3. RELAPSED/REFRACTORY MULTIPLE MYELOMA

EARLIER USE OF CILTACABTAGENE AUTOLEUCEL IS ASSOCIATED WITH BETTER IMMUNE FITNESS AND STRONGER IMMUNE EFFECTS AS SHOWN BY CORRELATIVE ANALYSIS OF PERIPHERAL BLOOD AND THE BONE MARROW TUMOR MICROENVIRONMENT FROM THE CARTITUDE-4 STUDY

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Introduction. Cilta-cel is approved in the US and EU for lenalidomide-refractory multiple myeloma (MM) after ≥1 prior line of therapy (pLOT), including a proteasome inhibitor and an immunomodulatory agent, based on CARTITUDE-1 (NCT03548207) and CARTITUDE-4 (NCT04181827). We investigated cilta-cel's mechanism of action by correlating peripheral blood and the bone marrow TME biomarkers with progression-free survival (PFS) and number of pLOT in patients with relapsed/refractory MM (RRMM) from CARTITUDE-1 and CARTITUDE-4.

Methods. Biomarker analyses used peripheral blood and bone marrow aspirates (BMAs) collected from CARTITUDE-1 and CARTITUDE-4. Flow cytometry immunophenotyping used peripheral blood at baseline/time of apheresis (samples from both trials). Immune fitness at baseline was determined by pLOT and in association with PFS. Gene set enrichment scores were derived from TME RNA sequencing data using BMAs. Mixed-effects models were used to recognize signatures/pathways modulated over time (Day 28 and at 6 months post infusion vs screening) and in association with PFS and pLOT.

Results. Cilta-cel was received as study treatment by 176 patients from CARTITUDE-4 and 97 from CARTITUDE-1. Immunophenotyping data were obtained from 248 peripheral blood samples (1 pLOT, n=56; 2 pLOT, n=61; ≥3 pLOT, n=131). At apheresis, CD4+ naïve T cells were higher with 1 or 2 pLOT vs ≥3 pLOT; no difference was found with 3–4 vs 5–6 vs ≥7 pLOT. Higher baseline levels of CD4+ naïve T cells were linked to longer PFS. TME gene expression data were obtained from 148 BMA samples (screening, n=50; Day 28, n=50; 6 months, n=48) from CARTITUDE-4. Gene expression signatures indicate depletion of B cells and antibodies at Day 28 post cilta-cel infusion (partial recovery at 6 months); these results were corroborated by flow cytometry and immunoglobulin quantification. Elevated expression was observed for myeloid- (including tumor-associated macrophages [TAM, likely M1]), and cytotoxic-T cell–associated genes at Day 28, while increased expression of genes linked to B cell receptors, T cell differentiation and activation, and cytokine signaling pathways were found at Day 28 and 6 months. Patients with >18 months PFS had higher levels of M1 TAM at Day 28; those with shorter PFS had higher regulatory T cells and more suppressed interferon pathway genes at 6 months. A more profound B cell depletion on Day 28, improved recovery at 6 months, and elevated B cell receptor signaling were inferred from gene expression in patients with fewer pLOT. Patients with 1 pLOT showed higher elevation of M1 TAM expression on Day 28 vs 3 pLOT.

Conclusions. Correlative biomarkers indicate that longer PFS is associated with improved immune fitness and responses post cilta-cel infusion. Peripheral immune fitness was more pronounced with 1 and 2 pLOT vs 3 pLOT and beyond, where deterioration plateaued, suggesting the impact of T cell immune fitness on PFS may be limited for >3 LOT. Other covariates may play a significant role in balancing this compromised intrinsic T cell immune fitness at apheresis, thereby contributing to PFS durability >3 pLOT. These results support the treatment of MM with cilta-cel in earlier LOTs.