Initial Dose-Escalation and Clinical Results from a Phase 1 Trial of PSMA-redirected/TGFβ-insensitive CAR-T cells in Metastatic Castration-Resistant Prostate Cancer

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Background:
Adoptive immunotherapy with CAR-T cells is a novel approach for the treatment of prostate cancer. However, the prostate cancer immunosuppressive microenvironment, including high levels of TGFβ, may limit the therapeutic potential of re-directed T cells upon tumor infiltration. The inhibition of TGFβ signaling via co-expression of a dominant negative TGFβ receptor (TGFβRdn) can enhance antitumor immunity. Co-expression of TGFβRdn on PSMA-redirected CAR-T cells in *in vivo* disseminated tumor models led to increased T cell proliferation, enhanced cytokine secretion, long-term persistence, and greater induction of tumor eradication.

Methods:
We are conducting a first-in-human phase 1 clinical trial evaluating the safety and preliminary efficacy of lentivirally-transduced PSMA-redirected/TGFβ-insensitive CAR-T cells (CART-PSMA-TGFβRdn) in metastatic CRPC (NCT03089203). In a 3+3 dose-escalation design, patients received a single dose of 1-3 x $10_7/m_2$ (Cohort 1) or 1-3 x $10_8/m_2$ (Cohort 2) CART-PSMA-TGFβRdn cells without lymphodepleting chemotherapy. In Cohort 3, 1-3 x $10_8/m_2$ CART-PSMA-TGFβRdn cells was administered following a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine. Quantitative PCR of CART-PSMA-TGFβRdn DNA was performed at serial time-points to evaluate for CAR-T expansion and persistence in peripheral blood and trafficking to target tissues.

Results:
Seven patients have received a single dose of CART-PSMA-TGFβRdn. All infusion products of CART-PSMA-TGFβRdn have met target transduction efficiency. Six patients received CART-PSMA-TGFβRdn cell infusions at the initial specified dose levels (Cohort 1, N=3; Cohort 2, N=3). In Cohort 2, two patients developed Grade 3 CRS requiring tocilizumab (anti-IL6R) rescue, and one patient developed Grade 3 CAR-T neurotoxicity requiring corticosteroids. These CRS events rapidly resolved with the above support, and no dose-limiting toxicities were observed. One patient had transient PSA decline. In Cohort 3, one treated patient developed grade 4 CRS requiring multi-modal immunosuppression. A rapid and robust PSA decline in this patient was observed from a peak value of 36 ng/ml on day 0 to <1 ng/ml by day +10. The patient ultimately died in the setting of enterococcal bacteremia, septic shock, and multi-organ failure. Marked increases in inflammatory cytokines (IL-6, IL-15, IL-2, IFNg) and ferritin correlated with all CRS events. A dose-dependent and lymphodepletion chemotherapy-dependent relationship was observed with CART-PSMA-TGFβRdn cell expansion in peripheral blood and with anti-tumor response as measured by PSA. Peak cytokine expression levels and CAR transgene levels in Cohort 3 were comparable to patients with acute lymphoblastic leukemia receiving anti-CD19 CAR-T.

Conclusions:
We have observed significant high-grade CRS in patients treated with CART-PSMA-TGFβRdn, which reflects an important clinical marker of bioactivity and potential anti-tumor efficacy. CRS appears to be dose- and lymphodepletion chemotherapy-dependent. A currently accruing modified protocol will seek to optimize the therapeutic window with CART-PSMA-TGFβRdn. Ongoing correlative analyses will interrogate the therapeutic contribution of TGFβRdn, as well as early markers of response and resistance to CART-PSMA-TGFβRdn therapy.

Conflict of Interest: None

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