Omega Therapeutics Announces First Patient Dosed in Landmark MYCHELANGELO™ I Trial of OTX-2002 in Hepatocellular Carcinoma and Other Solid Tumor Types Associated with the MYC Oncogene

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- *OTX-2002 is the First-Ever Epigenomic Controller in a New Class of Programmable mRNA Therapeutics to be Administered to Patients*

CAMBRIDGE, Mass., Oct. 27, 2022 /PRNewswire/ -- Omega Therapeutics, Inc. (NASDAQ: OMGA) ("Omega"), a clinical-stage biotechnology company pioneering the first systematic approach to use mRNA therapeutics as programmable epigenetic medicines, today announced dosing of the first patient in its Phase 1/2 MYCHELANGELO ™ I trial evaluating OTX-2002 for the treatment of relapsed or refractory hepatocellular carcinoma (HCC) and other solid tumor types associated with c-Myc (MYC) oncogene overexpression. OTX-2002, a novel epigenomic controller, is an mRNA therapeutic designed to downregulate MYC expression pre-transcriptionally through epigenetic modulation while potentially overcoming MYC autoregulation.

"Today's announcement marks a new era of therapeutic development utilizing precision genomic control intended to treat and cure serious diseases. As the first-ever Omega Epigenomic Controller ™ (OEC) to be dosed in a patient, this milestone for OTX-2002 and the MYCHELANGELO clinical program represents a significant step forward on our mission to deliver a new approach to bringing engineered, programmable mRNA therapeutics to patients," said Mahesh Karande, President and Chief Executive Officer of Omega Therapeutics. "OTX-2002 leverages our proprietary Omega Epigenomic Programming ™ platform and is designed for precise and durable tuning of MYC expression. We look forward to evaluating OTX-2002 for the treatment of HCC, and believe it has the potential to meaningfully transform the treatment landscape for patients in need."

Yan Moore, M.D., Chief Medical Officer of Omega Therapeutics added, "MYC has been a long sought-after target for cancer therapeutics given its critical role in disease progression, however properties of the MYC gene and protein have made it a historically undruggable target. Omega's unique approach has the potential to downregulate expression through epigenetic modulation by acting pre-transcriptionally to target MYC dysregulation at its source, a mechanism of action that could potentially lead to an enhanced efficacy and improved safety profile, for patients in need, compared to currently available treatments."

"HCC is one of the most rapidly increasing causes of cancer deaths worldwide, and MYC overexpression is associated with aggressive disease in up to 70% of these cases. Preclinical results of OTX-2002 showed downregulation of MYC in target cancer cells while sparing healthy cells and demonstrate the potential of this approach using Omega's unique epigenomic modulation technology," added Ildefonso Ismael Rodriguez, M.D., Medical Oncologist and Clinical Investigator at Next Oncology and principal investigator of the site. "I look forward to evaluating OTX-2002 in the clinical setting and building on the potential of this first-in-class therapy."

The Phase 1/2 MYCHELANGELO I trial (NCT05497453) will evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of OTX-2002 as a monotherapy (Part 1) and in combination with standard of care therapies (Part 2) in patients with relapsed or refractory HCC and other solid tumor types known for association with the MYC oncogene. The study is expected to enroll approximately 190 patients at clinical trial sites in the United States, Asia, and Europe.

Omega has previously announced preclinical data supporting OTX-2002's mechanism of action and antitumor activity in multiple *in vitro* and *in vivo* models. The Company demonstrated OTX-2002's ability to modulate the epigenetic profile of MYC and control its expression pre-transcriptionally in multiple *in vitro* studies. Preclinical studies also showed that OTX-2002 induced robust antitumor activity alone and in combination with standard of care therapies in multiple *in vivo* HCC models. Additionally, treatment with OTX-2002 resulted in successful pre-transcriptional downregulation of hepatocyte MYC expression in non-human primates. Cumulatively, these preclinical data support the clinical potential of OTX-2002 to provide a novel treatment strategy for patients with HCC.

About Hepatocellular Carcinoma and MYC

Hepatocellular carcinoma (HCC) is a leading cause of cancer deaths worldwide and represents an unmet clinical need with few therapeutic options. Tyrosine kinase inhibitors (TKIs) have been used as a systemic therapy for HCC, but patients frequently develop resistance with oncogenic MYC identified as a correlating prognostic factor. The MYC oncogene is associated with aggressive disease in up to 70% of patients with HCC.

About OTX-2002

OTX-2002 is a first-in-class Omega Epigenomic Controller ™ in development for the treatment of hepatocellular carcinoma (HCC). OTX-2002 is an mRNA therapeutic delivered via lipid nanoparticles (LNPs) and is designed to downregulate MYC expression pre-transcriptionally through epigenetic modulation while potentially overcoming MYC autoregulation. MYC is a master transcription factor that regulates cell proliferation, differentiation and apoptosis and plays a significant role in more than 50% of all human cancers. OTX-2002 is currently being evaluated in the Phase 1/2 MYCHELANGELO ™ I trial in patients with relapsed or refractory HCC and other solid tumor types known for association with the MYC oncogene; visit clinicaltrials.gov (NCT05497453) for more details.

About Omega Therapeutics

Omega Therapeutics, founded by Flagship Pioneering, is a clinical-stage biotechnology company pioneering the first systematic approach to use mRNA therapeutics as a new class of programmable epigenetic medicines. The company's OMEGA Epigenomic Programming ™ platform harnesses the power of epigenetics, the mechanism that controls gene expression and every aspect of an organism's life from cell genesis, growth, and differentiation to cell death. Using a suite of technologies, paired with Omega's process of systematic, rational, and integrative drug design, the OMEGA platform enables control of fundamental epigenetic processes to correct the root cause of disease by returning aberrant gene expression to a normal range without altering native nucleic acid sequences. Omega's modular and programmable mRNA medicines, Omega Epigenomic Controllers ™, are designed to target specific epigenomic loci within insulated genomic domains, EpiZips ™, from amongst thousands of unique, mapped, and validated genome-wide DNA-sequences, with high specificity to durably tune single or multiple genes to treat and cure diseases through Precision Genomic Control ™. Omega is currently advancing a broad pipeline of development candidates spanning a range of disease areas, including oncology, regenerative medicine, multigenic diseases including immunology, and select monogenic diseases, including alopecia.

For more information, visit omegatherapeutics.com, or follow us on Twitter and LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the timing and design of our Phase 1/2 MYCHELANGELO ™ I clinical trial; the potential of the OMEGA platform to engineer programmable epigenetic mRNA therapeutics that successfully regulate gene expression by targeting insulated genomic domains; expectations surrounding the potential of our product candidates, including our lead OEC candidate OTX-2002; and expectations regarding our pipeline, including trial design, initiation of preclinical studies and advancement of multiple preclinical development programs in oncology, immunology, regenerative medicine, and select monogenic diseases. 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 controller machines 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; potential delays in and unforeseen costs arising from our clinical trials; 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 OEC 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" in our Quarterly Report on Form 10-Q for the quarter ended June 30, 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 press release. Any such forward-looking statements represent management's estimates as of the date of this press release. 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.

Investor and Media Contact:
Eva Stroynowski
617.949.4370
estroynowski@omegatx.com

Media Contact:
Jason Braco
LifeSci Communications
646.751.4361
jbraco@lifescicomms.com

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