Kymera Therapeutics Presents Preclinical Data Demonstrating Activity of MDM2 Degraders in Acute Myeloid Leukemia and Merkel Cell Carcinoma

October 16, 2023

Preclinical models highlight the potential of KT-253 as a monotherapy and combined with the standard of care agent venetoclax for the treatment of Acute Myeloid Leukemia (AML)

MDM2 degraders shown to be highly active compared to MDM2 small molecule inhibitor in preclinical models of Merkel cell carcinoma (MCC)

WATERTOWN, Mass., Oct. 16, 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, reported preclinical data highlighting the therapeutic potential in liquid and solid tumors of potent and selective heterobifunctional degraders of MDM2, including KT-253. The data was presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics on October 11-15, 2023, in Boston, Massachusetts and will also be shared at the 10th International MDM2 Workshop taking place October 15-18, 2023, in Tokyo, Japan.

MDM2 is a crucial regulator of the most common tumor suppressor, p53. p53 remains intact (wild type) in approximately 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 cannot overcome the induced feedback loop that increases MDM2 protein levels, which can repress p53 and thereby limit their efficacy. In preclinical studies, MDM2 degraders have demonstrated the ability to overcome the MDM2 feedback loop observed with MDM2 SMIs and rapidly induce cell death in sensitive p53 wild-type cancer cell lines, even with brief compound exposure. This may enable an improved therapeutic index, which could result in a superior efficacy and safety profile over MDM2 SMIs.

The Company previously presented data on KT-253, its lead MDM2 degrader, showing greater than 200-fold higher growth inhibition potency *in vitro* against p53 wild-type cancer cell lines compared with MDM2 SMI and a favorable pharmacological profile. Results shared at the 10th International MDM2 workshop show potent *in vivo* activity of a single dose of KT-253 in models of AML and ALL as well as activity in combination with clinical and sub-clinical doses of venetoclax in a venetoclax-resistant AML model. KT-253 is currently being evaluated in a Phase 1 trial in liquid and solid tumors and the Company plans to share data regarding proof-of-mechanism from its Phase 1 trial later this year.

Work completed in collaboration with the Dana-Farber Cancer Institute and presented at both congresses support MDM2 degradation as a promising therapeutic approach in Merkel cell carcinoma (MCC), a high-grade neuroendocrine carcinoma of the skin. These data demonstrate *in vitro* efficacy of an MDM2 degrader, KTX-049, against p53 wild-type MCC cell lines that was achieved with brief compound exposure. In two MCC PDX models, KT-253 (referred to as KTX-169 in the presentation) demonstrated tumor regressions with weekly as well as every three-week dosing whereas an MDM2 SMI only showed modest tumor growth inhibition.

“These compelling results with MDM2 degraders exemplify our approach of selecting targets with strong genetic validation where we believe that targeted protein degradation provides the best chance for an effective treatment. They also support the potential of MDM2 degradation to overcome the inherent limitations of MDM2 SMIs to more effectively stabilize p53 and thereby induce cancer cell death in sensitive p53 wild type liquid and solid tumors, both alone and in combination with widely used treatments,” said Jared Gollob, M.D., Chief Medical Officer, Kymera Therapeutics. “We aim to drive meaningful improvements in efficacy as well as safety and tolerability over MDM2 small molecule inhibitors through intermittent dosing of our MDM2 degrader, and are currently evaluating KT-253 dosed every three weeks in a variety of liquid and solid tumors in our ongoing Phase 1 trial.”

Presentation at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics:

- Title: The MDM2 degrader KTX-049 is highly potent in TP53 wild-type (p53 WT) Merkel cell carcinoma (MCC).
  - Abstract Number: C134
  - Session Time: Poster Session C, 12:30 PM – 4:00 PM ET, October 14, 2023
  - Presenter: Varsha Ananthapadmanabhan, Ph.D., Department of Medical Oncology, Dana-Farber Cancer Institute, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School

Presentations at the 10th International MDM2 Workshop:

- Title: Development of KT-253, a highly potent and selective heterobifunctional MDM2 degrader, for the treatment of Acute Myeloid Leukemia
  - Abstract Number: 5
  - Session Time: 1:00 PM – 2:00 PM JST, October 16, 2023
  - Presenter: Yogesh Chutake, Ph.D., Principal Scientist, Translational Medicine, Kymera Therapeutics

- Title: Activity of MDM2 degrader KTX-049 in Merkel cell carcinoma
  - Abstract Number: ST19
  - Session Time: 10:35 AM – 10:50 AM JST, October 18, 2023
  - Presenter: James A. DeCaprio, M.D., Department of Medical Oncology, Dana-Farber Cancer Institute, Department

of Medicine, Brigham and Women's Hospital and Harvard Medical School

Copies of the presentations are available online in the Scientific Resources section of Kymera's website.

About 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 IRAK4, IRAKIMiD, STAT3, and MDM2 degrader programs; plans and timelines for the preclinical and 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 preclinical and clinical trials; the ability to initiate new clinical programs; and Kymera's financial condition and expected cash runway into the second half of 2025. The words "aim", "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 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 (SAR444656), 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; the risks associated with pandemics or epidemics; 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, 2022 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:

Justine Koenigsberg
Vice President, Investor Relations
investors@kymeratx.com
857-285-5300

Media Contact:

Todd Cooper
Senior Vice President, Corporate Affairs
media@kymeratx.com
857-285-5300