Kymera Therapeutics Presents Preclinical Data Highlighting Biological Superiority of MDM2 Degradation over Inhibition and Shares Profile of Clinical Candidate KT-253 at the American Association for Cancer Research (AACR) Annual Meeting 2022

April 8, 2022

MDM2 degradation demonstrated differentiated biological activity and superior cell killing compared to small molecule inhibition in p53 wild-type tumors and led to tumor regressions in xenograft models of ALL and AML

KT-253 is a highly potent and selective heterobifunctional MDM2 degrader whose mechanism of action overcomes the MDM2-p53 autoregulatory feedback loop that limits the activity of MDM2 small molecule inhibitors

WATERTOWN, Mass., April 08, 2022 (GLOBE NEWSWIRE) -- Kymera Therapeutics, Inc. (NASDAQ: KYMR), a clinical-stage biopharmaceutical company advancing targeted protein degradation to deliver novel small molecule protein degrader medicines, today presented preclinical data from its 4th development program, a novel MDM2 degrader, at the American Association for Cancer Research (AACR) Annual Meeting 2022, taking place from April 8 - 13, 2022 in New Orleans, Louisiana.

The murine double minute 2 (MDM2) oncoprotein is the E3 ligase that ubiquitinates and degrades the p53 tumor suppressor. While reversible small molecule inhibitors (SMIs) of the MDM2/p53 interaction have been developed to stabilize and upregulate p53 expression in order to induce cancer cell death in wild-type p53 tumors, they induce a feedback loop that upregulates MDM2 protein levels and thereby reduce p53 stabilization – limiting their biological activity and clinical application. Kymera is developing KT-253, an MDM2 protein degrader whose unique mechanism of action overcomes the MDM2-p53 autoregulatory feedback loop, allowing for a rapid apoptotic response and potentially superior efficacy and safety compared to SMIs.

The results showed that KT-253 inhibited tumor cell growth in the picomolar range and was >200-fold more potent than clinically active MDM2 SMIs across a panel of solid and hematological tumor cell lines. Short term (as brief as three to four hours) exposures of KT-253 in a p53 wild-type acute lymphoblastic leukemia (ALL) cell line more potently stabilized p53 compared to SMIs, leading to robust apoptosis that was not observed with SMIs.

In addition, a single low dose of KT-253 resulted in sustained tumor regression in a mouse xenograft model of ALL, correlating strongly with induction of pro-apoptotic p53 target genes. Administration of KT-253 every 3 weeks at exposures well-tolerated in NHP also achieved sustained tumor regression in a mouse xenograft AML model where SMIs only resulted in partial tumor growth inhibition.

“We are encouraged to see a clear biologic and therapeutic advantage over SMIs in preliminary studies of our novel MDM2 degrader,” said Juliet Williams, Senior Vice President and Head of Biology, Kymera Therapeutics. “KT-253 has demonstrated extremely potent *in vitro* cell killing and *in vivo* antitumor activity with intermittent dosing that is superior to existing SMIs and indicates the potential for improved efficacy and safety with the degrader approach in p53 wild-type tumors.”

KT-253 has broad franchise opportunities in p53 wild-type tumors, which comprise over 50% of all liquid and solid malignancies.

“Within the broad development landscape of p53 wild-type tumors, Kymera is focused on a biomarker selection strategy for identifying those tumor types where MDM2 degradation will elicit a rapid apoptotic response, which will enhance the therapeutic index,” said Nello Mainolfi, Ph.D., Co-Founder, President and CEO, Kymera Therapeutics. “We are excited to progress this compelling compound further into clinical trials in an anticipated broad set of indications in both liquid and solid tumors, and we anticipate filing an IND in 2022.”

Additional Research Highlights:

- MDM2 levels were maintained at undetectable levels with KT-253 while an SMI showed increased MDM2 protein expression at four hours post exposure.
- A single 1 mg/kg dose of KT-253 in RS4;11 ALL xenograft animal models led to tumor regression showing rapid increase in key apoptotic biomarkers such as p53, p21, and PUMA as early as 3 hours post dose.
- KT-253 also showed sustained tumor regression in MV-4-11 AML xenograft animal model and led to a rapid increase in GDF15, p21, and PUMA as early as 3 hours post dose.

Presentation at AACR Annual Meeting:

- Title: KT-253, a highly potent and selective heterobifunctional MDM2 degrader for the treatment of wild-type p53 tumors with superior potency and differentiated biological activity compared to small molecule inhibitors (SMI)
  - Abstract Number: 3934 / 8
  - Session Time: 9:00 AM – 12:30 PM CDT, April 13, 2022
  - Location: Section 22
  - Presenter: Yogesh Chutake, Principal Scientist, Oncology, Biology, Kymera Therapeutics

About MDM2 Degrader Program, KT-253

KT-253 is a potent and selective degrader of MDM2 with potential to be a best-in-class p53 stabilizer. Degradation of MDM2 has blocks the feedback loop which up-regulates MDM2 production and in doing so more effectively drives tumor cells to rapid apoptosis. As wild-type p53 is present in more than 50% of tumors, KT-253 represents another program with broad franchise potential in liquid and solid tumors. Kymera is focused on indications with specific sensitivity to this mechanism of action, such as AML, lymphomas, uveal melanoma, and others through a focused biomarker strategy. Kymera expects to file an IND for KT-253 in 2022.

About Kymera Therapeutics

Kymera Therapeutics (Nasdaq: KYMR) is a biopharmaceutical company pioneering the field of targeted protein degradation, a transformative approach to address disease targets and pathways inaccessible with conventional therapeutics. Kymera's Pegasus platform is a powerful drug discovery engine, advancing novel small molecule therapies that harness the body's innate protein recycling machinery to degrade dysregulated, disease-causing proteins. With a focus on undrugged nodes in validated pathways, Kymera is advancing a pipeline of novel therapeutics designed to address the most intractable pathways and provide new treatments for patients. Kymera's initial programs target IRAK4, IRAKIMiD, and STAT3 within the IL-1R/TLR or JAK/STAT pathways, providing the opportunity to treat patients with a broad range of immune-inflammatory diseases, hematologic malignancies, and solid tumors. For more information, visit www.kymeratx.com.

Founded in 2016, Kymera is headquartered in Watertown, Mass. Kymera has been named a "Fierce 15" biotechnology company by Fierce Biotech and has been recognized by the Boston Business Journal as one of Boston's "Best Places to Work." For more information about our people, science, and pipeline, please visit www.kymeratx.com or follow us on Twitter or LinkedIn.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding its: strategy, business plans and objectives for the MDM2 degrader program; and plans and timelines for the clinical development of Kymera Therapeutics' product candidates, including the therapeutic potential and clinical benefits thereof. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: the impact of COVID-19 on countries or regions in which we have operations or do business, as well as on the timing and anticipated results of our current preclinical studies and future clinical trials, strategy and future operations; the delay of any current preclinical studies or future clinical trials or the development of Kymera Therapeutics' drug candidates; the risk that the results of current preclinical studies may not be predictive of future results in connection with future clinical trials; Kymera Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of the Company's planned interactions with regulatory authorities; and obtaining, maintaining and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Quarterly Report on Form 10-K for the period ended December 31, 2021, filed on February 24, 2022, as well as discussions of potential risks, uncertainties, and other important factors in Kymera Therapeutics' subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Kymera Therapeutics' views only as of today and should not be relied upon as representing its views as of any subsequent date. Kymera Therapeutics explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

Investor Contact:
Bruce Jacobs
Chief Financial Officer
investors@kymeratx.com
857-285-5300

Chris Brinzey
Managing Director, Westwicke
chris.brinzey@westwicke.com
339-970-2843

Media Contact:
Tyler Gagnon
Director, Corporate Communications
tgagnon@kymeratx.com
508-904-9446