Abstract: P1222

Title: A MULTI-CENTER, OPEN-LABEL, PHASE 1/2 STUDY OF ONCT-808, A ROR1-TARGETING CAR-T CELL THERAPY, IN ADULTS WITH RELAPSED/REFRACTORY (R/R) AGGRESSIVE B CELL LYMPHOMAS (BCL)

Abstract Type: Poster Presentation

Topic: Aggressive Non-Hodgkin lymphoma - Clinical

Background:

ROR1 is an oncoembryonic pseudo-tyrosine kinase receptor overexpressed in a variety of hematologic and solid malignancies. After birth, ROR1 is largely expressed on malignant cells; this selective expression renders it a promising therapeutic target with potential for fewer toxicities due to off-target effects or non-specific immune activation.

The ROR1 binding moiety for ONCT-808 is derived from zilovertamab. Zilovertamab vedotin demonstrated promising antitumor activity in heavily pretreated aggressive lymphoma patients (pts), with no evidence of toxicities due to off-tumor effects (Wang 2022, Spurgeon 2023). Therapeutic approaches for BCL leverage several modalities, yet challenges remain, including variable response rates, treatment resistance, and toxicity.

Thus, ROR1-specific CAR T-cell therapy represents a promising potential advancement in the treatment of aggressive BCL in pts who have previously failed or were ineligible for CD19 CAR T therapy.

Aims:

To evaluate the safety and preliminary efficacy of ONCT-808, a ROR1-specific CAR T-cell therapy in R/R BCL patients including pts who failed prior CD19 CAR T.

Methods:

This is a multicenter phase 1/2 study of ONCT-808 in R/R BCL (mantle cell lymphoma [MCL], large BCL [LBCL]). Phase 1 consists of escalation at three provisional doses (1, 3, 10 x 106 cells/kg). ONCT-808 is given as a single infusion following lymphodepletion with fludarabine and cyclophosphamide. The primary objective of phase 1 is identifying dose-limiting toxicities (DLTs) and establishing a recommended phase 2 dose. Phase 2 involves expansion into two parallel cohorts with a primary endpoint of overall response rate (ORR). Adverse events (AEs) are graded using CTCAE v5.0, except for cytokine release syndrome (CRS) and IEC-associated neurotoxicity syndrome (ICANS) which are based on ASCTC grading. Secondary endpoints include efficacy and pharmacokinetics. 2014 Lugano criteria were used for response assessment.

Results:

To date, 5 pts have been enrolled and undergone leukapheresis as well as cellular manufacturing; 1 pt had a pre-treatment AE and withdrew prior to treatment. Of the 4 treated pts, 3 with R/R MCL (all male, median age 55 [range 50-57], 2 with prior CD19 CAR T), were treated at a dose of 1 x 106 viable ONCT-808 cells/kg with no DLTs reported during the 28-day evaluation window. Pt 4 (80-year-old male with diffuse LBCL) was treated at a dose of 3 x 106 cells/kg and died due to complications of CRS and ICANS. AEs in ≥2 pts during the DLT evaluation window included G3 pneumonia (2/4 pts), G1-2 CRS (3/4 pts); no other cases of ICANS were reported. Following the G5 event at 3 x 106 cells/kg dose, the protocol was amended to add screening for occult infection and revise dosing scheme to 0.3, 0.6, and 1 x 106 cells/kg.

Response assessments were evaluated in 3 pts treated with ONCT-808 at 1 x 106 viable ONCT-808 CAR T cells/kg. Complete response (CR) was observed at the Month 1 (M1) timepoint for 2 of 3 pts; the third pt experienced partial response (PR) at M1. One pt with CR had a confirmatory bone marrow biopsy at M1 and sustained CR at the M3 and M6 timepoints. Notably, pt 4 treated at the 3 x 106 cells/kg dose did not have evidence of lymphoma on autopsy despite 2 large tumor masses at baseline. Preliminary PK demonstrated

successful expansion and persistence of ROR1-positive CAR T cells at the M3 and M6 timepoints.

Summary/Conclusion:

ROR1 CAR T is tolerated at 1 x 106 viable cells/kg with promising efficacy for R/R BCL. Dosing at lower levels is ongoing to optimize safety profile and maintain efficacy.

Keywords: CAR-T, Cellular therapy, Mantle cell lymphoma, Diffuse large B cell lymphoma