Ciltacabtagene Autoleucel ± Lenalidomide Maintenance in Newly Diagnosed Multiple Myeloma With Suboptimal Response to Frontline Autologous Stem Cell Transplant: CARTITUDE-2 Cohort D

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CARTITUDE-2 Cohort D: Introduction

- Cilta-cel is a BCMA-targeting CAR-T cell therapy with a favorable benefit-to-risk profile across multiple LOT in RRMM[1-4]
  - Deep and durable responses in heavily pretreated patients with RRMM (CARTITUDE-1)[1,2]
  - Significant improvement in PFS vs SOC in lenalidomide-refractory patients with MM after 1–3 prior LOT (CARTITUDE-4)[3]
- Cilta-cel was recently approved for the treatment of adult patients with RRMM who have received at least 1 prior LOT, including a PI and an IMiD, and are refractory to lenalidomide[4]
- CARTITUDE-2 is a phase 2, multicohort study evaluating cilta-cel across various clinical settings of unmet need[5]
  - Cohort D evaluated cilta-cel ± lenalidomide maintenance in patients who achieved <CR after frontline ASCT
    - This patient population has historically poor clinical outcome[6-10]
    - For the first time, we present data from cilta-cel in a very early setting

Objective: To report initial efficacy and safety data from CARTITUDE-2 cohort D after a median follow-up of 22.4 months (range, 4.7–39.3)[a]

[a]Data cut-off date: September 5, 2023. ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; IMiD, immunomodulatory drug; LOT, line of therapy; MM, multiple myeloma; PFS, progression-free survival; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; SOC, standard of care.

1. Martin T, et al. *J Clin Oncol* 2023;41:1265-74. 2. Lin Y, et al. *J Clin Oncol* 2023;41:8009. 3. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47. 4. CARVYKTI® (ciltacabtagene autoleucel). Package insert. Horsham, PA: Janssen Biotech, Inc; 2024. 5. Hillengass J, et al. *Blood* 2023;142(suppl 1):1021. 6. Harousseau JL, et al. *Blood* 2009;114:3139-46. 7. Lahuerta JJ, et al. *J Clin Oncol* 2008;26:5775-82. 8. van de Velde HJ, et al. *Haematologica* 2007;92:1399-406. 9. Martínez-López J, et al. *Blood* 2011;118:529-34. 10. Chanan-Khan AA, et al. *J Clin Oncol* 2010;28:2612-24.

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CARTITUDE-2 Cohort D: Study Design and Endpoints

Key eligibility criteria

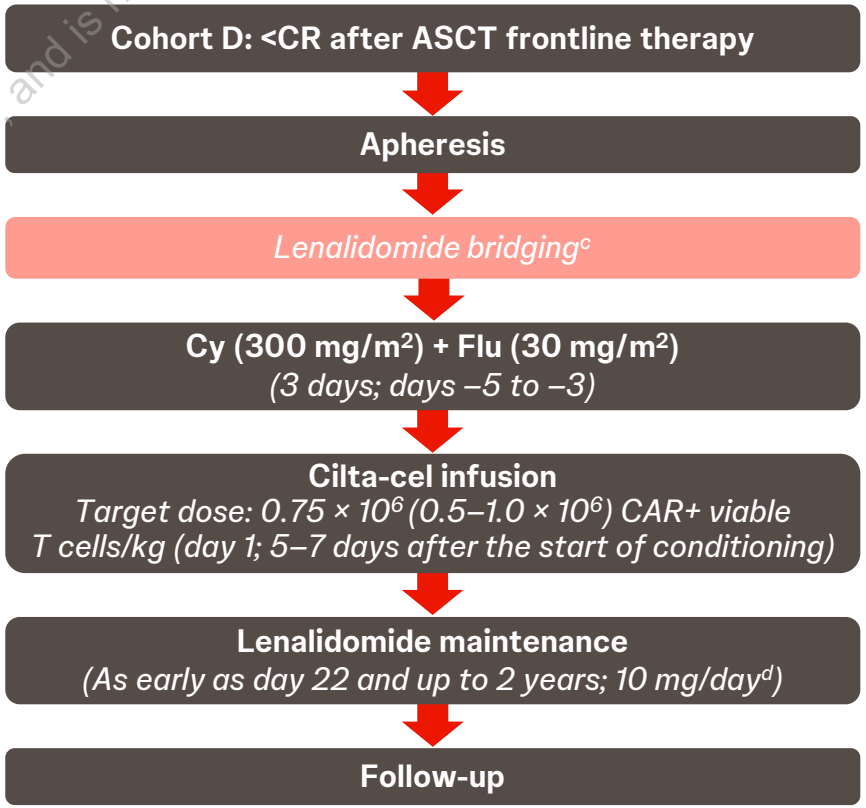
- History of 4–8 cycles of initial therapy, including induction, high-dose chemotherapy, and ASCT with or without consolidation
- Overall best response <CR

Primary endpoint

- MRD negativity (10^{-5} threshold) assessed by NGS or NGF

Key secondary endpoints

- ORR per IMWG response criteria[1]
- DOR
- Time to response
- PFS and OS
- Incidence and severity of AEs,[a] including CRS,[2,b] ICANS,[2,b] and neurotoxicity
- Pharmacokinetics



[a]Assessed per National Cancer Institute–Common Terminology Criteria for Adverse Events v5.0. [b]Graded per American Society for Transplantation and Cellular Therapy criteria. [c]Bridging therapy was allowed when clinically indicated; alternative bridging regimens instead of, or in addition to, lenalidomide were allowed. [d]Per protocol, safety was assessed in the first 5 patients with cilta-cel only; subsequently, 12 patients initiated continuous lenalidomide maintenance a minimum of 21 days post cilta-cel for ≤2 years. Dose of 10 mg daily upon adequate hematologic recovery.

AE, adverse event; ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; ICANS, immune effector cell–associated neurotoxicity syndrome; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

1. Kumar S, et al. *Lancet Oncol* 2016;17:e328-46. 2. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25:625-38.

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CARTITUDE-2 Cohort D: Post-Transplant Baseline Characteristics

Characteristic	N=17
Age, median (range), years	54.0 (37–69)
Male, n (%)	14 (82.4)
Race, n (%)	
White	14 (82.4)
Black/African American	1 (5.9)
Not reported	2 (11.8)
ECOG PS at screening, n (%)	
0	13 (76.5)
1	4 (23.5)
Time from initial diagnosis to enrollment, median (range), y	0.9 (0.6–1.4)
Myeloma type by immunofixation, n (%)	
IgG	11 (64.7)
IgA	2 (11.8)
Light chain, kappa	2 (11.8)
Negative immunofixation	2 (11.8)

Characteristic	N=17
Extramedullary plasmacytomas, n (%)	0
High-risk cytogenetics, n (%)[a]	1 (5.9)
Del(17p), n (%)	1 (5.9)
ISS stage I, n (%)	17 (100)
Prior ASCT, n (%)[b]	17 (100)
Prior PI and IMiD, n (%)	17 (100)
Prior anti-CD38 mAb, n (%)	3 (17.6)

[a]Cytogenetic risk abnormalities are based on central FISH testing, or local FISH testing and karyotype testing if central FISH not available. 1 patient was unknown. [b]1 patient received tandem ASCT, ie, underwent ASCT twice.
ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; Ig, immunoglobulin; IMiD, immunomodulatory drug; ISS, International Staging System; mAb, monoclonal antibody; PI, proteasome inhibitor.

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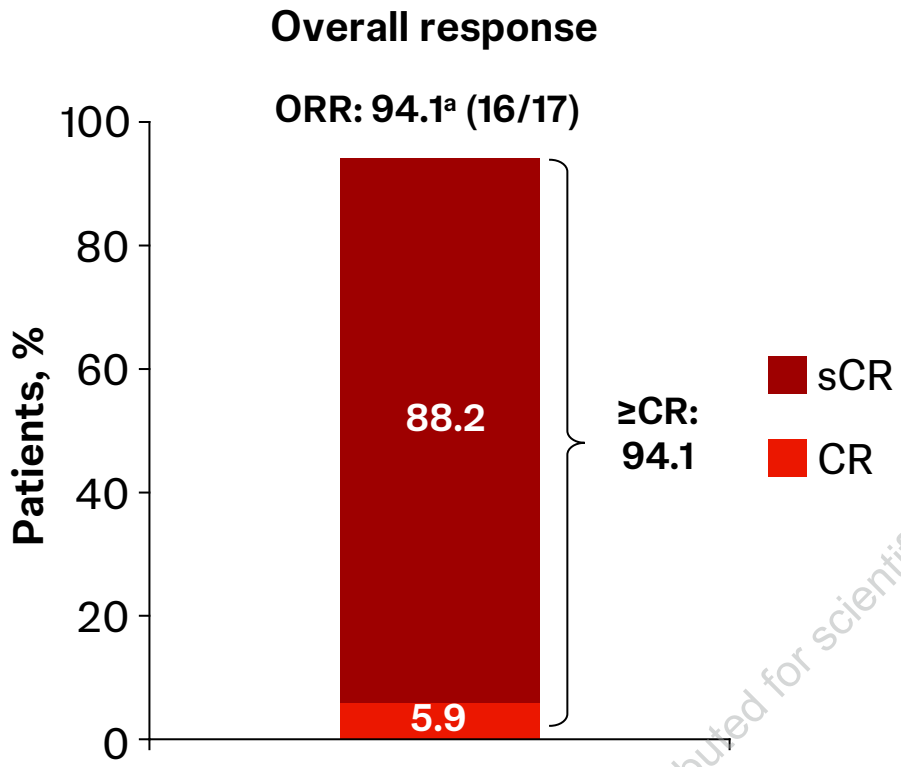
CARTITUDE-2 Cohort D: Lenalidomide Maintenance

- Per protocol, the first 5 patients did not receive lenalidomide maintenance after cilta-cel
- Subsequently, 12 patients initiated continuous lenalidomide maintenance after cilta-cel
  - Dose of 10 mg daily upon adequate hematologic recovery

Lenalidomide maintenance summary after cilta-cel	Lenalidomide maintenance (n=12)
Time to initiation, median (range), days	51.0 (21–214)
Duration, median (range), days	426.5 (70–716)
Cycles, median (range)	15.0 (3–26)
Overall relative dose intensity,[a] median (range), %	93.4 (68–100)

[a]Relative dose intensity is calculated as the percentage of total dose (mg) received in all relevant cycles divided by the sum of prescribed doses (mg) in those cycles.
cilta-cel, ciltacabtagene autoleucel.

CARTITUDE-2 Cohort D: Deep Responses Were Achieved With Cilta-cel



	Cohort D (N=17)
Time to response among responders, median (range), mo	
First response	1.3 (0.9–12.5)
Best response	1.9 (0.9–12.5)
≥CR	1.7 (0.9–12.5)
MRD negativity (10^{-5}), n/N (%)	
Overall	12/17 (70.6)
MRD-evaluable patients[b]	12/15 (80.0)

- 1 patient was lost to follow-up, and 1 patient was not evaluable for disease response

[a]ORR is defined as the proportion of patients who achieve a PR or better per IMWG criteria. Assessed using a validated computerized algorithm. [b]MRD evaluable denotes patients who had successful baseline calibration for NGS or who were assessed by NGF and had at least 1 postbaseline MRD sample with positive or negative result at the threshold of 10^{-5}.
cilta-cel, ciltacabtagene autoleucel; CR, complete response; IMWG, International Myeloma Working Group; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing; ORR, overall response rate; PR, partial response; sCR, stringent complete response.

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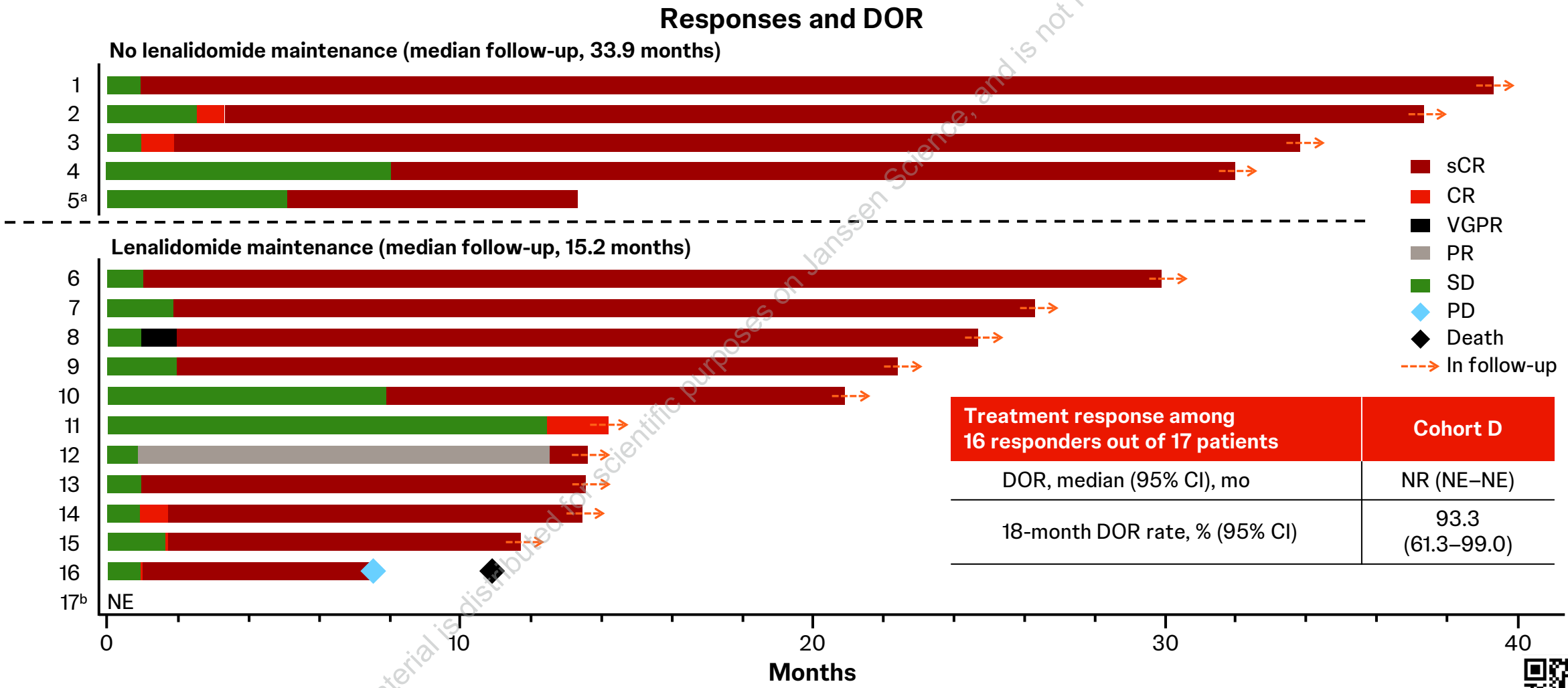
CARTITUDE-2 Cohort D: Responses Deepened Over Time and Were Durable With Cilta-cel



Treatment response among 16 responders out of 17 patients	Cohort D
DOR, median (95% CI), mo	NR (NE–NE)
18-month DOR rate, % (95% CI)	93.3 (61.3–99.0)

[a]1 patient was lost to follow-up. [b]1 patient was NE for disease response.
cilta-cel, ciltacabtagene autoleucel; CR, complete response; DOR, duration of response; MRD, minimal residual disease; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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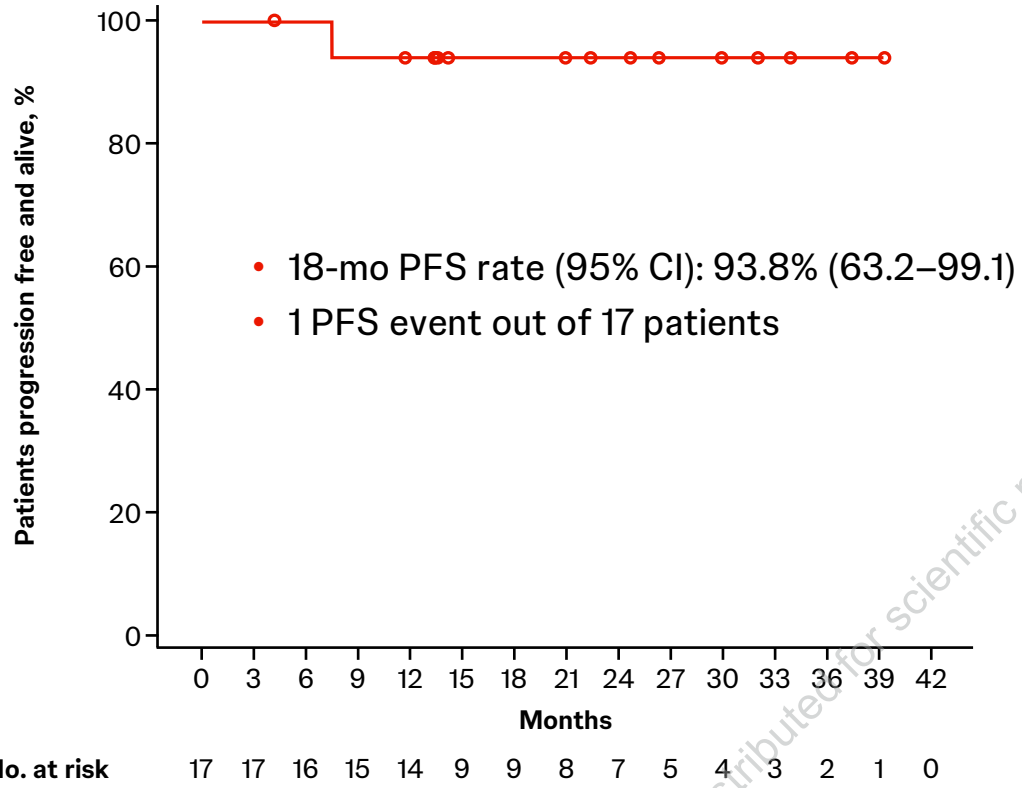
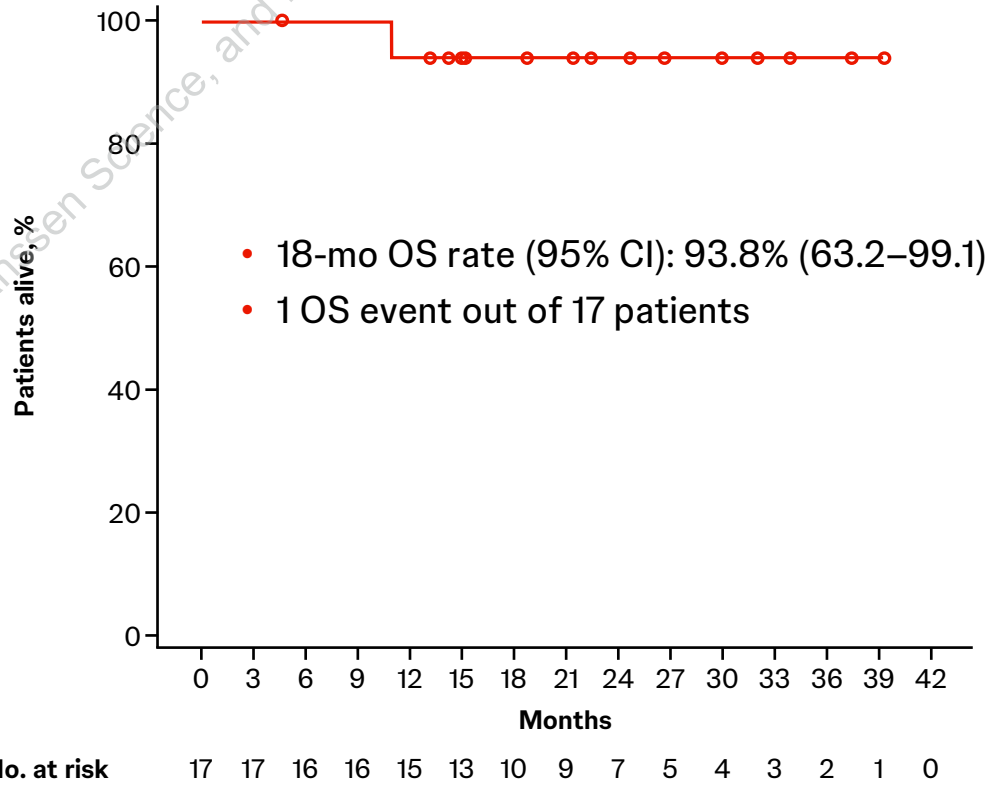
CARTITUDE-2 Cohort D: High PFS and OS Rates Were Achieved

PFS[a]



OS[a]



[a]Assessed using a validated computerized algorithm.
OS, overall survival; PFS, progression-free survival.

CARTITUDE-2 Cohort D: TEAEs Were Consistent With the Known Safety Profile of Cilta-cel

Select TEAEs, n (%)	Cohort D (N=17)	
	Any Grade	Grade 3/4
Any TEAE	17 (100)	17 (100)
Serious TEAE	10 (58.8)	9 (52.9)
Infections	12 (70.6)	5 (29.4)
Hematologic		
Neutropenia	16 (94.1)	14 (82.4)
Lymphopenia	11 (64.7)	10 (58.8)
Thrombocytopenia	8 (47.1)	4 (23.5)
Leukopenia	7 (41.2)	6 (35.3)
Anemia	5 (29.4)	1 (5.9)

	Cohort D (N=17)	Cohort D without lenalidomide (n=5)	Cohort D with lenalidomide (n=12)
Prolonged cytopenias,[a] n (%)			
Neutropenia	1 (5.9)	0	1 (8.3)
Lymphopenia	5 (29.4)	2 (40.0)	3 (25.0)
Thrombocytopenia	1 (5.9)	0	1 (8.3)
Grade 3/4 infections	5 (29.4)	1 (20.0)	4 (33.3)

- **Second primary malignancy**
  - 1 case of grade 3 myelodysplastic syndrome with onset on day 353[b]
- **No deaths due to TEAE at the time of data cut-off**

[a]Initial grade 3/4 cytopenias not recovered to grade ≤2 by day 60. [b]Not treatment related per investigator assessment.
ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; TEAE, treatment-emergent adverse event.

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CARTITUDE-2 Cohort D: AEs of Special Interest Were Consistent With the Known Safety Profile of Cilta-cel

AEs of special interest	Cohort D (N=17)			
	Any Grade, n (%)	Grade 3/4, n (%)	Time to onset, median, days	Duration, median, days
CRS	14 (82.4)	0	8.0	2.5
Neurotoxicity				
ICANS	1 (5.9)	0	7.0	1.0
Other neurotoxicity	6 (35.3)	1 (5.9)	21.0	111.0

- **Neurotoxicity**
  - No cases of MNTs/parkinsonism were observed
  - 1 patient with ICANS, which resolved
  - 6 patients experienced other neurotoxicities, mostly grade 1/2
    - 3 patients with cranial nerve VII disorders and associated symptoms (grade 1 [n=1], ongoing)[a]
    - 1 patient with diplopia[b] (grade 3) and hypoesthesia oral (both resolved)
    - 1 patient with paresthesia (grade 1, ongoing)
    - 1 patient with peripheral motor neuropathy, dysarthria, and dysphagia (resolved)

[a]Includes Bell's palsy, facial nerve palsy, facial nerve disorder, and dysarthria. 1 patient with facial nerve palsy not resolved by data cut-off. [b]Diplopia recovered after a duration of 43 days.
AE, adverse event; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; MNT, movement and neurocognitive treatment-emergent adverse event.

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CARTITUDE-2 Cohort D: CAR-T Cell Expansion Profile

	CARTITUDE-2 cohort D (N=17)	CARTITUDE-4 (N=176)[1]	CARTITUDE-1 (N=97)[1]
C_{max}, mean (SD), cells/µL	2129 (2113)	1451 (6169)[a]	1281 (1822)
T_{max}, median (range), days	11.74 (8.83–20.80)	12.91 (7.84–222.83)[a]	13.06 (8.72–300.84)
T_{last}, median (range), days	43 (26–210)	57 (13–631)	99 (19–911)
$AUC_{(0–6m)}$, mean (SD), day × cells/µL	10,376 (7803)	11,710 (56,994)[a,b]	13,376 (21,191)[b]

- In the cohort D population with low tumor burden, robust CAR-T cell expansion was observed

[a]For C_{max} and T_{max}, n=170; $AUC_{0–28d}$, n=169. [b]$AUC_{(0–28d)}$, area under the CAR+ T cells concentration-time curve from time 0 to 28 days. $AUC_{(0–6m)}$, area under the CAR+ T cells concentration-time curve from time 0 to 6 months; CAR, chimeric antigen receptor; C_{max}, maximum observed concentration of CAR+ T cells in blood; MM, multiple myeloma; T_{last}, sampling time (days post infusion) of last measurable concentration of CAR+ T cells; T_{max}, sampling time (days post infusion) to reach C_{max}.

1. de Larrea C, et al. Presented at IMS; September 27–30, 2023; Athens, Greece.

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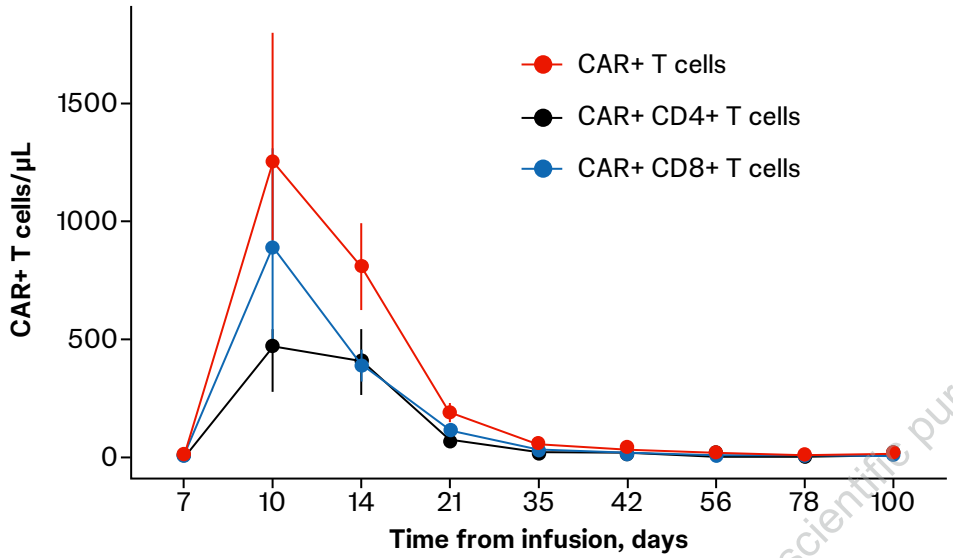
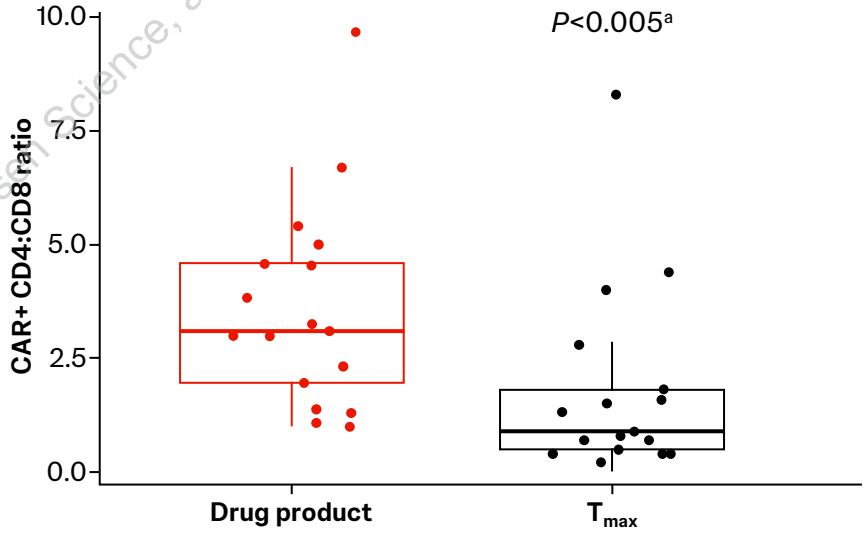
CARTITUDE-2 Cohort D: Preferential Expansion of CAR+ CD8 T Cells Post Infusion

CAR+ CD4 and CAR+ CD8 T-cell levels



CAR+ CD4:CD8 T-cell ratio



- Both CAR+ CD4 and CAR+ CD8 T cells expanded after infusion
- CAR+ CD4:CD8 T-cell ratios were lower in blood at ~T_{max} than in drug product

Consistent with CARTITUDE-4[1] and CARTITUDE-1,[2] CAR+ CD8 T cells expanded more than CAR+ CD4 T cells in blood in CARTITUDE-2 cohort D

[a]*P* value determined using the Wilcoxon test.
CAR, chimeric antigen receptor; C_{max}, maximum observed concentration of CAR+ T cells in blood; T_{max}, sampling time (days post infusion) to reach C_{max}.
1. de Larrea C, et al. Presented at IMS; September 27–30, 2023; Athens, Greece. 2. Zudaire E, et al. Presented at ASH; December 7–10, 2019; Orlando, FL, USA.

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CARTITUDE-2 Cohort D: Conclusions

- In patients with <CR after frontline ASCT, a single cilta-cel infusion ± lenalidomide maintenance demonstrated deep and durable responses
  - ORR was 94.1%, 18-month DOR was 93.3%, and 80% of patients achieved MRD negativity
  - 18-month PFS and OS rates were 93.8% each
  - CAR-T cell expansion was robust
- AEs were consistent with the known safety profile of cilta-cel
  - No cases of grade 3/4 CRS or ICANS
  - No cases of MNTs/parkinsonism
- Incidence of prolonged neutropenia and thrombocytopenia was low

In patients with a suboptimal response after ASCT frontline therapy, efficacy and safety with cilta-cel ± lenalidomide maintenance is promising, especially given the historically poorer clinical outcome of this patient population

AE, adverse event; ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; ICANS, immune effector cell–associated neurotoxicity syndrome; MM, multiple myeloma; MNT, movement and neurocognitive treatment-emergent adverse event; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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