First-in-human phase 1/2 Study (MYCHELANGELO I) of first-in-class Epigenomic Controller OTX-2002 targeting MYC oncogene in patients with hepatocellular carcinoma (HCC) and other solid tumors

Jonathan Mizrahi, William Senapedis, Charles W. O'Donnell, J. Graeme Hodgson, Joseph V. Newman, Stephen K. Siecinski, Chia-Chi Lin

Ochsner Clinic Foundation, New Orleans, LA; Omega Therapeutics, Cambridge, MA, USA; National Taiwan University Cancer Center, Taipei, Taiwan

ASCO Gastrointestinal Cancers Symposium 2025
Abstract #606

Introduction and Background

- Therapeutic modulation of the epigenome presents significant opportunities to leverage natural mechanisms to control and resolve gene dysregulation pre-transcriptionally. Omega Therapeutics, a clinical-stage biotechnology company, is designing programmable epigenomic mRNA therapeutics through an innovative platform capable of specifically, controllably and durably modifying epigenetic chromatin state to correct aberrant gene expression and treat disease.
- The c-MYC (*MYC*) oncogene is a master transcription factor of tumor cell and microenvironment regulation; it is often dysregulated in cancer, including hepatocellular carcinoma (HCC). OTX-2002 is a MYC-targeted Epigenomic Controller (MYC-EC), an mRNA drug substance encapsulated in a clinical lipid nanoparticle (LNP), designed to downregulate MYC expression pre-transcriptionally with high specificity and durability, inhibiting tumor cell viability while sparing normal cells.
- The MYCHELANGELO I trial (NCT05497453) investigates pre-transcriptional inhibition of *MYC* with OTX-2002 in patients with hepatocellular carcinoma (HCC) and other solid tumors. OTX-2002 encodes two proteins that durably modify chromatin, in part, through CpG DNA methylation at the *MYC* locus. We have previously shown that EC-directed *MYC* methylation leads to concomitant downregulation of *MYC* expression and loss of HCC cellular viability *in vitro* and inhibition of HCC xenograft growth *in vivo*.[1]

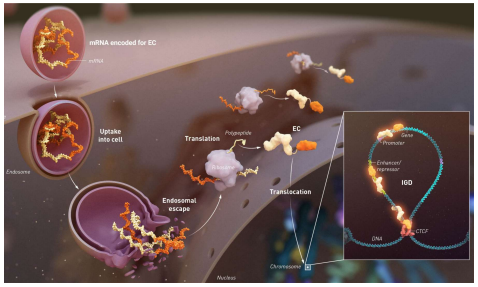

Figure 1. Structure and Mechanism of Action of an EC

Objectives

This Phase 1 study aimed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of OTX-2002 as a single agent in patients with hepatocellular carcinoma and other solid tumor types known for association with the *MYC* oncogene.

Trial Design and Methods

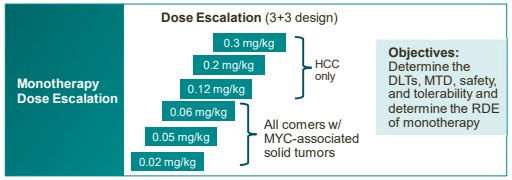

Figure 2. Monotherapy Dose Escalation design

- **Study Population:**
  - Adult participants with metastatic, advanced or recurrent solid tumors known for association with the *MYC* oncogene who experienced disease progression, relapse, or refractory disease to at least 1 prior systemic therapy, and without subsequent standard of care therapy options.
  - ECOG performance status of 0 or 1
  - Predicted life expectancy of at least 3 months
  - For HCC patients, BCLC Stage B or C with Child-Pugh A liver function, not amenable to or refractory to locoregional therapy and must have at least 1 lesion measurable according to mRECIST
  - Participants with chronic Hepatitis B virus (HBV) must have received antiviral therapy for at least 12 weeks and HBV viral load < 500 IU/mL prior to first dose of study drug
- **Primary Endpoints:**
  - Incidence of TEAEs, SAEs, and TEAEs leading to study drug discontinuation, graded according to CTCAE v5.0
- **Secondary and Exploratory Endpoints:**
  - ORR by mRECIST
  - We developed an investigational cell-free assay to evaluate changes in methylation at the MYC promoter in ctDNA[2]

Results

Patient Demographics

- 24 patients were enrolled and received OTX-2002 (Table 1)
  - 5 patients with non-HCC tumors were enrolled (Dose levels 1-3, per protocol)
  - 19 patients with HCC were enrolled (Dose levels 1-6)
- All patients had received at least 2 prior lines of anticancer therapy

	n = 24 Patients, n(%) (All patients)	n = 19 Patients, n(%) (HCC patients)
Age (years) Median (range)	61 (38-78)	61 (39-76)
Sex Male	17 (71%)	16 (84%)
Female	7 (29%)	3 (16%)
Race Asian	18 (75%)	15 (79%)
Caucasian	6 (25%)	4 (21%)
ECOG Performance Status* 0	8 (33%)	6 (32%)
1	16 (67%)	13 (68%)
Cancer Type at Initial Diagnosis Soft Tissue Sarcoma	1 (4%)	
Colorectal Cancer	1 (4%)	
Sarcoma	1 (4%)	
Cervical Cancer	1 (4%)	
Pancreatic Cancer	1 (4%)	
HCC	19 (80%)	19 (100%)
Number of Prior Lines of Therapy 2	12 (50%)	10 (53%)
3 or more	12 (50%)	9 (47%)

Table 1. Patient Demographics and Baseline Characteristics

Safety and Tolerability

- Favorable tolerability was observed at Dose Levels 1-4 (0.02 mg/kg – 0.12 mg/kg)
  - The majority of treatment-related adverse events were low grade (89%) with no DLTs
  - Infusion-related reactions (IRRs) were the most common AE (29%), consistent with known LNP profiles
  - Seven adverse events of AST elevation occurred in 4 of 17 (24%) participants with severities from Grade 2-4
  - 5 of 7 SAEs occurred in 3 participants and all SAEs resolved with supportive care
- Limited tolerability was observed at higher doses (0.2 mg/kg and 0.3 mg/kg) due to LNP-associated toxicities
  - MTD was exceeded at 0.3 mg/kg: 2 patients experienced DLTs (IRRs and AST/ALT elevation)
- Predictable and consistent pharmacokinetics profile with rapid clearance, minimal variability observed within and between patients, and no accumulation observed with repeat administration
- Recommended dose for expansion: 0.12 mg/kg, based on favorable safety and tolerability profile and preliminary antitumor activity.

Antitumor Activity

- Best overall response of stable disease was observed in 6/12 evaluable HCC patients, for a disease control rate (DCR) of 50%
- One HCC patient in Dose Level 2 (0.05 mg/kg) demonstrated durable stable disease for 45 weeks

Dose-Dependent, Persistent On-Target Epigenomic Signature Observed from Plasma cell-free DNA

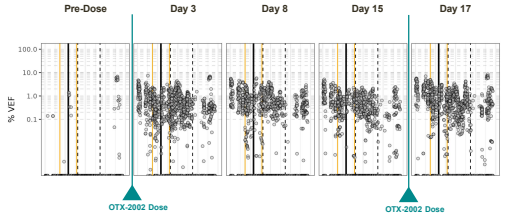

Figure 3. Significant, persistent increase in methylation signature seen across dose level 4 participants (0.12mg/kg, aggregate of N=6) over first 2 weeks of study. Individual CpG locations shown as points (x-axis), with epigenetic VEF[3] score (y-axis) calculated – indicating frequency of highly methylated (≥60%) cfDNA fragments localized from that CpG. OTX-2002 target indicated by vertical black line (orange: +/- 200bp) with the MYC first exon shown with dotted lines.

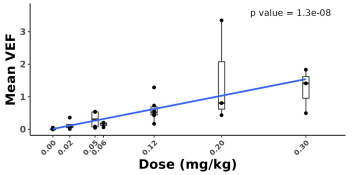

Figure 4. Mean VEF for the 1kb window around the target region of the MYC promoter at dose levels 0 (pre-treatment), 0.02, 0.05, 0.06, 0.12, 0.20, and 0.30 mg/kg. A significant positive linear relationship was observed between dose and on-target methylation signature (p-value = 1.3×10^{-8})

- Highly specific on-target, dose-dependent target engagement was observed with intended epigenetic changes at the target genomic loci, demonstrated by persistent increase in cell-free DNA MYC methylation signature following administration with OTX-2002.
- Increased MYC promoter methylation signature persisted throughout the two-week dosing interval
- Plasma MYC promoter methylation signatures increased with repeat administration across dosing cycles (data not shown)

Conclusions

This first-in-human trial establishes proof-of-mechanism for Omega's epigenomic controllers and demonstrates highly site-specific target engagement of the MYC locus in patients with HCC.

These data highlight epigenomic controllers as a new drug class with clinical applicability to Oncology and other diseases.

References

1. Senapedis, W. et al. (2024) https://doi.org/10.1038/s41467-024-52202-y
2. Chen, J. et al. (2024) https://doi.org/10.1158/1538-7445.AM2024-2417
3. Nikolaienko, O. et al. (2023) https://doi.org/10.1093/gigascience/giad087

Contact Information

Omega Therapeutics | 140 First Street | Cambridge, MA 02141 | odonnell@omegatx.com