Omega Therapeutics Announces Promising Preliminary Clinical Data for OTX-2002 from Ongoing MYCHELANGELO™ I Trial

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All 8 patients treated with OTX-2002 in initial two cohorts achieved highly specific on-target genomic engagement, intended epigenetic state change and robust downregulation in expression of c-MYC, a historically 'undruggable' target

First-known clinical observation of pre-transcriptional gene modulation using a programmable epigenomic mRNA candidate

Clinical proof-of-platform established; potential applicability across a broad range of diseases

Company to host webcast today at 8:00 a.m. ET

CAMBRIDGE, Mass., Sept. 26, 2023 (GLOBE NEWSWIRE) -- Omega Therapeutics, Inc. (Nasdaq: OMGA) ("Omega"), a clinical-stage biotechnology company pioneering the development of a new class of programmable epigenomic mRNA medicines, today announced encouraging preliminary safety, tolerability, pharmacokinetic and translational data from the initial two dose level cohorts (n=8) from Part 1 of its ongoing Phase 1/2 MYCHELANGELO™ I study evaluating OTX-2002 in patients with hepatocellular carcinoma (HCC) and other solid tumors associated with the c-MYC (MYC) gene. OTX-2002, the Company's lead development candidate, is designed to pre-transcriptionally downregulate MYC, a master oncogene implicated in more than 50% of all cancers and approximately 70% of HCC cases.

"We believe these promising data represent a landmark moment for Omega that supports the potential of our approach and marks a new era of therapeutic development utilizing programmable mRNA candidates for controlled epigenomic modulation," said Mahesh Karande, President and Chief Executive Officer of Omega Therapeutics. "For the first time ever in the clinical setting, we have site-specifically targeted and controllably modulated the expression of the MYC oncogene, one of the most promising targets in oncology that has proven difficult to successfully drug by other modalities. We are excited to continue advancing OTX-2002 as we aim to deliver a new class of medicines for patients in need."

"We are thrilled to see that all eight patients evaluated at these initial low doses demonstrated clear evidence of on-target epigenetic changes and correlated rapid, robust and durable decreases in MYC mRNA expression levels," added Thomas McCauley, Ph.D., Chief Scientific Officer of Omega Therapeutics. "These early clinical data are consistent with our preclinical experiments, giving us confidence that our approach has the potential to translate to anti-tumor activity and clinical benefit. Coupled with encouraging safety and predictable pharmacokinetics, we believe that OTX-2002 holds transformative potential for patients living with HCC."

MYCHELANGELO I (NCT05497453) is an ongoing Phase 1/2 open label trial evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor 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. These preliminary data cover the first two dose cohorts from the monotherapy dose escalation portion of the trial, which is currently being conducted at clinical sites across the United States and Asia. Patients were treated intravenously with either 0.02 mg/kg (n=4) or 0.05 mg/kg (n=4) of OTX-2002 once every two weeks. Changes in MYC DNA methylation and mRNA levels were analyzed through measurements of cell-free DNA and exosomal mRNA, respectively. As of the data cut-off date of September 18, 2023, one HCC patient in the 0.05 mg/kg dose level cohort remained on treatment.

Key Highlights:

Translational:

- Highly specific on-target engagement and intended epigenetic changes at the target genomic loci were observed for all eight patients across both dose levels, as evidenced by a robust increase in cell-free DNA MYC methylation signal following administration with OTX-2002. The increased methylation signal persisted throughout the two-week dosing interval.
- Epigenetic modulation of MYC translated to rapid, robust and durable downregulation of MYC expression in all eight patients, with mean reductions across both dose levels of approximately 55% observed 7 days following administration with OTX-2002.
- The increase in methylation and corresponding downregulation of MYC expression observed clinically are within the ranges that led to anti-tumor activity in preclinical xenograft models.

Pharmacokinetics:

- Consistent pharmacokinetic (PK) data across both dose levels with rapid clearance and minimal variability observed within and between patients.
- No accumulation was observed following repeat administration, and low, transient levels of immune response were observed with no related adverse events or impact on PK observed.

- Both initial dose levels are below the predicted threshold for anti-tumor activity based on preclinical models.

Safety and Tolerability:

- At both dose levels, OTX-2002 was generally well tolerated, with no dose-limiting toxicities.
- The majority of adverse events observed in the trial were grade 1 or 2.
- The most common treatment-related adverse events were infusion-related reactions (26%) including fever and chills, generally consistent with the known profile of other FDA-approved LNP-delivered therapeutics.

Gerard Evan, Ph.D., Principal Group Leader of the Francis Crick Institute in London and Professor of Cancer Biology, King's College London, added, "While MYC's role and importance in cancer progression has been long established, no clinical approach to date has effectively controlled its expression directly at its source. These new data, while early, are incredibly promising and highlight the potential of programmable epigenomic mRNA therapeutics to provide a groundbreaking new strategy to pre-transcriptionally control gene regulation. If successful, this approach could be applied broadly to a vast range of MYC-driven cancers where immense patient need remains."

Based on these encouraging data, OTX-2002 continues to advance in monotherapy dose escalation. Following the identification of a recommended dose, the Company expects to initiate expansion cohorts in monotherapy and in combination with standard of care therapies.

Company Investor Webcast and Conference Call

Omega will host a webcast and conference call for analysts and investors to review these data today, Tuesday, September 26, 2023, at 8:00 a.m. ET. The webcast will feature members of Omega's leadership team along with guest speaker, Gerard Evan Ph.D., Principal Group Leader of the Francis Crick Institute in London and Professor of Cancer Biology, King's College London. The live webcast can be accessed under "News & Events" on the investors section of Omega's website at https://ir.omegatherapeutics.com/news-events/event-calendar. To participate in the live call, please register using this link. It is recommended that participants register at least 15 minutes in advance of the call. Once registered, participants will be informed of the dial-in numbers, including PIN. The archived webcast will be available on Omega's website for approximately 90 days following the event.

About OTX-2002

OTX-2002 is an mRNA therapeutic delivered via lipid nanoparticles (LNPs) 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 has demonstrated the ability to control MYC expression pre-transcriptionally in multiple preclinical studies, including the successful downregulation of MYC in non-human primates. Additionally, OTX-2002 has shown robust anti-tumor activity alone and in combination with standard of care therapies *in vivo* in multiple preclinical models of HCC. Currently, OTX-2002 is being evaluated as a potential treatment for HCC and other solid tumors associated with MYC.

About Omega Therapeutics

Omega Therapeutics is a clinical-stage biotechnology company pioneering the development of a new class of programmable epigenomic mRNA medicines to treat or cure a broad range of diseases. By pre-transcriptionally modulating gene expression, Omega's approach enables controlled epigenomic modulation of nearly all human genes, including historically undruggable and difficult-to-treat targets, without altering native nucleic acid sequences. Founded in 2017 by Flagship Pioneering following breakthrough research by world-renowned experts in the field of epigenetics, Omega is led by a seasoned and accomplished leadership team with a track record of innovation and operational excellence. The Company is committed to revolutionizing genomic medicine and has a diverse pipeline of therapeutic candidates derived from its OMEGA platform spanning oncology, regenerative medicine, multigenic diseases including immunology, and select monogenic diseases.

For more information, visit omegatherapeutics.com, or follow us on X (formerly 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, progress and design of our Phase 1/2 MYCHELANGELO™ I clinical trial and our preclinical studies, as well as the anticipated impact and application of preliminary data related thereto; the potential of the OMEGA platform to engineer programmable epigenomic mRNA therapeutics that successfully and pre-transcriptionally regulate gene expression by targeting insulated genomic domains; expectations surrounding the potential of our product candidates, including OTX-2002; 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; and upcoming events and presentations. 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; 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, 2023, 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.

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