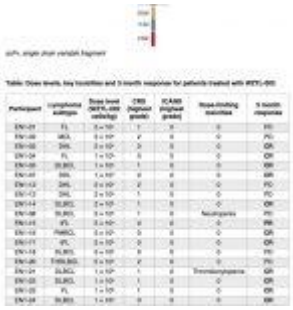
Advancements in CAR T-Cell Therapy: A Promising Clinical Outlook



A recent phase 1 dose escalation trial has unveiled compelling data on a new wave of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, marking a significant leap in the evolution of these therapies (Figure 1).

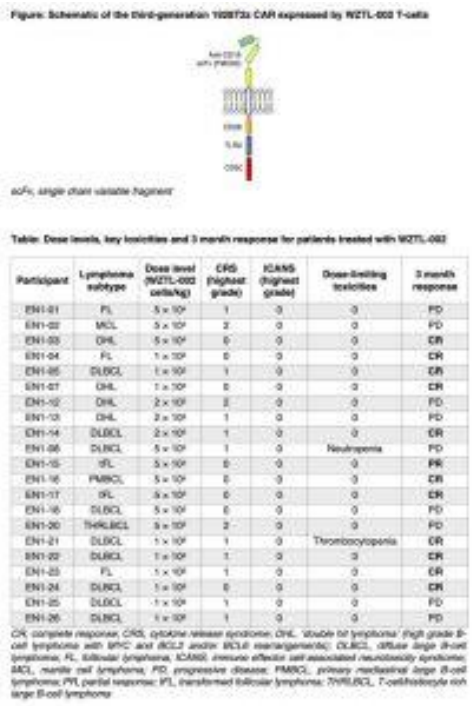


Table: Dose levels, key toxicities and 3 month response for patients treated with WZTL-002

Participant	Lymphoma subtype	Dose level (WZTL-002 cells/kg)	CRS (highest grade)	ICANS (highest grade)	Dose-limiting toxicities	3 month response
EN1-01	FL	5×10^6	1	0	0	PD
EN1-02	MCL	5×10^6	2	0	0	PD
EN1-03	DHL	5×10^6	0	0	0	CR
EN1-04	FL	1×10^6	0	0	0	CR
EN1-05	DLBCL	1×10^6	1	0	0	CR
EN1-07	DHL	1×10^6	0	0	0	CR
EN1-12	DHL	2×10^6	2	0	0	PD
EN1-13	DHL	2×10^6	1	0	0	PD
EN1-14	DLBCL	2×10^6	1	0	0	CR
EN1-06	DLBCL	5×10^6	1	0	Neutropenia	PD
EN1-15	tFL	5×10^6	0	0	0	PR
EN1-16	PMBCL	5×10^6	0	0	0	CR
EN1-17	tFL	5×10^6	0	0	0	CR
EN1-18	DLBCL	5×10^6	0	0	0	PD
EN1-20	THRLBCL	5×10^6	2	0	0	PD
EN1-21	DLBCL	1×10^6	1	0	Thrombocytopenia	CR
EN1-22	DLBCL	1×10^6	1	0	0	CR
EN1-23	FL	1×10^6	1	0	0	CR
EN1-24	DLBCL	1×10^6	0	0	0	CR
EN1-25	DLBCL	1×10^6	1	0	0	PD
EN1-26	DLBCL	1×10^6	1	0	0	PD

CR, complete response; CRS, cytokine release syndrome; DHL, 'double hit lymphoma' (high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements); DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; MCL, mantle cell lymphoma; PD, progressive disease; PMBCL, primary mediastinal large B-cell lymphoma; PR, partial response; tFL, transformed follicular lymphoma; THRLBCL, T-cell/histiocyte rich large B-cell lymphoma

Figure 1.

Current CAR T-cell therapies utilizing anti-CD19 with CD28 co-stimulation, like axicabtagene ciloleucel and brexucabtagene autoleucel, showcase potent efficacy against B-cell non-Hodgkin lymphomas. However, their association with

neurotoxicity (immune effector cell-associated neurotoxicity syndrome, ICANS) in nearly half of recipients, along with cytokine release syndrome (CRS) affecting up to 90%, has been a limiting factor.

This groundbreaking study centers on a novel third-generation autologous anti-CD19 CAR T-cell product integrating CD28 with a toll-like receptor 2 (TLR2) co-stimulatory domain. Preclinical investigations reveal that the addition of the TLR2 domain not only maintains or enhances efficacy but also significantly reduces the production of pro-inflammatory cytokines IFN-γ and GM-CSF, which are implicated in CRS and ICANS. Importantly, this reduction in cytokines is compared to CARs with CD28 co-stimulation alone.

These promising trial results represent a significant milestone in advancing novel CAR T technology, propelling the future landscape of CAR T therapies globally. Furthermore, this breakthrough holds promise in addressing unmet needs within markets not yet targeted by major pharmaceutical companies.

The reduced side effect profile exhibited by WZTL-002 CAR T-cell therapy presents a compelling opportunity to address these unmet needs, hinting at a new era of CAR T-cell therapies with potentially improved safety profiles and broader market applications.

Journal article: Weinkove, R., et al. 2023. 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*****.**

Summary by Stefan Botha