TPS7084 Poster Session

A phase 2 trial to evaluate the efficacy and safety of WZTL-002, a third-generation anti-CD19 CAR T-cell therapy, in patients with relapsed or refractory large B-cell lymphoma (ENABLE-2).

Aine Hurley, Philip George, Giulia Giunti, Brittany Lavender, Amy Holmes, Clinton Lewis, Robert Weinkove; Malaghan Institute of Medical Research, Wellington, New Zealand; Canterbury District Health Board, Christchurch Hospital, Wellington, New Zealand; Auckland City Hospital, Auckland, New Zealand

Background: Autologous chimeric antigen receptor (CAR) T-cells directed against CD19 are a standard of care for relapsed or refractory (r/r) large B-cell lymphoma (LBCL). CAR T-cells incorporating a CD28 costimulatory domain are among the most effective CAR T-cell therapies for LBCL, but are associated with high rates of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In a phase I dose escalation and expansion study (ENABLE-1, NCT04049513), a new 'third-generation' CAR T-cell incorporating a TLR2 co-stimulatory domain alongside CD28 (WZTL-002) demonstrated low rates of CRS and ICANS and promising efficacy. a recommended phase 2 dose (RP2D) of $0.5 – 1.0 \times 10^6$ CAR^+ cells/kg was selected following dose escalation, and outpatient management and automated closed-system WZTL-002 manufacture were implemented within a dose expansion cohort. ENABLE-2 (ClinicalTrials.gov NCT06486051) is a multicentre phase 2 that aims to assess the efficacy and safety of WZTL-002 in patients with r/r LBCL. **Methods:** Eligible participants are age 18 – 75 years with relapsed or refractory LBCL (either de novo or transformed from follicular or marginal zone lymphoma) following 1 or 2 prior lines of therapy, have assessable disease and satisfactory organ function. Leukapheresis is conducted to obtain autologous T-cells, which are transduced *ex vivo* to express a third-generation CD19-directed CAR incorporating CD28, TLR2 and CD3zeta stimulatory domains (1928T2z). Bridging therapy is permitted pending WZTL-002 manufacture and product release. Lymphodepletion comprises intravenous fludarabine (30mg/m^2) and cyclophosphamide (500mg/m^2) daily for 3 days. Two days later a single dose of WZTL-002 is administered at $0.5 – 1.0 \times 10^6$ CAR^+ cells/kg (capped at 10^8 CAR^+ cells). Participants undergo daily outpatient assessments for toxicities including CRS and ICANS for the first 11 days after WZTL-002 administration, and at days 14 and 28. Disease response is assessed by PET/CT scans at day 28, 3 months and 6 months, and duration of response by CT scan at months 12 and 24. The co-primary endpoints are complete response rate (Lugano criteria) and ICANS rate (any grade) 3 months after WZTL-002 administration. Secondary outcomes include safety (with CRS, ICANS and cytopenias as adverse events of special interest), and progression-free, event-free and overall survival. The first participant was enrolled on 13 August 2024. Clinical trial information: NCT06486051. Research Sponsor: None.