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# 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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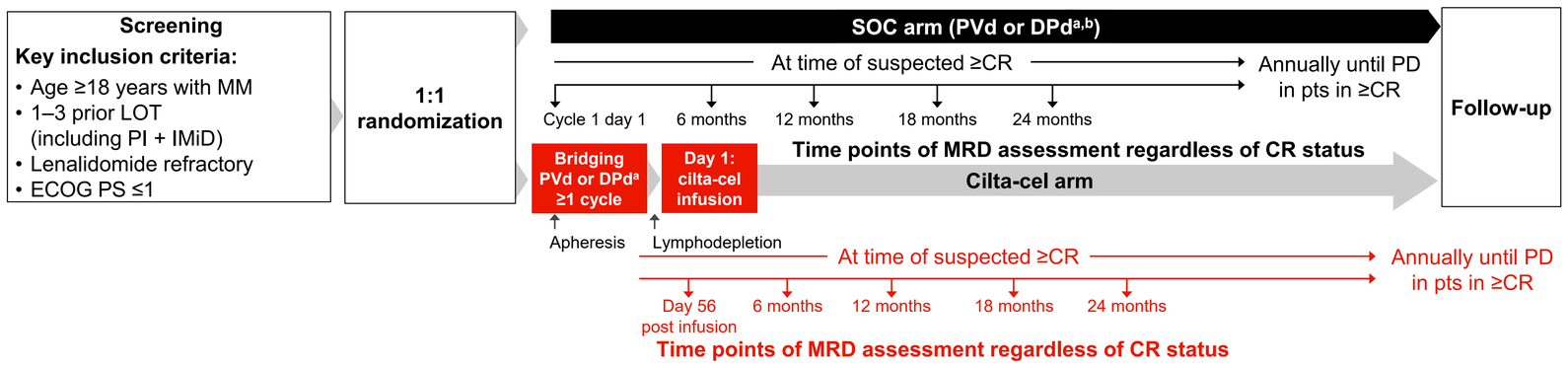
## INTRODUCTION

- There is an increasing recognition of minimal residual disease (MRD) as a primary clinical endpoint in multiple myeloma (MM) as it is linked to improved progression-free survival (PFS) and overall survival (OS)[1-5]
- In CARTITUDE-4, patients who were randomized to ciltacabtagene autoleucel (cilta-cel) had[6]
  - Significantly improved PFS vs standard of care (SOC); hazard ratio (HR), 0.29 (95% CI, 0.22–0.39); nominal *P*<0.0001
  - Median PFS was not reached with cilta-cel
  - Data cut-off date: May 1, 2024
- Cilta-cel also showed an OS benefit over SOC with HR, 0.55 (95% CI, 0.39–0.79); *P*=0.0009[6]
  - Median OS was not reached
  - Data cut-off date: May 1, 2024
- 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 complete response (CR) or better, at a median follow-up of 33.6 months in CARTITUDE-4

## METHODS

- The study design for CARTITUDE-4 is shown in **Figure 1**
- PFS was the primary endpoint; ≥CR rate, overall response rate, overall MRD-negativity rate, and OS were key secondary endpoints
- MRD was assessed centrally via next-generation sequencing (clonoSEQ v2.0; Adaptive Biotechnologies)
  - Timing of MRD assessment was from cycle 1 day 1 for SOC and from cilta-cel infusion for the cilta-cel arm
- Sustained MRD negativity ($10^{-5}$) was defined as confirmed MRD negativity ≥12 months apart without MRD positivity in between
- Patients were evaluable for sustained MRD negativity if they achieved MRD negativity and had ≥1 evaluable MRD sample ≥12 months after the first negative result or progressed/died/started subsequent treatment <12 months after the first negative result

**Figure 1: Study design of phase 3 CARTITUDE-4 cohorts**

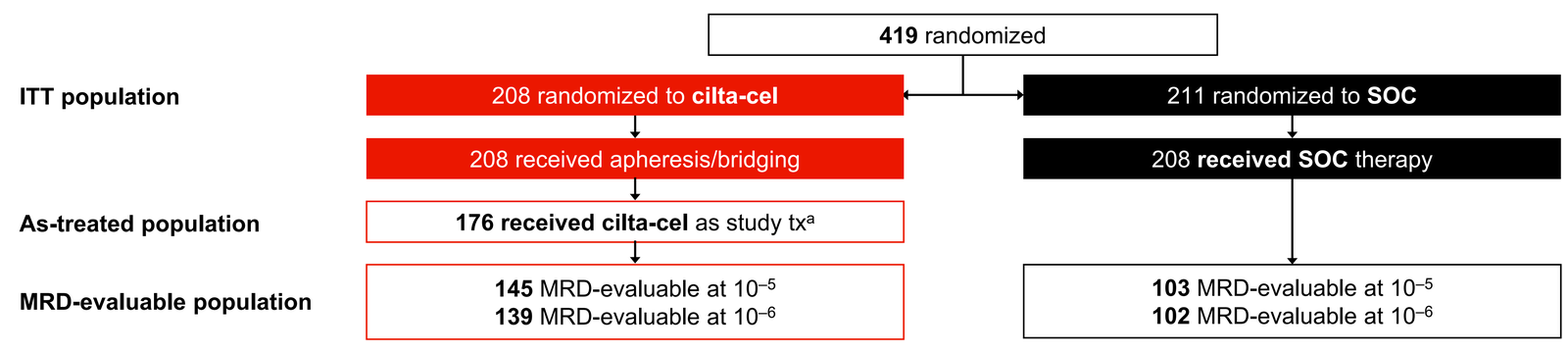



[a]Physician's choice. [b]Administered until disease progression. DPd, daratumumab, pomalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; LOT, line of therapy; PD, progressive disease; PI, proteasome inhibitor; PVd, pomalidomide, bortezomib, and dexamethasone; pts, patients.

## RESULTS

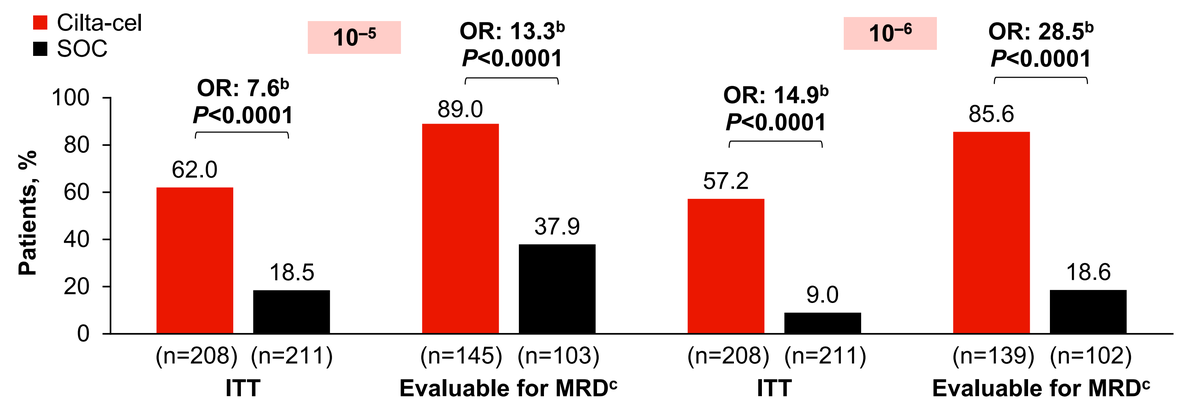
- The study population and MRD evaluability is shown in **Figure 2**
- MRD-evaluable samples passed calibration and quality control (QC), and include sufficient cells for evaluation at the respective testing threshold
- At median 33.6-month follow-up, 145 patients (cilta-cel) and 103 (SOC) were evaluable for MRD ($10^{-5}$)
- High rates of overall MRD negativity were rapidly achieved with cilta-cel, and almost all cilta-cel patients negative at $10^{-5}$ were also negative at $10^{-6}$ (**Figure 3**)
- 69% of evaluable patients achieved MRD negativity ($10^{-5}$) by day 56 (intent to treat [ITT], 48%), rising to 86% (ITT, 60%) by 6 months post cilta-cel infusion (**Figure 4**)
- Across subgroups, cilta-cel increased overall MRD-negativity rates at the $10^{-5}$ threshold vs SOC

**Figure 2 :Study population and MRD evaluability**



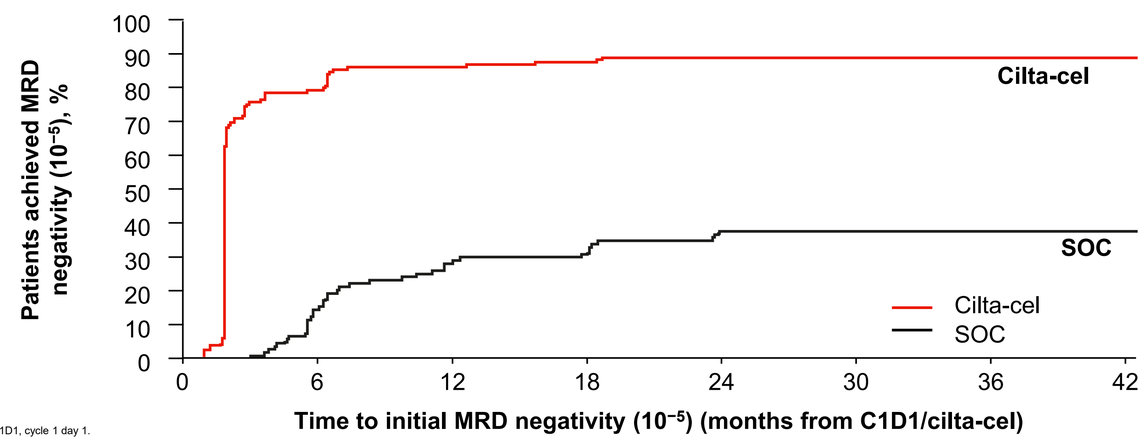

[a]32 did not receive cilta-cel as study treatment (n=30 due to disease progression; n=2 due to death during bridging therapy/lymphodepletion), of which 20 received cilta-cel as subsequent LOT. tx, treatment.

**Figure 3: Overall MRD negativity[a]**




[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. OR, odds ratio.

**Figure 4: Time to MRD negativity ($10^{-5}$) in evaluable patients**




C1D1, cycle 1 day 1.

- At the data cut-off, >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 (**Figure 5**)
- 30-month PFS and OS rates were >93% in patients with sustained (≥12 months) MRD-negative ≥CR (**Figures 6** and **7**)
  - 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

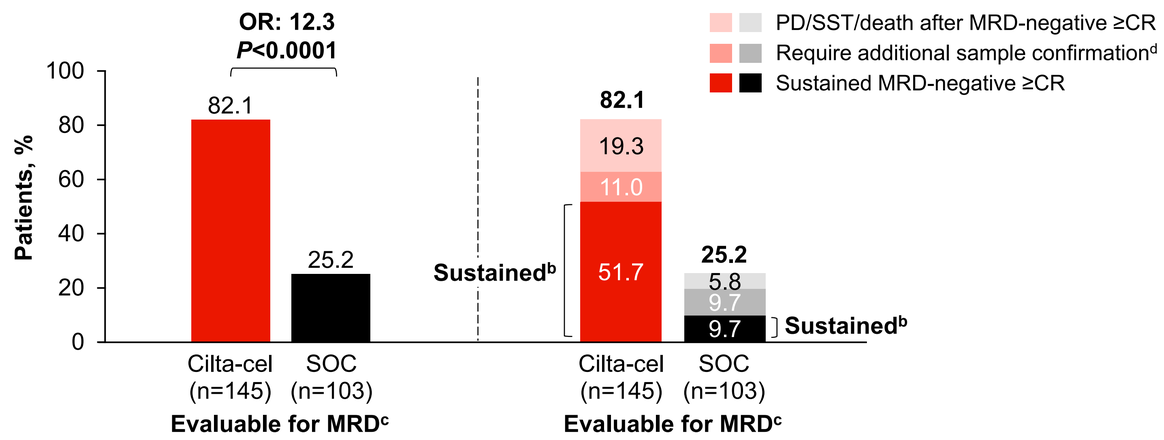
### Biologic correlates

- MRD-negative ≥CR status was associated with enhanced immune fitness at apheresis, lower inflammatory cytokines pre infusion, and higher chimeric antigen receptor (CAR+) T-cell expansion vs those with MRD-positive ≥CR; these covariates were previously associated with longer PFS in CARTITUDE-1[7]

### CARTITUDE-4 vs CARTITUDE-1

- Higher rates of MRD negativity were observed in CARTITUDE-4 (1–3 prior LOT) than in CARTITUDE-1 (3+ prior LOT)
  - 73.3% vs 58.8% ($10^{-5}$)
  - 67.6% vs 40.2% ($10^{-6}$)
- This corresponded to increased rates of 30-month PFS (68.4% vs 54.2%) and OS (84.3% vs 68.0%)

**Figure 5: Overall MRD-negative ≥CR ($10^{-5}$)[a] and sustained (≥12 months) MRD-negative ≥CR ($10^{-5}$)[b]**




[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. SST, subsequent systemic therapy.

**Figure 6: 30-month PFS rate**

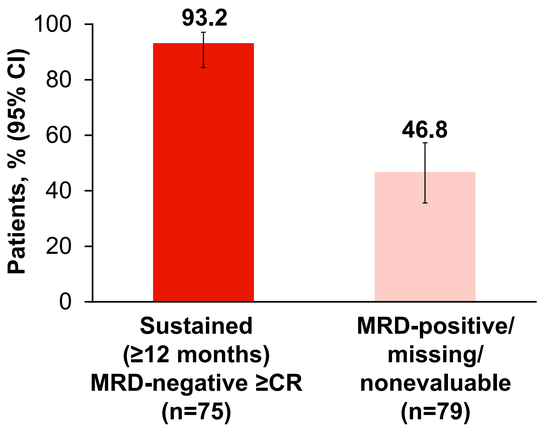
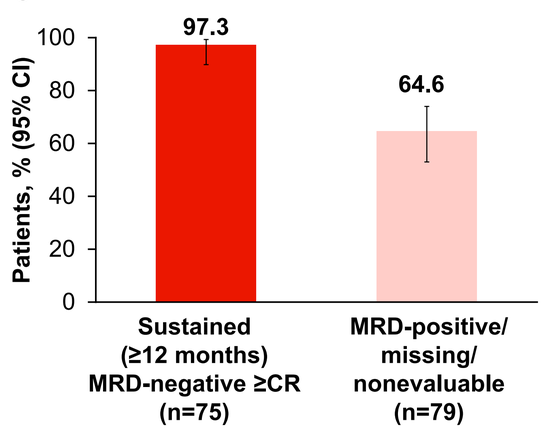



**Figure 7: 30-month OS rate**




## KEY TAKEAWAY

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

## CONCLUSIONS

- Cilta-cel significantly increased overall MRD-negativity rates compared with SOC at $10^{-5}$ threshold (89% vs 38% of evaluable patients)
  - All prespecified subgroups showed an MRD benefit with cilta-cel
  - Higher rates of MRD negativity were observed in CARTITUDE-4 vs CARTITUDE-1
- Patients treated with cilta-cel achieved rapid and deep MRD negativity ($10^{-5}$ and $10^{-6}$)
- Sustained MRD-negative ≥CR with cilta-cel corresponded to high rates of PFS and OS, supporting its prognostic value in patients treated with CAR-T cell therapy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**DISCLOSURES**

**LK** has been a consultant for Amgen, Celgene, GSK, Johnson & Johnson, and Takeda, and has received honoraria from AbbVie, Amgen, Celgene, Johnson & Johnson, Sanofi, and Takeda.

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