Cilta-cel Extends Overall Survival in Lenalidomide-Refractory Multiple Myeloma

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Multiple myeloma remains a challenging hematologic malignancy, particularly for patients whose disease progresses after initial therapies. Lenalidomide-refractory disease represents a critical juncture where effective treatment options are needed. The CARTITUDE-4 trial has previously shown that ciltacabtagene autoleucel (cilta-cel), a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell therapy, significantly prolonged progression-free survival in this patient population. An updated analysis now provides longer-term data, including overall survival outcomes, which could reshape treatment strategies for relapsed or refractory multiple myeloma.

KEY TAKEAWAYS

- The Pivot: Cilta-cel, a CAR T-cell therapy, now demonstrates a significant overall survival benefit in lenalidomide-refractory multiple myeloma, beyond its previously reported progression-free survival advantage.
- The Data: Median overall survival was not reached in the cilta-cel group versus not reached (37.7 months-not evaluable) in the standard-of-care group (HR 0.55 [95% CI 0.39-0.79]; p=0.0009).
- The Action: These findings support considering cilta-cel earlier in the treatment sequence for patients with relapsed or refractory multiple myeloma, potentially after first relapse.

Background on Multiple Myeloma and Treatment Challenges

Multiple myeloma is a plasma cell malignancy characterized by the proliferation of abnormal plasma cells in the bone marrow. Despite advances in treatment, most patients eventually experience relapse or become refractory to initial therapies. Lenalidomide, an immunomodulatory drug, is a cornerstone of multiple myeloma treatment, and resistance to it poses a significant clinical challenge. For patients with lenalidomide-refractory multiple myeloma who have received one to three prior lines of therapy, effective treatment options are crucial to improve outcomes and extend survival. CAR T-cell therapies, such as ciltacabtagene autoleucel (cilta-cel), represent a novel approach by engineering a patient's own T-cells to target BCMA, a protein highly expressed on multiple myeloma cells.

Study Design and Methods: The CARTITUDE-4 Trial

The CARTITUDE-4 trial is an open-label, multicenter, randomized, phase 3 study conducted across 81 hospital sites in the USA, Europe, Asia, and Australia. The trial enrolled adult patients (aged >18 years) with lenalidomide-refractory multiple myeloma who had received one to three previous treatment lines, including a proteasome inhibitor and an immunomodulatory drug. Patients were required to have an Eastern Cooperative Oncology Group performance

status of 0 or 1. A key amendment during the trial lowered the threshold for measurable disease to 0.5 g/dL from 1.0 g/dL serum monoclonal paraprotein to broaden access. Patients were randomly assigned (1:1) to receive either a single infusion of cilta-cel or standard of care (physician's choice of pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone)1.

The cilta-cel arm involved apheresis, bridging therapy (at least one cycle of pomalidomide-bortezomib-dexamethasone or daratumumab-pomalidomide-dexamethasone), lymphodepletion, followed by a cilta-cel infusion (0.75×10⁶ CAR T cells per kg). The standard-of-care regimens were administered in cycles as per established protocols. The primary endpoint was progression-free survival (PFS), which has been previously published. This updated report focuses on a prespecified second interim analysis of overall survival (OS) and a longer-term analysis of PFS in the intention-to-treat population. The trial is registered at ClinicalTrials.gov (NCT04181827) and is ongoing1.

Cilta-cel Significantly Extends Progression-Free Survival

Between July 10, 2020, and November 17, 2021, 208 patients were assigned to the cilta-cel group and 211 to the standard-of-care group. At a median follow-up of 33.6 months (interquartile range [IQR] 20.3-35.0), the median progression-free survival was not reached (95% CI 34.5 months-not evaluable) in the cilta-cel group, compared to 11.8 months (9.7-14.0) in the standard-of-care group. This translates to a hazard ratio (HR) of 0.29 (95% CI 0.22-0.39), indicating a substantial reduction in the risk of disease progression or death with cilta-cel1.

Overall Survival Benefit and Safety Profile

The updated analysis revealed a statistically significant improvement in overall survival. Median overall survival was not reached (95% CI not evaluable) in the cilta-cel group, whereas it was not reached (37.7 months-not evaluable) in the standard-of-care group (HR 0.55 [95% CI 0.39-0.79]; p=0.0009). This demonstrates a significant survival advantage for patients treated with cilta-cel1.

Regarding safety, maximum grade 3 treatment-emergent adverse events (TEAEs) occurred in 30 (14%) of 208 patients in the cilta-cel group and 77 (37%) of 208 in the standard-of-care group. The most common grade 3 TEAEs were anemia (35%) in the cilta-cel group and neutropenia (28%) in the standard-of-care group. Maximum grade 4 TEAEs were more frequent in the cilta-cel group (75%) compared to standard of care (56%), primarily due to neutropenia (73% with cilta-cel vs. 54% with standard of care). Serious TEAEs occurred in 98 (47%) patients in each group. Deaths in the safety population occurred in 50 (24%) in the cilta-cel group and 82 (39%) in the standard-of-care group. Treatment-related adverse events led to death in six (3%) patients in the cilta-cel group (four due to infection) and five (2%) in the standard-of-care group (all due to infection)1.

Clinical Implications and Future Directions

The significantly improved overall survival and progression-free survival observed with cilta-cel in the CARTITUDE-4 trial provide compelling evidence for its efficacy in lenalidomide-refractory multiple myeloma. These findings suggest that cilta-cel could be considered earlier in the treatment paradigm for patients with relapsed or refractory multiple myeloma, potentially after first relapse, rather than reserving it for later lines of therapy. The safety profile, while including higher rates of some grade 4 hematologic events like neutropenia with cilta-cel, is manageable within the context of CAR T-cell therapy and its associated monitoring and supportive care protocols.

Why this matters for clinical practice today: The demonstration of an overall survival benefit with cilta-cel in earlier

lines of therapy for lenalidomide-refractory multiple myeloma is a pivotal development. Clinicians managing these patients now have stronger evidence to consider CAR T-cell therapy earlier, potentially before patients become heavily pretreated and less fit for intensive treatments. This shift could lead to better long-term outcomes for patients who have limited options after failing lenalidomide-based regimens. Careful patient selection, robust supportive care, and access to specialized CAR T-cell centers will be critical for optimal implementation.

Limitations and Next Steps

While the CARTITUDE-4 trial provides robust data, some limitations should be considered. The open-label design could introduce some bias, although objective endpoints like PFS and OS are less susceptible. The follow-up duration, while extended, is still evolving, and longer-term data on durability and late-onset adverse events will be important. Further research is needed to understand the optimal sequencing of cilta-cel with other emerging therapies and to identify patient subgroups who may benefit most from earlier intervention. Ongoing follow-up of the CARTITUDE-4 trial will continue to provide valuable insights into the long-term efficacy and safety of cilta-cel in this patient population1.

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REFERENCES

1. 1. Einsele H, San-Miguel J, Dhakal B, et al. Cilta-cel in lenalidomide-refractory multiple myeloma (CARTITUDE-4): an updated analysis including overall survival from an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2026;27(2):254-268. doi:10.1016/S1470-2045(25)00653-9

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