ROR1: A PROMISING TARGET IN B-NHL (MCL, CLL, MZL, DLBCL)
CLINICAL EXPERIENCE WITH A FULLY-HUMANIZED mAb AND NOVEL CAR T-CELL THERAPY

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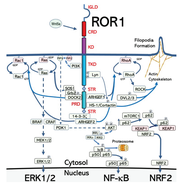
ONCTERNAL therapeutics

DAVA Oncology:
2024 Whistler Global Summit
on Hematologic Malignancies

ZILOVERTAMAB: HUMANIZED ANTI-ROR1 mAb

ROR1-TARGETING mAb

- ROR1 is an onco-embryonic kinase-like receptor not present on healthy adult tissues, but highly expressed by many solid and hematologic malignancies (including MCL, CLL, MZL)
- Wnt5a can activate ROR1 signaling, enhancing gene expression via activated ERK 1/2, NF-κB, and NRF2 – promoting cancer cell growth, migration, self-renewal, and resistance to therapy
- Zilovertamab (Zilo; formerly cirmtuzumab) is a fully humanized anti-ROR1 mAb designed to inhibit ROR1-signaling

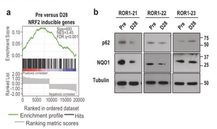


ROR1: receptor tyrosine kinase-like orphan receptor 1; ERK 1/2: extracellular signal-regulated kinase 1/2; NF-κB: nuclear factor kappa B; NRF2: nuclear factor erythroid 2-related factor 2. Source: Kipps, Blood 2022

ZILOVERTAMAB MECHANISM OF ACTION

Treatment of Patients with Zilovertamab Inhibits Expression of NRF2-Target Genes In vivo

- Besides inhibiting ROR1 signal transduction, Zilo inhibits CLL cell expression of genes induced by activated ERK1/2, NF-κB, STAT3, and NRF2 that may promote the survival and growth of CLL cells with mutated TP53 of patients treated with BTKi



Source: Sanchez-Lopez, E., NF-κB-p62-NRF2 survival signaling is associated with high RORt expression in chronic lymphocytic leukemia. Cell Death & Differentiation 2020; 27(7): 2206-2216.

STUDY CIRM-0001 DESIGN

NCT03088878

Phase 1	Phase 2	
Part 1 (MCL & CLL)	**Part 2 (MCL, CLL & MZL)**	**Part 3 (CLL)**
DOSE-FINDING COHORT	**DOSE-EXPANSION COHORT**	**RANDOMIZED EFFICACY**
• 2, 4, 8 and 16mg/kg and 300 and 600mg doses of zilovertamab[a] evaluated • Ibrutinib added after 1 month safety run-in (420mg CLL, 560mg MCL, qd po) • RP2D;[b] 600mg IV Q2W x 3 then Q4W in combination with ibrutinib at approved doses	• Primary Endpoints: safety, preliminary efficacy, pharmacology at RP2D • Confirm RP2D of zilovertamab (600mg) + ibrutinib at approved dose (420mg CLL, 560mg MCL and MZL)	• Zilovertamab + ibrutnib vs. ibrutinib • 2:1 randomization • Evaluate objective responses, PFS, biomarkers

[a] Formerly cirmtuzumab; [b] RP2D: recommended Phase 2 dose

	Parts 1 & 2[c]		Part 3	
	MCL zilo + ibrutinib	CLL zilo + ibrutinib	CLL zilo + ibrutinib	CLL ibrutinib
Study Population				
Patients Enrolled, n	33	34	21	10
Safety Population,[a] n	33	34	21	10
Efficacy Population,[b] n (%)	28 (84.8)	34 (100)	16 (88.9)	7 (70.0)
Ongoing, n (%)	13 (39.4)	0	2 (11.1)	10 (10.0)
Discontinued from Treatment,[d] n (%)	20 (60.6)	34 (100)	16 (88.9)	9 (90.0)

a, Safety population is comprised of all enrolled subjects who received at least one dose of zilovertamab (or ibrutinib if Part 3 ibrutinib alone arm); b, Efficacy population is comprised of enrolled subjects who have received at least one dose of zilovertamab and have at least one post-baseline tumor assessment; c, At the time of the data cut (11Oct2022), there were no MZL patients evaluable for efficacy, so MZL patients are not included in the analyses; d, most common reason for discontinuing for CLL patients is completed 2 years of treatment, for MCL is disease progression.

ZILO + IBRUTINIB IN TP53-ABERRANT CLL

CLL Efficacy by TP53 mutation/del17p: Clinical Response Rates

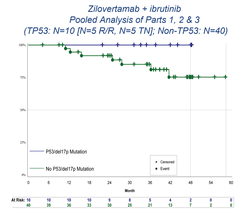
High response rates and durable responses CLL patients with TP53 mutation/del17p

Endpoints	Parts 1 & 2 (N=34)	Part 3 – Zilo + Ibr (N=16)	Part 3 – Ibr (N=7)	TP53 mutation/del17p (N=10)
Overall Response Rate (ORR), n (%)	31 (91.2)	15 (93.8)	7 (100.0)	10 (100.0)
Complete Response (CR), n (%)	3 (8.8)[a]	0	1 (14.3)	1 (10.0)
Partial Response (PR), n (%)	28 (82.4)[b]	15 (93.8)	6 (85.7)	9 (90.0)[b]
Stable Disease (SD), n (%)	3 (8.8)	1 (6.3)	0	0
Median Duration of response, months (95% CI)	40.3 (33.5, NE)	NR (22.2, NE)	NR (8.3, NE)	40.3 (NE, NE)

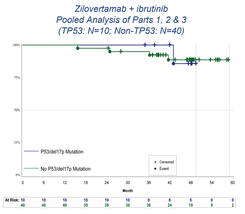
N: number of evaluable patients; NE: not estimable; a: includes 1 unconfirmed CR, b: includes 1 PR-L

CLL Efficacy: PFS and OS by TP53 mutation/del17p Status

Very encouraging landmark PFS at ~48 mo



PFS for TP53 mutation at ~48 months was 100%



OS for TP53 mutation at ~42 months was 100%

Note: One TP53 subject received new anti-cancer treatment, hence was censored for the PFS analysis. This subject subsequently died and is reflected in the OS analysis.

STUDY CIRM-0001 SUMMARY AND CONCLUSIONS

- Zilovertamab is a humanized mAb designed to inhibit the tumor promoting activity of ROR1.
  - In CLL patients with TP53 mutation who have been treated with BTKi, zilovertamab inhibits CLL-cell expression of genes induced by activated ERK1/2, NF-kB, STAT3, and NRF2
- In patients with MCL and CLL, the combination of zilovertamab + ibrutinib was well tolerated, with a safety profile comparable to ibrutinib alone. Some side effects appeared less frequently than expected.
- The ORR was 89.3%, CRR 42.9% and median DOR 34.1 months for patients with R/R MCL on zilovertamab + ibrutinib
- PFS for zilovertamab + ibrutinib was ~95% at 24 months in patients with R/R CLL (median 2 prior LOT)
- Very encouraging PFS in CLL patients was 100% at ~48 months for patients with TP53 mutation/del17p

ACKNOWLEDGEMENTS

- To all patients and their families and caregivers
- To investigators, staff and institutions
- To Pharmacyclics LLC, an AbbVie Company, for the generous donation of ibrutinib

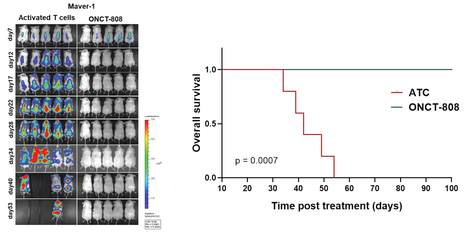
THANK YOU

- Funding for this research was provided by the California Institute for Regenerative Medicine and Oncternal Therapeutics, Inc.

ONCT-808: ROR1-TARGETING CAR T

ONCT-808: PRECLINICAL MODELS

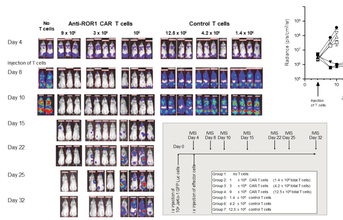
ONCT-808 Exhibits Anti-Tumor Activity in ROR1+ Model: Maver-1 MCL Xenograft



Maver FF-luc (2x cells per mouse, 5 mice per treatment arm)
a. Activated T cells (6x10⁶ cells per mouse)
b. ONCT-808 CAR T cells (6x10⁶ CAR+ cells per mouse)

Collaboration with Dr. Michael Wang (MDACC)

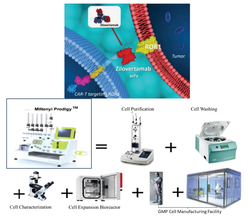
ONCT-808 Exerts Anti-Tumor Activity in ROR1+ Model: Jeko-1 MCL



Data generated in collaboration with Dr. Evren Alici (Karolinska Institutet), presented at EHA 2022

DESIGN AND MANUFACTURING OF ONCT-808 CAR T CELLS

- ROR1 targeting CAR construct optimized with high potency against ROR1+ cancer cells; lentiviral vector
- Flexible, closed, fully-automated Prodigy system eliminates manual processing
  - ≤ 8-day production process
  - Up to 2 billion CAR+ T cells produced
  - Encouraging CAR T cell phenotypes likely to persist and expand



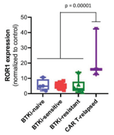
STATUS

- ONCT-808 is currently active and enrolling patients in the dose escalation phase.
- Contact: ***clinops@oncternal.com***

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

SUPPORT FOR A ROR1-TARGETING CAR T IN AGGRESSIVE B-NHL

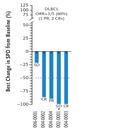
Preclinical data



ROR1 expression was highest in brexucabtagene autoleucel (Tecartus®)–relapsed samples (n = 3) among analyzed cell samples from MCL patients

Jiang 2021 J Hematol Oncol

Phase 1 ADC Efficacy Data*



Patients with DLBCL responses had 3, 7, and 7 prior regimens (including HDT/HSCT in 1 patient and CAR T cells in 3 patients)

Wang 2022 NEJM Evid

Phase 1 ADC Safety Data*

"…as expected with a monomethyl auristatin E-containing antibody–drug conjugate, adverse events (AEs) included acute neutropenia and cumulative neuropathy…"

"…no clinically-concerning AEs occurred to suggest ROR1-mediated toxicities or nonspecific zilovertamab vedotin binding to normal tissues…"

Wang 2022 NEJM Evid

ONCT-808-101: ROR1 CAR T PHASE 1/2 STUDY

NCT05588440

Eligibility:
- Aggressive B-cell NHL
  - LBCL
  - MCL
- Failed chemo-immunotherapy
- Failed or ineligible for CD19 CAR T therapy (Phase 1 only)
- Able to undergo CAR T cell treatment

CAR T cell manufacturing at Dana Farber CMCF

Dose Level 1: 0.3x10⁶ CAR+ T cells/kg

Dose Level 2: 0.6x10⁶ CAR + T cells/kg

Dose Level 3: 1x10⁶ CAR + T cells/kg

3+3 Dose escalation

Phase 1 Objectives:
- Safety & tolerability
- Determine MTD or MAD
- Select 2 Phase 2 doses

Dose Level A N = 7-18 evaluable

Dose Level B N = 7-18 evaluable

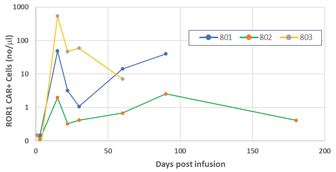
Randomized to 2 dose levels

Phase 2 Objectives:
- Risk/benefit of ONCT-808
- Safety & tolerability
- Efficacy (ORR, CRR, DOR)
- PK of ONCT-808

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; MTD: Maximum Tolerated Dose; MAD: Maximum Administered Dose; RP2D: Recommended Phase 2 Dose; ORR: Objective Response Rate; CRR: Complete Response Rate; DOR: Duration of Response.

CLINICAL DATA – ROR1-TARGETING CAR T

- Promising tolerability and activity at initial dose level, 1x10⁶ CAR T cells/kg
  - TEAEs: Grade 1-2 CRS, no reported ICANS; pneumonia, cytopenias
  - 2/3 patients achieved complete metabolic response (CMR) by PET-CT
  - 1/3 patient achieved partial response (PR) by PET-CT
- Following a G5 SAE at the highest dose level (3x10⁶ CAR T cells/kg) in an 80yo with bulky DLBCL, protocol was revised to evaluate lower dose levels given potency of ONCT-808
  - There was no evidence of lymphoma in either of 6cm masses present at baseline on autopsy



- ONCT-808 CAR T cells expand and are persistent for the first three patients in the 1 x 10⁶ CAR T cells/kg cohort up to 6 months

Data as of January 04, 2024