Xencor Presents Data from Multiple Preclinical XmAb® Bispecific Antibody and Cytokine Programs at the SITC Annual Meeting

November 9, 2020

MONROVIA, Calif.--(BUSINESS WIRE)--Nov. 9, 2020-- Xencor, Inc. (NASDAQ:XNCR), a clinical-stage biopharmaceutical company developing engineered monoclonal antibodies 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 at the 35th Annual Meeting of the Society for Immunotherapy of Cancer (SITC).

"Our XmAb bispecific Fc domains were specifically created to enable the rapid design and simplified development of a wide range of multi-specific antibodies and other protein structures, such as our engineered cytokines," said John Desjarlais, Ph.D., senior vice president and chief scientific officer at Xencor. "At SITC, we are presenting new data from multiple preclinical programs, including CD28 bispecific antibodies, our second class of T cell engagers, that we have designed to conditionally co-stimulate T cells when they are bound to tumor cells. For the first time, we also show data from two selective TGFβ inhibitors engineered with XmAb bispecific Fc domains."

Poster presentations and audio descriptions are available to registrants of the SITC Annual Meeting. The posters will also be archived under "Events & Presentations" in the Investors section of the Company's website located at www.xencor.com.

CD28 Bispecific Antibody Platform

- Poster 697, “Tumor-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 often not expressed on tumor cells. Targeted CD28 bispecific antibodies 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 two XmAb bispecific antibodies, B7-H3 x CD28 and PD-L1 x CD28, to provide conditional co-stimulation of T cells, activating them when bound to tumor cells. B7-H3 is an immune receptor highly expressed on a wide range of solid tumors and has low expression on normal tissue, and it is associated with poor clinical outcomes. PD-L1, which is also expressed on many types of tumors, suppresses anti-tumor responses by the immune system.

The B7-H3 x CD28 bispecific antibody activated T cells only in the presence of the B7-H3 antigen and did not demonstrate super-agonism, consistent with Xencor's CD28 platform design. The combination of B7-H3 x CD28 and a PSMA x CD3 T cell engaging bispecific antibody generated enhanced T cell activation and proliferation in a PSMA-positive cell line compared to the PSMA x CD3 alone; importantly, no activity was observed in a PSMA-negative cell line, demonstrating that both antigens are required for T cell activation. A combination of B7-H3 x CD28 and a B7-H3 x CD3 bispecific antibody enhanced anti-tumor activity compared to either bispecific antibody alone in an *in vivo* model of breast cancer.

Further, the combination of the PD-L1 x CD28 and a B7-H3 x CD3 T cell engaging bispecific antibody demonstrated superior T cell activation and proliferation compared to a bivalent anti-PD-L1 antibody and B7-H3 x CD3 combination. *In vivo*, PD-L1 x CD28 inhibited tumor growth more effectively than a bivalent anti-PD-L1 antibody.

PD-1 x TGFβR2 Bispecific Antibody Program

- Poster 714, “PD-1 x TGFβR2 bispecifics selectively block TGFβR2 on PD-1-positive T cells, promote T cell activation, and elicit an anti-tumor response in solid tumors”

TGFβ is an inhibitory cytokine, and its production by solid tumors and the tumor microenvironment 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-high T cell populations. Additionally, PD-1 x TGFβR2 was active *in vivo* and promoted T cell engraftment and anti-tumor response. Anti-tumor activity was enhanced when combined with an

anti-PD-1 antibody, compared to anti-PD-1 alone or an anti-PD-L1/TGFβ trap. Similar *in vivo* evaluation of CD5 x TGFβR2 is underway.

IL-12-Fc

- Poster 564, “Potency-reduced and extended half-life IL-12 heterodimeric Fc-fusions exhibit strong antitumor activity with potentially improved therapeutic index compared to native IL-12 agents”

IL-12 is a proinflammatory cytokine produced by activated antigen-presenting cells, and it leads to proliferation of T cells and NK cells and increased cytotoxicity through high levels of interferon gamma signaling. As a potent immune stimulating protein, IL-12 can have a significant effect on shrinking tumors; however, prior clinical studies have demonstrated it to have a narrow therapeutic window, limiting potential response rates.

Xencor's IL-12-Fc cytokine program builds on Xencor’s prior work with IL-15-Fc fusions in oncology, where reduced potency led to improved pharmacokinetics, pharmacodynamics and safety in preclinical studies. IL-12-Fc fusions were engineered with reduced potency in order to improve potential tolerability, slow receptor-mediated clearance and prolong the fusions' half-lives *in vivo*, compared to native IL-12. These potency-reduced IL-12-Fc fusions demonstrated significant anti-tumor activity concurrent with activation and proliferation of CD8+ T cells, increased PD-1 checkpoint expression and increased levels of interferon gamma in serum. Anti-tumor activity was enhanced when combined with an anti-PD-1 antibody.

About Xencor, Inc.

Xencor is a clinical-stage biopharmaceutical company developing engineered monoclonal antibodies for the treatment of cancer and autoimmune diseases. Currently, 18 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 monoclonal antibodies resulting in new mechanisms of therapeutic action. For more information, please visit www.xencor.com.

Forward-Looking Statements

Statements contained in this press release regarding matters that are not historical facts are forward-looking statements within the meaning of applicable securities laws, including, but not limited to, the quotations from Xencor's chief scientific officer and any expectations relating to future product candidates and Xencor's research and development programs. Such statements involve 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 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, 2019 as well as Xencor's subsequent filings with the Securities and Exchange Commission. All forward-looking statements are based on Xencor's current information and belief as well as assumptions made by Xencor. 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. 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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