



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

652.Multiple Myeloma: Clinical and Epidemiological

A Novel Composite Endpoint of Toxicity- and Progression-Free Survival after B-Cell Maturation Antigen (BCMA)-Directed Chimeric Antigen Receptor T-Cell Therapy for Relapsed/Refractory Multiple Myeloma

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Introduction: BCMA-directed chimeric antigen receptor T-cell therapy (CAR T), idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), are approved for patients with relapsed and/or refractory (R/R) multiple myeloma (MM). Pivotal KaRMMA and CARTITUDE-1 trials as well as real-world data demonstrated heterogeneity in toxicity and efficacy between ide-cel and cilta-cel. To account for such differences, we have established a novel composite endpoint of toxicity-free, progression-free survival within 3 months (TPFS3) after anti-BCMA CAR T therapy. We also studied factors associated with TPFS3 across ide-cel and cilta-cel and the impact of TPFS3 on overall survival (OS) after CAR T.

Methods: We analyzed a retrospective cohort of 133 consecutive recipients of ide-cel or cilta-cel at Moffitt Cancer Center (05/2021-03/2023). TPFS3 was defined as absence of severe (Grade \geq 3) cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenia(s), myeloma progression/stable disease (PD/SD), and non-relapse mortality (NRM) within 3 months after CAR-T infusion. CRS and ICANS were graded according to ASTCT Consensus grading. Cytopenias were graded according to CTCAE v5.0 and defined as two (or more) timepoint uni- or multilineage cytopenia, including any Grade \geq 2 cytopenia at post-CAR T Day 30 deepening to at least Grade \geq 3 at Day 60 and/or Day 90. Factors associated with TPFS3 were assessed via multivariate logistic regression analysis (MVA). Landmark Cox survival analysis at the 3-month timepoint examined the impact of TPFS3 on subsequent overall survival (OS). All analyses were performed using SAS and R.

Results: In total, 48.1% (N= 64; median age=66 years [range, 45-82]; male=44%) of the patients were alive, toxicity- and progression-free by 3 months after CAR T infusion. TPFS3 components included PD/SD (N=30, 43.5%), severe cytopenias (N=26, 37.7%), ICANS (N=8, 11.6%), CRS (N=3, 4.3%), and NRM (N=2, 2.9%) (Figure 1A). In the univariate analysis, TPFS3 patients differed from the rest of the cohort according to lower marrow burden ($p=0.025$), revised international staging system (R-ISS) (I/II vs III; $p=0.015$), CRP ($p=0.019$) and ferritin ($p=0.002$) levels at lymphodepletion (LD). The use of ide-cel (N=109) vs cilta-cel (N=24) was not significantly associated with TPFS3 ($p=0.119$).

In the MVA logistic regression, lower ferritin level (median cut off=228 ng/mL) at LD was associated with TPFS3 (odds ratio [OR]=0.37 [95%CI, 0.18-0.78], $p=0.008$) after adjusting for age, myeloma marrow burden, presence of extramedullary disease, R-ISS, CAR T product (all $p>0.1$), and CRP (median cut off=0.41mg/dL) at LD (OR=0.51 for lower vs higher, [95%CI, 0.25-1.05], $p=0.069$) included in the final model together with ferritin. In the landmark Cox survival analysis at 3 months, TPFS3 was

associated with 6.54-fold superior OS (hazard ratio [HR]=0.15, 95%CI 0.05-0.52, $p=0.003$) (Figure 1B) after adjustment for potential confounders (age, gender, CRP, CAR-T product, marrow burden, R-ISS, extramedullary disease; all $p>0.1$). Other prognostic risks associated with inferior OS in the final model of the landmark analysis included the use of bridging therapy (HR=3.98 [95%CI, 1.30-12.20], $p=0.016$), ECOG ≥ 2 at LD (HR=4.53 [95%CI, 1.57-13.07], $p=0.005$) and higher ferritin level at LD (HR=2.60 [95%CI, 0.95-7.13], $p=0.063$).

Conclusions: We found that 48.1% of anti-BCMA CAR T recipients with R/R MM were alive and free of TPFS3-defining events. Myeloma response failure, cytopenias and severe ICANS were the top leading components of TPFS3 which was best predicted by ferritin level at LD. TPFS3 independently predicted long-term OS. Thus, TPFS3 may serve as an ideal composite safety and efficacy endpoint in future myeloma trials with BCMA-directed CAR T.

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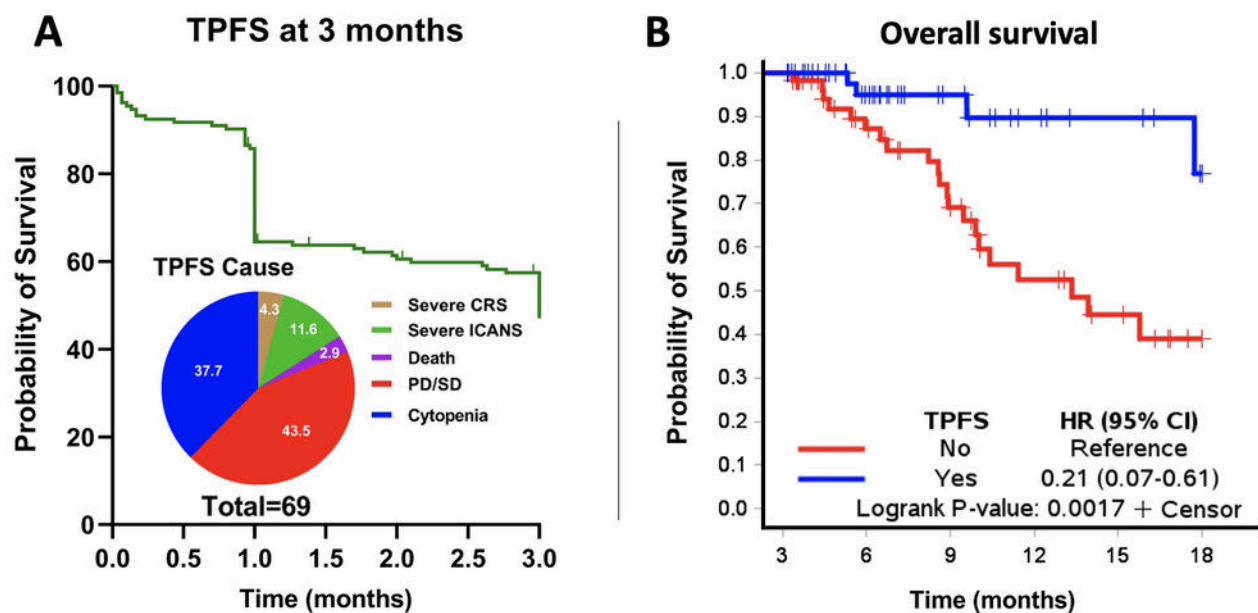


Figure 1. A Kaplan-Meier curve of TPFS3 and distribution of its components; B. Overall survival predicted by TPFS3 in the landmark analysis at 3-months

Figure 1

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