Kymera Therapeutics to Disclose IRAKIMiD Degrader Program and Present Preclinical Data Demonstrating Potent Immunomodulatory and Antitumor Activity for its Novel STAT3 Degraders in Immuno-oncology

June 11, 2020

Data to be presented at the 2020 American Association for Cancer Research (AACR) Virtual Annual Meeting II

Cambridge, Mass. (June 11, 2020) – Kymera Therapeutics, Inc., a biotechnology company pioneering targeted protein degradation to invent breakthrough protein degrader medicines for patients, today announced that it will present preclinical data on its potent and highly selective STAT3 degraders as well as the first data from its novel IRAKIMiD degraders combining IRAK4 and IMiD substrate degradation. Data will be shared in two separate presentations (Abstracts #10165 and #4349, respectively) during the 2020 American Association for Cancer Research (AACR) Virtual Annual Meeting II on Monday, June 22 at 9:00 AM EDT.

STAT3 is an attractive but elusive target known to regulate genes implicated in oncogenesis, tumor immune evasion, inflammation and fibrosis. In cancer, STAT3 has been shown to drive tumor growth and promote an immunosuppressive tumor microenvironment (TME). Kymera has previously reported the ability of its highly selective STAT3 degraders to achieve tumor regression in mouse xenograft models of STAT3-dependent hematologic malignancies. The company will present preclinical data demonstrating that its STAT3 degraders downregulated immune checkpoint signals on tumor cells and positively modulated composition and activity of immune cells in the TME, leading to *in vivo* antitumor activity in a solid tumor model refractory compared to standard anti-PD-1/L1 immunotherapy. These findings demonstrate the potential for STAT3 degraders to drive antitumor responses through both tumor cell-intrinsic and -extrinsic immunomodulation as well as direct antitumor effects.

Kymera will also present the first data from its potent IRAKIMiD degraders in development for the treatment of MYD88-mutant lymphomas, which constitute approximately one quarter of all diffuse large B-cell lymphomas (DLBCL). IRAKIMiDs are novel heterobifunctional degraders that target degradation of both IRAK4 and IMiD substrates with a single small molecule. While IRAK4 degradation alone offers a viable therapeutic approach that we believe is superior to IRAK4 kinase inhibition, targeting two complementary pathways in lymphoma biology addresses potential tumor escape mechanisms and shows synergistic activity in MYD88-mutant lymphomas compared to IRAK4 degraders or IMiDs alone. In fact, IRAKIMiDs demonstrated improved cell death and breadth of activity relative to IMiDs or IRAK4-selective degraders, and drove strong *in vivo* tumor regressions in multiple models of MYD88-mutant B cell lymphoma that Kymera believes are superior to what has been observed in preclinical studies with other agents such as BTK inhibitors and IMiDs.

“Our STAT3 and IRAKIMiD programs exemplify the tremendous potential of targeted protein degradation in oncology, allowing us to inhibit well-validated, high impact disease pathways through targets like STAT3 previously considered undruggable, and through selective multi-targeting of IRAK4 and IMiD substrates with a single degrader,” said Jared Gollob, MD, Chief Medical Officer. “The dual effects of STAT3 degraders on both tumor cells and the tumor microenvironment, as well as the dual effects of IRAKIMiDs on multiple pathways involved in tumor cell growth and survival in MYD88-mutant lymphomas, drive robust antitumor responses in preclinical models that support progression of both programs into the clinic in 2021.”

AACR Study Highlights

ABSTRACT #10165 / POSTER #LB-088, “A STAT3 selective targeted protein degrader decreases the immune-suppressive tumor microenvironment and drives antitumor activity in preclinical models,” presented by Fred Csibi, PhD, Associate Director, Oncology Biology at Kymera Therapeutics.

- KTX-201 (formerly known as KYM-003) is a potent and highly selective STAT3 degrader with activity in immune and tumor cells.
- Degradation of STAT3 with KTX-201 in both immune and tumor cells reversed expression of genes that contribute to immune suppression.
- KTX-201 treatment resulted in reversal of immunosuppression in an *in vitro* non-small cell lung cancer model as well as antitumor activity in a mouse colorectal cancer model resistant to immune checkpoint inhibitors.

ABSTRACT #4349 / POSTER #5222, “Degraders targeting both IRAK4 and IMiD substrates show combinatorial effects leading to broader activity with durable and complete regressions in MYD88 mutant lymphoma xenografts *in vivo*,” presented by Duncan H. Walker, PhD, VP of Oncology at Kymera Therapeutics.

- IRAK4 degradation, but not IRAK4 kinase inhibition, showed additive and synergistic activity with IMiDs *in vitro*; IRAKIMiDs, which combine these activities in a single molecule, showed potent *in vitro* and *in vivo*
- Degradation of both IRAK4 and IMiD substrates correlated with *in vitro* cell growth inhibition, consistent with a requirement for both activities for cell death.
- Regressions observed in xenograft models of MYD88-mutant lymphoma were associated with degradation of both IRAK4 and IMiD substrates, consistent with the dual-targeting activities of these molecules.

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About Kymera Therapeutics

Kymera Therapeutics is a biotechnology company pioneering a transformative new approach to treating previously untreatable diseases. The company is advancing the field of targeted protein degradation, accessing the body's innate protein recycling machinery to degrade dysregulated, disease-causing proteins. Powered by Pegasus™, a game-changing integrated degradation platform, 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. 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.