Phase III Randomized Evidence for BCMA-Directed CAR T-Cell Therapy Versus Standard Regimens in Relapsed/Refractory Multiple Myeloma: A Systematic Review and Meta-Analysis

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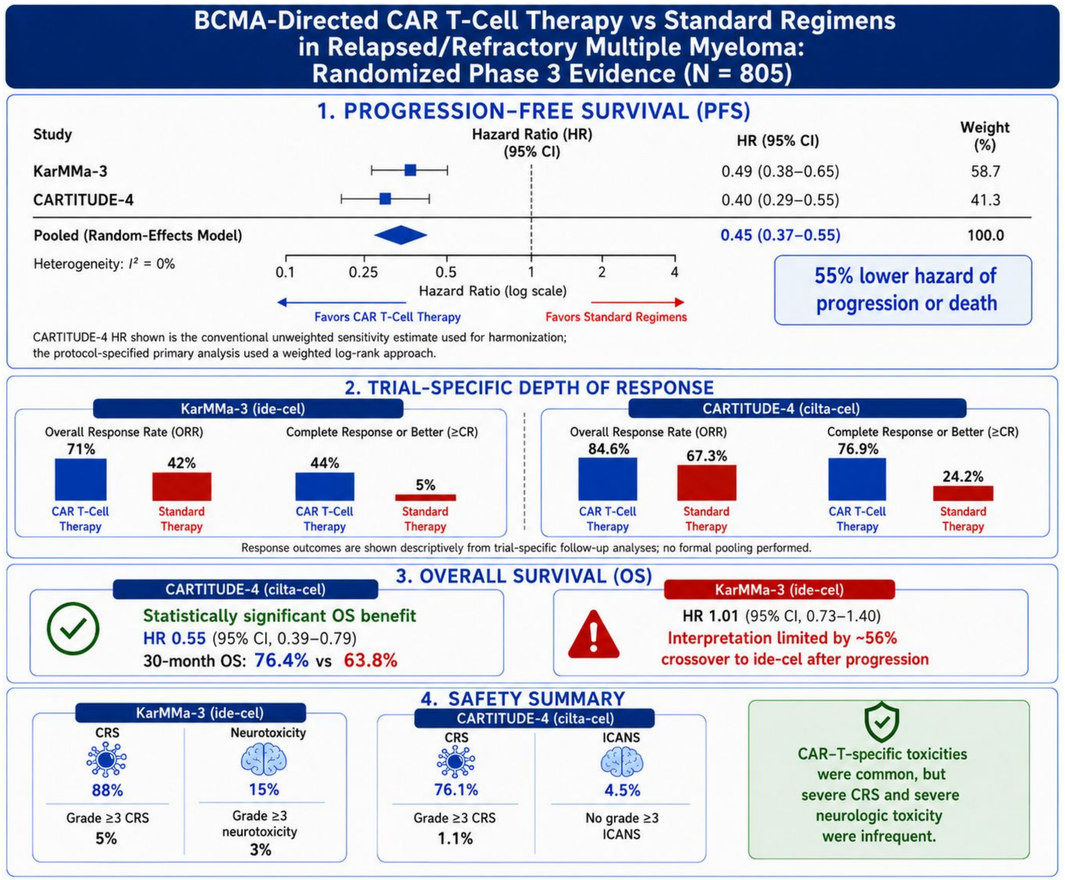
INTRODUCTION

BCMA-directed chimeric antigen receptor T-cell (CAR-T) therapy has transformed the treatment of relapsed/refractory multiple myeloma (RRMM), producing deep and durable responses in patients previously exposed to proteasome inhibitors, immunomodulatory agents, and anti-CD38 therapy. Initial approvals were largely supported by single-arm studies in heavily pretreated populations; however, randomized phase 3 trials now provide direct comparisons with contemporary standard regimens. We performed a systematic review and meta-analysis of randomized phase 3 evidence evaluating BCMA-directed CAR-T therapy versus standard-of-care treatment in RRMM, focusing on progression-free survival (PFS), depth of response, overall survival (OS), and toxicity.

METHODS

PubMed/MEDLINE, Embase, ClinicalTrials.gov, and major hematology conference proceedings were searched through May 2026 for randomized phase 3 trials comparing BCMA-directed CAR-T therapy with standard regimens in adults with RRMM. The primary endpoint was PFS; secondary outcomes included OS, overall response rate (ORR), complete response (CR) or better, minimal residual disease (MRD) negativity, and treatment-related toxicities. PFS hazard ratios (HRs) were pooled using inverse-variance methods, with heterogeneity assessed using the I^2 statistic. Because CARTITUDE-4 used a protocol-specified weighted PFS analysis due to early non-proportional hazards, the conventional unweighted HR was used in the harmonized pooled analysis to improve comparability with KarMMa-3.



RESULTS

Two randomized phase 3 trials comprising 805 patients met eligibility criteria. KarMMa-3 compared idecabtagene vicleucel (ide-cel) with investigator-selected standard regimens after 2–4 prior therapies, while CARTITUDE-4 compared ciltacabtagene autoleucel (cilta-cel) with pomalidomide-based therapy after 1–3 prior lines in lenalidomide-refractory disease. PFS significantly favored CAR-T therapy in both KarMMa-3 (HR 0.49; 95% CI, 0.38–0.65) and CARTITUDE-4 using the unweighted sensitivity estimate (HR 0.40; 95% CI, 0.29–0.55). The pooled analysis demonstrated a 55% reduction in the risk of progression or death (HR 0.45; 95% CI, 0.37–0.55), with no observed heterogeneity (I^2=0%). Both trials also demonstrated substantially higher ORR, CR-or-better, and MRD-negativity rates with CAR-T therapy. Updated CARTITUDE-4 follow-up demonstrated an OS benefit with cilta-cel, whereas OS interpretation in KarMMa-3 was complicated by substantial crossover to ide-cel. CRS and neurotoxicity were common but predominantly low grade.

CONCLUSIONS

Randomized phase 3 evidence demonstrates a large and consistent PFS benefit with BCMA-directed CAR-T therapy compared with active standard regimens in RRMM, with a pooled 55% reduction in progression or death and no observed statistical heterogeneity. CAR-T therapy also produced substantially deeper responses and greater MRD negativity, while longer-term CARTITUDE-4 data demonstrate an emerging survival advantage. These findings support moving BCMA-directed CAR-T therapy earlier in the treatment course of appropriately selected patients with RRMM rather than reserving cellular therapy exclusively for heavily pretreated disease.