Kymera Therapeutics Presents Preclinical Data on IRAKIMiD and STAT3 Programs at Virtual 62nd American Society of Hematology (ASH) Annual Meeting

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WATERTOWN, Mass., Dec. 07, 2020 (GLOBE NEWSWIRE) -- Kymera Therapeutics, Inc. (NASDAQ: KYMR), a biopharmaceutical company advancing targeted protein degradation to deliver novel, small molecule protein degrader therapeutics, today announced the company presented preclinical data that further support development of its highly selective and potent IRAKIMiD and STAT3 protein degraders scheduled to enter the clinic in 2021. Data were presented at the virtual 62nd American Society of Hematology (ASH) Annual Meeting, Dec. 5-8, 2020 in three separate poster presentations.

IRAKIMiD Program

ABSTRACT #2088, "KTX-120, A Novel IRAKIMiD Degrader of IRAK4 and IMiD Substrates, Shows Preferential Activity and Induces Regressions in MYD88-Mutant DLBCL Cell and Patient Derived Xenograft Models," presented by Duncan H. Walker, PhD, Vice President of Oncology at Kymera Therapeutics. Poster Session II: Sunday, Dec. 6th (7:00 AM - 3:30 PM PT)

IRAKIMiDs are novel, heterobifunctional degraders in development for MYD88-mutant ($MYD88^{MT}$) diffuse large B cell lymphoma (DLBCL) that selectively target and degrade both IRAK4 and IMiD substrates to elicit more profound and durable anti-tumor activity than targeting IRAK4 or IMiD substrates alone. New data presented on Kymera's IRAKIMiD development candidate, KT-413 (formerly KTX-120), continue to support the potential for a first-in-class targeted therapy in $MYD88^{MT}$ DLBCL.

Research highlights:

- KT-413 selectively degraded IRAK4 and IMiD substrates in peripheral blood mononuclear cells and activated type I interferon signaling in $MYD88^{MT}$ DLBCL.
- KT-413 showed superior activity *in vitro* compared to the potent IMiD CC-220 across $MYD88^{MT}$ DLBCL cell lines, irrespective of co-mutations such as CD79B, TNFAIP3, IRF4, and/or BCL6.
- PK/PD in tumors showed sustained >80% degradation of both IRAK4 and IMiD substrates associated with tumor regressions irrespective of co-mutations in multiple $MYD88^{MT}$ DLBCL mouse CDX and PDX *in vivo* models with intermittent PO or IV dosing.
- KT-413 is on track for initiation of a Phase 1 trial in advanced lymphoma in 2H 2021.

ABSTRACT #3013, "Targeting MYD88-Mutant DLBCL with IRAKIMiDs: A Comparison to IRAK4 Kinase Inhibition and Evaluation of Synergy with Rational Combinations," presented by Jennifer K. Lue, MD of Columbia University Irving Medical Center. Poster Session III: Monday, Dec. 7th (7:00 AM - 3:30 PM PT)

IRAKIMiD degraders KTX-475 and KTX-582 demonstrated potent cell killing across a panel of $MYD88^{MT}$ DLBCL cell lines that was superior to clinically-active IMiDs or IRAK4 kinase inhibitors. In addition, KTX-475 showed synergistic killing of $MYD88^{MT}$ DLBCL in combination with BTK, PI3K, or BCL2 inhibitors *in vitro*.

Additional research highlights:

- KTX-582 induced apoptosis in association with IRAK4 degradation in $MYD88^{MT}$ DLBCL whereas the IRAK4 kinase inhibitor CA-4948 did not.
- IRAKIMiDs showed more potent cell killing activity in $MYD88^{MT}$ DLBCL, compared to $MYD88^{WT}$, that was superior to the IMiDs lenalidomide, pomalidomide, and CC-220 and the IRAK4 kinase inhibitor CA-4948.
- Combinations of KTX-475 and ibrutinib (BTK), venetoclax (BCL2), or umbralisib (PI3K) were synergistic in the OCI-LY10 cell line model of $MYD88^{MT}$ DLBCL.

"The broad and robust anti-tumor activity of IRAKIMiDs in $MYD88^{MT}$ DLBCL CDX and PDX models, irrespective of co-mutations, supports their initial development in this genetically-defined subset of relapsed/refractory patients, comprising approximately 25% of all DLBCL, and we look forward to initiating our KT-413 Phase 1 trial in the second half of next year," said Jared Gollob, MD, Chief Medical Officer at Kymera Therapeutics. "We are also encouraged by the synergy observed with select combinations, which may provide expanded development paths for KT-413 in DLBCL beyond the exciting monotherapy opportunity."

STAT3 Program

ABSTRACT #2090, "Mechanisms of Anti-tumor Activity of STAT3 Degraders in Lymphoma," presented by Haojing Rong, PhD, Vice President of Pre-Clinical Development. Poster Session II: Sunday, Dec. 6th (7:00 AM - 3:30 PM PT)

STAT3 hyperactivation is prominent in numerous solid and liquid tumors, including clinically aggressive lymphomas. Kymera's potent and selective STAT3 degrader, KTX-201, has been shown to strongly repress cancer cell growth in preclinical models of STAT3-dependent heme malignancies, including ALK+ ALCL. Data presented for the first time at ASH revealed the molecular mechanisms (both tumor cell-intrinsic and -extrinsic) underlying the anti-tumor effect of STAT3 degradation in mouse models of lymphoma as well as the PK/PD/efficacy relationship of KTX-201 *in vivo*.

Additional research highlights:

- KTX-201 demonstrated potent cell killing *in vitro* in the ALK+ ALCL cell line SU-DHL-1, associated with >90% STAT3 degradation, and induced complete tumor regressions *in vivo* with IV weekly dosing.
- *In vivo* PK/PD analysis revealed prolonged KTX-201 tumor half-life, resulting in sustained >90% STAT3 degradation for 48-96 hours that was sufficient for efficacy with a weekly dosing schedule.
- Time course proteomic analysis of SU-DHL-1 cells treated with KTX-201 showed that STAT3 degradation resulted in early downregulation of known STAT3-dependent proteins (e.g. SOCS3, Myc, and granzyme B) followed by downregulation of key signaling nodes involved in cell cycling and cytokine response.
- KTX-201, as expected, did not include cell killing *in vitro* in the A20 lymphoma cell line but did demonstrate anti-tumor activity *in vivo* that was associated with STAT3 reduction in the tumor microenvironment, supporting a cell-extrinsic mechanism of action for KTX-201.

“The tumor cell-intrinsic effects of our STAT3 degraders, as well as the immunomodulatory, cell-extrinsic effects on the tumor microenvironment, suggest tremendous potential for the treatment of both liquid and solid tumors,” said Nello Mainolfi, PhD, Co-Founder, President and CEO, Kymera Therapeutics. “Our enhanced mechanistic understanding of both the cytotoxic and immunomodulatory effects of STAT3 degradation, as well as the *in vivo* PK/PD required for that activity, are key steps towards indication prioritization and expansion as we approach our clinical entry in 2H 2021.”

About Kymera Therapeutics
Kymera Therapeutics is a biopharmaceutical company focused on a transformative new approach to address previously intractable disease targets. Kymera is advancing the field of targeted protein degradation, accessing the body’s innate protein recycling machinery to degrade dysregulated, disease-causing proteins. Kymera’s Pegasus targeted protein degradation platform harnesses the body’s natural protein recycling machinery to degrade disease-causing proteins, with a focus on un-drugged nodes in validated pathways currently inaccessible with conventional therapeutics. Kymera is accelerating drug discovery with an unmatched ability to target and degrade the most intractable of proteins, and advance new treatment options 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 a broad range of immune-inflammatory diseases, hematologic malignancies, and solid tumors. For more information, visit www.kymeratx.com.

About Pegasus™
Pegasus™ is Kymera Therapeutics’ proprietary protein degradation platform, created by its team of experienced drug hunters to improve the effectiveness of targeted protein degradation and generate a pipeline of novel therapeutics for previously undruggable diseases. The platform consists of informatics-driven target identification, novel E3 ligases, proprietary ternary complex predictive modeling capabilities, and degradation tools.

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 IRAKIMiD and STAT3 degrader programs; 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-Q for the period ended September 30, 2020, filed on November 5, 2020, 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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