TPS7087 **Poster Session**

CD5-deleted chimeric antigen receptor cells (Senza5 CART5) to enhance immunotherapy against T-cell non-Hodgkin lymphoma: A first-in-human phase I clinical trial (NCT06420089).

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Background: Autologous CART options for patients with relapsed or refractory (R/R) T-cell lymphomas (TCL) have faced challenges such as T-cell fratricide during CART manufacture and safety concerns regarding depletion of normal T cells. To overcome these obstacles, we proposed a dual cell population CART product, which contained both autologous 4-1BB co-stimulated CART cells against CD5 and healthy T-cells, with both populations knocked out for CD5 (CRISPR-Cas9 CD5 short-guide RNA to delete CD5 - Senza5). In vivo experiments using the dual population product of (Senza5 CART5) demonstrated increased CART5 expansion and enhanced antitumor efficacy in TCL xenograft models compared to wild-type (WT) CART5. For clinical use, a novel 5-day manufacturing process was designed to obtain a less differentiated and less exhausted product, with enhanced in vivo expansion and fitness. **Methods:** A human phase I trial was designed to determine the safety, effectiveness and recommended phase 2 dose (RP2D) of Senza5 CART5 cells in participants with R/R TCL with ≥50% expression of CD5 on malignant cells, and no circulating CD5+ cells. Participants must have a suitable backup stem cell product or donor identified in the unlikely event of T-cell aplasia. Patients with prior allo HCT are currently excluded. Cohorts of patients are treated with escalating doses of Senza5 CART5 cells ($3x10^6$ to $1.25x10^8$) using a Bayesian Optimal Interval design following lymphodepletion. The study will enroll and treat participants until a maximum of 9 participants are infused and evaluable for dose limiting toxicity (DLT) assessments at a given dose level, or a maximum of 30 DLT-evaluable participants from all dose levels are infused. The RP2D will be determined based on both safety and biological evidence of efficacy. Study objectives include frequency and severity of treatment-related adverse events, as well as efficacy by assessing overall and complete response rates, duration of response, progression-free and overall survival. Manufacturing feasibility will be determined by the frequency of product release failures and occurrence of dose failures (inability to meet targeted dose). Exploratory objectives will evaluate the persistence and trafficking of Senza5 CART5 cells in blood and tumor by characterizing the kinetics of the infused cells by flow cytometry and qPCR gene expression. We will perform profiling of the tumor microenvironment and measure systemic soluble cytokines before and after treatment. We will also assess the impact of CART5 on normal T cells, and the persistence of CD5KO untransduced T cells that are infused as part of the Senza5 CART5 product by multicolor flow cytometry and qPCR. The trial is sponsored by Vittoria Biotherapeutics and is registered at clinicaltrials.gov as NCT06420089. Enrollment in this trial has begun. Clinical trial information: NCT06420089. Research Sponsor: Vittoria Biotherapeutics.