EDITORIAL

Toward functional cure in relapsed/refractory multiple myeloma: long-term outcomes from CARTITUDE-1 study cement the role of CAR-T cells

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The introduction of T-cell directed therapies, including chimeric antigen receptor (CAR)-T cell therapy and bispecific antibodies, for patients with relapsed/refractory (RR) multiple myeloma (MM), has significantly improved outcomes, allowing the possibility for long-term disease control and a potential cure for a proportion of patients [1–4]. This has been further supported by the long-term outcomes from the CARTITUDE-1 study, which enrolled a heavily pretreated challenging population of patients, including 25% with high-risk cytogenetics [1]. Jagannath et al. reported a median overall survival (OS) of 60.7 months and importantly a sustained response with durable progression-free survival (PFS) in one-third of patients treated with a single infusion of ciltacabtagene autoleucel (cilta-cel), without maintenance therapy, reinforcing the concept of functional cure for a selected group of patients [1].

The CARTITUDE-1 study, a phase Ib/II, open-label, multicenter trial, enrolled 97 triple-class-exposed RRMM patients (87.6% triple-class refractory and 97% resistant to daratumumab) [2]. This represents a particularly difficult-to-treat population, with aggressive disease biology and poor outcomes historically—median OS rarely exceeding 12 months in previous reports [5, 6]. In this context, a median OS of 60.7 months following a single infusion of cilta-cel is remarkable [1]. At a median follow up of 61.3 months, 32 of the 97 patients (33%) remained progression-free, with no additional therapy; of those all but 1 patient achieved a stringent complete response (sCR) as best response. Importantly, a subgroup of 12 patients treated at a single center, achieving sCR, with complete follow-up, had persistent MRD negativity (at 10^{-5} threshold) and PET-negativity at year five [1, 7]. This depth and durability of response in a high-risk population represent a meaningful milestone, supporting the increasingly realistic concept of a "functional cure" in myeloma, as demonstrated with cilta-cel [1].

Additionally, correlative biomarker analyses from CARTITUDE-1 provide valuable insights into long-term remission determinants, specifically lower tumor burden at time of infusion, and better hematologic parameters (higher hemoglobin levels, platelet counts, and T-cell to neutrophil ratios), suggesting the impact of an intact host immune competence. At the cellular level, patients with durable remission had apheresis products enriched in naïve and memory T-cells, pointing to superior T-cell fitness at the time of CAR-T manufacturing. Furthermore, they exhibited a higher effector-to-target (E:T) ratio, potentially enabling more robust and sustained anti-myeloma activity [1]. These findings may help define predictive biomarkers for future patient selection and CAR-T product optimization.

Encouragingly, the long-term safety profile showed no new concerns. No new late-onset neurotoxicity events—such as Parkinsonism—were observed beyond year five, and the incidence of grade ≥3 infections and second primary malignancies remained low [1]. These data strengthen the case for cilta-cel as a well-tolerated, one-time treatment option with the potential for durable disease control.

One of the most compelling aspects of CARTITUDE-1 is long-term follow-up. With a median of over five years, it represents, together with the LEGEND-2 study [8], the longest follow-up reported to date for BCMA-targeted CAR-T therapy in MM. The depth and durability of response, particularly in the absence of maintenance therapy—positions cilta-cel at the forefront of emerging treatment strategies for patients with RRMM, suggesting the potential for cure for a select population of patients, given the sustained MRD negativity [1].

Beyond clinical efficacy, the study provides useful insights into biomarkers linked to long-term benefit. Patients with durable responses tended to have better T-cell fitness, lower tumor burden, and more favorable immune profiles at baseline [1]. These findings support a more personalized use of CAR-T therapy in the future, helping to guide patient selection and possibly improve product design.

Finally, these results are not only statistically significant but also highly relevant in the current real-world practice. In triple-class refractory patients—where treatment choices are limited and outcomes have been poor [5]—these results may help reshape expectations for this high-risk population, both in trial design and routine care.

Despite its historic significance, and as with any single-arm trial, CARTITUDE-1 has important limitations that should be discussed and acknowledged.

In addition to the lack of a control group which limits the ability to interpret the survival benefit, the small sample size, and the highly selected population of patients, the exploratory nature of this post-hoc long-term analysis—without adjustment for multiplicity—may indicate that statistical comparisons should be considered as hypothesis-generating rather than confirmatory with a susceptibility for confirmation bias.

In addition, the subgroup of 12 patients with complete MRD and PET data at year five came from a single center, raising the possibility of selection bias and limiting the generalizability of the findings [1]. While their outcomes are encouraging, they may not fully reflect the entire study population, or general MM patients.

Another important limitation is the lack of standardized assessments beyond year three, with patients having been rolled over to the CARTinue follow-up study, where evaluations were performed per local standard of care, resulting in incomplete long-term data on MRD status and immune monitoring [9]. Future

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studies should aim to preserve standardized data collection beyond protocol closure to better understand late relapses and predictors of sustained benefit.

The CARTITUDE-1 long-term report provides a transformative impact on clinical practice and represents a pivotal benchmark in the field, which helps in redefining expectations in the treatment paradigm of multiple myeloma after showing that a single infusion of cilta-cel can achieve sustained remission and long-term survival in a heavily pretreated population of patients [1]. These results support rethinking of how, when, and for whom CAR-T therapy should be used. They, however, raise important questions about the use of biomarkers for patient selection, the optimal treatment sequencing, the role of autologous stem cell transplantation (ASCT), and most importantly, challenge the previously widely accepted assumption that myeloma is incurable.

Building on these findings, the CARTITUDE-4 study has already shown that moving cilta-cel earlier in the treatment course can improve outcomes compared to standard regimens in lenalidomide-refractory patients after one to three prior lines [10]. Notably, MRD negativity was achieved in 73% of patients, exceeding the 59% seen in CARTITUDE-1 and reinforcing the idea that earlier intervention may further improve the depth and durability of response.

Ongoing trials, including CARTITUDE-5 and -6, are now exploring cilta-cel in newly diagnosed patients [11, 12]. These studies might help refine the role of ASCT as well as maintenance therapy during earlier lines of treatment.

At the same time, the biomarker insights from CARTITUDE-1 provide the possibility for a more refined patient selection, potentially identifying those most likely to achieve long-term benefit based on baseline immune competence and tumor characteristics [1]. Nonetheless, additional studies are needed to identify the important thresholds for hematological and immune parameters, for efficacy as well as safety.

Similar to historic studies, these results also pave the way for additional evaluation for single therapies versus combination treatments, but most importantly with the reported durable efficacy future efforts should target both role of CAR-T cell therapy for frail patients, in addition to the equitable access globally for CAR-T and other novel therapies.

As the field continues to evolve, it's becoming increasingly clear that the therapeutic landscape is shifting. In a disease historically defined by continuous treatment and inevitable relapse, data from cilta-cel and other CAR-T therapies, suggest that, for some patients, durable, treatment-free remission—and even the possibility of cure— may no longer be out of reach [1, 9–12].

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DATA AVAILABILITY

Data sharing not applicable to this article as no new datasets were generated or analyzed during the current study.

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AUTHOR CONTRIBUTIONS

TdS drafted the first version of the manuscript. NM revised and edited the manuscript. MM critically revised and finalized the manuscript. All authors approved the final version.

COMPETING INTERESTS

MM declares receiving honoraria from Celgene, Amgen, Bristol Myers Squibb, Janssen, Takeda, Pfizer, Novartis, Jazz Pharmaceuticals, Sanofi, Medac; and has a consulting or Advisory Role for Jazz Pharmaceuticals, Sanofi, MaaT Pharma, Novartis, GlaxoSmithKline, Johnson & Johnson/Janssen. TdS and NM declare no relevant conflict of interests in this review.