Ciltacabtagene Autoleucel vs Standard of Care in Patients With Lenalidomide-Refractory Multiple Myeloma After 1–3 Lines of Therapy: Minimal Residual Disease Negativity in the Phase 3 CARTITUDE-4 Trial

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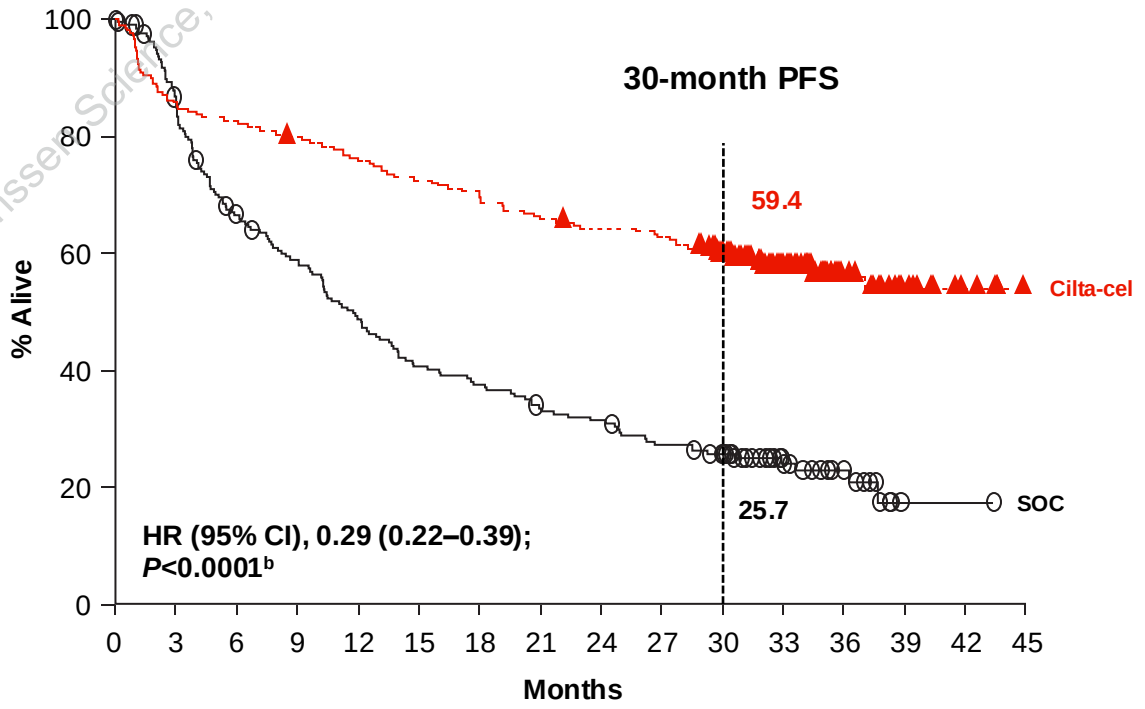
CARTITUDE-4: Introduction

- There is an increasing recognition of MRD as a primary clinical endpoint in MM as it is linked to improved PFS and OS[1-5]
- In CARTITUDE-4, patients who were randomized to cilta-cel had[6,a]
  - Significantly improved PFS vs SOC **(HR [95% CI], 0.29 [0.22–0.39]; *P*<0.0001[b])**
  - Median PFS was not reached with cilta-cel

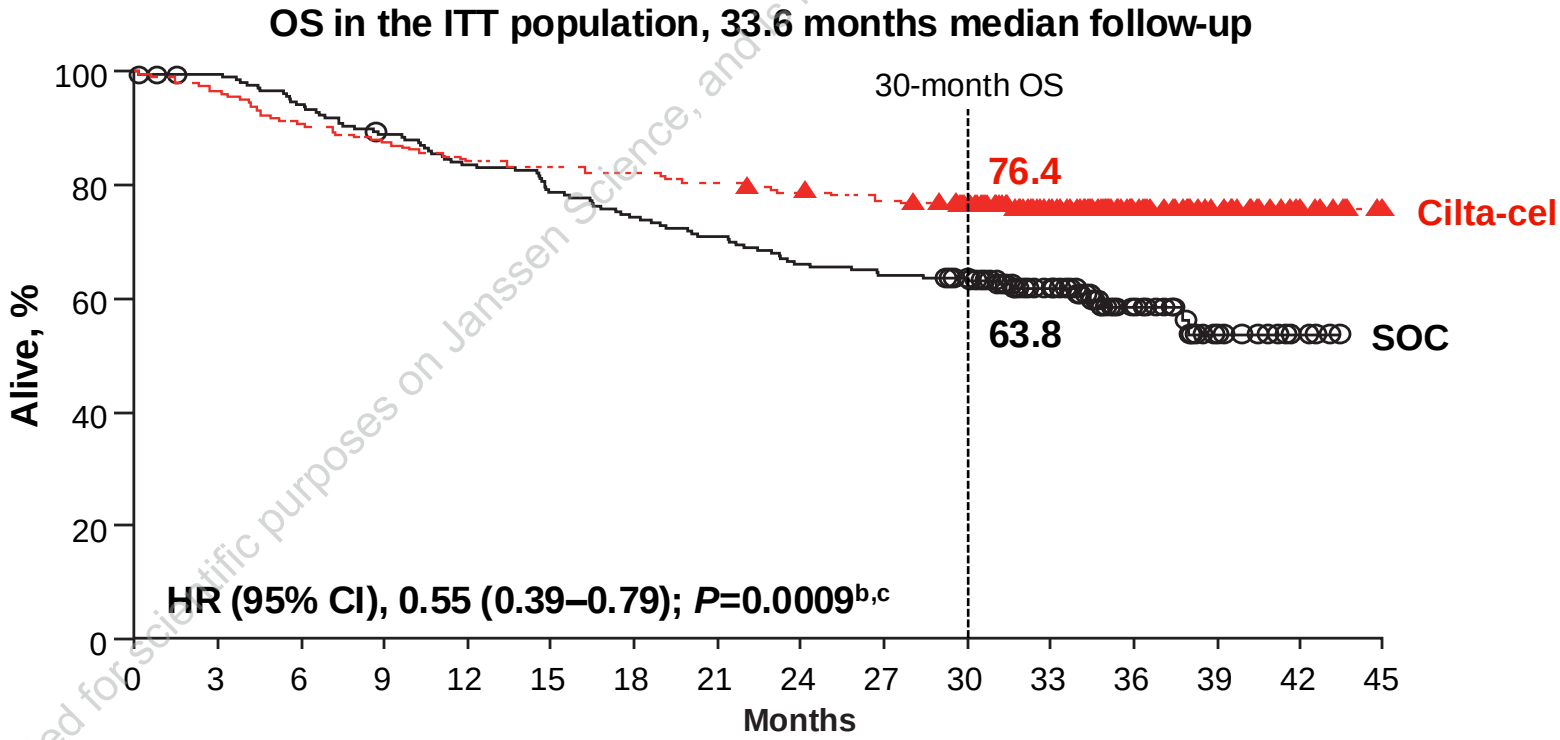
PFS in the ITT population, 33.6 months median follow-up



[a]Data cut-off date: May 1, 2024. [b]Nominal *P* value.
cilta-cel, ciltacabtagene autoleucel; HR, hazard ratio; ITT, intent-to-treat; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; SOC, standard of care.
1. US Food and Drug Administration. https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024#event-materials. Accessed November 30, 2024. 2. Avet-Loiseau H, et al. *Clin Lymphoma Myeloma Leuk* 2020;20:e30-e37. 3. Munshi NC, et al. *Blood Adv* 2020;4:5988-99. 4. Cavo M, et al. *Blood* 2022;139:835-44. 5. Landgren O, et al. *Blood* 2024;144:359-67. 6. Mateos MV, et al. Presented at IMS; September 25–28, 2024; Rio de Janeiro, Brazil. Oral #1437.

CARTITUDE-4: Introduction (Cont'd)

- Cilta-cel also showed an OS benefit over SOC, with **HR, 0.55 (95% CI, 0.39–0.79; *P*=0.0009)[1,a]**
  - Median OS was not reached
- Overall MRD negativity, a secondary endpoint, was also higher in patients randomized to cilta-cel vs SOC (62.0% vs 18.5%)



We report MRD-negativity outcomes, including overall and sustained MRD-negative ≥CR, at a median follow-up of 33.6 months in CARTITUDE-4[a]

[a]Data cut-off date: May 1, 2024. [b]Log-rank test. *P* value, 0.0009, crossed the prespecified boundary of 0.0108 as implemented by the Kim-DeMets spending function with parameter=2. [c]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

cilta-cel, ciltacabtagene autoleucel; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; MRD, minimal residual disease; OS, overall survival; SOC, standard of care.

1. Mateos MV, et al. Presented at IMS; September 25–28, 2024; Rio de Janeiro, Brazil. Oral #1437.

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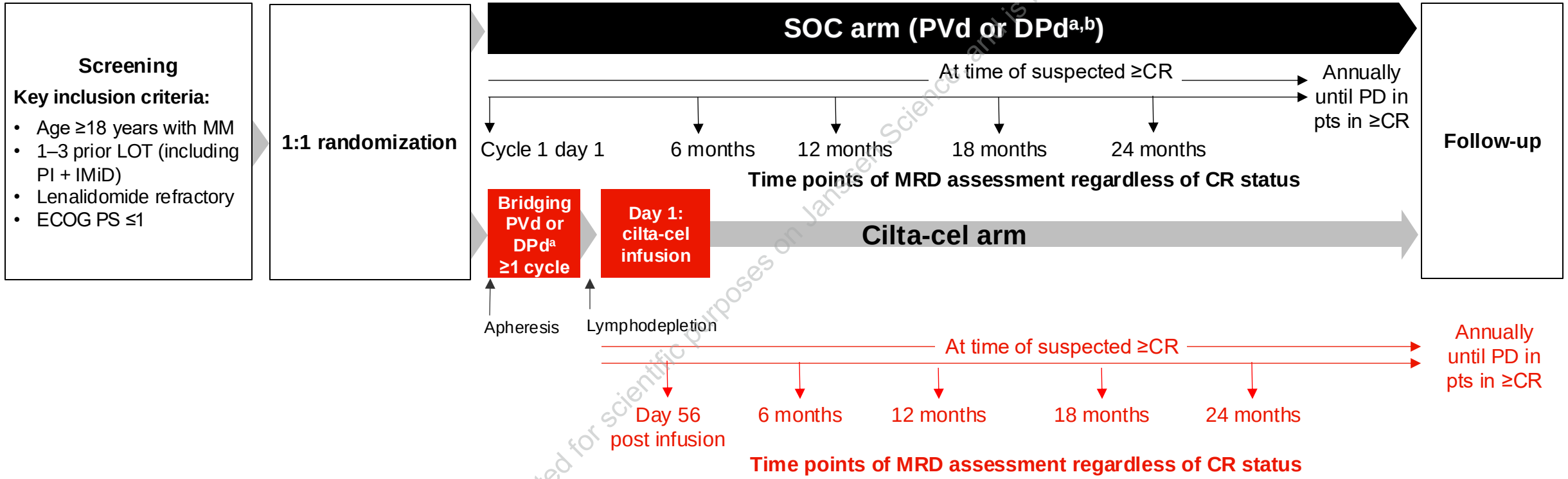
CARTITUDE-4: Study Design and MRD Assessments



- Next-generation sequencing at the 10^{-5} and 10^{-6} sensitivity thresholds
- Timing of MRD assessment is from cycle 1 day 1 for SOC and from cilta-cel infusion for cilta-cel arm

[a]Physician's choice. [b]Administered until disease progression.
cilta-cel, ciltacabtagene autoleucel; CR, complete response; DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease; PD, progressive disease; PI, proteasome inhibitor; PVd, pomalidomide, bortezomib, and dexamethasone; pts, patients; SOC, standard of care.

1. San-Miguel J, et al. *N Engl J Med* 2023;389:335-47.

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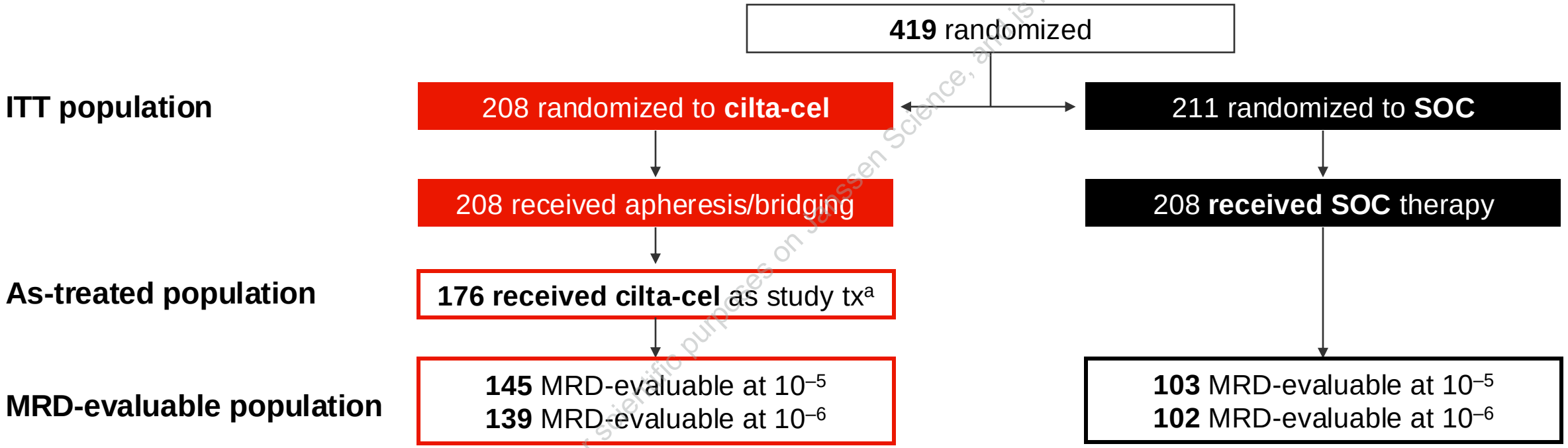
CARTITUDE-4: Study Population and MRD Evaluability



MRD-evaluable samples:

- Passed calibration and QC and include sufficient cells for evaluation at the respective testing threshold

[a]32 did not receive cilta-cel as study treatment (n=30 due to disease progression; n=2 due to death during bridging therapy/lymphodepletion), of which 20 received cilta-cel as subsequent LOT.
cilta-cel, ciltacabtagene autoleucel; ITT, intent-to-treat; LOT, line of therapy; MRD, minimal residual disease; QC, quality control; SOC, standard of care; tx, treatment.

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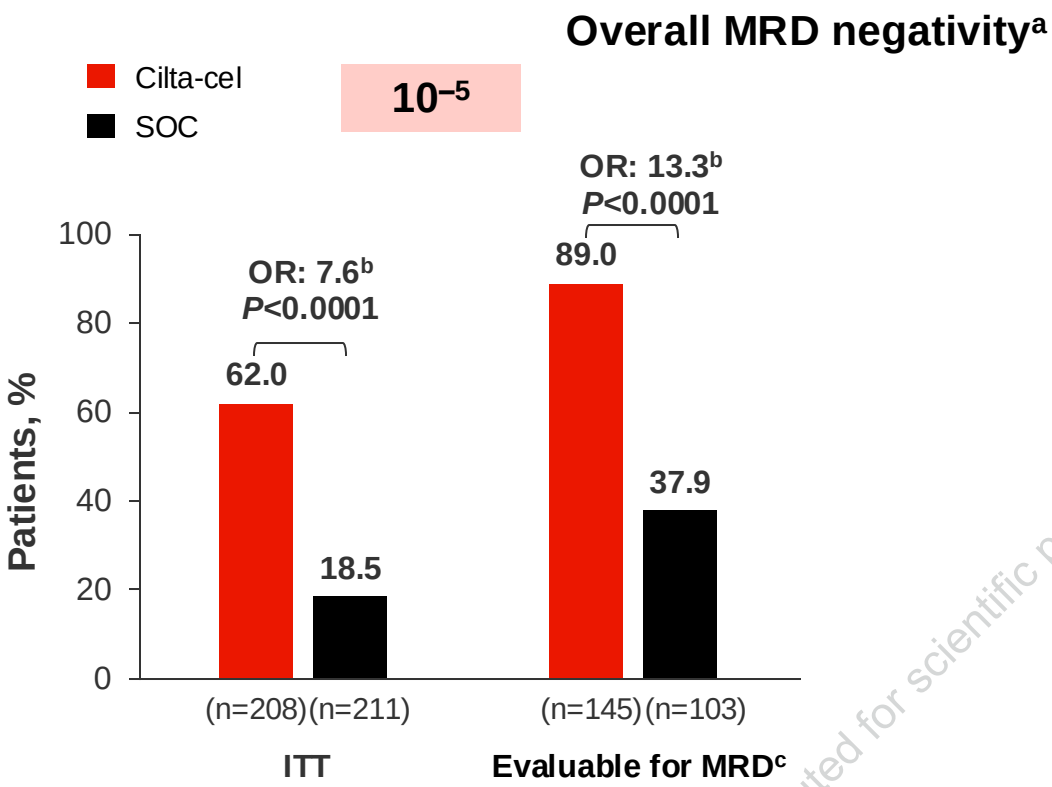
CARTITUDE-4: Overall MRD Negativity



High rates of overall MRD negativity are rapidly achieved with cilta-cel, and almost all cilta-cel patients negative at 10^{-5} were also negative at 10^{-6}

[a]Achievement of MRD negativity at any time after randomization and before next therapy. [b]Stratified Cochran-Mantel-Haenszel test. [c]Evaluable samples were those that passed calibration and QC and included sufficient cells for evaluation at the respective testing threshold.
cilta-cel, ciltacabtagene autoleucel; C1D1, cycle 1 day 1; ITT, intent-to-treat; MRD, minimal residual disease; OR, odds ratio; QC, quality control; SOC, standard of care.

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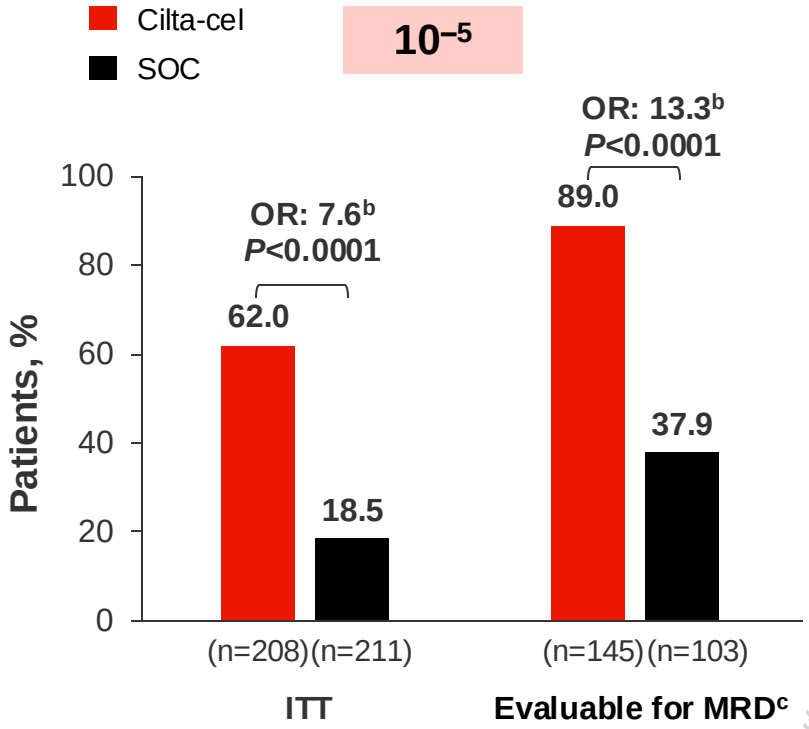
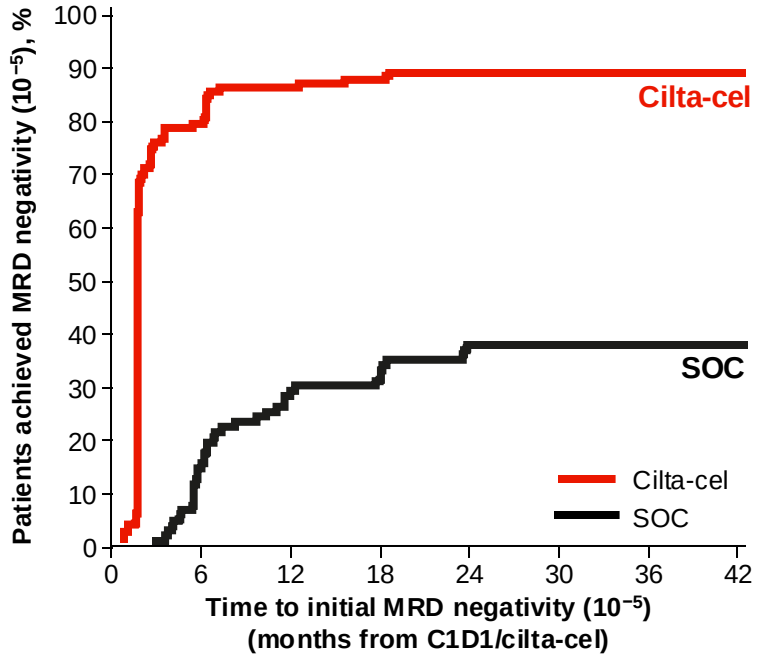
CARTITUDE-4: Overall MRD Negativity

Overall MRD negativity[a]



Time to MRD negativity (10^{-5}) in evaluable patients



- 69% of evaluable patients achieved MRD negativity (10^{-5}) by day 56 (ITT, 48%), rising to 86% (ITT, 60%) by 6 months post cilta-cel infusion

High rates of overall MRD negativity are rapidly achieved with cilta-cel, and almost all cilta-cel patients negative at 10^{-5} were also negative at 10^{-6}

[a]Achievement of MRD negativity at any time after randomization and before next therapy. [b]Stratified Cochran-Mantel-Haenszel test. [c]Evaluable samples were those that passed calibration and QC and included sufficient cells for evaluation at the respective testing threshold.
cilta-cel, ciltacabtagene autoleucel; C1D1, cycle 1 day 1; ITT, intent-to-treat; MRD, minimal residual disease; OR, odds ratio; QC, quality control; SOC, standard of care.

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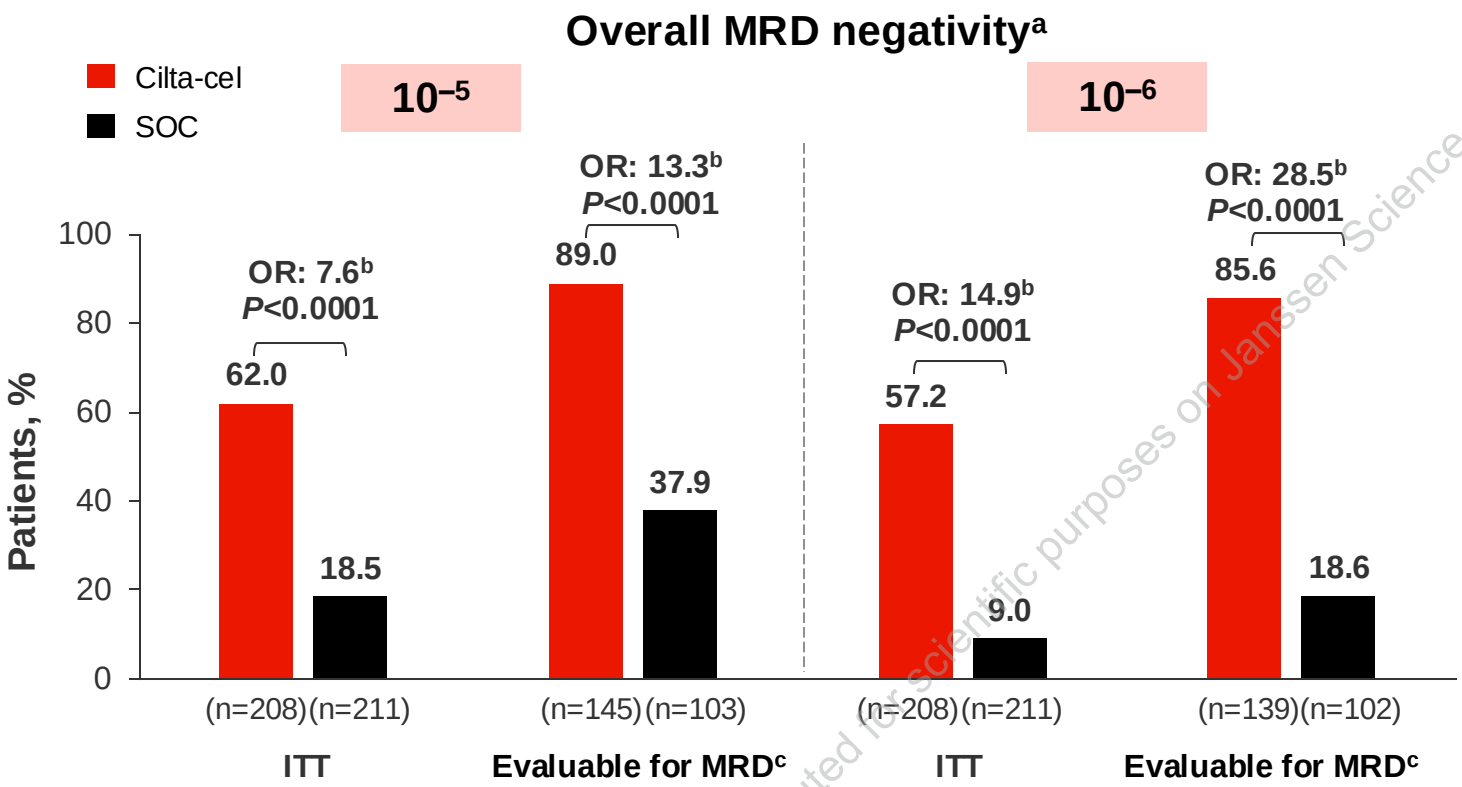
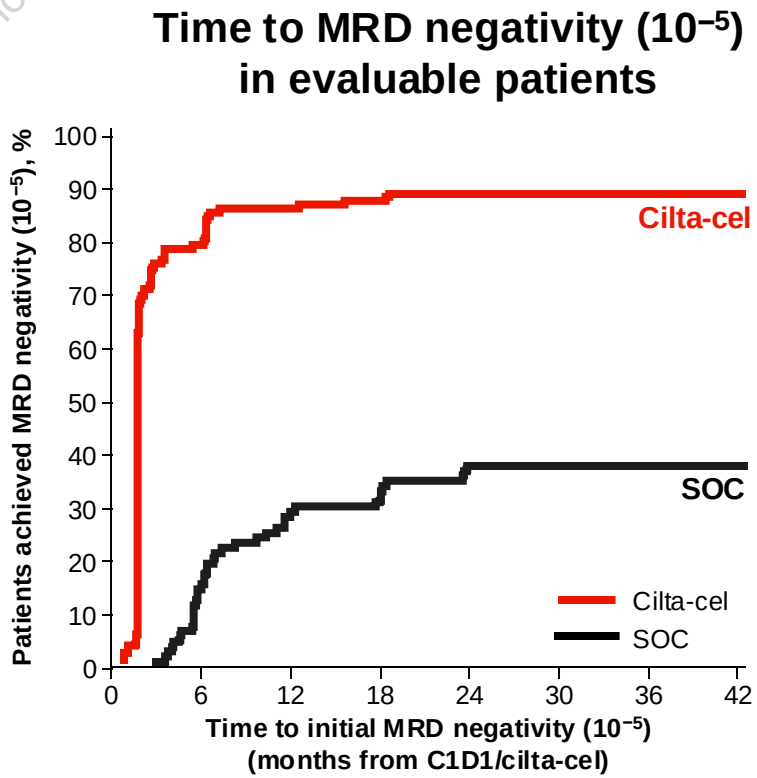
CARTITUDE-4: Overall MRD Negativity





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cilta-cel, ciltacabtagene autoleucel; C1D1, cycle 1 day 1; ITT, intent-to-treat; MRD, minimal residual disease; OR, odds ratio; QC, quality control; SOC, standard of care.

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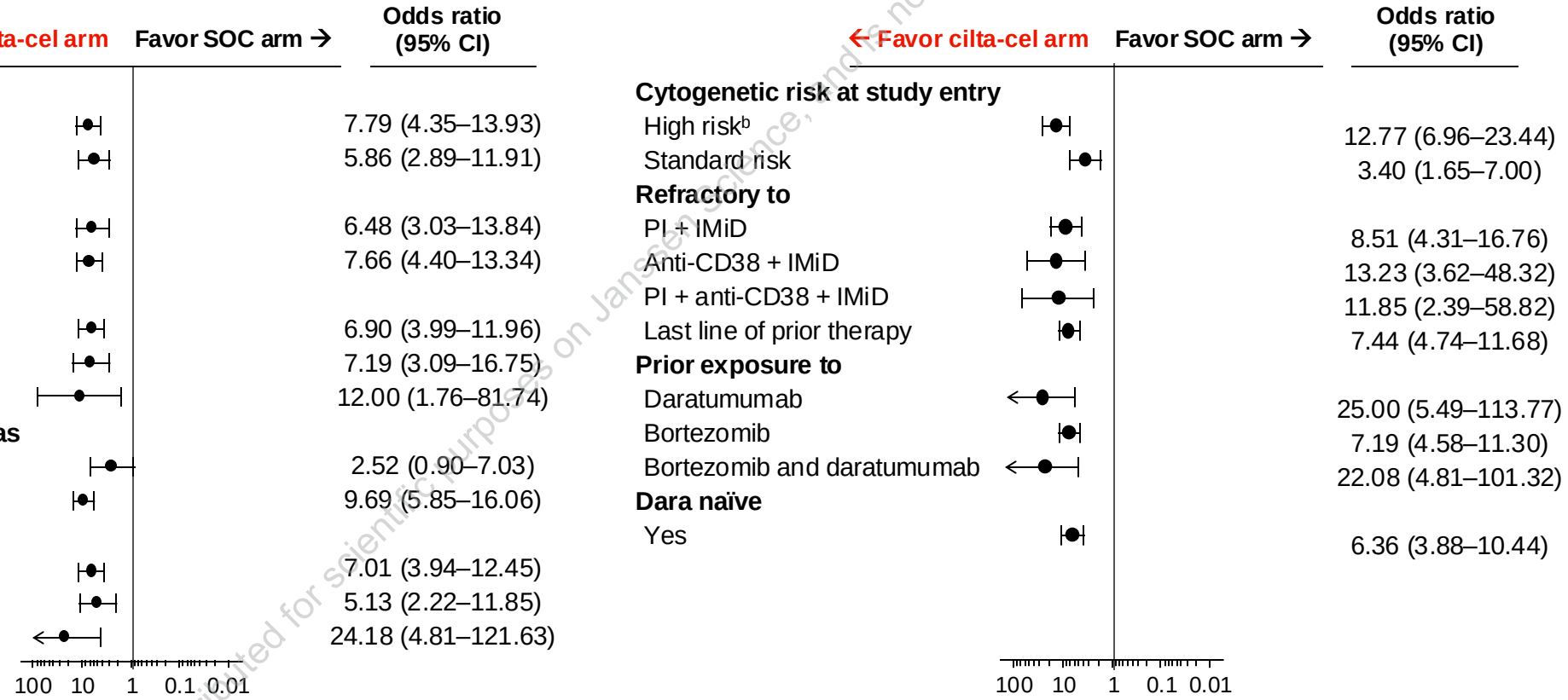
CARTITUDE-4: Overall MRD Negativity in Subgroups (ITT)



Across subgroups, cilta-cel increased overall MRD-negativity rates at the 10^{-5} threshold vs SOC

[a]ISS staging is derived based on serum β-2 microglobulin and albumin. [b]High risk includes the subjects who are positive for any of del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH testing.
cilta-cel, ciltacabtagene autoleucel; FISH, fluorescence in situ hybridization; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intent-to-treat; MRD, minimal residual disease; OS, overall survival; PI, proteasome inhibitor; SOC, standard of care.

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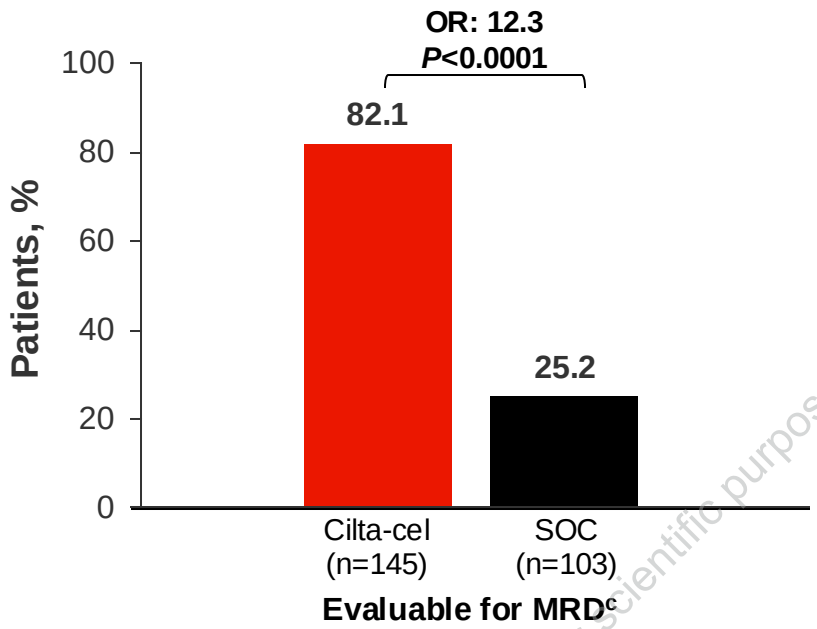
CARTITUDE-4: Overall MRD-Negative ≥CR (10^{-5}) and Sustained (≥12 Months) MRD-Negative ≥CR (10^{-5})



At the data cut-off, more than 50% of evaluable patients in the cilta-cel arm achieved sustained (≥12 months) MRD-negative ≥CR, compared with <10% of patients in the SOC arm

[a]Overall MRD-negative ≥CR was defined as the proportion of patients achieving MRD negativity within 3 months of achieving ≥CR post randomization and prior to disease progression or initiation of subsequent antimyeloma therapy. [b]Achievement of MRD-negative and CR status in succession and confirmed by at least 1 year apart without MRD-positive status or disease progression or subsequent antimyeloma therapy in between. [c]Evaluable samples were those that passed calibration and QC and included sufficient cells for evaluation at the respective testing threshold. [d]1 patient in the cilta-cel arm and 2 patients in the SOC arm had an MRD-positive result but did not have PD at data cutoff. Cilta-cel, ciltacabtagene autoleucel; CR, complete response; ITT, intent-to-treat; MRD, minimal residual disease; OR, odds ratio; PD, progressive disease; QC, quality control; SOC, standard of care; SST, subsequent systemic therapy.

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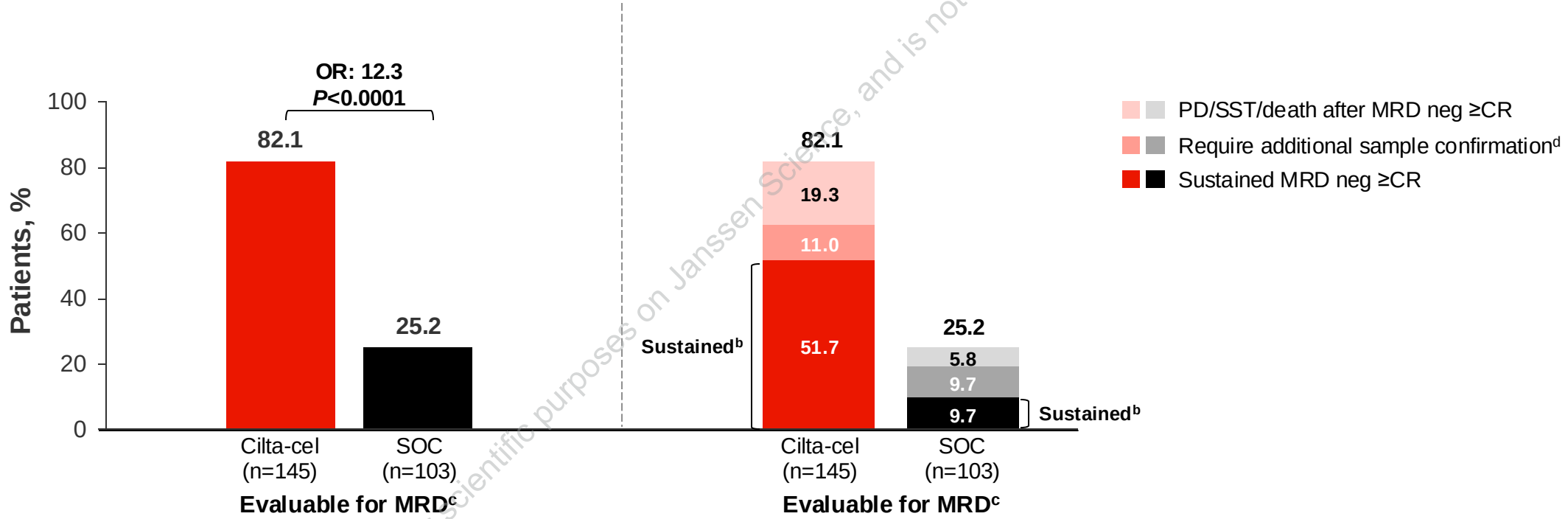
CARTITUDE-4: Overall MRD-Negative ≥CR (10^{-5}) and Sustained (≥12 Months) MRD-Negative ≥CR (10^{-5})



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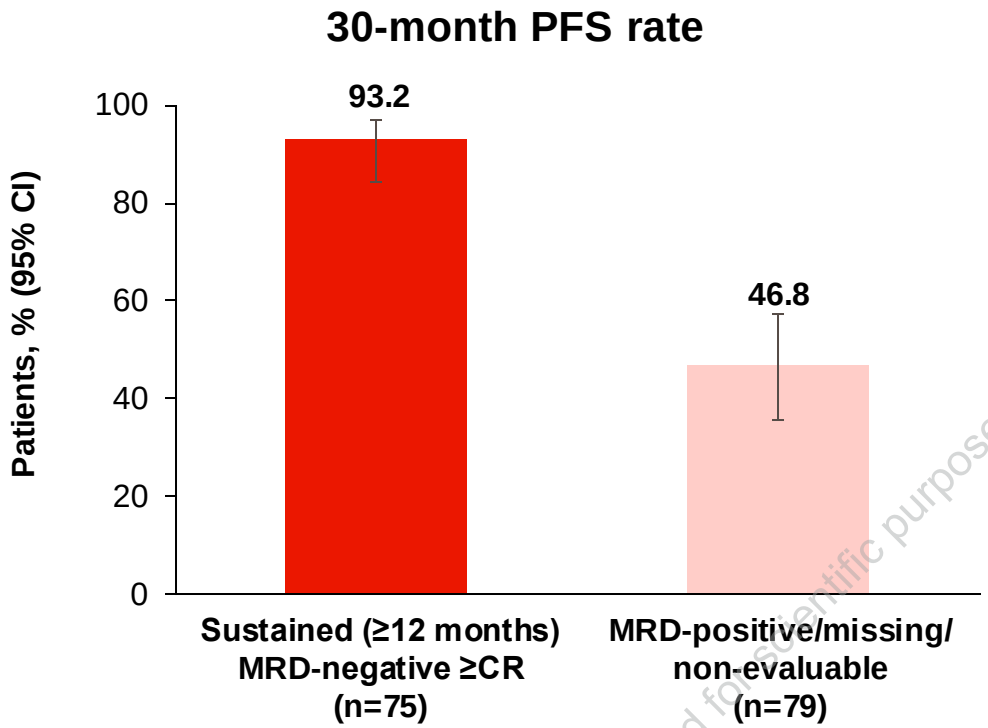
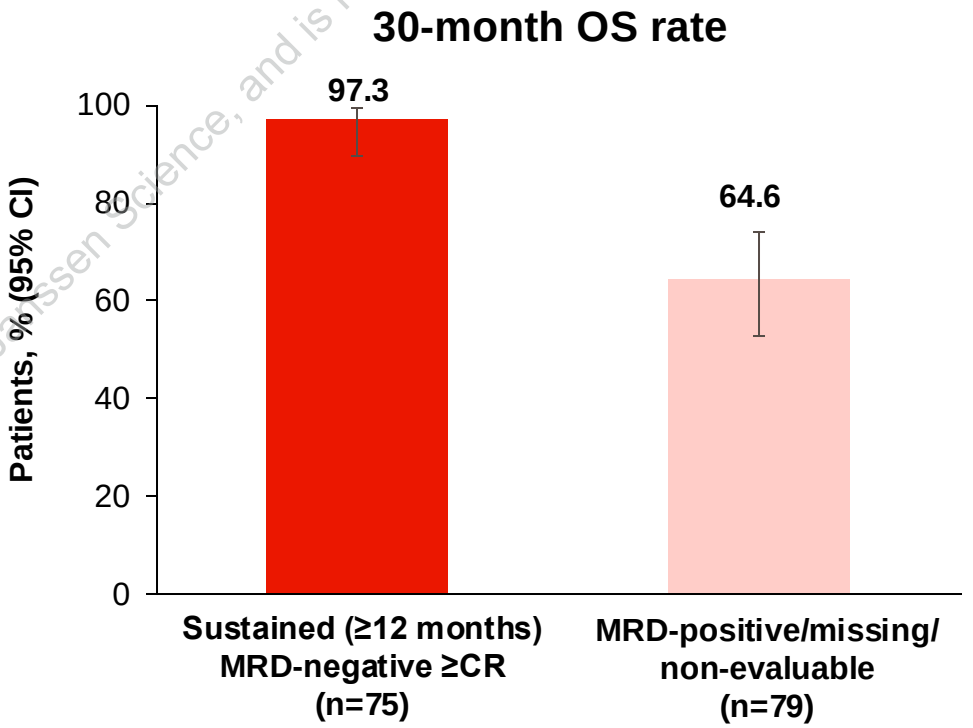
CARTITUDE-4: Survival Outcomes in Patients With Sustained MRD-Negative ≥CR Post Cilta-cel





30-month PFS and OS rates were >93% in patients with sustained (≥12 months) MRD-negative ≥CR[a]

[a]Achievement of MRD-negative and CR status in succession and confirmed by at least 1 year apart without MRD-positive status or disease progression or subsequent antimyeloma therapy in between.
cilta-cel, ciltacabtagene autoleucel; CR, complete response; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival.

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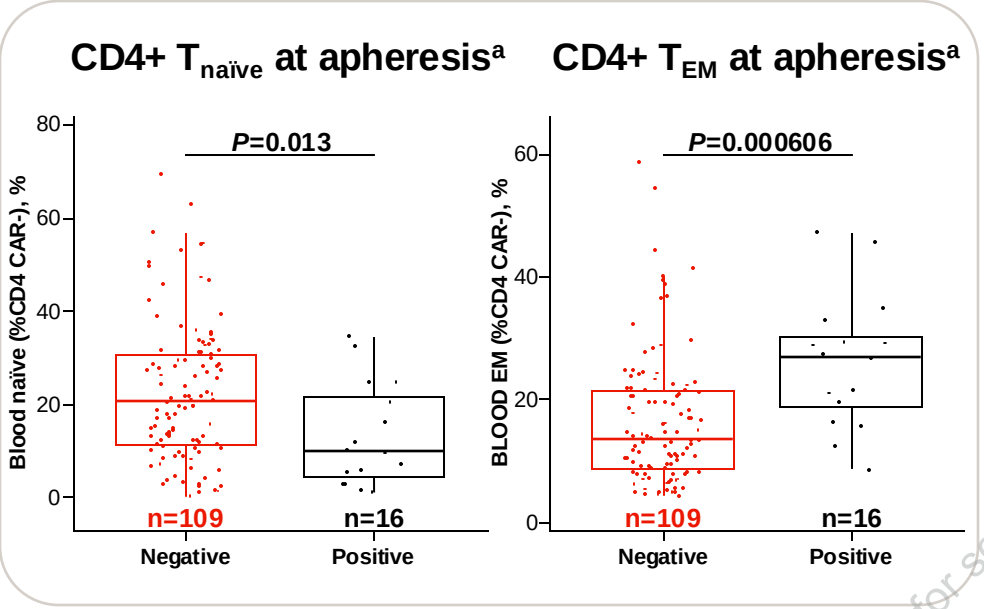
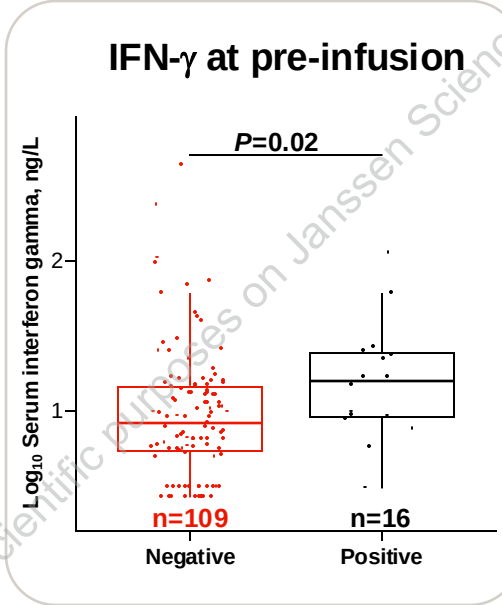
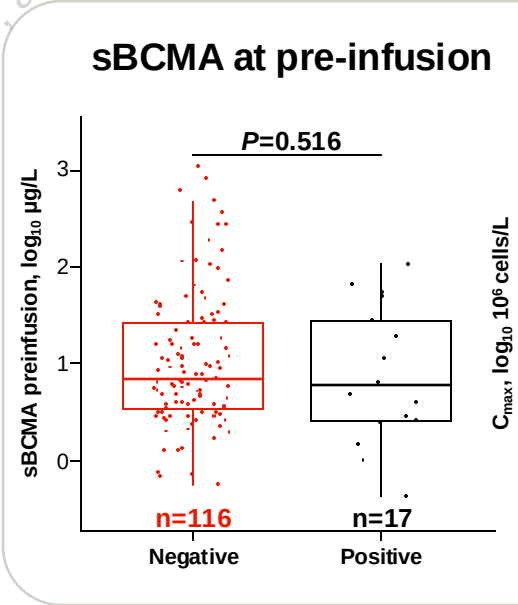
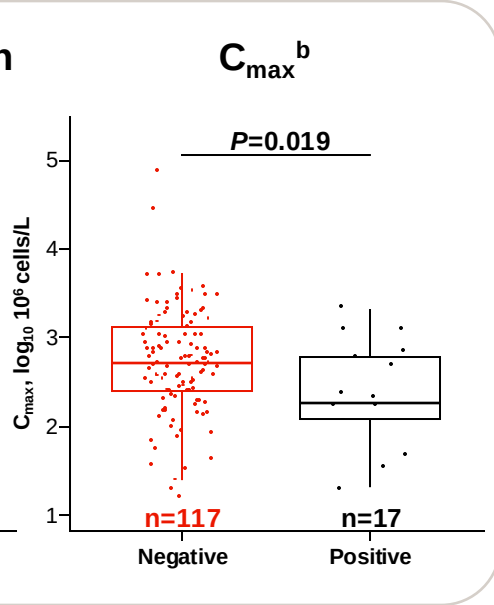
CARTITUDE-4: Biological Correlates of MRD-Negative ≥CR in the Cilta-cel Arm

- Comparison of patients with MRD-positive ≥CR and patients with MRD-negative ≥CR









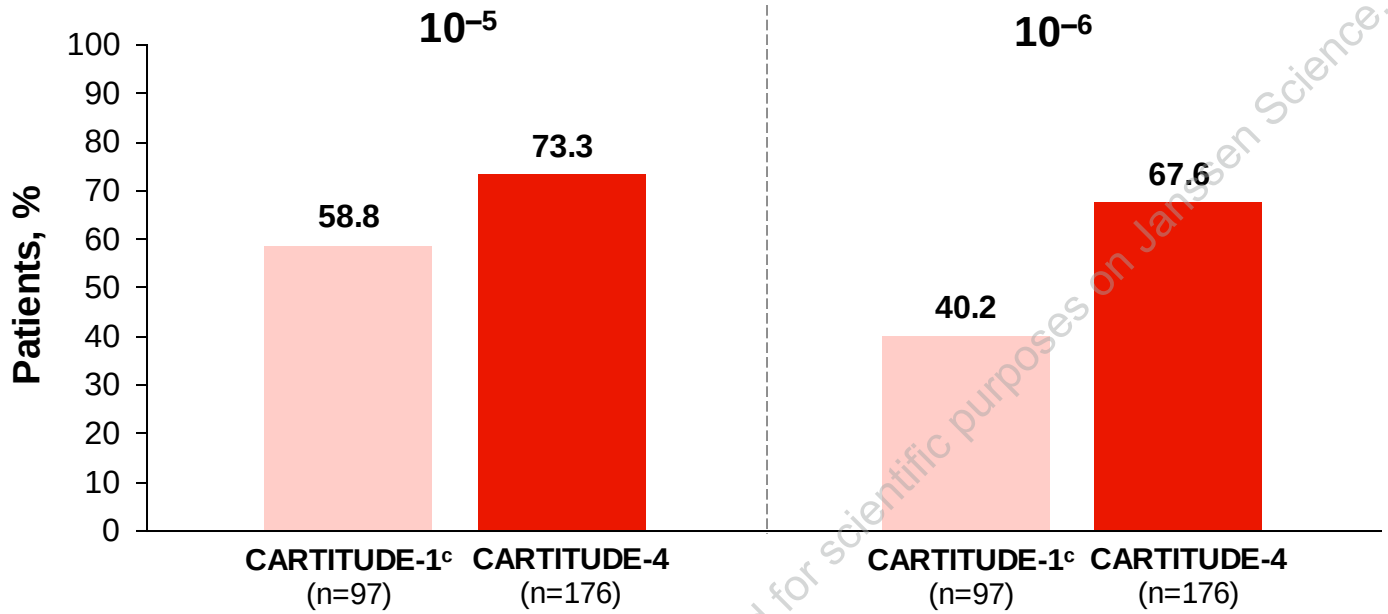
MRD-negative ≥CR status was associated with enhanced immune fitness at apheresis, lower inflammatory cytokines pre-infusion, and higher CAR+ T-cell expansion vs those with MRD-positive ≥CR; these covariates were previously associated with longer PFS in CARTITUDE-1[1]

[a]Consistent finding in CD8+ T cells at apheresis. [b]Assessed by flow cytometry.
CAR, chimeric antigen receptor; C_{max}, maximum concentration; CR, complete response; EM, effector memory; IFN, interferon; MRD; minimal residual disease; PFS, progression-free survival; sBCMA, serum B-cell maturation antigen.

1. Montes de Oca, et al. Presented at ASH; December 8–12, 2023; San Diego, CA, USA. Poster #2099.

MRD Negativity in CARTITUDE-4 vs CARTITUDE-1

Overall MRD negativity[a,b] in patients who received cilta-cel as study treatment



	CARTITUDE-1 (n=97)	CARTITUDE-4 (n=176)
30-month PFS rate, %	54.2	68.4
30-month OS rate, %	68.0	84.3

Higher rates of MRD negativity were observed in CARTITUDE-4 (1–3 prior LOT) than in CARTITUDE-1 (3+ prior LOT), corresponding to increased rates of 30-month PFS and OS

[a]Assessed by next-generation sequencing. [b]Proportion of patients who have MRD-negative status (at 10^{-5} or 10^{-6}) by bone marrow aspirate at any time after the date of randomization and prior to progressive disease or subsequent antimyeloma therapy. [c]CARTITUDE-1 data cut-off October 2022; median follow-up 33.4 months.
cilta-cel, ciltacabtagene autoleucel; LOT, line of therapy; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival.

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CARTITUDE-4: Conclusions

- Cilta-cel significantly increased overall MRD-negativity rates compared with SOC at 10^{-5} threshold (89% vs 38% of evaluable patients)
  - MRD responses with cilta-cel were deeper (10^{-6}) than with SOC (86% vs 19%)
  - MRD-negativity onset was rapid with cilta-cel (typically within 2 months from infusion)
  - All prespecified subgroups showed an MRD benefit with cilta-cel
  - Higher rates of MRD negativity were observed in CARTITUDE-4 vs CARTITUDE-1
- More patients achieved sustained (≥12 months) MRD-negative ≥CR with cilta-cel vs SOC (52% vs 10% of evaluable patients; *P*<0.0001), corresponding with high rates of PFS (93.2%) and OS (97.3%) at 30 months
- Patients achieving MRD-negative ≥CR after cilta-cel had lower baseline inflammatory cytokines, improved immune fitness at apheresis, and increased CAR-T cell expansion vs MRD-positive ≥CR patients

Patients treated with cilta-cel achieved rapid and deep MRD negativity (10^{-5} and 10^{-6}); sustained MRD-negative ≥CR corresponded to high rates of PFS and OS, supporting its prognostic value in patients treated with CAR-T cell therapy

cilta-cel, ciltacabtagene autoleucel; CAR, chimeric antigen receptor; CR, complete response; LOT, line of therapy; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

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