

ANALYSES OF SEVERE IMMUNE-MEDIATED TOXICITY IN PATIENTS WITH ADVANCED MCRPC TREATED WITH A PSMA-TARGETED ARMORED CAR T-CELLS

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Background We previously reported preliminary safety and efficacy results from a multi-center Phase 1 trial of CART-PSMA-TGFβRDN T-cells (TmPSMA-01; NCT04227275) in patients (pts) with metastatic castration resistant prostate cancer (mCRPC). Nine pts were dosed with TmPSMA-01 across three doses ranging from 1×10^7 - 3×10^8 CAR+ cells. Evidence of clinical activity was observed, however, two pts developed severe immune-mediated toxicity and experienced Grade (Gr) 5 events. These pts had no known clinically relevant risk-factors and demonstrated disparate pre- and post-infusion clinical courses. Translational research efforts to evaluate the mechanisms of immune-mediated toxicity to TmPSMA-01 were undertaken. Results are summarized herein.

Methods Pt samples collected per clinical protocol were subjected to correlative analysis platforms. Longitudinal serum and peripheral blood specimens were evaluated for soluble factors by immunoassays and TmPSMA-01 kinetics by molecular techniques, respectively. Biomarker comparisons between patients with Gr5 events and those without were made. As available, pt tissues (tumor and autopsy samples) were evaluated for TmPSMA-01 infiltration by RNA-ISH. Additionally, an *in vitro* model of immune toxicity was applied to evaluate TmPSMA-01 product potency and new CAR candidates.

Results Serum cytokines from all pts showed patterns consistent with an immune-effector response but pts with Gr5 events demonstrated an elevated inflammatory signature with higher levels of IL2, IL6, GM-CSF and IL-18, among others. Peripheral expansion of TmPSMA-01 was observed and kinetics correlated with cytokine response. Autopsy evaluation from one pt with a Gr5 event showed TmPSMA-01 lymph node tumor infiltration but no presence in the sampled brain, despite clinical presentation of immune effector cell associated neurotoxicity. Finally, *in vitro* modeling of immune-toxicity demonstrated higher cytokine levels in TmPSMA-01 cell products from Gr5 pts. Using the same assay, substituting CD2 for 41BB showed a reduction in cytokine levels without impacting efficacy.

Conclusions Correlative studies from pts who demonstrated severe immune-mediated toxicity following TmPSMA-01 revealed trends toward patient-intrinsic hyperinflammation. Biomarker findings suggest a contribution of IL-18 to TmPSMA-01-associated cytokine response which can be further explored for toxicity management. Moreover, we found no evidence of on-target, off-tumor involvement in the examined tissues. While a clear mechanism explaining the excessive immune-mediated response in 2 pts following TmPSMA-01 is not fully elucidated, our preclinical data demonstrate potential risk mitigation by replacing the 41BB co-stimulatory domain with CD2. Knowledge gained from these studies supported the development of a next-generation PSMA-targeting CAR, TmPSMA-02, to improve safety while maintaining anti-tumor activity and will be explored in a multi-center, Ph1/2 trial for pts with mCRPC.

Ethics Approval Patients were enrolled on a WCG Institutional Review Board (IRB) approved protocol, IRB#20191909, titled

“A Phase 1 Open-Label, Multi-Center Study of PSMA Targeted Genetically Modified Chimeric Antigen Receptor T Cells in Patients with Metastatic Castration Resistant Prostate Cancer.” This clinical study was designed and implemented, and the results of the trial reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice with applicable local regulations and international guidances, including the 21 CFR and all ethical principles written in the Declaration of Helsinki. The clinical study protocol and the informed consent form (ICF) were both reviewed and approved by the properly chartered IRBs and Independent Ethics Committee before the study commenced. Patients enrolled in the study underwent the appropriate Screening procedures only after providing the appropriate written consent using the approved ICF for this study.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0335>