Kymera Therapeutics Presents Data Demonstrating Superior Efficacy of KT-253, a Potent and Selective Heterobifunctional MDM2 Degrader, Compared to Small Molecule Inhibitor in Preclinical Leukemia Models at the European Hematology Association Congress

June 9, 2023

A single dose of KT-253 drives tumor regression and demonstrates differentiated pharmacology compared to small molecule inhibitor (SMI) in preclinical models of ALL and AML

WATERTOWN, Mass., June 09, 2023 (GLOBE NEWSWIRE) -- Kymera Therapeutics, Inc. (NASDAQ: KYMR), a clinical-stage biopharmaceutical company advancing targeted protein degradation (TPD) to deliver novel small molecule protein degrader medicines, will present preclinical data on KT-253, a potent and selective heterobifunctional MDM2 degrader. The data will be presented at the European Hematology Association (EHA) Congress, taking place from June 8-15, 2023, in Frankfurt, Germany.

KT-253 targets MDM2, the crucial regulator of the most common tumor suppressor, p53. p53 remains intact (wild type) in close to 50% of cancers, meaning that it retains its ability to modulate cancer cell growth. While small molecule inhibitors (SMIs) have been developed to stabilize and upregulate p53 expression, they have been found to induce a feedback loop that increases MDM2 protein levels, which can repress p53 and limit their efficacy. In preclinical studies, KT-253 has shown the ability to overcome the MDM2 feedback loop and rapidly induce cancer cell death with brief exposures, providing the opportunity for an improved efficacy and safety profile.

New results show that a single, high dose of KT-253 administered intravenously (IV) in preclinical models of acute lymphoblastic leukemia (RS4;11 ALL) and acute myeloid leukemia (MV4;11 AML) led to >90% MDM2 degradation in tumors within one hour of dosing, strong p53 upregulation and induction of apoptosis within the first 8-24 hours, and sustained tumor regressions. In contrast, lower doses of KT-253 administered IV more frequently or repeat dosing with an oral MDM2 SMI led only to relatively weak p53 activation and apoptosis induction and modest tumor growth inhibition. These results suggest that a pulse IV dosing regimen of KT-253 has the potential for an improved efficacy and safety profile over MDM2 SMIs currently in the clinic.

“KT-253 exemplifies our approach of selecting targets with strong genetic validation where we believe that targeted protein degradation provides the best chance for an effective treatment. These findings in models of AML and ALL demonstrate that acute and potent MDM2 degradation with IV pulse dosing of KT-253 enables the most effective upregulation of the p53 pathway in vulnerable p53 wild-type tumor cells while limiting the duration of pathway modulation in normal cells, thereby potentially improving the therapeutic index for MDM2 targeting,” said Nello Mainolfi, Ph.D., Founder, President and CEO, Kymera Therapeutics. “This hit-and-run approach with our MDM2 degrader has the potential to overcome the inherent limitations of small molecule MDM2 inhibitors against this promising target, and we look forward to investigating the activity of KT-253 in a variety of liquid and solid tumors in our ongoing clinical studies.”

Presentation at EHA:

- Title: Pulse Dosing of Potent and Selective Heterobifunctional MDM2 Degrader KT-253 Drives Tumor Regression and Demonstrates Differentiated Pharmacology Compared to p53/MDM2 Small Molecule Inhibitors
  - Abstract Number: P464
  - Session Time: 6:00 PM – 7:00 PM CEST, June 9, 2023
  - Presenter: Nancy Dumont, Director, In Vivo Pharmacology, Kymera Therapeutics

MDM2 Degrader Program (KT-253)

The KT-253 Phase 1 trial initiated in March 2023 will evaluate the safety, tolerability, pharmacokinetics/ pharmacodynamics, and clinical activity of KT-253 in patients with relapsed or refractory high grade myeloid malignancies, including acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), lymphoma and solid tumors. Patients in the KT-253 Phase 1 dose escalation study will receive IV doses of KT-253 administered once every 3 weeks. The open-label study is intended to identify the recommended Phase 2 dose for KT-253, and is comprised of two arms, with ascending doses of KT-253 in each arm. The first arm will consist of patients with lymphomas and advanced solid tumors and the second arm will consist of patients with high grade myeloid malignancies and ALL.

More information on the Phase 1 study can be found at www.clinicaltrials.gov, identifier NCT05775406.

About Kymera Therapeutics

Kymera 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 programs designed to 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 therapeutic candidates designed to address the most promising targets and provide patients with more effective treatments. Kymera’s initial programs target IRAK4, IRAKIMiD, and STAT3 within the IL-1R/TLR or JAK/STAT pathways, and the MDM2 oncoprotein, providing the opportunity to treat patients with a broad range of immune-inflammatory diseases, hematologic malignancies, and solid tumors.

Founded in 2016, Kymera is headquartered in Watertown, Mass. Kymera has been named a “Fierce 15” 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 MDM2 degrader program; plans and timelines for the preclinical and clinical development of KT-253, including the therapeutic potential, clinical

benefits and safety thereof; expectations regarding timing and, success and data announcements of current ongoing preclinical and clinical trials. 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 or any future pandemics 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 current or future preclinical and clinical trials, including those for KT-474, KT-333, KT-413 and KT-253; 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 Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 filed on May 4, 2023, 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.

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