OMEGA™ THERAPEUTICS

MYCHELANGELO™ I:
Preliminary Phase 1 Clinical Update

September 26, 2023

Disclaimer and Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding our expectations surrounding the potential of our product candidates, including our lead epigenomic controller (EC) candidate OTX-2002; development timelines; anticipated timing of regulatory submissions and filings; and expectations regarding our pipeline, including trial design, initiation of preclinical studies and our goal of declaring additional EC development candidates. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: the novel technology on which our product candidates are based makes it difficult to predict the time and cost of preclinical and clinical development and subsequently obtaining regulatory approval, if at all; the substantial development and regulatory risks associated with epigenomic controllers due to the novel and unprecedented nature of this new category of medicines; our limited operating history; the incurrence of significant losses and the fact that we expect to continue to incur significant additional losses for the foreseeable future; our need for substantial additional financing; our investments in research and development efforts that further enhance the OMEGA platform, and their impact on our results; uncertainty regarding preclinical development, especially for a new class of medicines such as epigenomic controllers; the fact that our product candidates may be associated with serious adverse events, undesirable side effects or have other properties that could halt their regulatory development, prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences; the impact of increased demand for the manufacture of mRNA and LNP based vaccines to treat COVID-19 on our development plans; difficulties manufacturing the novel technology on which our EC candidates are based; our ability to adapt to rapid and significant technological change; our reliance on third parties for the manufacture of materials; our ability to successfully acquire and establish our own manufacturing facilities and infrastructure; our reliance on a limited number of suppliers for lipid excipients used in our product candidates; our ability to advance our product candidates to clinical development; and our ability to obtain, maintain, enforce and adequately protect our intellectual property rights. These and other important factors discussed under the caption “Risk Factors” our most recent Quarterly Report on Form 10-Q and our Annual Report on Form 10-K for the year ended December 31, 2022, and our other filings with the SEC could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management’s estimates as of the date of this presentation. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change.

Today's Agenda

Welcome and Introductory Remarks

- **Mahesh Karande**, President and Chief Executive Officer

Review of Preliminary Phase 1 Clinical Data from Ongoing MYCHELANGELO™ I Trial

- **Thomas McCauley, Ph.D.**, Chief Scientific Officer

Guest Speaker

- **Gerard Evan, Ph.D.**, Principal Group Leader of the Francis Crick Institute in London; Professor of Cancer Biology at Kings College London

Closing Remarks

- **Mahesh Karande**

Q&A with Management

- **Mahesh Karande**
- **Thomas McCauley**

Introduction

Mahesh Karande
President and Chief Executive Officer

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Pioneering A New Era of Therapeutic Development

Encouraging Preliminary Data for OTX-2002: Power of Precision Epigenomic Control

- ✓ Unlocks potential of MYC, a historically ‘undruggable’ target
- ✓ Establishes clinical proof-of-platform; potential applicability across broad range of diseases
- ✓ Supports potential of epigenomic controllers as a new class of programmable mRNA medicines

Delivering on the Promise of Epigenetics

Omega's Controlled Epigenomic Modulation Approach Is a Significant Technological Advance

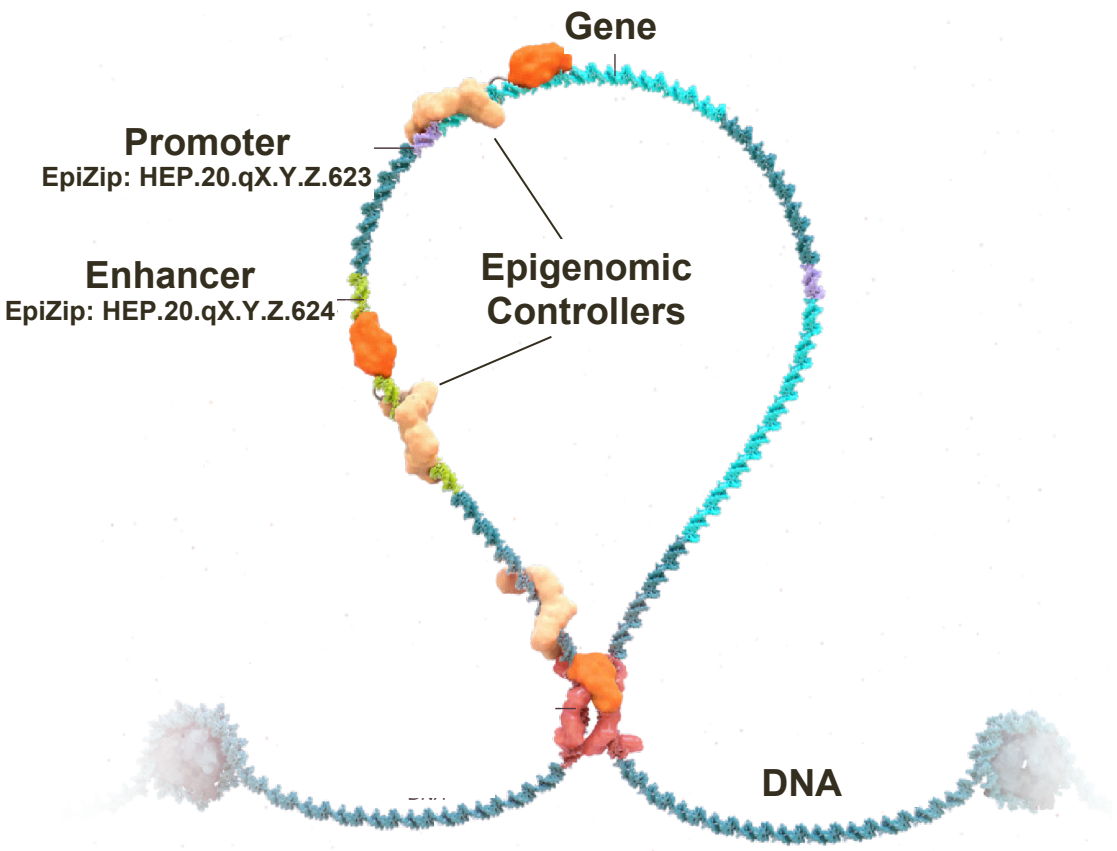
Existing modalities have limitations

- Restricted to druggable target structures or can only address narrow therapeutic areas
- Wide opportunity space in drug development remains

Epigenomic controllers solve multiple challenges in drug development

- Independent of structure, chemistry or location of target
- Address undruggable or inaccessible targets
- Both up or down regulation for therapeutic benefit
- Avoid liabilities of permanent genetic alterations
- Applicable to any human gene or disease process
- Speed to development candidates and INDs

OMEGA Platform Engineers Programmable mRNA Therapeutics to Control Gene Expression Through Epigenetics



DNA / Insulated Genomic Domain (IGD)

Fundamental Biology: Nature's Control System

- IGDs: Contain genes and their controlling regulators
- EpiZips: Unique target regulatory sequences

mRNA Therapeutics: Epigenomic Controllers

- Bind to EpiZips (proprietary library of targets)
- Controllably modulate gene expression

Preclinical Proof-of-Platform Across Diverse Therapeutic Areas

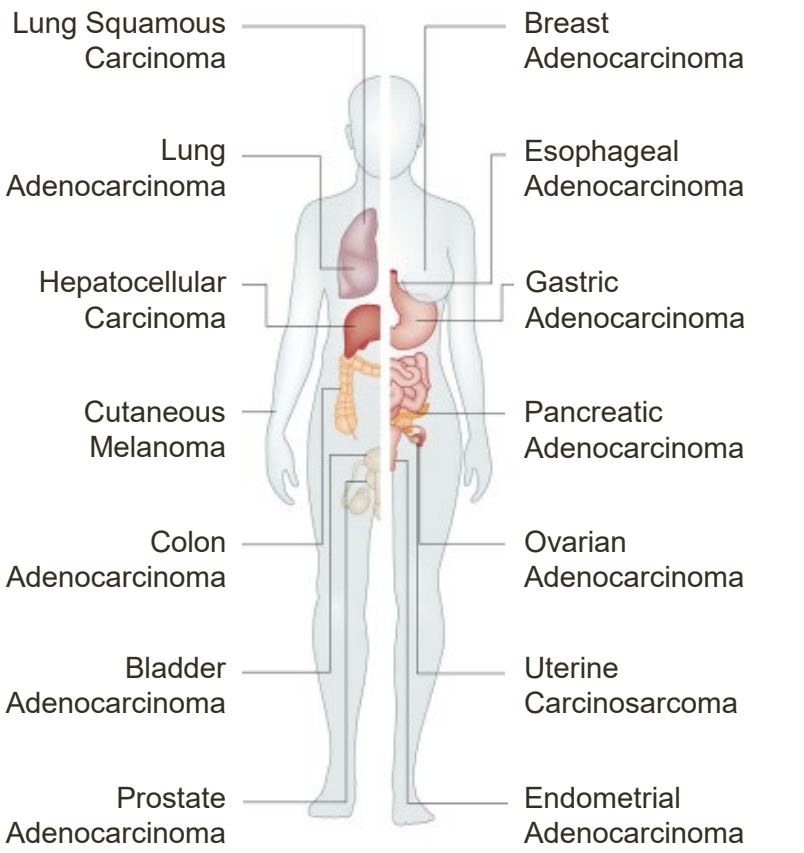
	Target Gene(s)	Indication	EC	Discovery	Preclinical	Clinical		
						Phase 1	Phase 2	Phase 3
Oncology	**MYC**	Hepatocellular carcinoma	OTX-2002*	*Phase 1/2 MYCHELANGELO™ Study*				
	MYC	Non-small cell lung cancer	OTX-2101	*IND-Enabling Studies Ongoing*				
	Undisclosed	Small cell lung cancer						
Multigenic Diseases	**CXCL 1-8**	Potential franchise of programs**						
	Undisclosed	Idiopathic pulmonary fibrosis						
Regenerative Medicine	**HNF4A**	Liver regeneration						
	Undisclosed	Corneal regeneration						
Monogenic Diseases	**SFRP1**	Alopecia						

Route of Administration (top to bottom): IV (HCC), IV (NSCLC), IV (SCLC), IV/Pulmonary, IV/Pulmonary (IPF), IV (Liver Regeneration), Topical (Corneal Regeneration), Topical (Alopecia)
*In November 2022, OTX-2002 received Orphan Drug Designation from the FDA for the treatment of hepatocellular carcinoma
**Potential indications for CXCL-targeting EC include neutrophilic asthma, acute respiratory distress syndrome (including COVID-related), dermatological and rheumatological indications, and oncology

MYC: The Holy Grail of Master Oncogenes

- Primary driver of cancer growth and immune evasion in more than 50% of human cancers
- Strongly correlated with metastases and poor patient prognosis
- Historically ‘undruggable’ due to its disordered protein structure and autoregulation
- Potential solution: Controlled epigenomic modulation
  - OTX-2002 in development for treatment of HCC (70% MYC-associated)

MYC is a master oncogene that contributes to many human cancers

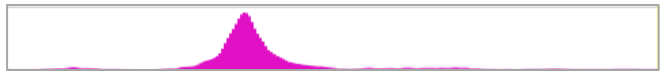


Reference: Dhanasekaran R, et al. *Nat Rev Clin Oncol*. 2022 Jan;19(1):23-36.

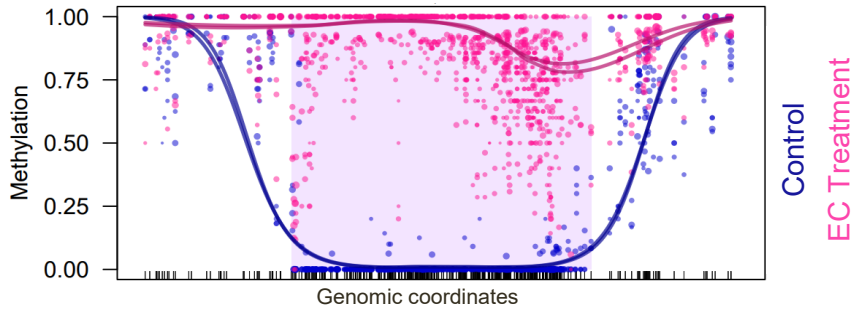
OTX-2002 Mechanism of Action

Preclinical Data Confirms Proof-of-Concept Through Epigenetic Modulation of MYC

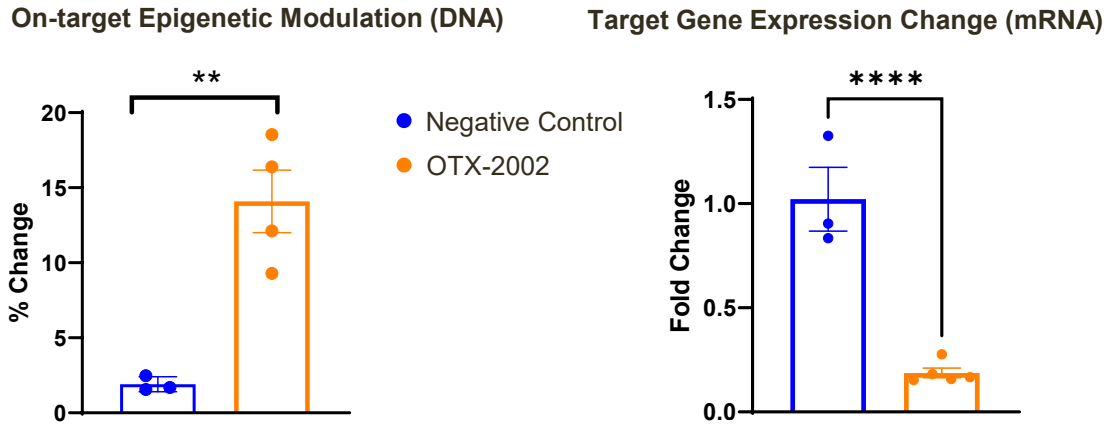
1 Site-specific target engagement



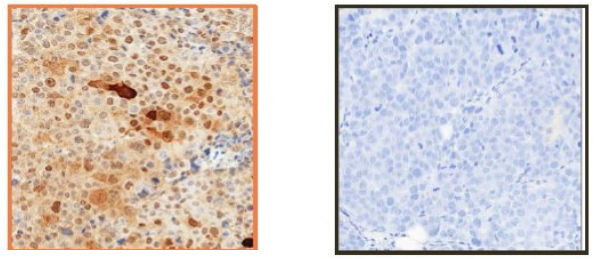
2 Site-specific epigenetic state change (*in vitro*)



3 Site-specific epigenetic change and reduction in mRNA levels (*in vivo*)



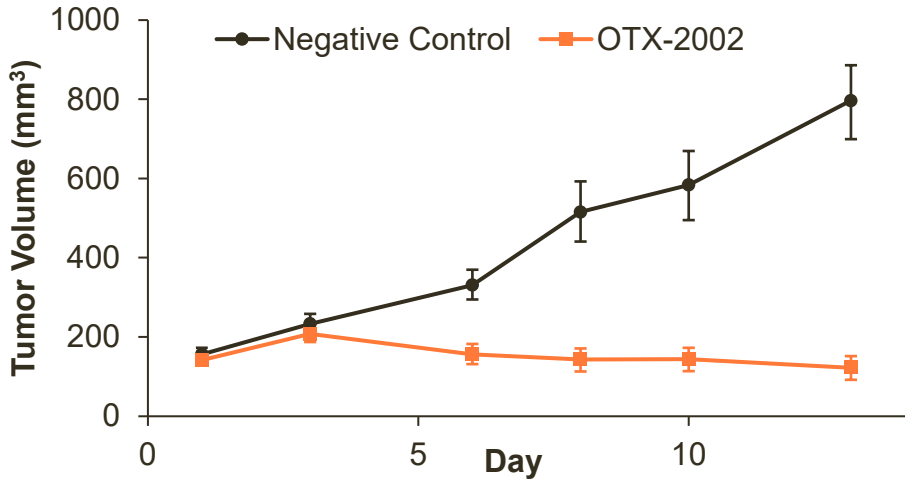
4 Biomarker changes in tissue (*in vivo* change in protein)



Negative control

OTX-2002 treated

5 *In vivo* efficacy



Early Clinical Data Demonstrate Promising Potential of OTX-2002

First Known Clinical Observation of Pre-Transcriptional Epigenetic Control of Gene Expression

8/8 Patients in First Two Dose Levels Showed:

- ✓ Highly-specific binding at target genomic loci
- ✓ Intended epigenetic state change with on-target increase in methylation signature
- ✓ Rapid, robust and durable downregulation of MYC expression
- ✓ Encouraging safety and consistent PK profile

Replication of OTX-2002 mechanism from preclinical to clinical settings provides strong scientific rationale for translation to anti-tumor activity in patients

Unlocks potential for MYC, a historically 'undruggable' target

Establishes clinical proof-of-platform

Validates epigenomic controllers as a new class

MYCHELANGELO™ I
Preliminary Data Overview

Thomas McCauley, Ph.D.
Chief Scientific Officer

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MYCHELANGELO™ I: Ongoing Phase 1/2 Clinical Trial of OTX-2002 in HCC*

Global Two-Part Study of OTX-2002 as Monotherapy and in Combination with Standard of Care**

OTX-2002: IV dosing, once-every-two-weeks; Patients to be enrolled across U.S., Asia, and Europe

Part 1: Monotherapy

Dose Escalation

TBD
Cohort 3
Cohort 2
Cohort 1

3+3 design

- Patients with HCC and other solid tumors known for association with the *MYC* oncogene

Objectives: Determine the DLTs, MTD, safety, and tolerability and determine the RDE of monotherapy

HCC Expansion

Recommended Dose for Monotherapy Expansion

- Patients with advanced HCC

Objectives: Determine the preliminary antitumor activity of monotherapy by ORR and DOR

Part 2: Combination

Safety Run-In Phase

OTX-2002 + Standard of Care**

- Patients with advanced HCC

Objectives: Determine the DLTs, MTD, safety, and tolerability and determine the RDE of combinations

Combination HCC Expansion

Recommended Dose for Combination Expansion + Standard of Care**

- Patients with advanced HCC

Objectives: Determine the preliminary antitumor activity of combinations by ORR and DOR

* Patients with HCC who progressed, relapsed, refractory or intolerant of >1 prior systemic therapy and without available subsequent SOC
** Tyrosine kinase inhibitors, and checkpoint inhibitors including anti-PD-1 and anti-PD-L1 monoclonal antibodies. Dose of SOC in accordance with approved dose in local region.
Definitions: HCC (hepatocellular carcinoma); RDE (recommended dose for expansion); ORR (objective response rate); DOR (duration of response); SOC (standard of care)

Encouraging Emerging Safety Profile for OTX-2002*

Phase 1 Study Enrolled Difficult-to-Treat, Heavily Pretreated Population

Dose Level	Demographics	Cancer Type at Initial Diagnosis	# Prior Lines of Therapy
Dose Level 1 0.02 mg/kg	78 / F / White	Soft Tissue Sarcoma (Oct 2015)	3+
	51 / M / Asian	HCC (Feb 2020)	3+
	70 / M / White	Colorectal Cancer (Sep 2016)	3+
	69 / F / Asian	Sarcoma (Mar 2022)	2
Dose Level 2 0.05 mg/kg	46 / F / Asian	Cervical Cancer (Jan 2014)	2
	68 / M / White	Pancreatic Cancer (Oct 2021)	3+
	56 / M / Asian	HCC (Apr 2020)	3
	66 / M / Asian**	HCC (Aug 2015)	2

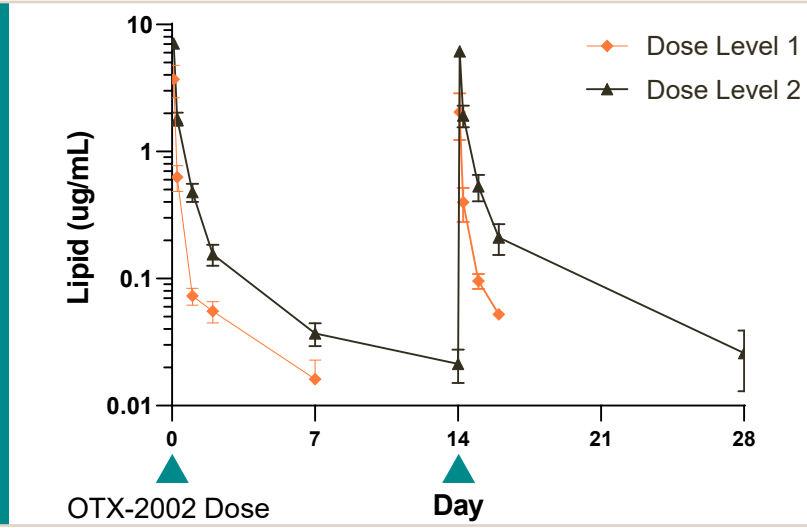
- OTX-2002 was generally well tolerated with no DLTs; MTD not reached
- Majority of AEs were grade 1 or 2 (87%)
- Most common treatment-related AEs were infusion-related reactions (26%); generally consistent with known profile of other FDA-approved LNP-delivered therapeutics
- One grade 4 AST elevation SAE was reported after end of DLT period; resolved within 4 days with minimal intervention (supportive care); no clear etiology or causality
- No dose interruption or modification due to treatment-related AEs

*Data cut-off date of September 18, 2023. **Patient remains on treatment.

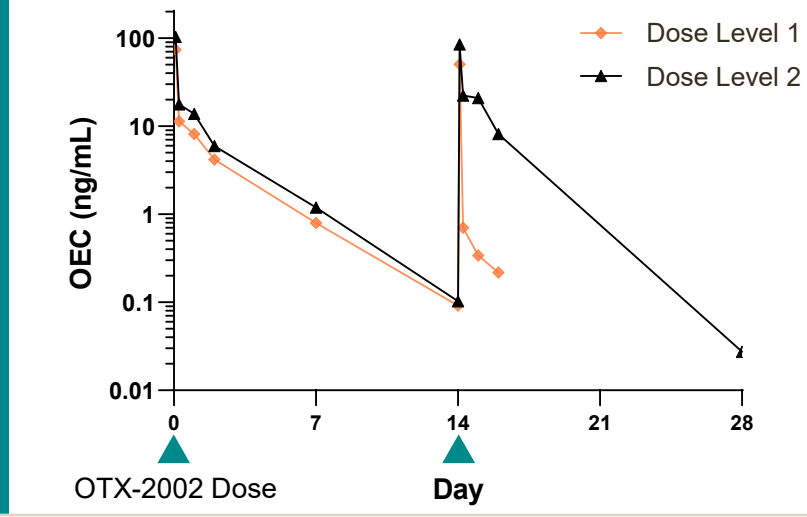
Predictable Pharmacokinetics with Rapid Clearance of Drug Product Observed

Clinical Pharmacokinetics and Lack of Immunogenicity Directly Translate from Preclinical Experience

LNP



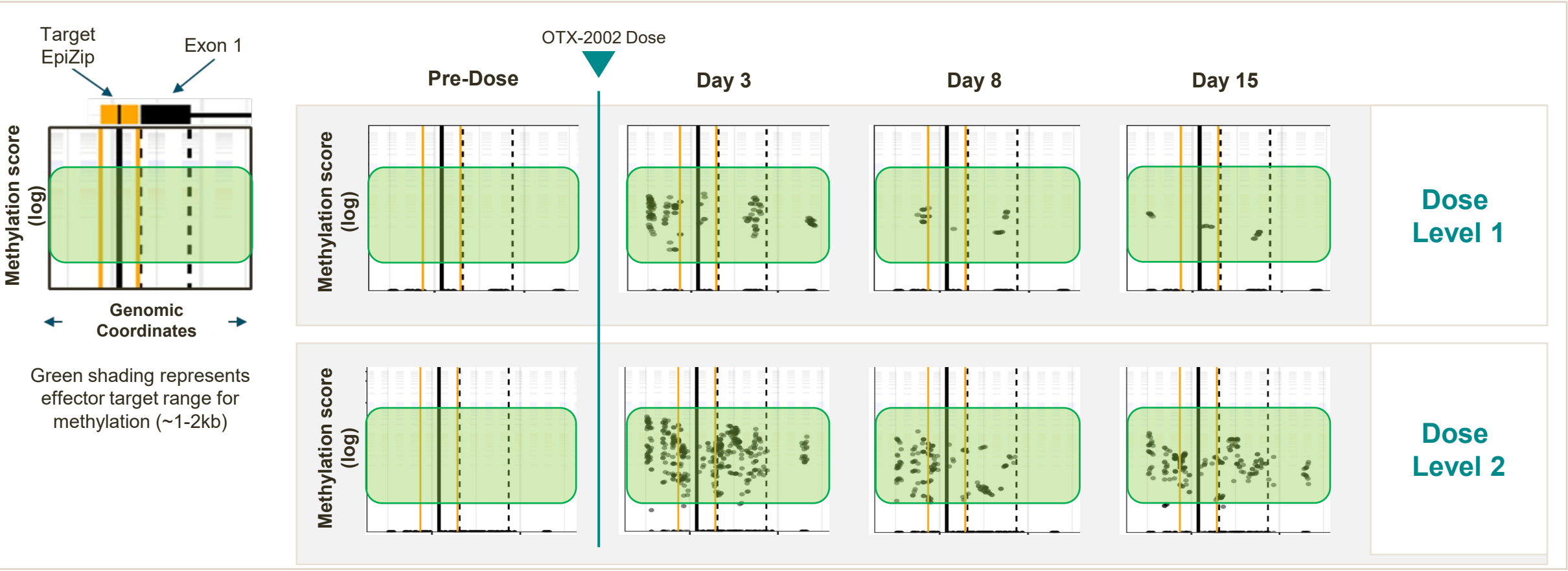
Epigenomic Controller mRNA



- OTX-2002 was cleared rapidly from systemic circulation
- No accumulation observed with repeat doses
- Low levels of immune response; no related adverse events or impact on PK observed
- PK profile of both LNP and mRNA components of OTX-2002 were consistent overall between patients across both cohorts
- Dose levels 1 and 2 are below predicted dose range for activity based on preclinical modeling; dose escalation continues

Highly-Specific Target Engagement and Intended Epigenetic State Change at Target Genomic Loci within MYC IGD Observed

- On-target increase in cell-free DNA MYC methylation signal, persistent over two-week dosing cycle

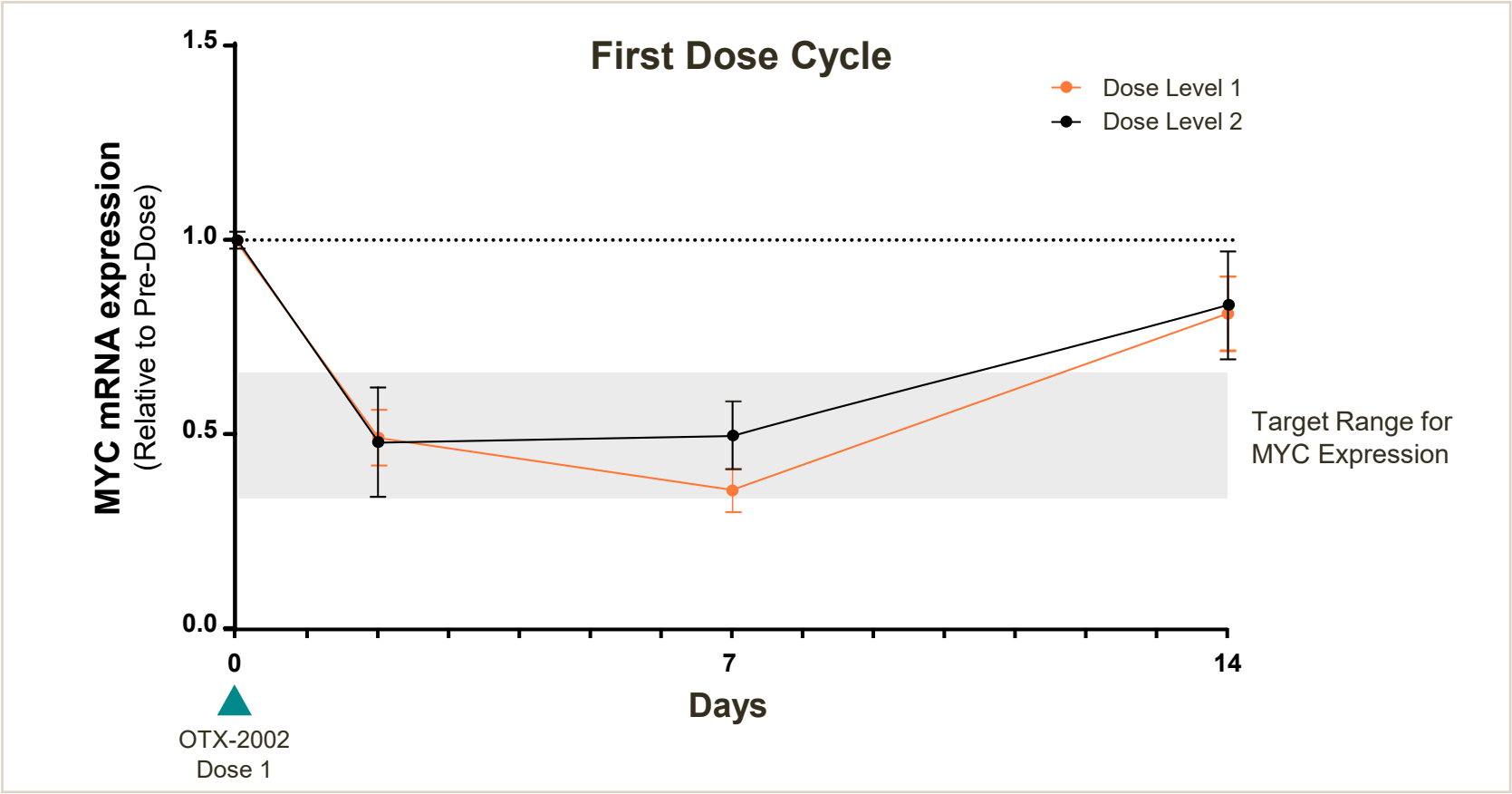


First-in-human demonstration of controlled epigenomic modulation

*Data represent aggregate methylation for all patients in each cohort (dose level 1, n=4; dose level 2, n=4)

Rapid, Robust & Durable Downregulation of MYC mRNA Expression Observed

- OTX-2002 reduced MYC mRNA levels in all 8 patients across dose levels 1 and 2



Clinical MYC downregulation consistent with levels that led to robust anti-tumor efficacy in preclinical settings

*Data represent mean expression data for all patients in each cohort (dose level 1, n=4; dose level 2, n=4)

Preliminary Data Show Promising Potential of OTX-2002 and MYC Modulation

Key Takeaways

- ✓ First known clinical observation of pre-transcriptional control of gene expression using a programmable mRNA development candidate
- ✓ OTX-2002 directly targeted and therapeutically controlled historically 'undruggable' MYC in 8/8 patients
- ✓ Rapid, robust and durable downregulation of MYC expression to levels therapeutically relevant in literature and preclinical settings
- ✓ Encouraging safety, predictable PK and demonstration of intended epigenetic effects support continued development of OTX-2002

Next Steps

- Continue monotherapy dose escalation
- Provide additional updates on clinical data
- Select recommended dose for expansion
- Initiate monotherapy expansion and combination with standard of care

Preliminary data support overall translation of preclinical experience to clinical performance

Guest Speaker

Gerard Evan, Ph.D.

Principal Group Leader of the Francis Crick Institute in London;
Professor of Cancer Biology at Kings College London

Closing Remarks

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Q&A

Mahesh Karande
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Thank You