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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Trial-in-Progress: A Phase 1/2 Multi-Center Study of Onct-808, a ROR1-Specific CAR T, in Adult Patients with Relapsed/Refractory Aggressive B Cell Lymphoma

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BACKGROUND: The therapeutic landscape for B-cell lymphomas (BCL) leverages several modalities, including chemotherapy, targeted agents, adoptive cell therapy, and immunotherapy. While these approaches have shown clinical benefit, challenges remain, such as variable response rates, treatment resistance, and toxicities. ROR1-specific CAR T-cell therapy represents a promising potential advancement in the treatment of aggressive BCL in patients (pts) who have failed previous CD19 CAR T therapy.

ROR1-targeted CAR T therapy offers several advantages that could address these challenges. By directing CAR T cells to specifically recognize and eliminate ROR1-expressing tumor cells, it offers a highly targeted approach with the potential for enhanced efficacy. Moreover, ROR1 is often highly expressed on aggressive BCL, making it a suitable therapeutic target. This focused approach may help overcome the limitations associated with current treatments and improve response rates. After birth ROR1 is predominantly expressed on malignant cells; therefore, this selective expression pattern may reduce the risk of toxicities, including off-tumor target elimination and non-specific activation of immune cells.

The development of ROR1-specific CAR T holds promise in enhancing the treatment outcomes for patients with aggressive BCL. With targeted action and potential to reduce toxicity, ROR1-specific CAR T cell therapy offers an innovative and novel strategy for improving patient outcomes in BCL. The ROR1 binding moiety for ONCT-808 is derived from zilovertamab. Zilovertamab vedotin showed preliminary evidence of efficacy and no evidence of on-target off-tumor toxicity in patients with advanced B cell malignancies (Wang 2022).

METHODS: This is a Phase 1/2, single-arm, open-label, multi-center trial to evaluate the safety and efficacy of ONCT-808 in pts with aggressive BCL, including large B-cell lymphoma (LBCL) and mantle cell lymphoma (MCL) with no approved therapy available. The study comprises two distinct phases: Phase 1 for dose escalation followed by Phase 2 for dose expansion.

In Phase 1, a standard 3+3 dose escalation design will be used with 3 provisional dose levels and expected sample size of up to 18 patients. Subjects will receive a conditioning regimen of intravenous (IV) cyclophosphamide and fludarabine, followed by ONCT-808 IV infusion. The dose of ONCT-808 will be sequentially escalated to determine the recommended Phase 2 dose (RP2D) for LBCL and MCL cohorts. Bridging therapy is permitted if clinically indicated. Phase 2 will enroll LBCL and MCL patients into separate dose expansion cohorts at the RP2D determined in Phase 1. ONCT-808 will be administered as a single IV infusion of autologous CAR T cells.

The primary outcomes include assessing the incidence, severity, and relationship of Dose Limiting Toxicities (DLT), Treatment Emergent Adverse Events (TEAE), and RP2D selection of ONCT-808. Secondary outcomes include evaluating the Overall Response Rate (ORR), Complete Response (CR) rate, Duration of Response (DOR), pharmacokinetics of ONCT-808, expansion, persistence of ROR1 CAR-positive T cells, overall safety and tolerability. Key inclusion criteria include histologically confirmed aggressive B-cell NHL, measurable lesions per Lugano criteria (Cheson, 2014), and relapsed/refractory (R/R) disease without available therapy (must be previously treated with systemic therapy, progressed after or ineligible for autologous HSCT, and received prior approved anti-CD19 CAR-T at least 6 months prior to enrollment unless refused/ineligible). Key exclusion criteria include previous ROR1-targeted therapy, ongoing immunosuppression, and CNS involvement.

The trial is currently active and patients have been treated in the phase 1 dose escalation.

Clinical Trial Identifier: NCT05588440

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