Xencor Presents Early Clinical Data from Combination Study of Vudalimab and New Data from Multiple Preclinical-stage XmAb® Programs at the SITC Annual Meeting

November 10, 2022

MONROVIA, Calif.--(BUSINESS WIRE)--Nov. 10, 2022-- Xencor, Inc. (NASDAQ:XNCR), a clinical-stage biopharmaceutical company developing engineered antibodies and cytokines for the treatment of cancer and autoimmune diseases, today announced the presentation of data from the first patients in the Phase 2 combination study of vudalimab, a selective PD-1 x CTLA-4 XmAb® bispecific antibody, in patients with metastatic castration-resistant prostate cancer (mCRPC) and data from multiple preclinical-stage XmAb programs at the 37th Annual Meeting of the Society for Immunotherapy of Cancer (SITC) in Boston.

“Evaluating chemotherapy combinations with vudalimab is an important part of our Phase 2 development plan due to the breadth of tumor types we could address with dual PD-1/CTLA-4 blockade and chemotherapy,” said Allen Yang, M.D., Ph.D., senior vice president and chief medical officer at Xencor. “Our initial combination data examines vudalimab with the aggressive chemotherapy regimen of a carboplatin and a taxane. Though we observed clinical activity, including multiple PSA50 responses and a partial response even in this small number of patients with advanced mCRPC, tolerability was a concern, so we are de-intensifying the chemotherapy regimen and maintaining the vudalimab dose. Consistent with our strategy of pursuing indications that checkpoint inhibitors have not yet addressed, we will continue to study a combination of platinum and taxane in patients with aggressive variant prostate cancer and a more broadly applicable chemotherapy combination with vudalimab and a taxane for other patients with mCRPC.”

Posters will be available in the poster hall and virtually to registrants of the SITC Annual Meeting. In the poster hall, odd numbered posters will be displayed on Thursday, November 10, and even numbered posters will be displayed on Friday, November 11. The posters will be archived under "Events & Presentations" in the Investors section of the Company's website located at www.xencor.com.

Abstract 668, “A Phase 2 study of vudalimab, a PD-1 x CTLA-4 bispecific antibody, plus chemotherapy or targeted therapy in patients with molecularly defined subtypes of metastatic castration-resistant prostate cancer”

Xencor is advancing vudalimab, a selective dual checkpoint inhibitor, in multiple Phase 2 clinical studies. The Company is conducting a Phase 2 study of vudalimab in patients with mCRPC, as a monotherapy or in combination with standard-of-care chemotherapy or a PARP inhibitor. A Phase 2 monotherapy study in patients with advanced gynecologic and clinically defined high-risk mCRPC is also ongoing.

The trials in progress poster included clinical data from the safety run-in portion of the first Phase 2 study, which enrolled nine patients with mCRPC. Eight of the nine patients received vudalimab plus carboplatin and a taxane (either cabazitaxel or docetaxel). Patients were categorized into five cohorts, depending on their molecularly defined mCRPC subtype: aggressive variant prostate cancer (Cohort A; n=2), prior PARPi progressor (Cohort B; n=1), PARPi naïve (Cohort C; n=1), MSI-high or MMRD (Cohort D; n=0) and no targetable mutations (Cohort E; n=5).

Efficacy Analysis

As of the data cut on September 7, 2022, prostate-specific antigen (PSA) reductions of more than 50% from baseline (PSA50) had been observed in three of nine patients, inclusive of all cohorts and time on study. A patient in Cohort E with an 89% reduction in PSA from baseline experienced a partial response (PR) at week 18 and was continuing treatment at 35 weeks. Treatment was continuing for one additional patient in Cohort C, at 4 weeks. In addition to the patient experiencing a PR in Cohort E, six other patients were efficacy evaluable and experienced a best response of stable disease (n=5) or non-complete response/non-progressive disease (non-CR/non-PD; n=1).

Safety Analysis

The review of data from the safety run-in portion of the study guided the Company to revise the chemotherapy dosing regimens in combination cohorts in the study (Cohorts A, B and E). Vudalimab dosing in all cohorts remains at 10 mg/kg, administered every two weeks. The chemotherapy regimen was changed to taxane alone in Cohorts B and E or reduced dose intensity for the first cycle of treatment in Cohort A, the aggressive variant.

- Eight patients in Cohorts A, B and E received the combination of vudalimab, carboplatin and either cabazitaxel or docetaxel, depending on prior docetaxel exposure. Treatment-related serious adverse events (SAEs) occurring within the first cycle of therapy were reported for five of eight patients. All events resolved with medical management, including steroids when appropriate, treatment interruption or treatment cessation. Overall, four patients discontinued treatment due to AEs. The types of irAEs observed were largely consistent with the Phase 1 vudalimab monotherapy study of 110 patients.
- No immune related adverse events (irAEs) or treatment-related AEs were reported for the patient in Cohort C, who

received vudalimab and olaparib, a PARP inhibitor.

Preclinical Program Posters

Abstract 1067, "Synergistic combination of Natural Killer cell engagers (NKEs) 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. In addition to stimulating NK cells, NKG2D-targeting NKEs also provide costimulation to CD8 T cells, though this may induce the potential killing by the NK cells. Therefore, NKG2D affinity was tuned to balance desired anti-tumor activity with off-target effector cell effects.

In parallel, Xencor also engineered NKEs targeting B7-H3 and NKG2D's ligands, MICA and MICB (MICA/B). The molecule's design is intended to engage the activating receptors NKG2D and CD16; however, indirect targeting of NKG2D via its ligands MICA/B may avoid off-target effector cell effects.

In vitro, B7-H3 x NKG2D and MICA/B x B7H3 NKEs activated NK cells and enhanced NK cell mediated lysis of tumor cells. Additionally, *in vitro* anti-tumor activity was enhanced when combined with an analog of the proinflammatory IL15-Fc cytokine, XmAb306.

Abstract 1073, "Costimulatory CD28 trispecific antibodies targeting PDL1 and PDL2 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.

Xencor designed a PDL1 x PDL2 x CD28 XmAb trispecific antibody to provide CD28 costimulation in the presence of TCR engagement and either PDL1 or PDL2 antigens. Since PDL1 and PDL2 can engage PD-1 to suppress the immune system's anti-tumor responses, the trispecific is designed to simultaneously block CD28's suppression by PD-1. *In vitro*, the trispecific enhanced the activity of a CD3 bispecific antibody, a modality known to indirectly promote PDL1 and PDL2 expression.

Abstract 1079, "LAG3-targeted IL15/IL15Rα-Fc (LAG3 x IL15) fusion proteins for preferential TIL expansion via cis delivery of IL15 to LAG3+ cells"

IL-2 and IL-15 are cytokines that cause the activation and proliferation of T cells and NK cells. Their therapeutic potential has been well established in preclinical models and clinical studies; however, when given systemically, these potent cytokines have historically provided a poor therapeutic window, as they are not well tolerated and are quickly cleared from circulation. LAG-3 is an immune checkpoint expressed on tumor-infiltrating lymphocytes (TILs), is frequently co-expressed with PD-1 and has limited expression in non-activated T cells.

Xencor engineered LAG3-targeted, reduced potency IL15/IL15Rα-Fc cytokine/antibody fusion proteins (LAG-3 x IL-15) for selective activation of LAG3-positive immune cells, which may potentially avoid systemic toxicities arising from off-target activation and expansion of peripheral immune cells. An XmAb heterodimeric Fc domain serves as a molecular scaffold, and Xtend™ technology promotes longer circulating half-life. Recently, anti-LAG3 agents have generated promising results in clinical studies, and LAG-3 x IL-15 agents could be combined with anti-PD1 agents. Xencor's LAG-3 x IL-15 candidate molecules demonstrated high selectivity for LAG3-positive cell populations in multiple *in vitro* and *in vivo* models. In a preclinical tumor model, a combination of LAG-3 x IL-15 and an anti-PD1 antibody inhibited tumor growth better than anti-PD1 antibody alone.

Abstract 1372, "XmAb143, an engineered IL18 heterodimeric Fc-fusion, features improved stability, reduced potency, and insensitivity to IL18BP"

IL-18 is a proinflammatory cytokine that modulates both the innate and adaptive immune responses. IL-18 receptor 1, the primary co-receptor for IL-18, is expressed on activated T cells and NK cells, which are critical for anti-tumor responses. Additional preclinical studies of IL-18 have demonstrated its anti-tumor activity, including synergy with immune checkpoint inhibitors and CAR-T therapies. In contrast with other potent cytokines, IL-18 has been well tolerated in clinical trials but demonstrated a lack of efficacy despite heavy dosing. IL-18 participates in a negative feedback loop with a high affinity natural inhibitor, IL18BP, which was observed to be upregulated in early phase clinical studies and may have directly resulted in IL-18's limited clinical performance.

Xencor engineered stabilized, potency-reduced, monovalent IL-18 cytokines fused to an XmAb heterodimeric Fc domain with Xtend Fc technology for longer half-life (IL18-Fc). Importantly, these IL18-Fc candidates were engineered to avoid binding its inhibitor IL18BP. In a preclinical mouse model of graft-versus-host disease, IL18-Fc led to the expansion and proliferation of target immune cells and induced high levels of interferon gamma. In a preclinical tumor model, IL18-Fc and an anti-PD1 antibody inhibited tumor growth and expanded NK cells and CD8 T cells more than the anti-PD1 antibody alone. Further, it was well tolerated in non-human primates and exhibited superior pharmacokinetics.

Additional Posters (Clinical Trials in Progress)

Abstract 667, "A Phase 1, multiple-dose study to evaluate the safety and tolerability of XmAb819 (ENPP3 x CD3) in subjects with relapsed or refractory clear cell renal cell carcinoma (RCC)"

Abstract 733, "A Phase 2 study of vudalimab (XmAb717), an anti-PD-1/CTLA-4 bispecific antibody, in patients with selected gynecological malignancies and high-risk metastatic castration-resistant prostate-cancer"

About Vudalimab

Vudalimab is an XmAb bispecific antibody that simultaneously targets immune checkpoint receptors PD-1 and CTLA-4 and is designed to promote tumor-selective T-cell activation. Xencor's approach to dual checkpoint inhibition reduces the need for multiple antibodies and allows for more selective targeting of T cells with high checkpoint expression of both targets, which may potentially improve the therapeutic index of combination immunotherapies. In preclinical studies, dual blockade of PD-1 and CTLA-4 with vudalimab significantly enhanced T cell proliferation and activation,

and anti-tumor activity in vivo. Xencor is conducting a Phase 2 clinical study of vudalimab in patients with metastatic castration resistant prostate cancer (mCRPC), plus chemotherapy for certain patient populations, and a Phase 2 clinical study in patients with advanced gynecologic and genitourinary malignancies, as well as high-risk mCRPC.

About XmAb®819

XmAb®819 is a tumor-targeted, T-cell engaging XmAb 2+1 bispecific antibody in development for patients with renal cell carcinoma (RCC). XmAb819 engages the immune system by activating T cells for highly potent and targeted killing of tumor cells expressing ENPP3, an antigen highly expressed on kidney cancers. ENPP3 is differentially expressed between RCC (high expression) and normal tissues (low expression). To attack RCC cells selectively, XmAb819 was engineered as an XmAb 2+1 bispecific antibody with two binding domains against ENPP3 and one cytotoxic T-cell binding domain against CD3, a component of the T-cell receptor (TCR) complex. Xencor's XmAb Bispecific Fc Domain serves as the scaffold for these binding domains and provides long circulating half-life, stability and ease of manufacture. Xencor is conducting a Phase 1 study of XmAb819 in patients with advanced renal cell carcinoma.

About Xencor

Xencor is a clinical-stage biopharmaceutical company developing engineered antibodies and cytokines for the treatment of patients with cancer and autoimmune diseases. More than 20 candidates engineered with Xencor's XmAb® technology are in clinical development, and three XmAb medicines are marketed by partners. Xencor's XmAb engineering technology enables small changes to a protein's structure that result 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 presentations of clinical trial data for vudalimab generally, planned clinical trials, the quotations from Xencor's senior vice president and chief medical 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, 2021 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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