# 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)

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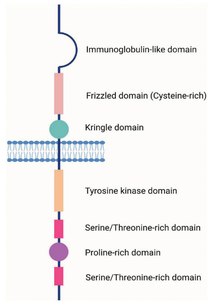
## INTRODUCTION

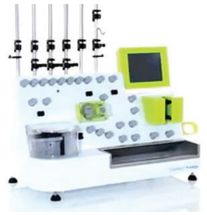
- Receptor tyrosine kinase-like orphan receptor 1 (ROR1) chimeric antigen receptor (CAR) expressing T-cell therapy is a promising potential treatment for aggressive B Cell Lymphoma (BCL), including patients who have relapsed following CD19 CAR T therapy.
- Although essential during embryogenesis, ROR1 has no known physiologic role in adults and is predominantly expressed on malignant cells, frequently by cancers with more aggressive features.
- 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).
- By directing CAR T cells to specifically recognize and eliminate ROR1-expressing tumor cells, this approach stands to minimize off-target toxicity while enhancing targeted destruction.




### ONCT-808 Manufacturing Overview

***Clinical ROR1 CAR T cell production process: closed, automated cell Processing platform (Prodigy CliniMACS 250)***

- Greater than 2 billion ROR1 CAR T cells produced (> 4 billion cells) with over 60% CAR+ expression from healthy donor leukapaks
- Greater than 1.3 billion ROR1 + CAR T cells produced (3 billion total viable cells) with over 42% average CAR+ expression with patient cells
- High percentage of CAR T cells with juvenile phenotypes (stem central memory T cells) favorable for expansion and persistence in healthy donor runs



## AIM AND METHODS

- 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.
- ONCT-808 is given as a single infusion following lymphodepletion with fludarabine and cyclophosphamide.
- Phase 1 has a standard 3+3 dose escalation design. The primary objective of Phase 1 is identifying DLTs and establishing a recommended Phase 2 dose. Phase 2 involves expansion into two parallel cohorts with a primary endpoint of 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. The 2014 Lugano criteria are used for response assessment.

## OBJECTIVES AND ENDPOINTS

### PHASE 1 PORTION

- Incidence, severity, and relationship of DLTs
- Safety and tolerability
- Selection of Phase 2 doses
- Preliminary anti-tumor activity
- Engraftment, expansion, persistence, and immunophenotype of ROR1 CAR-positive T cells

### PHASE 2 PORTION

- Risk/Benefit assessment (2 doses)
  - Safety and tolerability
  - ORR, CR rate, and DOR
- Engraftment, expansion, persistence, and immunophenotype of ROR1 CAR-positive T cells

## KEY ELIGIBILITY CRITERIA

### INCLUSION CRITERIA

- Adults with histologically confirmed aggressive B-cell NHL (MCL, LBCL)
- Relapsed/refractory (R/R) disease without available therapy, previous CD19 CAR T-cell therapy (unless ineligible/refused)
- Measurable disease
- ECOG 0-1
- Adequate bone marrow, renal, hepatic, pulmonary function

### EXCLUSION CRITERIA

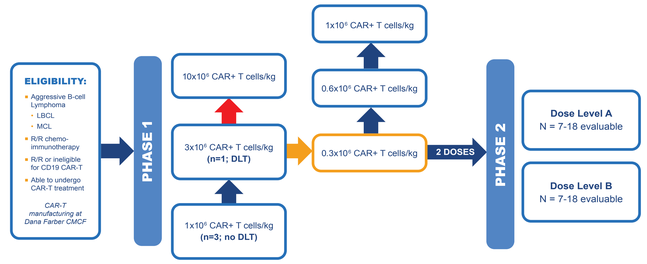
- CNS involvement or CNS disease
- Systemic immunosuppressive therapy
- Unable to tolerate CAR T therapy due to medical condition

### Patient Status and Safety

| | Patient 801<br>1x10$^6$ Car+ T cells/kg | Patient 802<br>1x10$^6$ Car+ T cells/kg | Patient 803<br>1x10$^6$ Car+ T cells/kg | Patient 805*<br>3x10$^6$ Car+ T cells/kg |
|---|---|---|---|---|
| Age/Disease Type | 55M with R/R MCL | 57M with R/R MCL | 50M with R/R MCL | 80M with R/R DLBCL; Bulky Disease |
| Prior CD19/Progression | Brex-cel/April 2023 | None | Brex-cel/July 2023 | Liso-cel/March 2023 |
| Additional PRIOR LOTs | • BR<br>• Ibrutinib<br>• Pirobrutnib | • R-CHOP<br>• Velcade<br>• LOXO-305 | • R-HyperCVAD + Intrathecal (IT) chemo<br>• R-ibrutnib + IT chemo | • R-CHOP<br>• R-polatuzuman vedotin<br>• Loncastuximab teserine |
| Bridging Therapy | RCD | None | R-Hypercytoxan+ Dex+ radiation | Dex+Prednisone |
| Dosed | June 2023 | July 2023 | September 2023 | November 2023 |
| TEAEs | G3 pneumonia | G2 CRS (SAE; resolved) | G1 CRS<br>G3 Infection (SAE)<br>G3 lactic acidosis | G4 CRS<br>G3 ICANS<br>Died on Day 8** |

*Possible pretreatment occult infection with fever, procalcitonin >6x ULN, CRP was 166.
**TEAE of G5 shock.

### ONCT-808: Phase 1/2 Study Design




LBCL: Large B-Cell Lymphoma (Diffuse LBCL NOS, Primary mediastinal LBCL, High-grade BCL, DLBCL arising from indolent lymphoma or CLL, Follicular lymphoma grade 3B, Richter's syndrome); MCL: Mantle Cell Lymphoma; CMCF: Cell Manipulation Core Facility;
Represents current active cohort.

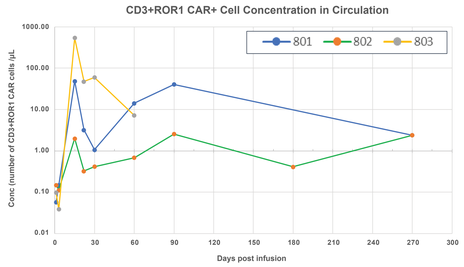
### Response Assessments

| | Patient 801<br>1x10$^6$ Car+ T cells/kg | Patient 802<br>1x10$^6$ Car+ T cells/kg | Patient 803<br>1x10$^6$ Car+ T cells/kg |
|---|---|---|---|
| **Month 1** | **Lugano:** PD<br>**PET-CT:** PMR | **Lugano:** CR<br>**PET-CT:** CMR | **Lugano:** PR<br>**PET-CT:** CMR |
| **Month 3** | **Lugano:** PD<br>**PET-CT:** PMR | **Lugano:** CR<br>**PET-CT:** CMR | **Lugano:** PD<br>**PET-CT:** PMD |
| **Month 6** | N/A | **Lugano:** CR<br>**PET-CT:** CMR | N/A |
| **Month 9** | N/A | **Lugano:** PD<br>**PET-CT:** PMD | N/A |

PR – Partial response; PMR – Partial metabolic response; CR – Complete response; CMR – Complete metabolic response; PD – Progressive disease; PMD – Progressive metabolic disease

Note: Patient 805, treated with 3x10$^6$ CAR+ cells/kg had no evidence of lymphoma on autopsy despite two 6 cm tumor masses at baseline.

### ONCT-808-101 – ONCT-808 CAR T Expansion and Persistence




- ONCT-808 CAR T cells expand and are persistent in all three patients from the 1 x 10$^6$ CAR T cells/kg cohort up to 9 months
- Expansion has been associated with response (e.g. prior Axi-Cel study, Neelapu NEJM 2017)

## STATUS

- ONCT-808 is currently active and enrolling patients in the dose escalation phase.
- Partnering site

City of Hope. Massachusetts General Hospital Founding Member, Mass General Brigham. Dana-Farber Cancer Institute. THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

## REFERENCES

Wang M, Barrientos JC, Furman RR, et al. Zilovertamab Vedotin Targeting of ROR1 as Therapy for Lymphoid Cancers. NEJM Evid 2022; 1 (1).

Kipps TJ. ROR1: an orphan becomes apparent. Blood 2022; 140 (14).

Specht JM, Lee S, Turtle CJ, et al. Abstract CT131: A phase I study of adoptive immunotherapy for advanced ROR1+ malignancies with defined subsets of autologous T cells expressing a ROR1-specific chimeric antigen receptor (ROR1-CAR). Cancer Res. 2018;78 (Supp 13).

## CONCLUSIONS

- ROR1 CAR T is well tolerated at 1 x 10$^6$ CAR + T cells/kg with promising early evidence of anti-tumoractivity.
- Following a Grade 5 TEAE, the protocol was amended with modified eligibility criteria, increased monitoring for infection, and evaluating lower doses of ONCT-808 CAR+ T cells.
- ONCT-808 is a promising CAR T cell therapy targeting ROR1 in aggressive lymphomas
- The ONCT-808-101 study is active and proceeding through dose escalation

EHA 2024

Clinical Trial: NCT05588440