Third-generation anti-CD19 CAR T-cells show efficacy without neurotoxicity in B-cell lymphoma phase 1 clinical trial

December 11 2023

Malaghan Institute GMP lab where CAR T-cells were manufactured for the phase 1 trial. Credit: Malaghan Institute of Medical Research

The Malaghan Institute of Medical Research, in collaboration with

Wellington Zhaotai Therapies Limited, today announced results of its phase 1 dose escalation trial of a new third generation anti-CD19 chimeric antigen receptor (CAR) T-cell therapy to be presented at the American Society of Hematology (ASH) Annual Meeting in San Diego on 11 December. The research is also published in the journal *Blood*.

Anti-CD19 CAR T-cells with a CD28 co-stimulatory domain, such as axicabtagene ciloleucel and brexucabtagene autoleucel, are among the most effective CAR T-cell therapies for B-cell non-Hodgkin lymphomas but are associated with neurotoxicity (immune effector cell-associated neurotoxicity syndrome, ICANS) in around half of recipients, and cytokine release syndrome (CRS) in up to 90%.

The Malaghan Institute and Wellington Zhaotai Therapies Limited have developed a third generation autologous anti-CD19 CAR T-cell product, which combines CD28 with a toll-like receptor 2 (TLR2) co-stimulatory domain. In preclinical studies, adding the TLR2 domain maintained or improved efficacy, while lowering production of the pro-inflammatory cytokines IFN-γ and GM-CSF, which are implicated in CRS and ICANS, compared to a CAR with CD28 co-stimulation alone.

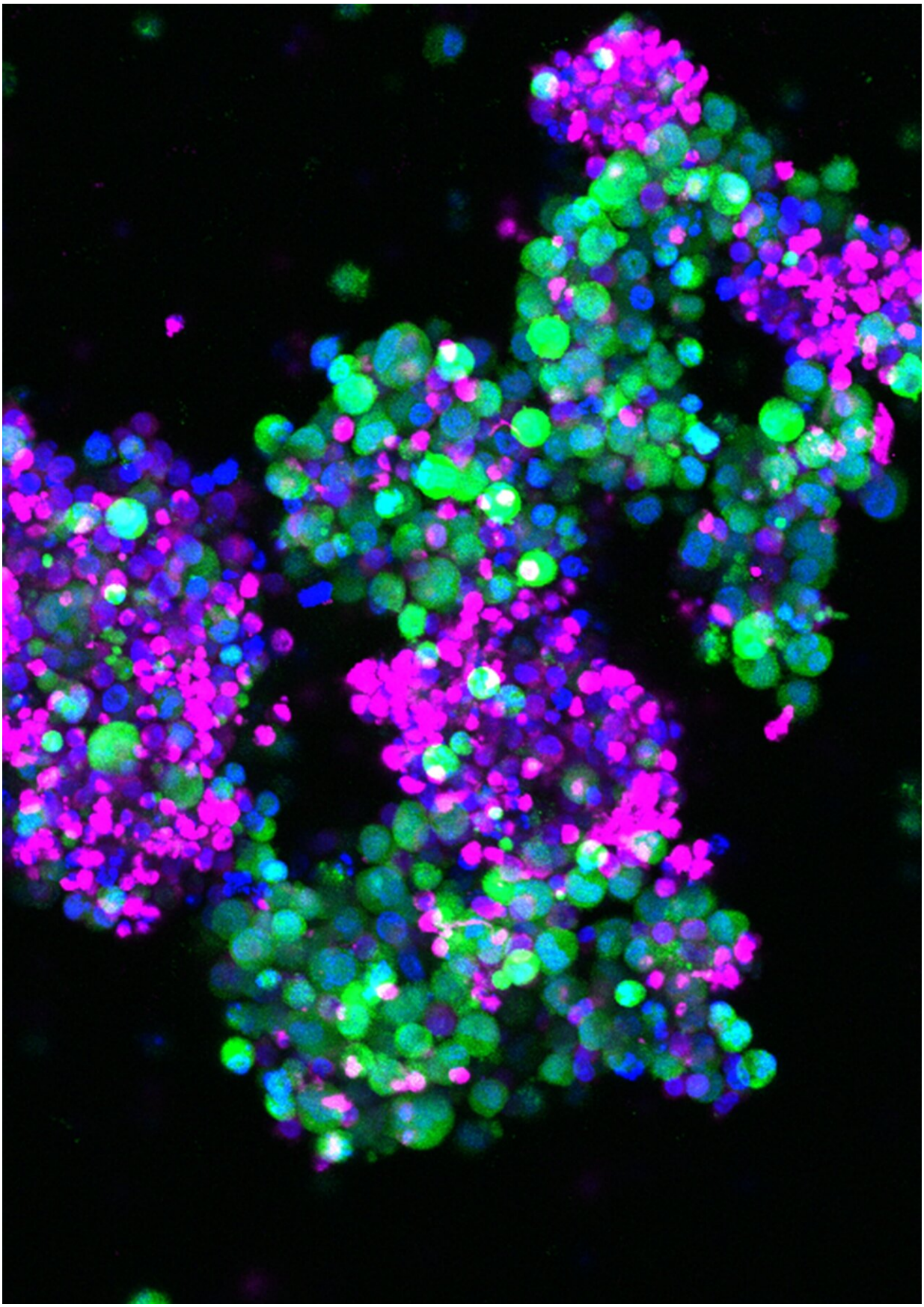
Twenty-one patients with relapsed or refractory B-cell non-Hodgkin lymphomas were treated in the dose escalation cohort of a phase 1 trial and completed the primary follow-up period. Median age was 57 years, 19% were Māori, participants had received a median of four prior lines of therapy.

No dose limiting toxicities occurred at doses of 5×10^4 to 1×10^6 CAR T-cells/kg. Grade 1 or 2 CRS occurred in 13 patients (62%); no severe (grade ≥ 3) CRS occurred. Notably, no ICANS of any grade occurred. Clinical responses were seen at all dose levels, with a 3-month complete response rate of 52%. WZTL-002 CAR T-cell expansion was robust. A phase 2 dose range of 5×10^5 to 1×10^6 cells/kg was recommended. A

further four patients have since been treated at this dose within a dose expansion cohort and have reached the DLT assessment timepoint; among these four additional patients, no grade ≥ 3 CRS or ICANS of any grade occurred.

"The absence of neurotoxicity with a CD28-based anti-CD19 CAR T-cell therapy is remarkable. Adding the intracellular TLR2 domain with CD28 and CD3ζ alters the CAR T-cell cytokine profile, and may account for our clinical findings," says Malaghan Institute Clinical Director and Principal Investigator Dr. Robert Weinkove.

"We are enrolling to a dose expansion cohort, with outpatient management and automated manufacture of WZTL-002 CAR T-cells. This is helping us prepare for a phase 2 trial in early 2024, to assess efficacy and safety in a larger number of patients."

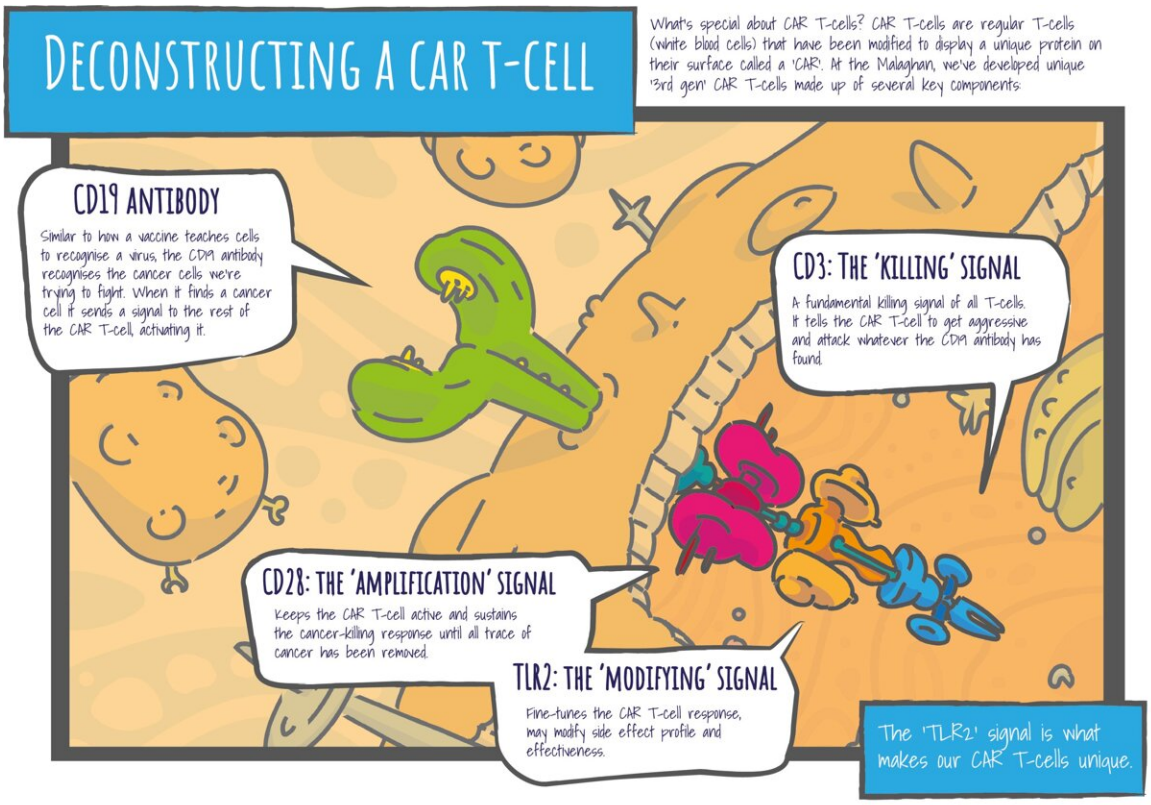


CAR T-cells in action. Pink CAR T-cells, manufactured at the Malaghan Institute, are shown attacking a clump of green blood cancer cells. As the cancer cells die they turn blue. Credit: Malaghan Institute of Medical Research

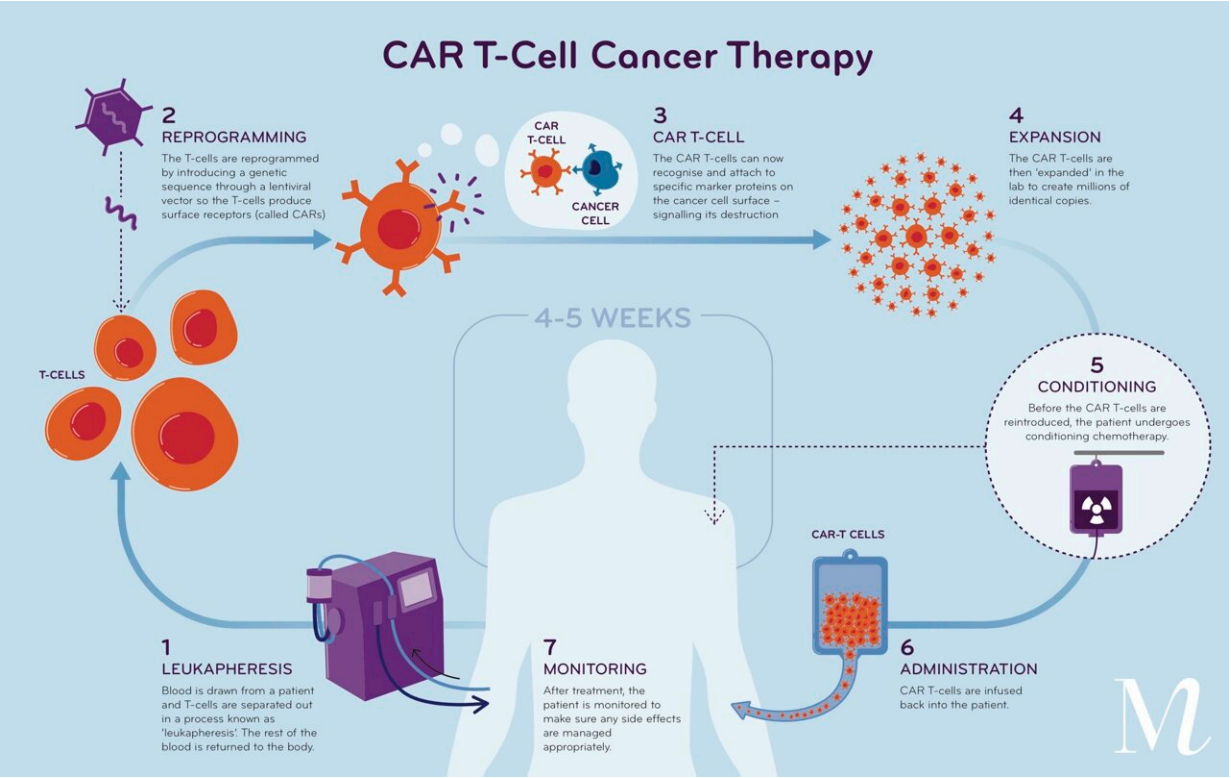
The original TLR2-containing CAR T constructs were developed at the Guangzhou Institute of Biomedicine and Health in China in collaboration with the Hunan Zhaotai Medical Group. In 2017, Wellington Zhaotai Therapies Limited was formed as a joint venture between the Malaghan Institute and Hunan Zhaotai Medical Group to develop this technology for international markets. The clinical trial of autologous anti-CD19 CAR T-cell therapy combining CD28 and TLR2 costimulation, WZTL-002, commenced in 2019. In 2023, Wellington Zhaotai Therapies Limited entered into a license agreement with Dr. Reddy's Laboratories to develop a CAR T-cell therapy incorporating this construct.

"These results are another exciting milestone in the development of our novel CAR T technology and the future of CAR T therapies globally," says Peter Lai, Wellington Zhaotai Therapies Limited Executive Director.

"There is a huge need and opportunity to extend CAR T-cell therapies into markets not yet addressed by major pharmaceutical companies. The reduced side effect profile of WZTL-002 creates a promising opportunity to address this unmet need."



Deconstructing a CAR T-cell—what's unique about our CAR T-cell construct? Credit: Malaghan Institute of Medical Research



How CAR T-cell therapy is administered. Credit: Malaghan Institute of Medical Research

One of the objectives of the dose expansion cohort study is to move CAR T-cell manufacture onto an automated platform, in partnership with New Zealand company BioOra Limited. Professor Carl June, BioOra board member and CAR T-cell therapy pioneer, says the ENABLE trial's phase 1 CAR T data are a step forward for the treatment of CD19-expressing lymphomas.

"Dr. Weinkove and his team at the Malaghan Institute have shown efficacy that is on par with commercial CAR T, but the safety signal appears superior. This lays the foundation for outpatient delivery and management and expanding indications for their CAR T program."

More information: Robert Weinkove et al, A Phase 1 Dose Escalation Trial of Third-Generation CD19-Directed CAR T-Cells Incorporating CD28 and Toll-like Receptor 2 (TLR2) Intracellular Domains for Relapsed or Refractory B-Cell Non-Hodgkin Lymphomas (ENABLE), *Blood* (2023). DOI: 10.1182/blood-2023-178872