TPS627: A phase 1/2 open-label study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of OTX-2002 as a single agent and in combination with standard of care in patients with hepatocellular carcinoma and other solid tumor types known for association with the MYC oncogene (MYCHELANGELO I)

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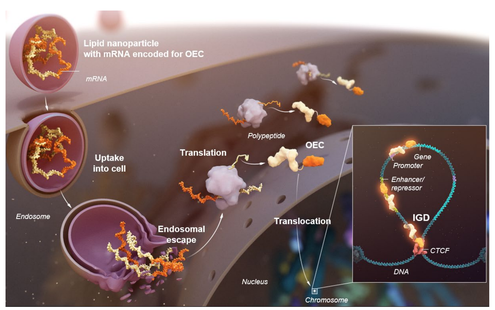
BACKGROUND

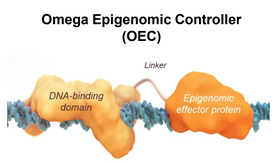
- MYC, or c-MYC, is a master regulator of gene expression that controls cell growth and proliferation.
- Dysregulation of MYC is frequently identified in various cancer types and reduction of MYC expression has been associated with antitumor efficacy in a wide variety of tumor types in animal models.[1]
- MYC is overexpressed in up to 70% of viral and alcohol-related hepatocellular carcinoma (HCC). [2]
- MYC has historically been considered undruggable due to a lack of a structured binding pocket and tightly autoregulated expression.
- *MYC* resides alone within its 2.8 Mb insulated genomic domain (IGD) and is a potential target for gene regulation via an epigenetic approach.[3]

INVESTIGATIONAL PRODUCT

- OTX-2002 is an Omega Epigenomic Controller (OEC) mRNA medicine delivered by lipid nanoparticles that aims to controllably and durably downregulate MYC expression pre-transcriptionally by targeting specific regulatory elements within the MYC IGD.
- In cells that take up OTX-2002, the bicistronic mRNA translates into two modular proteins each comprised of a DNA binding domain and an epigenomic effector domain.
- The expressed proteins bind to the regulatory genomic sequences in the MYC IGD, coupled with laying down epigenetic marks leading to downregulation of MYC expression.
- In HCC xenograft mouse models, OTX-2002 demonstrated anti-tumor activity as monotherapy and in combinations with standard of care therapies in HCC.[4]
- OTX-2002 is dosed intravenously every two weeks at sub mg/kg levels.

Figure 1. Structure and Mechanism of Action of OECs

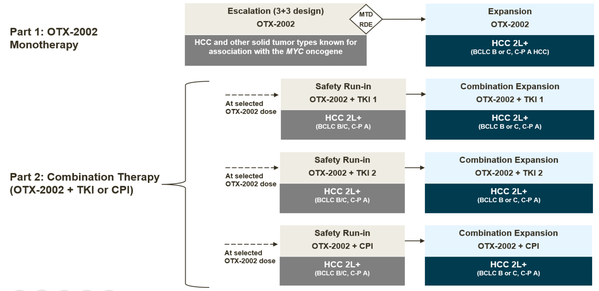




STUDY DESIGN

- MYCHELANGELO I study comprised of Part 1: OTX-2002 monotherapy and Part 2: combination therapy.
- Part 1 dose escalation explores ascending doses of OTX-2002 to identify dose limiting toxicities, maximum tolerated dose, and recommended dose for expansion (RDE) in patients with HCC and other solid tumors using a classic 3+3 design. Upon identification of the RDE, a monotherapy expansion in advanced HCC patients is planned to explore the preliminary anti-tumor activity of OTX-2002.
- Part 2 will evaluate OTX-2002 in combinations with a tyrosine kinase inhibitor or immune checkpoint inhibitor in the same HCC population as that of Part 1 expansion. The safety of the combinations at selected doses will be evaluated in a safety run-in; expansion will follow to identify the preliminary anti-tumor activity of the combinations.

Figure 2. MYCHELANGELO I Study Schema



STUDY OBJECTIVES AND ENDPOINTS

Table 1. Primary and Secondary Study Objectives and Endpoints

	Part 1 Dose Escalation & Part 2 Safety Run-in		Part 1 & Part 2 Expansion	
	Objective	Endpoint	Objective	Endpoint
Primary	• Determine the DLTs, MTD, safety, and tolerability and determine the RDE of OTX-2002 as a single agent in solid tumor participants in monotherapy dose escalation and in combination in HCC participants in safety run-in	• DLTs, MTD • Incidence of TEAEs	• Determine the preliminary antitumor activity of OTX-2002 as a single agent and in combinations	• ORR • DoR
Secondary	• Determine the preliminary antitumor activity of OTX-2002 as a single agent and in combinations • Determine the PK of OTX-2002 as a single agent and in combinations	• ORR • DoR • PK parameters	• Determine the safety and tolerability of OTX-2002 as a single agent and in combination in participants with HCC • Evaluate the survival and response pattern of OTX-2002 as a single agent and in combination in participants with HCC	• Incidence of TEAEs • PFS • OS • TTR • TTP

DLT=dose limiting toxicity; MTD=maximum tolerated dose; TEAE=treatment emerging adverse event; ORR=objective response rate; DoR=duration of response; PK=pharmacokinetics; PFS=progression-free survival; OS=overall survival; TTR=time to response; TTP=time to progression

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria

- Metastatic, advanced, or recurrent solid tumor types known for association with the MYC oncogene, including, but not limited to hepatocellular carcinoma, breast, bladder, lung, pancreatic, ovarian, uterine, endometrial, gastric, esophageal, hepatobiliary, colorectal, soft tissue sarcoma, and neuroblastoma, who progressed on, relapsed after, are refractory to, or intolerant to standard of care for which no alternative standard treatment exists (*only applies to monotherapy escalation*)
- Clinical or histological confirmed HCC, BCLC B or C
- Child-Pugh A liver function
- Received at least 1 line, and no more than 3 lines of systemic therapy (*only applies to HCC patients*)
- Met liver function requirements: T-bil. ≤ 2.0 mg/dL; AST and ALT ≤ 5 × ULN ; INR ≤ 2.0

Key Exclusion Criteria

- Main portal vein thrombosis (Vp4)
- Tumor occupies >50% of the liver parenchyma
- Encephalopathy
- Uncontrolled ascites
- Active CNS metastasis
- Varices bleeding that required interventional treatment within 6 months
- Fibrolamellar, sarcomatoid or mixed cholangio-HCC tumors
- Prior anti-PD1/PD-L1 in the CPI cohort
- Prior exposure to the same TKI in the TKI cohorts

REFERENCE

1. Allen-Petersen et al. BioDrugs. 2019;33:539-553
2. Lin et al. World J Hepatol. 2010;2:16–20.
3. Hnisz et al. Cell. 2016;167:1188–1200
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