Kymera Therapeutics Announces Scientific Presentations at the American Association for Cancer Research 2024 Annual Meeting

April 8, 2024

New preclinical data on novel E3 pairing and structural mechanisms for KT-333, a First-in-Class STAT3 degrader, presented in AACR's late-breaking poster session

Nello Mainolfi, Founder, President and CEO of Kymera, invited as a featured speaker in AACR's Major Symposium to discuss drug discovery and clinical translation strategies for STAT3 and MDM2 degrader programs

KT-333 and KT-253 Phase 1 dose escalation studies ongoing with additional data expected in 2024

WATERTOWN, Mass., April 08, 2024 (GLOBE NEWSWIRE) -- Kymera Therapeutics, Inc. (NASDAQ: KYMR), a clinical-stage biopharmaceutical company advancing a new class of small molecule medicines using targeted protein degradation (TPD), today announced that new preclinical data showing the structural and molecular mechanisms underlying anti-tumor activity of its novel STAT3 degrader, KT-333, were presented in a late-breaking research poster session at the AACR Annual Meeting taking place April 5-10, 2024, in San Diego, California. Additionally, Nello Mainolfi, PhD, Founder, President and CEO, will present in the Major Symposium at the conference highlighting the Company's unique target selection strategy and strong preclinical to clinical translation observed across the Company's first-in-class oncology programs, KT-333 and KT-253, a potent and selective degrader of MDM2.

"Guided by our drug development principles and innovative platform capabilities and know-how, we have designed highly potent and selective degraders against undrugged and poorly drugged targets, including oncogenic proteins in key signaling pathways, that have disruptive therapeutic potential," said Dr. Mainolfi. "Our precise understanding of E3 ligase pairing, ternary complex molecular mechanisms at the atomic level, and accuracy of PK and PD, as presented at AACR, has resulted in impeccable translation of our pipeline in the clinic and continues to validate our differentiated molecular design, target selection, and translational strategies to advance a new generation of medicines for patients."

STAT3 is recognized as a key component of the JAK-STAT signaling pathway with both tumor cell intrinsic and tumor cell extrinsic effects on the tumor microenvironment. Although multiple drugs have been approved that target upstream effectors signaling through STAT3, no known drugs selectively block STAT3 broadly across all relevant cell types or address both phosphorylation-dependent and -independent functions of STAT3. For these reasons, STAT3 degraders may provide a solution to the development of targeted and selective drugs to address multiple STAT3 dependent pathologies. New findings presented for the first time show KT-333 induces a strong ternary complex between STAT3 and the VHL E3 ligase in a positively cooperative manner, exhibiting properties of native protein complexes, leading to potent, selective, rapid, and consistent degradation as observed *in vitro* and *in vivo*. Innovative structure-based design with cryo-electron microscopy, biochemical, and proteomics techniques provide mechanistic and structural insights further validating VHL as the E3 ligase of choice for STAT3 degradation in cancer. In the STAT3-dependent SUDHL-1 lymphoma xenograft model, reduced expression of canonical STAT3 targets and down-regulation of cytokine-mediated signaling and cell cycle signature genes indicated that cell cycle arrest and subsequent apoptosis were the main drivers of efficacy for KT-333. Additionally, this unique mechanism of action led to induction of proinflammatory anti-tumorigenic transcriptional signatures in the tumor microenvironment. This has resulted in robust antitumor activity in patients, as reported in the Company's latest clinical update at the American Society of Hematology (ASH) Annual Meeting in December 2023.

The Phase 1a trials for KT-333 and KT-253 are currently ongoing. The Company expects to complete both studies and share additional clinical data to inform the programs' next development steps in 2024 at upcoming medical meetings.

Presentations at the American Association for Cancer Research (AACR) Annual Meeting

Poster Session: Late-Breaking Research, Chemistry
Abstract Number: LB037/19
Title: E3 Pairing and Structural Mechanism Underlying Anti-Tumor Activity of Clinical STAT3 Degrader KT-333
Presenter: Kirti Sharma, PhD, Senior Director, Proteomics
Time: April 7, 2024, from 1:30 PM – 5:00 PM PT
Abstract available on the AACR website.

Major Symposium SY12: Molecular Glues, PROTACs, and Next-Gen Degraders: Discovery and Early Preclinical Advances
Title: Targeting Validated but Un-Drugged Oncogenes with Small Molecule Protein Degraders
Presenter: Nello Mainolfi, PhD, Founder, President and CEO
Time: April 9, 2024, from 10:16 AM-10:36 AM PT
Abstract available on the AACR website.

Copies of both the poster and symposium presentation will be available in the Resource Library section of Kymera's website.

About KT-333 STAT3 Degrader
KT-333 is a potent, highly selective degrader of STAT3 in development for the treatment of multiple STAT3-dependent pathologies, including hematological malignancies and solid tumors. STAT3 is an undrugged transcription factor activated through a variety of different cytokine and growth factor receptors via Janus kinases (JAKs), as well as through oncogenic fusion proteins and mutations in STAT3 itself. In certain malignant cells, STAT3 activation is set into overdrive, leading to a dampened immune response, tumor progression, and metastasis. STAT3's role as a cancer driver and tumor microenvironment modulator has been validated in a multitude of studies, making it a strong candidate to target in the treatment of cancer. KT-333 was the first degrader against an undrugged transcription factor to enter the clinic and the Phase 1 clinical trial is designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of KT-333 dosed weekly in adult patients with relapsed and/or refractory lymphomas, leukemias, and solid tumors. Clinical data from the KT-333 Phase 1 trial has shown evidence of STAT3 targeted protein degradation in humans with associated STAT3 pathway inhibition, along with early signs of antitumor activity, highlighting the potential of heterobifunctional degraders for targeting this previously undruggable transcription factor. Dose escalation in the KT-333 Phase 1 study is ongoing.

About KT-253 MDM2 Degrader

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 unable to show meaningful clinical benefits of p53 stabilization, with acceptable safety margins, likely due to their inability to overcome a feedback loop that increases MDM2 protein levels when p53 is upregulated. 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. The Phase 1 study of KT-253 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), lymphomas, and solid tumors. KT-253 has achieved clinical proof-of-mechanism in the Phase 1 trial and shown early signs of anti-tumor activity. Dose escalation in the KT-253 Phase 1 study is ongoing.

About Kymera Therapeutics
Kymera is a clinical-stage biotechnology company pioneering the field of targeted protein degradation (TPD) to develop medicines that address critical health problems and have the potential to dramatically improve patients' lives. Kymera is deploying TPD to address disease targets and pathways inaccessible with conventional therapeutics. Having advanced the first degrader into the clinic for immunological diseases, Kymera is focused on delivering oral small molecule degraders to provide a new generation of convenient, highly effective therapies for patients with these conditions. Kymera is also progressing degrader oncology programs that target undrugged or poorly drugged proteins to create new ways to fight cancer. Founded in 2016, Kymera has been recognized as one of Boston's top workplaces for the past several years. For more information about our science, pipeline and people, please visit www.kymeratx.com or follow us on X (previously 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 its clinical 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 first half of 2027. 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 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-333 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, 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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