Real-world patient cases

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

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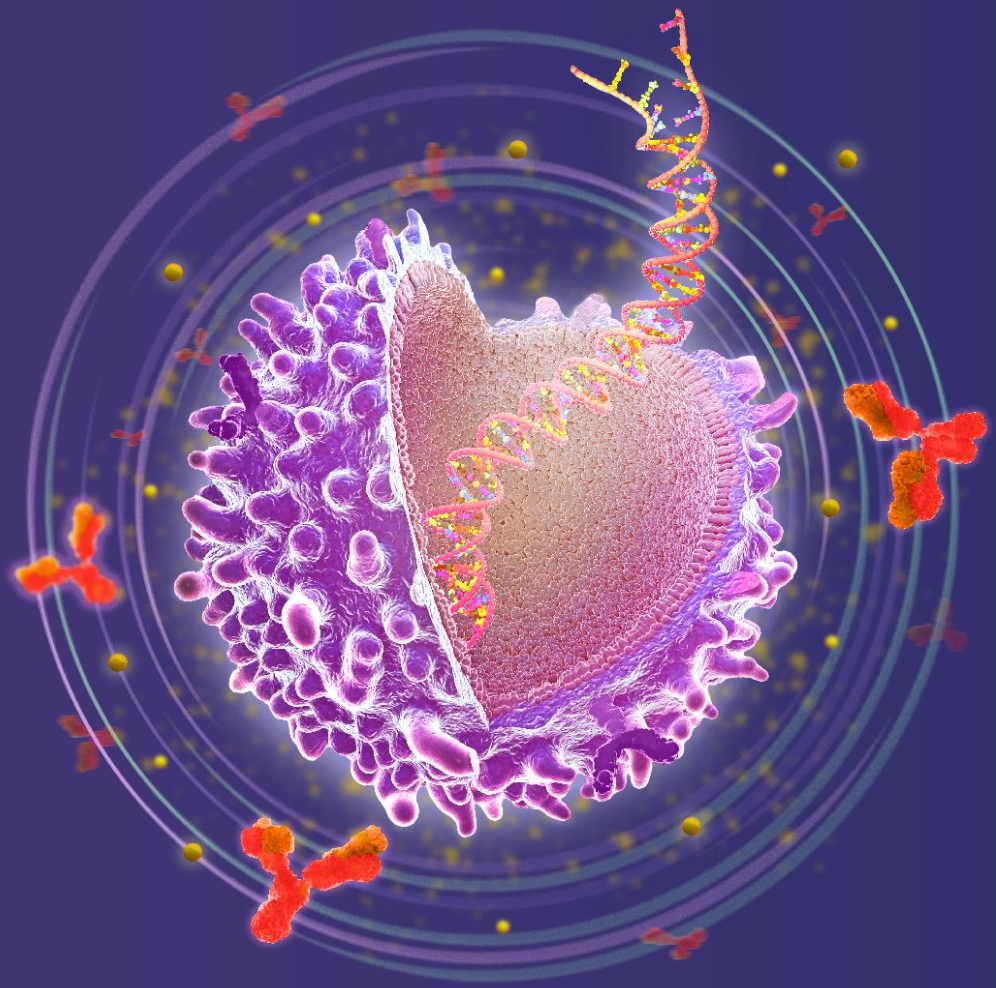

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Disclosures

- The following declarations are made for the last 3 years and the following 12 months (where arrangements have already been made):
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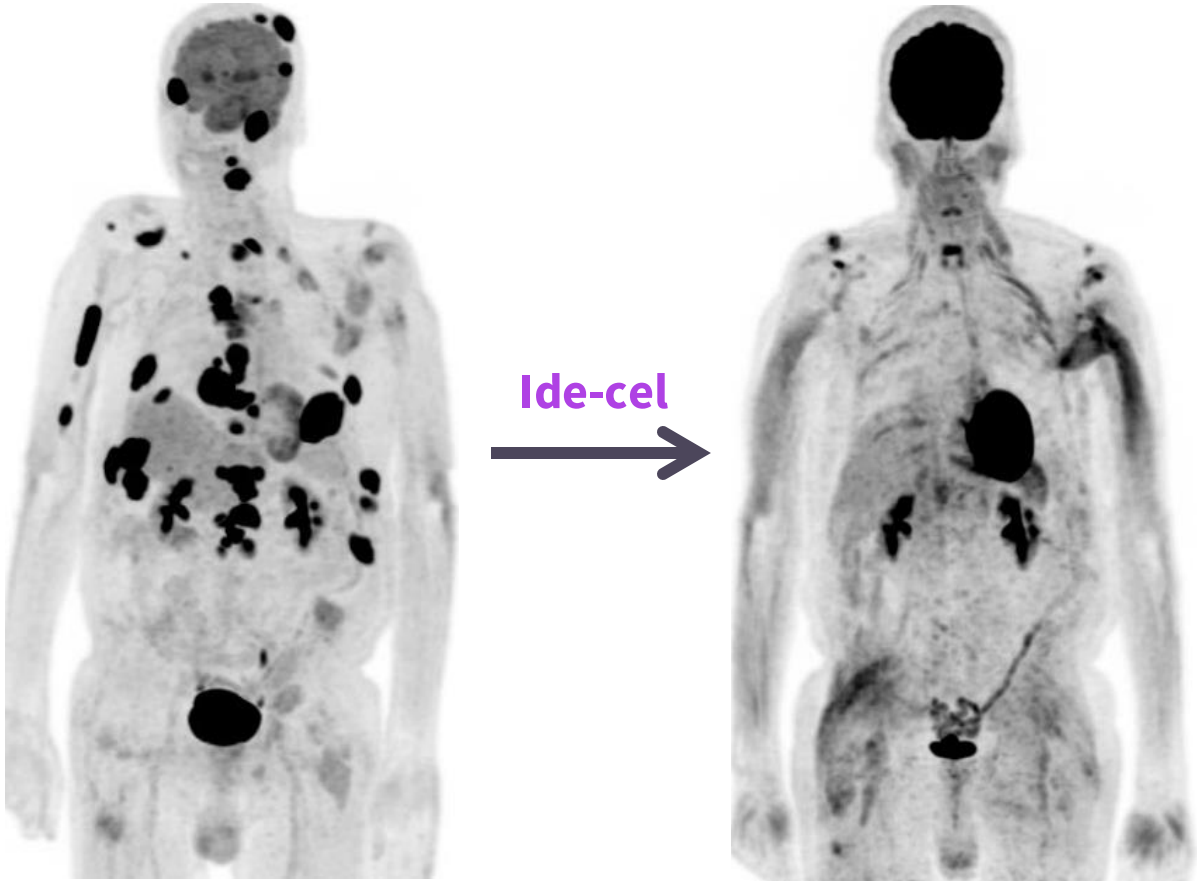
Can a patient older than 70 years be safely treated with CAR T-cell therapy?

1. Yes
2. Yes, with special measures
3. No
4. I’m not sure

Case #1 Subject with multiple comorbidities and prior BCMA

- 78-year-old Caucasian male with R-ISS II, standard risk, IgG lambda multiple myeloma s/p ide-cel 11/23/21 with 324 × 106 CAR T cells.
- Prior therapies: 8
  - Td → HCT
  - Rd
  - KPd
  - Ixa-Pd
  - Dara-Vd
  - Isa-Pd
  - Cyclo-Pd
  - Belantamab mafodotin
- Comorbidities
  - ECOG performance status 3
  - CAD/NSTEMI
  - EF: 40–45%
  - IDDM II

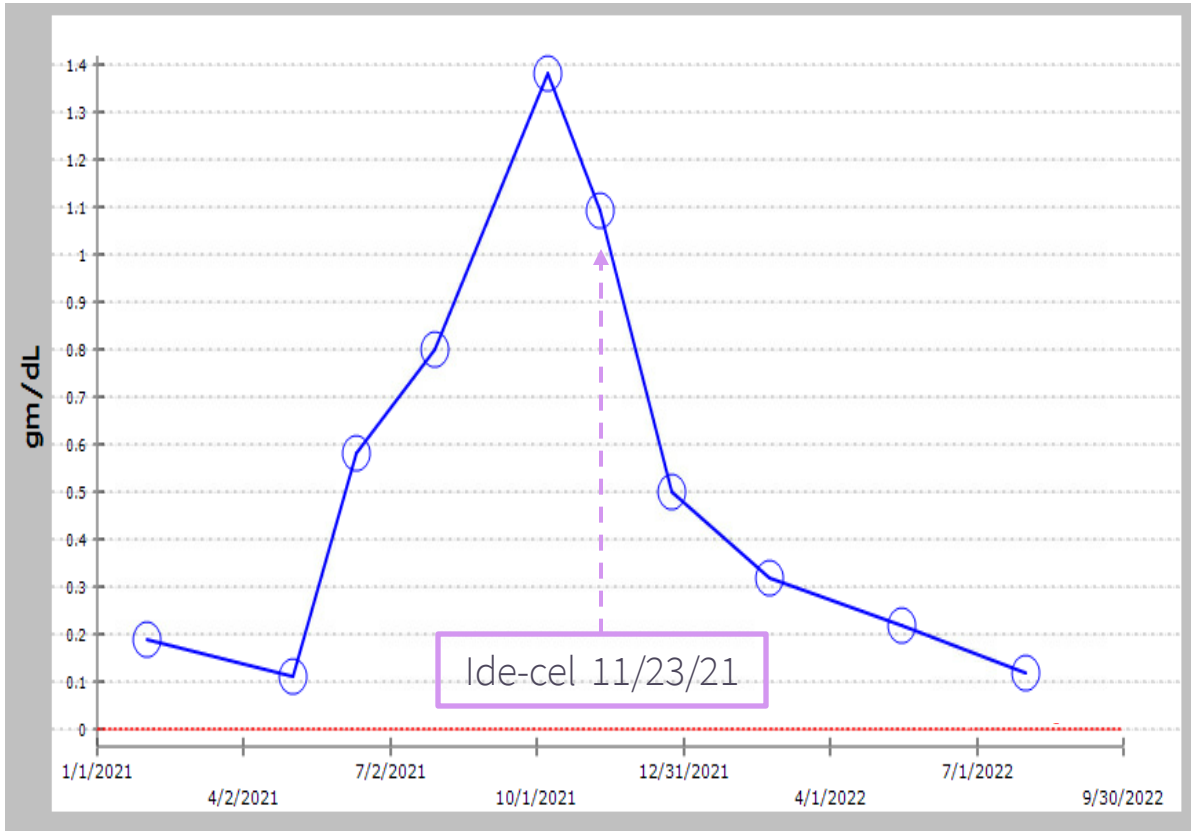


BCMA, B-cell maturation antigen; CAD/NSTEMI, coronary artery disease/non-ST-elevation myocardial infarction; CAR, chimeric antigen receptor; Cyclo; cyclophosphamide; Dara, daratumumab; d, dexamethasone; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; HCT, hematopoietic stem cell transplant; IDDM, insulin-dependent diabetes mellitus 2; ide-cel, idecabtagene vicleucel; Ig, immunoglobulin; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; MM, multiple myeloma; P, pomalidomide; R, lenalidomide; R-ISS, revised International Staging System; s/p, status post; T, thalidomide; V, bortezomib.
Doris Hansen. Personal communication; Jun 9, 2023.

Subject responses deepened over time

- Response to ide-cel by IMWG response criteria:
  - 1 month: PR
  - 3 months: PR
  - 6 months: PR
  - 12 months: PR, near VGPR
  - 16 months: CR
- Co-morbidities which would have deemed patient KarMMa ineligible:
  - ECOG performance status 3
  - Cardiac dysfunction (NSTEMI within 3 months of CAR T-cell therapy and EF of 40–45%)
  - Prior use of anti-BCMA therapy

Serum M-spike



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction ; Ide-cel, idecabtagene vicleucel; IMWG, International Myeloma Working Group; NSTEMI, non-ST-elevation myocardial infarction; PR, partial response.
Doris Hansen. Personal communication; Jun 9, 2023.

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.

Characteristics differentiating real-world patients from KarMMa[1]

75% (N = 120) of patients would have been ineligible for participation in the KarMMa clinical trial

KarMMa exclusion criteria	n (%)
Organ dysfunction (renal, cardiac, hepatic)	45 (28)
Prior anti-BCMA therapy	33 (21)
Platelets <50,000/µL	33 (21)
ECOG performance status ≥2	28 (18)
Hemoglobin <8 g/dL	25 (16)
ANC <1,000/µL	22 (14)
CNS myeloma and other CNS pathology	13 (8)
PCL, POEMS, amyloidosis, non-secretory	11 (7)
Prior allogeneic SCT	9 (6)
Other malignancies	10 (6)

ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PCL, plasma cell leukemia; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; SCT, stem cell transplant.

1. Hansen D, et al. *J Clin Oncol.* 2023;41(11);2087-2097.

Safety of idecabtagene vicleucel in the real world[1]

Characteristic	SOC ide-cel[1] (N = 159)	KarMMa[2] (N = 128)
Any CRS*, n (%)	131 (82)	107 (84)
Grade ≥3	5 (3)	7 (5)
Any neurotoxicity*, n (%)	29 (18)	23 (18)
Grade ≥3	9 (6)	4 (3)
Tocilizumab use, n (%)	113 (71)	67 (52)
Steroid use, n (%)	42 (26)	19 (15)

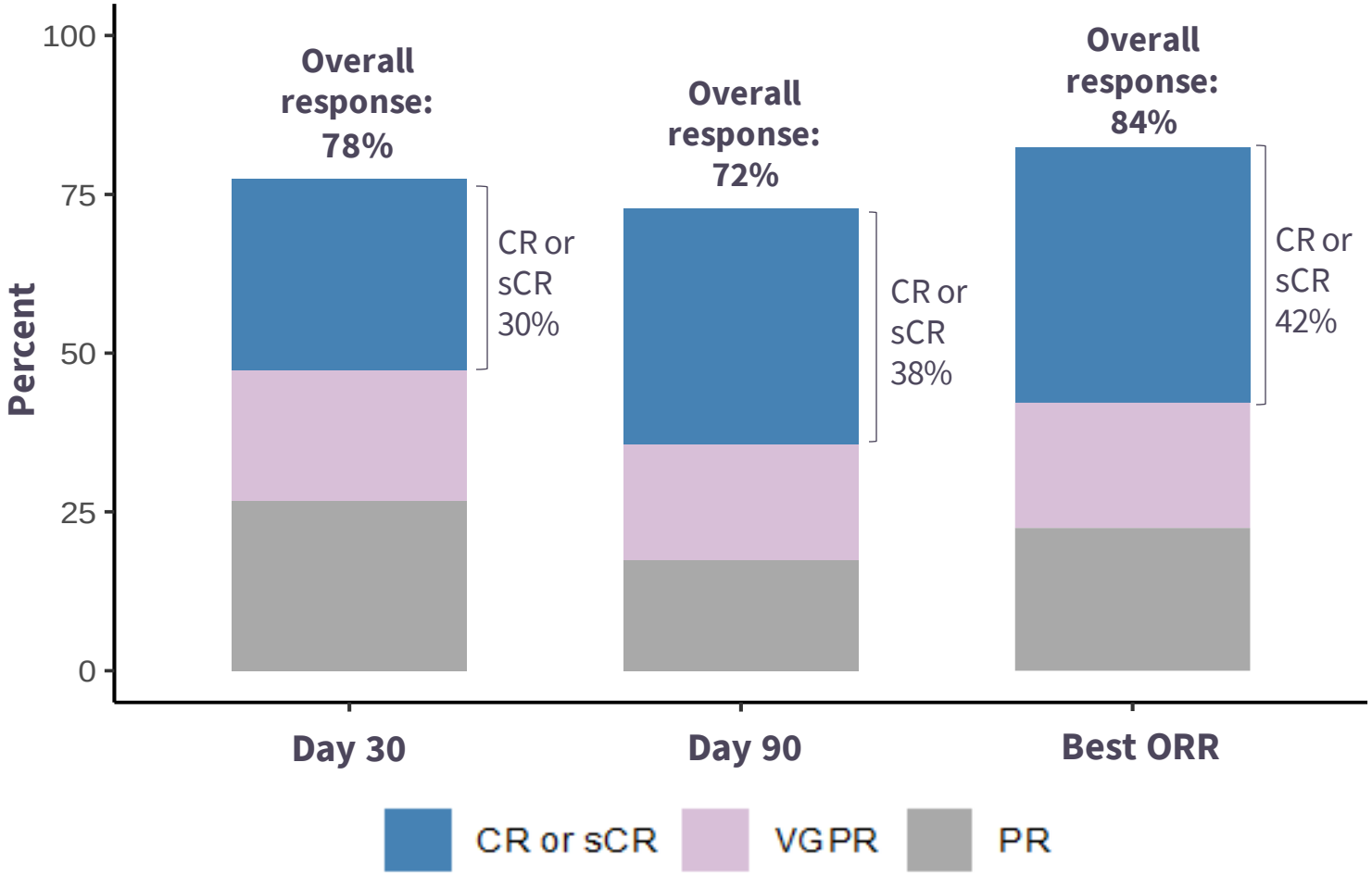
Total of 30 (19%) deaths in SOC population[1]:

- n = 20 (13%) due to progression
- n = 8 (5%) due to NRM
  - Toxicity (n = 3)
  - Infection (n = 3; Covid-19)
  - Cardiomyopathy (n = 2)
- n = 2 (1%) unknown

CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ide-cel, idecabtagene vicleucel; NRM, non-relapse mortality; NT, neurotoxicity; SOC, standard of care.
*ASTCT criteria used for grading CRS and NT.

1. Hansen D, et al. *J Clin Oncol.* 2023;41(11);2087-2097. **2.** Munshi, et al. *NEJM.* 2021;384(8):705-716.

Day 30, Day 90, and best overall tumor responses for standard of care ide-cel[1,2]



CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

1. Hansen D, et al. *J Clin Oncol.* 2023;41(11);2087-2097. **2.** Doris Hansen. Personal communication; Jun 9, 2023.

Multivariable analysis for idecabtagene vicleucel efficacy[1]

Characteristic	Best response ≥CR		Estimated ORR		PFS	
	OR	p	OR	p	HR	p
Prior anti-BCMA	0.48	0.2	0.46	0.2	2.81	**0.003**
High-risk cytogenetics	0.74	0.4	0.43	0.7	2.31	**0.003**
ECOG performance status ≥2	0.44	0.1	0.55	0.4	2.19	**0.02**
Patient age	1.00	>0.9	0.87	0.4	0.97	**0.04**

Model also included extramedullary disease, penta-refractory status, cell dose ≥400 $\times 10^6$ CAR T cells, and number of prior lines of therapy.

Prior use of BCMA-directed therapy, high risk cytogenetics, ECOG performance status ≥2, and younger age are **associated with inferior outcomes**. Additional investigation is warranted to include combinatorial approaches and consolidation or maintenance strategies for prior BCMA-treated patients.

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OR, odds ratio; ORR, overall response rate; PFS, progression-free survival.

1. Hansen D, et al. *J Clin Oncol.* 2023;41(11);2087-2097.

Ciltacabtagene autoleucel in the real world: Baseline characteristics (57% CARTITUDE-1 ineligible)

Characteristic	Cilta-cel (N = 143)[1]	CARTITUDE-1 (N = 97)[2,3]
Median age (range)	64 (30–79)	61 (56-68)
Male, n (%)	81 (57)	57 (59)
Extramedullary disease, n (%)	44 (31)	13 (13)
Oligosecretory/non-secretory, n (%)	23 (16)	0
Plasma cell leukemia, n (%)	10 (7)	0
ECOG performance status, n (%)		
0–1	116 (89)	93 (96)
2–4	14(11)	4 (4)
R-ISS/ISS, n (%)		
I	31 (32)	61 (63)
II	44 (46)	22 (23)
III	21 (22)	14 (14)
High-risk cytogenetics, n (%)		
Any high-risk cytogenetics	51 (41)	23 (24)
BT, n (%)	114 (80)	73 (75)
Response to BT (≥ PR), n (%)	30 (30)	15 (21)
Prior BCMA therapy, n (%)	16 (11)	0
Median prior lines of therapy (range)	6 (3–18)	6 (4–8)
LD chemotherapy, n (%)		
Fludarabine + cytoxan	120 (84)	97(100)
Others	23 (16)	0
Refractory status, n (%)		
Triple-refractory	102 (71)	85 (88)
Penta-refractory	48 (34)	41 (42)

BCMA, B-cell maturation antigen; BT, bridging therapy; cilta-cel, ciltacabtagene autoleucel; ECOG, Eastern Cooperative Oncology Group; LD, low dose; R-ISS, revised International Staging System.
*22% of patients (n = 31) received out of specification product under EAP. Unknown/missing/not included.
1. Hansen DK. Abstract #8012. 2023 ASCO Annual Meeting. Jun 5, 2023; Chicago, US. **2.** Martin T, et al. *J Clin Oncol.* 2023;41(6):1265-1274. **3.** Berdeja JG, et al. *Lancet*. 2021;398(10297):314-324.

Safety of cilta-cel in the real world

Characteristic	Cilta-cel (N = 143)[1]	CARTITUDE-1 (N = 97)[2,3]
Any CRS, n (%)*	114 (80)	92 (95)
Grade ≥3	7 (5)	4 (4)
Any ICANS, n (%)*	24 (18)	16 (17)
Grade ≥ 3	8 (6)	2 (2)
Any delayed NT, n (%)	17 (12)	12 (12)
Parkinsonism	2 (1)	4 (4)
Bell's/CN Palsy	9 (6)	2 (2)
Other	6 (4)	6 (6)
Median day of onset (IQR)	25 (21–32)	27 (16–73)
Delayed NT resolution	6 (35)	6 (50)
Median time to resolution (IQR), days	58 (33–94)	75 (28–159)

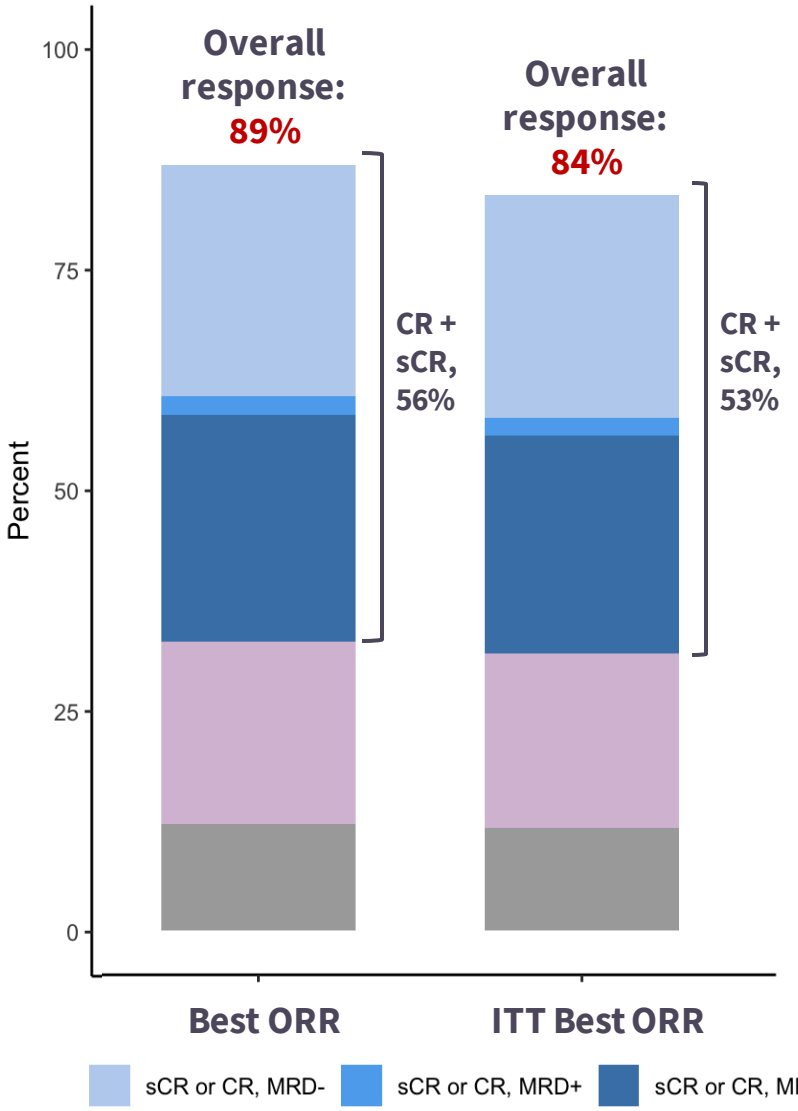
Total of 22 deaths (15%) in SOC population:

- n = 8 due to myeloma progression
- n = 14 (10%) due to NRM
  - Grade 5 CRS (n = 3), concomitant CRS/infection (n = 1), Grade 5 ICANS (n = 1), delayed NT (n = 2), IEC-associated HLH-like syndrome (n = 1), and infections (n = 6)

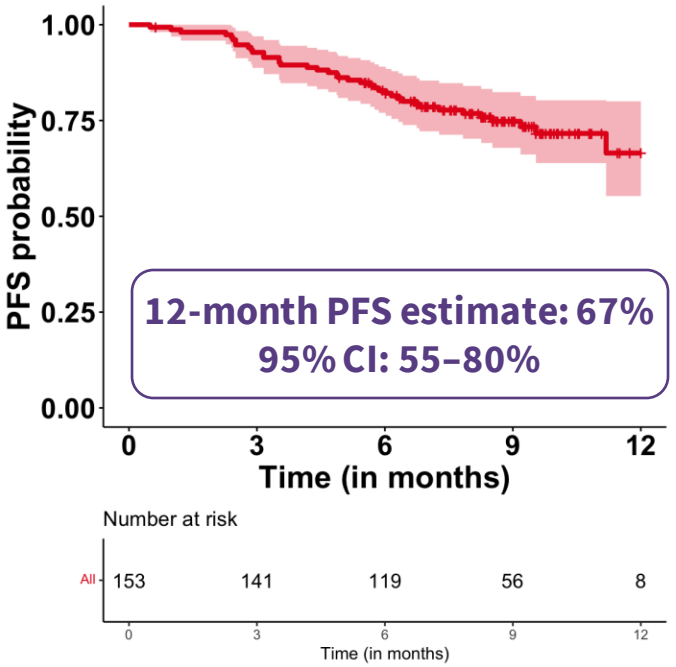
cilta-cel, ciltacabtagene autoleucel; CN, cranial nerve; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; IEC, immune effector cell; IQR, interquartile range; NRM, non-relapse mortality; NT, neurotoxicity; SOC, standard of care.
*ASTCT criteria used for grading of CRS and NT.

1. Hansen DK. Abstract #8012. 2023 ASCO Annual Meeting. Jun 5, 2023; Chicago, US. **2.** Martin T, et al. *J Clin Oncol.* 2023;41(6):1265-1274. **3.** Berdeja JG, et al. *Lancet.* 2021;398(10297):314-324.

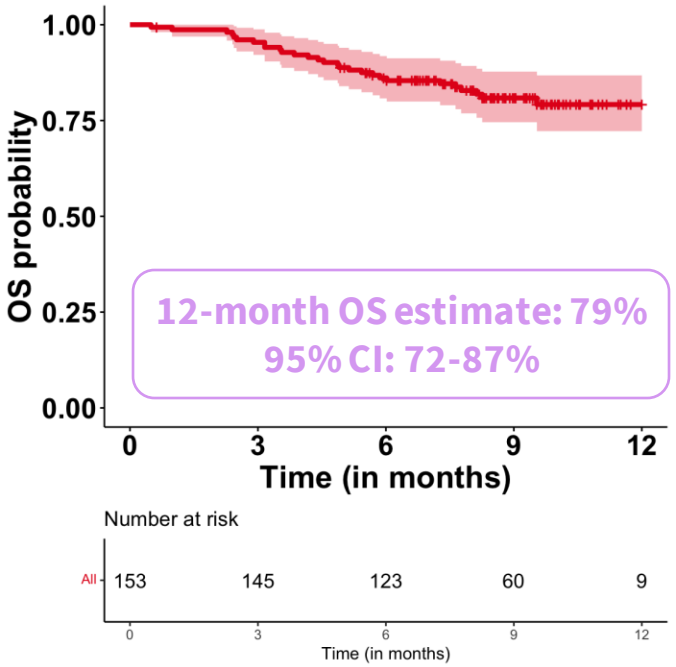
Best ORR, ITT tumor response, real-world PFS and OS for standard of care cilta-cel[1]



Real-world PFS



Real-world OS



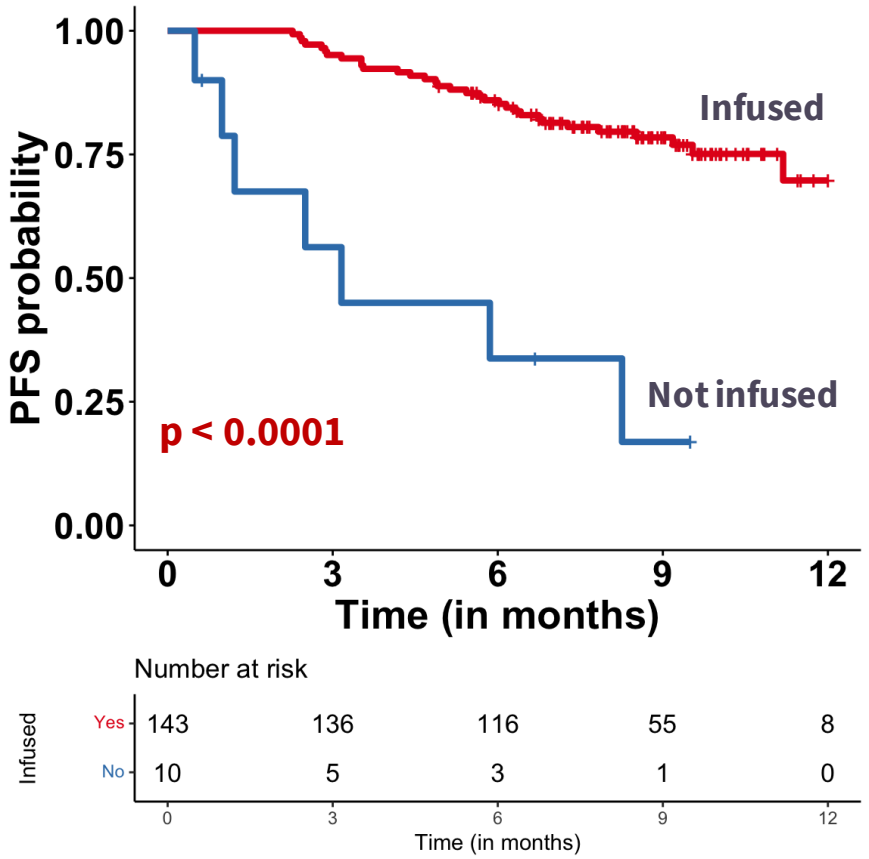
ITT; median follow up, 8.4 months

CI, confidence interval; ITT, intention to treat; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

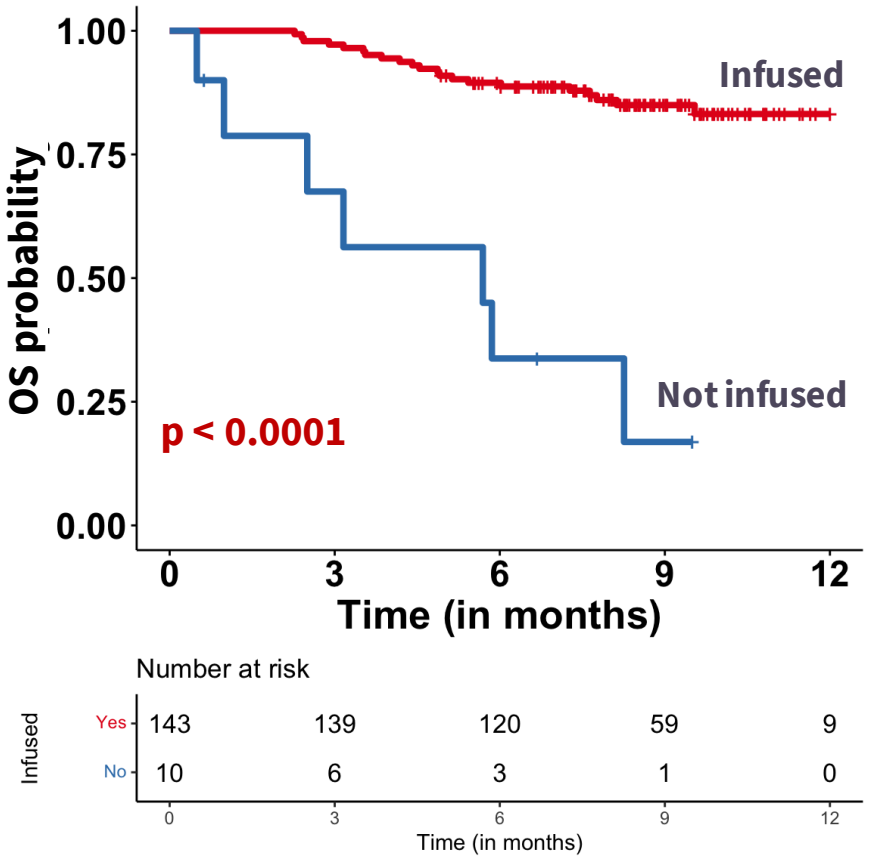
1. Hansen DK. Abstract #8012. 2023 ASCO Annual Meeting. Jun 5, 2023; Chicago, US.

Standard of care cilta-cel: PFS and OS by infusion among apheresed patients[1]

Real-world PFS



Real-world OS



OS, overall survival; PFS, progression-free survival.

1. Hansen DK. Abstract #8012. 2023 ASCO Annual Meeting. Jun 5, 2023; Chicago, US.

Standard of care cilta-cel: Multivariable analysis for efficacy[1]

- Models also included prior use of BCMA-TT, extramedullary disease, ECOG performance status ≥2, penta-refractory status, CAR T-cell dose <0.7 × 10^6 CAR T cells, patient age, conditioning chemotherapy, and number of lines of therapy.

Characteristic	Best ORR			PFS			OS		
	OR	95% CI	p	OR	95% CI	p	HR	95% CI	p
High-risk cytogenetics	0.29	0.08, 0.95	0.046	3.31	1.53, 7.19	0.002	2.93	1.08, 7.95	0.035

- High-risk cytogenetics is an independent predictor of inferior outcomes impacting best ORR, PFS, and OS.
  - LD chemotherapy and **prior use of BCMA-TT did not impact survival outcomes**.

BCMA-TT, B-cell maturation antigen targeted therapy; CAR, chimeric antigen receptor; CI, confidence interval; ECOG, Eastern Coop erative Oncology Group; LD, low dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Hansen DK. Abstract #8012. 2023 ASCO Annual Meeting. Jun 5, 2023; Chicago, US.

Conclusions

- Our multicenter experience demonstrated favorable efficacy and toxicity in patients commercially treated with ide-cel and cilta-cel relative to the KarMMa and CARTITUDE-1 trials despite >50% of our patients being ineligible for trial inclusion.
- Treatment with ide-cel and cilta-cel is feasible outside of the clinical trial.
- Patients do not need to meet pivotal clinical trial inclusion criteria to benefit from cilta-cel and ide-cel

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Our patients and their families
US Multiple Myeloma Immunotherapy Consortium
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