Kymera Therapeutics Presents Preclinical Data Demonstrating Activity of KT-253, a Selective Heterobifunctional MDM2 Degrader, in Acute Myeloid Leukemia at the American Society of Hematology Annual Meeting

December 11, 2022

A single dose of KT-253 induced rapid apoptosis and sustained tumor regression in xenograft models of AML

KT-253 showed combinatorial benefit with BCL-2 inhibitor venetoclax in model of venetoclax-resistant AML

KT-253 also active in other hematologic malignancies including DLBCL

WATERTOWN, Mass., Dec. 11, 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 showing that KT-253, a novel MDM2 degrader, inhibited tumor growth as single agent and in combination with venetoclax in AML xenograft models. The data was presented at the American Society of Hematology (ASH) Annual Meeting, taking place from December 10 - 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 p53 in order to induce cancer cell death in wildtype (WT) p53 tumors, they induce a feedback loop that upregulates MDM2 protein and thereby reduces p53 protein levels – limiting their biological activity and clinical application. Recent clinical trials with MDM2 inhibitors, especially in relapsed/refractory Acute Myeloid Leukemia (AML), have resulted in suboptimal clinical activity, highlighting the need for novel therapeutic approaches to treat WT p53 hematologic and solid tumor malignancies. MDM2 degraders, because of their catalytic mechanism, can overcome the feedback loop and lead to more efficient p53 stabilization and induction of an acute apoptotic response in tumor cells.

Kymera previously showed that KT-253, a novel, highly potent and selective heterobifunctional MDM2 degrader, has superior activity compared to MDM2 SMIs and demonstrated greater than 200-fold improvements in both in vitro cell growth inhibition and apoptosis. Because of the distinct pharmacological profile compared to MDM2/p53 SMIs, a single dose of KT-253 was sufficient to induce rapid apoptosis and sustained tumor regression in the MV4;11 AML and RS4;11 ALL cell line-derived (CDX) mouse xenograft models.

New results in AML now demonstrate that KT-253 administered once every three weeks led to tumor regression in the CTG-2227 AML patient-derived xenograft (PDX) model and responses in CTG-2240 and CTG-2700 AML PDX models. These data support an intermittent dosing schedule of KT-253 in AML which has the potential for improved efficacy and safety using the degrader approach. In addition, in an AML CDX model resistant to the standard of care BCL-2 inhibitor venetoclax, KT-253 administered once every three weeks in combination with venetoclax achieved durable tumor regression. This suggests a potential benefit of KT-253 combined with AML standard of care agents that could further expand the development possibilities in AML.

KT-253 also showed activity in additional hematological malignancies, including both in vitro and in vivo single-agent responses in DLBCL, supporting the development of KT-253 in additional indications such as lymphoma.

“Our KT-253 degrader, unlike small molecule inhibitors, has the potential to overcome the feedback loop which upregulates MDM2 production and more effectively stabilize the tumor suppressor p53, alone and in combination with widely used treatments,” said Nello Mainolfi, Ph.D., Co-Founder, President and CEO, Kymera Therapeutics. “Given that P53 dependency is seen across a large number of tumor types, we’re excited to advance this compound into clinical trials to evaluate its impact on the treatment of AML and other p53 wild-type cancers.”

Presentation at ASH Annual Meeting:

- Title: Development of KT-253, a Highly Potent and Selective Heterobifunctional MDM2 Degrader for the Treatment of Acute Myeloid Leukemia
  - Abstract Number: 2776
  - Session Time: 6:00 PM – 8:00 PM CT, December 11, 2022
  - Location: Ernest N. Morial Convention Center, Hall D
  - Presenter: Stefanie Schalm, Senior Director, 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 overcomes 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, and solid tumors through a focused biomarker strategy. Kymera expects to clear an IND for KT-253 by Q4 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 both the Boston Globe and the Boston Business Journal as one of Boston’s top workplaces. 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 by Kymera Therapeutics regarding its: strategy, business plans and objectives for the IRAK4, IRAKIMiD,STAT3 and MDM2 degrader programs; plans and timelines for the clinical development of its product candidates, including the therapeutic potential, clinical benefits and safety thereof; expectations regarding timing, success and data announcements of current ongoing clinical trials; the ability to initiate new clinical programs; and cash position and expected runway. 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 and future preclinical studies and clinical trials, supply chain, strategy and future operations; the delay of any current and future preclinical studies or clinical trials or the development of Kymera Therapeutics' drug candidates; the risk that the results of current preclinical studies and clinical trials 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 Kymera Therapeutics' planned interactions with regulatory authorities; obtaining, maintaining and protecting its intellectual property; and Kymera Therapeutics' relationships with its existing and future collaboration partners. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Annual Report on Form 10-K for the period ended December 31, 2021 and most recent Quarterly Report on Form 10-Q, 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:
Todd Cooper
Senior Vice President, Corporate Affairs
media@kymeratx.com
857-285-5300