Xencor Presents Data from Multiple Preclinical XmAb® Bispecific Antibody Programs and IL-12 Cytokine, XmAb662, at the SITC Annual Meeting

November 12, 2021

MONROVIA, Calif.--(BUSINESS WIRE)--Nov. 12, 2021-- Xencor, Inc. (NASDAQ:XNCR), a clinical-stage biopharmaceutical company developing engineered monoclonal antibodies and cytokines for the treatment of cancer and autoimmune diseases, today announced the presentation of new data from multiple preclinical XmAb® bispecific antibody programs and its preclinical IL-12-Fc cytokine program, XmAb662, at the 36th Annual Meeting of the Society for Immunotherapy of Cancer (SITC).

"XmAb bispecific Fc domains enable the rapid design and simplified development of a wide range of multi-specific antibodies and other protein structures, such as engineered cytokines. At SITC, we are presenting new data from multiple preclinical programs, including our first presentation of XmAb NK cell engagers, an exciting modality that mechanistically synergizes with our investigational engineered cytokine candidates," said John Desjarlais, Ph.D., senior vice president and chief scientific officer at Xencor. "Our preclinical programs show the power of Xencor's platform to create exciting XmAb drug candidates that access new biologies and continually supply our clinical pipeline with differentiated molecules."

The posters will be archived under "Events & Presentations" in the Investors section of the Company's website located at www.xencor.com.

Abstract 707, "IL12 Fc-fusions engineered for reduced potency and extended half-life exhibit strong anti-tumor activity and improved therapeutic index compared to wild-type IL12 agents"

IL-12 is a potent pro-inflammatory cytokine that promotes high levels of interferon gamma secretion from T-cells and NK cells, increasing their cytotoxicity and the immunogenicity of the tumor microenvironment by making tumor antigens more visible to the immune system. Prior clinical studies have demonstrated IL-12 has significant anti-tumor activity; however, its toxicity has limited its potential. Xencor's IL-12 program follows the same potency reduction design strategy as the Company's IL15-Fc fusions in oncology, where reduced potency led to improved pharmacokinetics, pharmacodynamics and safety in preclinical studies. In addition, preliminary clinical data from Xencor's IL15-Fc program, XmAb306, showed generally good tolerability and robust and sustained immune cell expansion.

IL12-Fc fusions were engineered with reduced potency in order to improve potential tolerability, slow receptor-mediated clearance and prolong half-life in vivo, compared to native IL-12. These potency-reduced IL12-Fc fusions demonstrated significant anti-tumor activity in vivo, concurrent with activation and proliferation of CD8+ T cells and with interferon gamma production.

The addition of Xencor's half-life extending Xtend™ Fc mutations further improved exposure of the molecules over time. In non-human primates, the engineered cytokines had an improved pharmacokinetic profile and therapeutic window compared to a native cytokine-Fc fusion, with superior exposure, a more gradual dose response and similar levels of cytokine production in serum.

XmAb662 was selected for further development and demonstrated significant anti-tumor activity in vivo, concurrent with increases in NK cells, T cells, serum IP10 and serum interferon gamma, which were further enhanced when combined with an anti-PD-1 antibody. The Company anticipates submitting an IND application for XmAb662 in 2022.

Abstract 698, "PDL1-targeted CD28 costimulatory bispecific antibodies enhance T cell activation in solid tumors"

T cells in the tumor microenvironment require both T cell receptor (TCR) and co-stimulatory receptor engagement to achieve full activation. CD28 is a key immune co-stimulatory receptor on T cells; however, the ligands that activate T cells through CD28 are usually not expressed on tumor cells. Targeted CD28 bispecific antibodies, a new class of T cell engager, may provide conditional co-stimulation of T cells, for example, to T cells recognizing neoantigens or in concert with CD3 T-cell engaging bispecific antibodies.

Xencor engineered PD-L1 x CD28 bispecific antibodies to provide conditional co-stimulation of T cells, activating them when bound to PD-L1+ cells. PD-L1, which is expressed on many types of tumors, suppresses anti-tumor responses by the immune system and can inhibit CD28 by engaging PD-1. A PD-L1 x CD28 bispecific antibody, therefore, may promote CD28 co-stimulation and simultaneously block CD28's suppression by PD-1.

In vitro, the combination of the PD-L1 x CD28 and a CD3 T cell engager enhanced T cell activation and proliferation compared to the CD3 bispecific alone. PD-L1 x CD28 also enhanced the interaction between T cells and antigen presenting cells and exhibited strong CD28-dependent anti-tumor activity in mice. PD-L1 x CD28 was well tolerated in non-human primates and exhibited favorable pharmacokinetics. Modeling and preclinical data suggest a dosing schedule consistent with typical checkpoint inhibitor regimens.

Abstract 872, "PD1 x TGFβR2 and CD5 x TGFβR2 bispecifics selectively block TGFβR2 on target-positive T cells, promote T cell activation, and elicit an anti-tumor response in solid tumors"

TGFβ is an inhibitory cytokine, and its production in solid tumors is a significant mechanism used by tumors to avoid recognition by the immune system. While TGFβ inhibition is expected to promote an anti-tumor response, systemic blockade of TGFβ has also been associated with toxicity.

Xencor engineered two XmAb bispecific antibodies, PD-1 x TGFβR2 and CD5 x TGFβR2, to selectively block the suppressive activity of TGFβ on specific T-cell populations and to enhance their anti-tumor activity while avoiding the toxicity associated with systemic blockade. PD-1 and CD5 were selected to direct TGFβ blockade to activated or all T cells, respectively.

In vitro, both bispecific antibodies exhibited highly selective blocking of TGFβ activity in PD-1-high and CD5-positive T cell populations. PD-1 x TGFβR2 and CD5 x TGFβR2 were active in vivo and promoted T cell engraftment and anti-tumor response. Anti-tumor activity was significantly enhanced when combined with an anti-PD-1 antibody, compared to either anti-PD-1 or the bispecific antibody alone.

Abstract 787, “Natural killer cell engagers activate innate and adaptive immunity and show synergy with proinflammatory cytokines”

Xencor’s XmAb natural killer cell engagers (NKEs) are multifunctional antibodies that target multiple activating receptors on the surface of NK cells and bind to tumor associated antigens.

Xencor engineered a B7-H3 x NKG2D NKE bispecific antibody with a modified Fc domain to enhance FcγR binding. The molecule’s design is intended to engage NK cells through the simultaneous binding to B7-H3 on tumor cells and the activating receptors NKG2D and CD16. Additionally, NKEs may provide co-stimulation to T cells through NKG2D expressed on T cells.

In vitro, B7-H3 x NKG2D NKEs activated NK cells, enhanced NK cell mediated lysis of tumor cells and provided co-stimulation to T cells. Additionally, in vitro anti-tumor activity was enhanced when combined with proinflammatory cytokines: an analog of the IL15-Fc cytokine XmAb306 and the IL12-Fc cytokine XmAb662.

About Xencor, Inc.

Xencor is a clinical-stage biopharmaceutical company developing engineered monoclonal antibodies and cytokines for the treatment of cancer and autoimmune diseases. Currently, 22 candidates engineered with Xencor's XmAb® technology are in clinical development internally and with partners. Xencor's XmAb antibody engineering technology enables small changes to the structure of proteins resulting in new mechanisms of therapeutic action. For more information, please visit www.xencor.com.

Forward-Looking Statements

Certain statements contained in this press release may constitute forward-looking statements within the meaning of applicable securities laws. Forward-looking statements include statements that are not purely statements of historical fact, and can generally be identified by the use of words such as “potential,” “can,” “will,” “plan,” “may,” “could,” “would,” “expect,” “anticipate,” “seek,” “look forward,” “believe,” “committed,” “investigational,” and similar terms, or by express or implied discussions relating to Xencor’s business, including, but not limited to, statements regarding any expectations relating to future or potential product candidates, research and development programs, planned IND filings or additional clinical trials, the quotations from Xencor's senior vice president and chief scientific officer and other statements that are not purely statements of historical fact. Such statements are made on the basis of the current beliefs, expectations, and assumptions of the management of Xencor and are subject to significant known and unknown risks, uncertainties and other factors that may cause actual results, performance or achievements and the timing of events to be materially different from those implied by such statements, and therefore these statements should not be read as guarantees of future performance or results. Such risks include, without limitation, the risks associated with the process of discovering, developing, manufacturing and commercializing drugs that are safe and effective for use as human therapeutics and other risks, including the ability of publicly disclosed preliminary clinical trial data to support continued clinical development and regulatory approval for specific treatments, in each case as described in Xencor's public securities filings. For a discussion of these and other factors, please refer to Xencor's annual report on Form 10-K for the year ended December 31, 2020 as well as Xencor's subsequent filings with the Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended to date. All forward-looking statements are qualified in their entirety by this cautionary statement and Xencor undertakes no obligation to revise or update this press release to reflect events or circumstances after the date hereof, except as required by law.

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Charles Liles
cliles@xencor.com

Media Contact
Jason I. Spark
Canale Communications
619-849-6005
jason@canalecomm.com

Source: Xencor, Inc.