EHA2023. Oral abstract #S202.

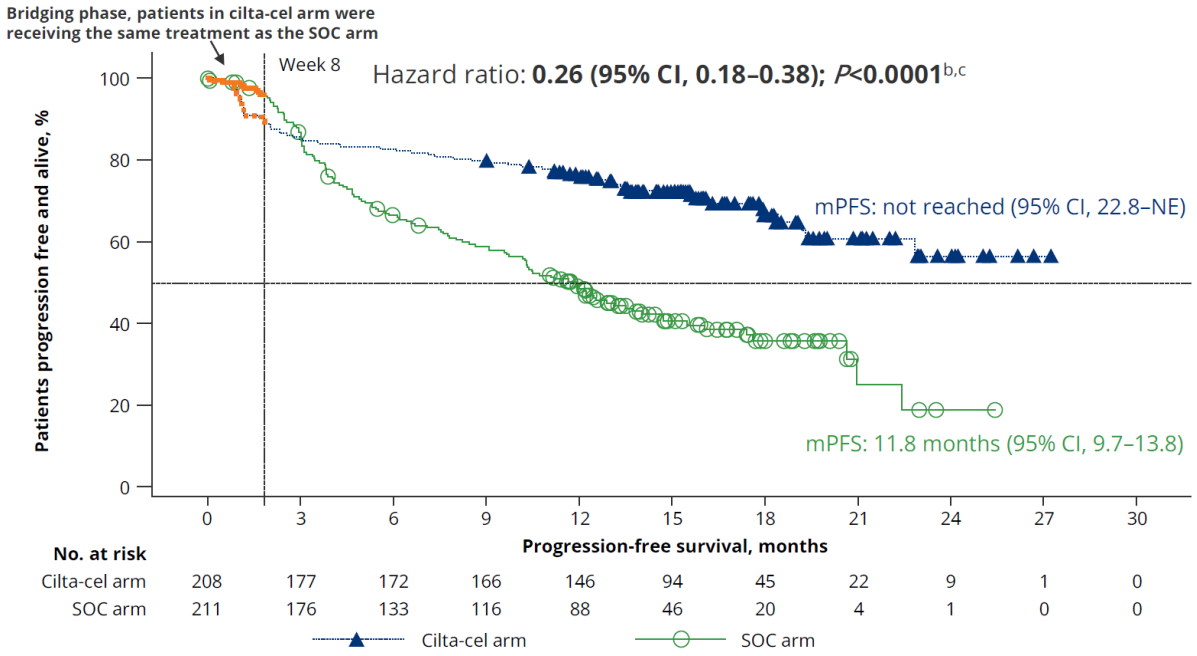
CAR-T in earlier lines of treatment: Ide-cel or cilta-cel vs SOC (KarMMa-3[1] and CARTITUDE-4[2])

Progression-free survival

KarMMa-3[1]
Ide-cel vs SOC



CARTITUDE-4[2]
Cilta-cel vs SOC



CI, confidence interval; HR, hazard ratio; ide-cel, idecabtagene vilecleucel; mo, month; SOC, standard of care.

1. Rodriguez-Otero P. 5th European CAR T-Cell Meeting. Oral abstract #BA02-7. Feb 10, 2023; Rotterdam, NL. **2.** Dhakal B. 2023 ASCO Annual Meeting. Oral abstract #LBA106. Jun 5, 2023; Chicago, US.

Most common challenges when considering CAR T-cell therapy in MM

- Age
  - Increased toxicity with older patients
- Comorbidities
  - Increases potential AE profile
- Rapid progression
  - Inability to wait for product manufacture
- Prior BCMA-directed therapy
  - Potential target loss
- Extramedullary disease, high-risk MM
  - Reduced durability of response
- High tumor burden
  - Increased risk of CRS, ICANS

AE, adverse event; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; MM, multiple myeloma.
Shaji Kumar. Personal communication; Jun 9, 2023

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AE, adverse event; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; MM, multiple myeloma.
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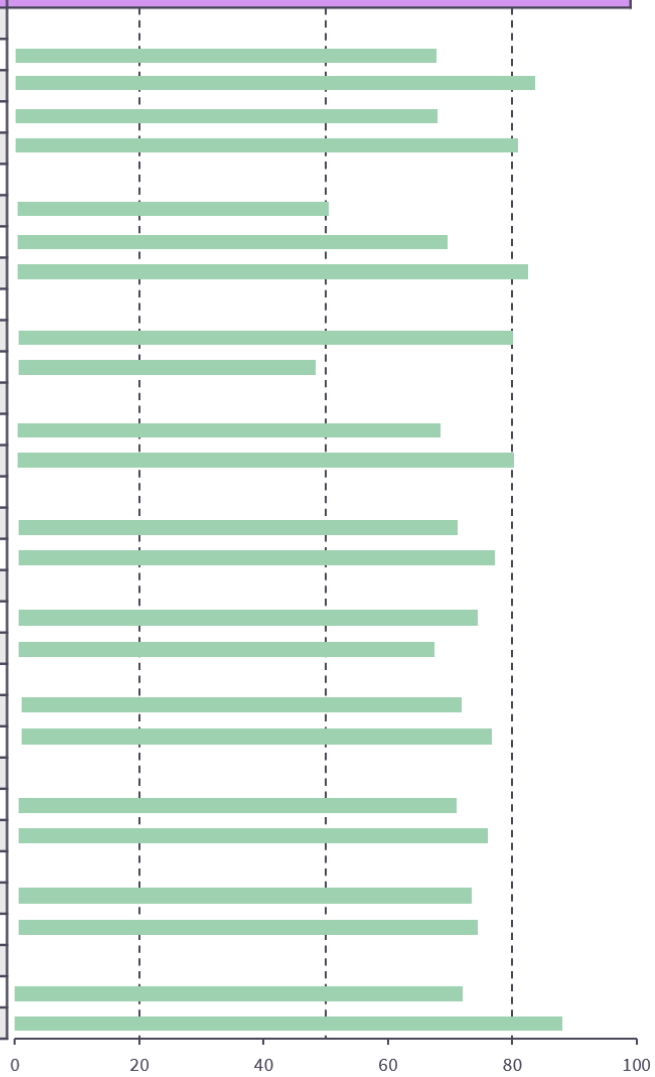
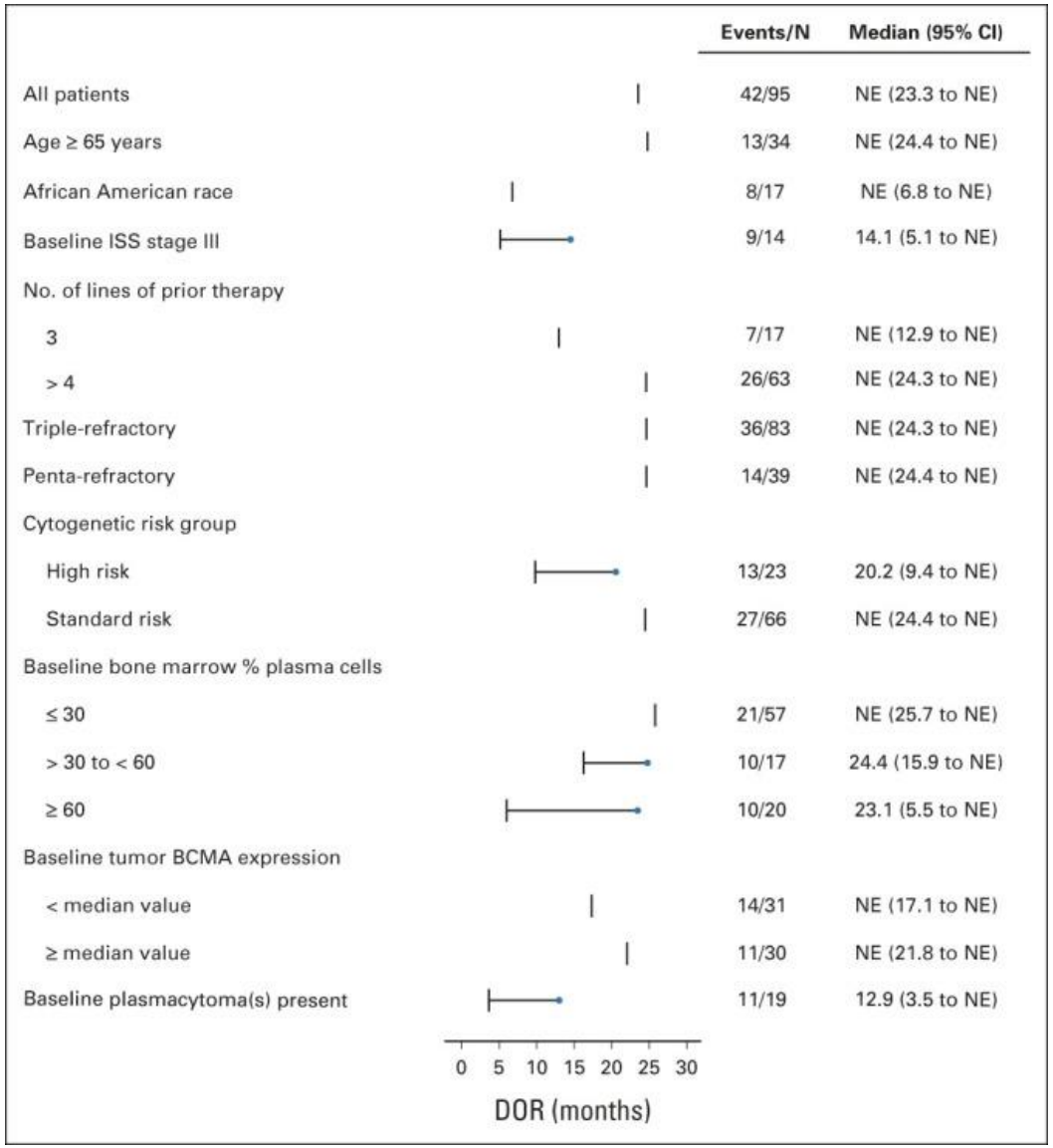
Factors affecting outcomes

Subgroup	Patients, n
Age, years	
<65	83
≥65	45
Male	76
Female	52
Ide-cel target dose	
150 × 10^6 CAR$^+$ T cells	4
300 × 10^6 CAR$^+$ T cells	70
450 × 10^6 CAR$^+$ T cells	54
R-ISS stage at enrolment	
I or II	104
III	21
High risk cytogenetic abnormality	
Yes	45
No	66
Tumor burden at baseline	
≥50% BMPCs	65
<50% BMPCs	57
Tumor BCMA expression	
≥50%	109
<50%	3
Extramedullary disease	
Yes	50
No	78
Triple-refractory disease	
Yes	108
No	20
Penta-refractory disease	
Yes	33
No	95
Bridging therapy	
Yes	112
No	16



Adapted from Munshi NC, et al. *N Engl J Med* 2021; 384:705-716.



Martin T, et al. *J Clin Oncol*. 2023;41(6):1265-1274.

BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; CAR, chimeric antigen receptor; CI, confidence interval; DOR, duration of response; ide-cel, idecabtagene vicleuce; ORR, overall response rate; R-ISS, revised International Staging System.

Experience with CAR T cells in patients who received prior BCMA-directed therapy

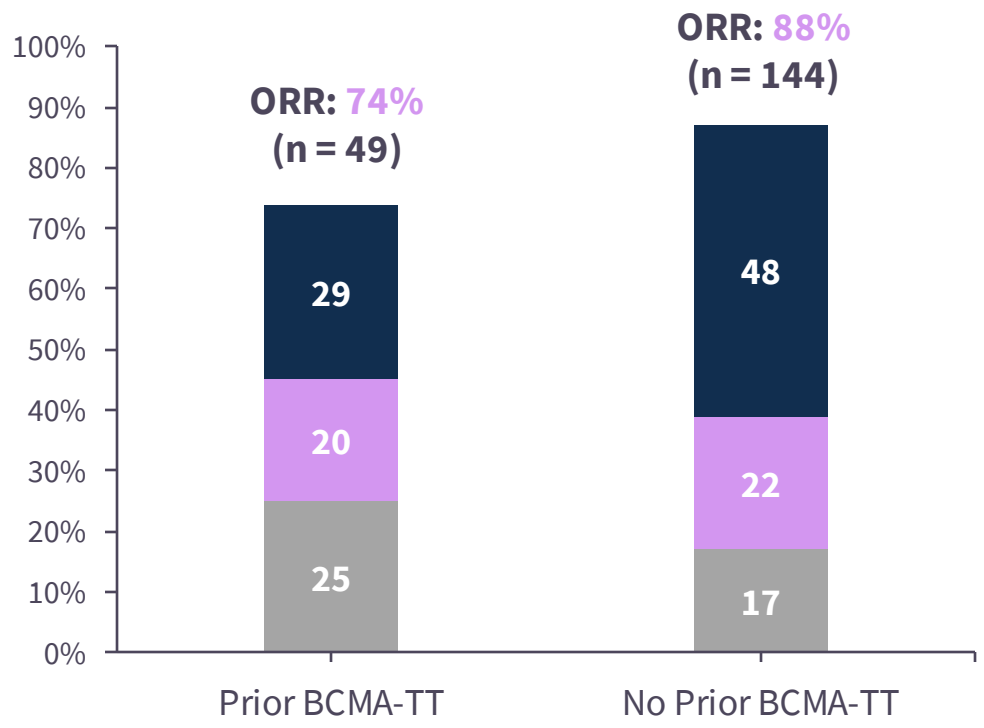
Idecabtagene vicleucel in the real world: Baseline characteristics

Characteristic*	SOC ide-cel (N = 159)[1]	KarMMa (N = 128)[2]
Median age (range), years	64 (36–83)	61 (33–78)
Male, n (%)	91 (57)	76 (59)
Extramedullary disease, n (%)	76 (48)	50 (39)
ECOG performance status, n (%)		
0–1	127 (81)	125 (98)
2–4	29 (19)	3 (2)
R-ISS, n (%)		
I–II	93 (72)	104 (81)
III	35 (27)	21 (16)
High-risk cytogenetics, n (%)		
Any high-risk cytogenetics	49 (35)	45 (35)
del (17p)	32 (22)	23 (18)
t(4;14)	19 (14)	23 (18)
t(14;16)	6 (4)	6 (5)
Bridging therapy/ORR, n (%)	123/13 (77/11)	112 (88)
Prior BCMA therapy, n (%)	33 (21)	0
Median prior lines of therapy (range), n	7 (4–18)	6 (3–16)
Autologous HCT, n (%)	134 (84)	120 (94)
Refractory status, n (%)		
Triple-refractory	134 (84)	108 (84)
Penta-refractory	70 (44)	33 (26)

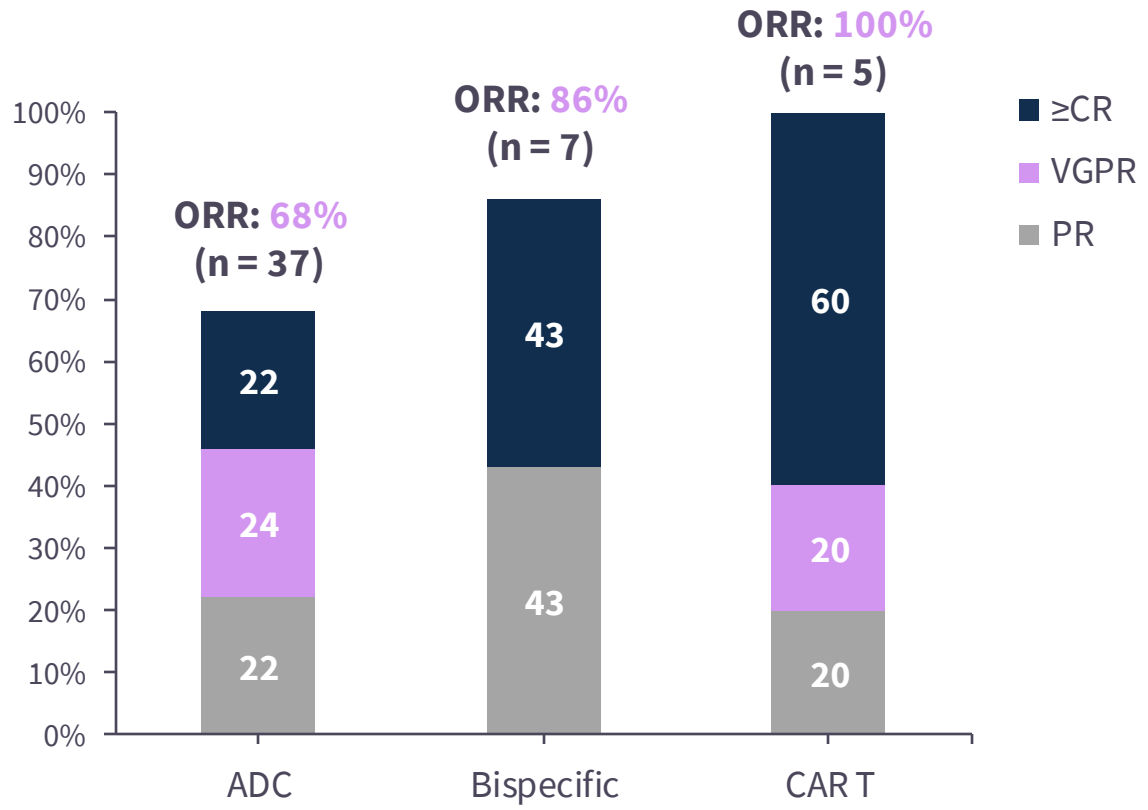
BCMA, B-cell maturation antigen; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic stem cell transplant; ide-cel, idecabtagene vicleucel; ORR, overall response rate; R-ISS, revised International Staging System.
*Patients with unknown ECOG performance status, R-ISS, and high-risk cytogenetics are not included in the table.
1. Hansen D, et al. *J Clin Oncol.* 2023;41(11);2087-2097. **2.** Munshi, et al. *NEJM.* 2021;384(8):705-716.

Efficacy outcomes by prior BCMA therapy (N = 49)[1,2]

ORR by any vs no BCMA



ORR by type of prior BCMA

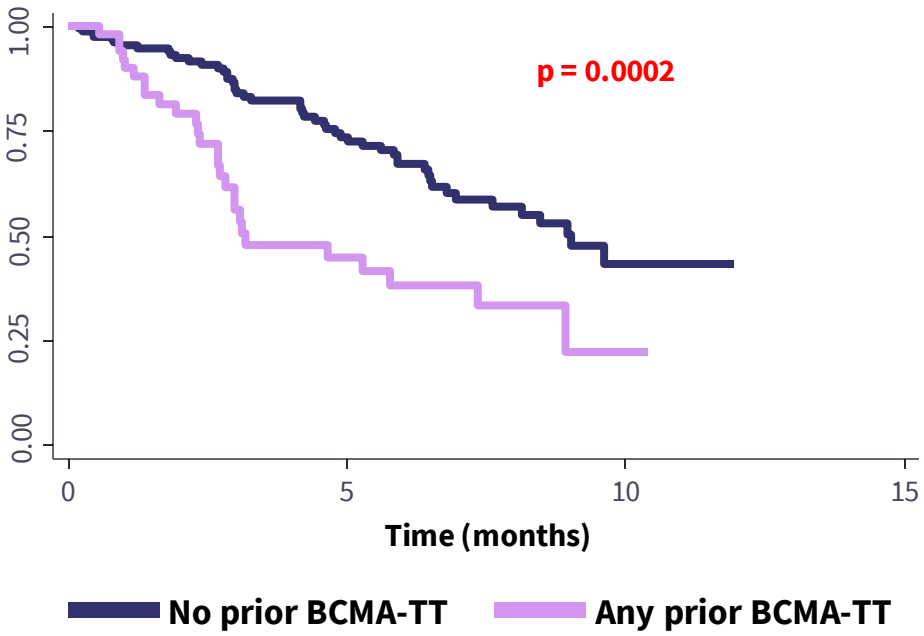


ADC, antibody–drug conjugate; BCMA-TT, B-cell maturation antigen-targeted therapy; CAR T, chimeric antigen receptor T-cell therapy; CR, complete response; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

1. Ferreri CJ. Oral abstract #766. 64th ASH Annual Meeting & Exposition. Dec 12, 2022; New Orleans, US. **2.** Doris Hansen. Personal communication; Jun 9, 2023.

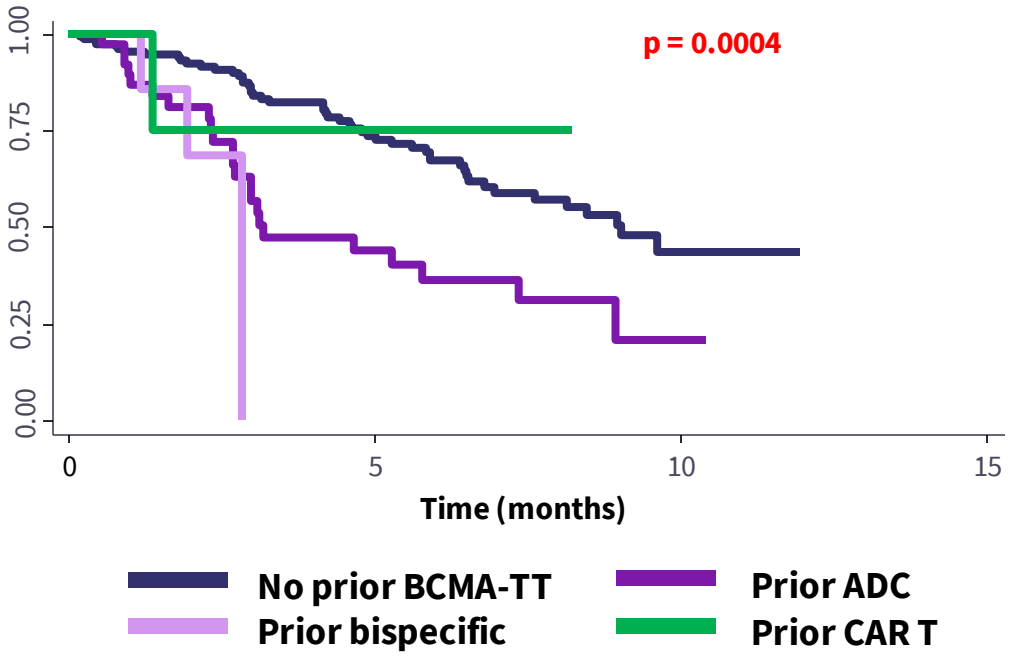
PFS outcomes by prior BCMA therapy[1,2]

PFS by any prior BCMA therapy



Median PFS: 9.0 months
Median PFS: 3.2 months

PFS by type of BCMA therapy



Median PFS: 9.03 months **Median PFS: 2.83 months**
Median PFS: 3.19 months **Median PFS: Not reached**

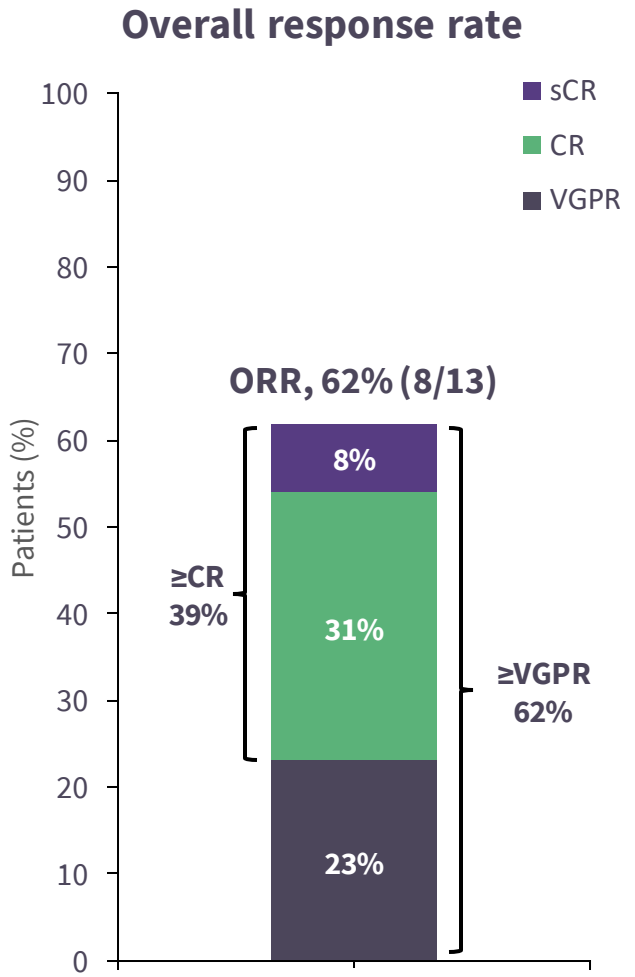
ADC, antibody-drug conjugate; BCMA-TT, B-cell maturation antigen-targeted therapy; CART, chimeric antigen receptor T-cell therapy; PFS, progression-free survival.

1. Ferreri CJ. Oral abstract #766. 64th ASH Annual Meeting & Exposition. Dec 12, 2022; New Orleans, US. **2.** Doris Hansen. Personal communication; Jun 9, 2023.

Efficacy of cilta-cel in patients treated with prior ADC [1]

CARTITUDE-2 (NCT04133636) Cohort C

- Overall, 5 of 7 patients in the MRD-evaluable subset* were MRD-negative at the 10^{-5} threshold
  - The 5 MRD-negative patients achieved best responses of sCR (n = 1), CR (n = 1), VGPR (n = 2), and PD (n = 1 [due to increased plasmacytoma size])
- ORR = 61.5% (95% CI, 31.6–86.1)
- Median time to first response = 1 month (range, 0.9–5.1 months)
  - Median time to best response = 2.6 months (range, 0.9–9.9 months)

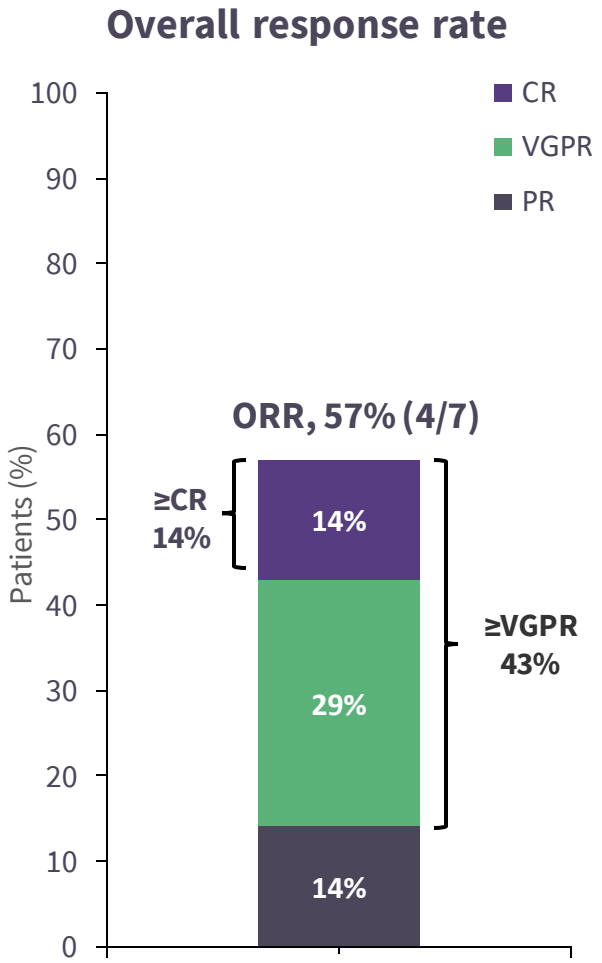


ADC, antibody–drug conjugate; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PD, progressive disease ; sCR, stringent CR; VGPR, very good partial response.
*Evaluable samples are those that pass calibration and quality control and include sufficient cells for evaluation at 10^{-5} threshold.
1. Rodriguez-Otero. Immunotherapy and bispecifics: a real-life case discussion. 9th COMy World Congress; May 14, 2023; Virtual.

Efficacy of cilta-cel in patients with prior BsAb[1]

CARTITUDE-2 (NCT04133636) Cohort C

- 2 of 3 patients in the MRD-evaluable subset* were MRD-negative at the 10^{-5} threshold
  - The 2 MRD-negative patients achieved CR and VGPR
- ORR = 57% (95% CI, 18.4–90.1)
  - 2 patients died before confirmed response
- Median time to first response = 0.9 months (range, 0.9–6.0 months)
  - Median time to best response = 1.4 months (range, 0.9–7.0 months)



BsAb, bispecific antibody; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; VGPR, very good partial response.
*Evaluable samples are those that pass calibration and quality control and include sufficient cells for evaluation at 10^{-5} threshold.
1. Rodriguez-Otero. Immunotherapy and bispecifics: a real-life case discussion. 9th COMy World Congress; May 14, 2023; Virtual.

Current limitations[1]

Patient selection
- Stable or progressive disease after CT
- Relapsed or ineligible for ASCT
- Good medical condition

Production platforms
- Long-term vs short-term genetic modification
- Random vs site-specific transgene integration
- *Ex vivo* vs *in vivo* transduction
- Off-the-shelf CAR T cells

Toxicity
CRS
- Most prevalent adverse effect
- Elevated inflammatory cytokines due to immune activation

On-target off-tumor recognition
- Shared target antigen expression on malignant and healthy tissue
- Severity from manageable to severe toxicity (death)

Neurotoxicity
- Reversible in most cases and pathophysiology remains unknown

Relapse

ALL adults **21–45%**
Park, *et al*. 2018; Turtle, *et al*. 2016.

ALL children **20–67%**
Maude, *et al*. 2014 and 2018; Fry, *et al*. 2018.

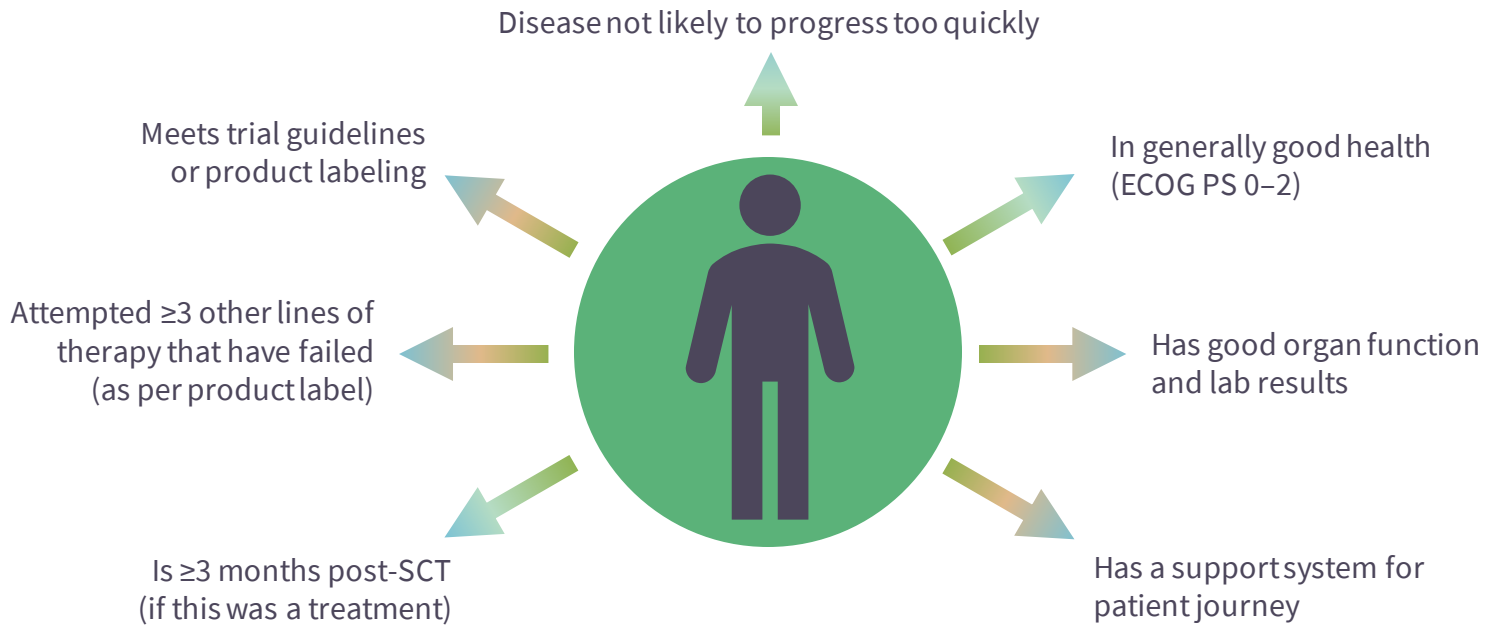
CLL **0–35%**
Porter, *et al*. 2015; Turtle, *et al*. 2017.

DLBCL **0–11%**
Turtle, *et al*. 2016. Schuster, *et al*. 2017

ALL, acute lymphoblastic leukemia; ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; CT, chemotherapy; DLBCL, diffuse large B-cell lymphoma.

1. Lesch S, et al. *Semin Cancer Biol*. 2020;65:80-90.

Eligibility for CAR T-cell therapy?



In general, more patients would be eligible for CAR T-cell therapy compared to stem cell transplantation

CAR, chimeric antigen receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; SCT, stem cell transplant

1. Dave H, et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569. **2.** Beaupierre A, et al. *Clin J Oncol Nursing*. 2019;23(2):27-34. **3.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141. **4.** Cohen AD. American Society of Clinical Oncology Educational Book 38 (May 23, 2018) e6-e15.

Logistical considerations[1,2]

How far is the closest treatment center and what CAR-T products do they offer?

Can the patient travel or remain close to the center for extended periods of time (~4 weeks)?

Does the patient have the ability to pay for treatment either through insurance coverage or other financing options?

When is the optimal time to harvest cells for best results?

CAR, chimeric antigen receptor.

1. Dave H, et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569. **2.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141. **3.** Beaupierre A, et al. *Clin J Oncol Nursing*. 2019;23(2):27-34.

- Sequencing same-target agents
- Risk-adapted therapy
- Use of maintenance
- Reinfusion

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