Xencor Reports Initial Dose-Escalation Data from Phase 1 Study of XmAb®20717, PD-1 x CTLA-4 Bispecific Antibody, in Solid Tumors

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-- XmAb20717 generally well-tolerated and a confirmed complete response (CR) observed at highest dose level tested --

-- Robust, dose-dependent immune activation consistent with inhibition of both PD-1 and CTLA-4 checkpoints --

-- Further dose-escalation and expansion cohorts continue to enroll patients with advanced solid tumors --

MONROVIA, Calif.--(BUSINESS WIRE)--May 13, 2020-- Xencor, Inc. (NASDAQ:XNCR), a clinical-stage biopharmaceutical company developing engineered monoclonal antibodies for the treatment of cancer and autoimmune diseases, today reported initial dose-escalation data from the Phase 1 study evaluating XmAb®20717, a PD-1 x CTLA-4 bispecific antibody and Xencor's first tumor microenvironment activator, in patients with advanced solid tumors (DUET-2). The American Society of Clinical Oncology (ASCO) has published an abstract (e15001) with initial clinical data from the study on its website today.

"In our first six dose-escalation cohorts, we observed XmAb20717 to be generally well-tolerated in heavily pretreated patients with advanced solid tumors. We observed dose-dependent increases in T-cell activation biomarkers, and from the cohort of seven patients receiving the highest dose of 10 mg/kg, we are encouraged that a patient with melanoma, who was treated previously with prior checkpoint therapy, achieved a confirmed complete response. Based on these data and to further characterize safety and activity, we opened expansion cohorts in several tumor types at 10 mg/kg. Also, we did not reach a maximum tolerated dose and expanded the study to enroll patients into additional escalation cohorts, currently at 15 mg/kg and potentially at 20 mg/kg dose levels, and the possibility remains to modify the expansion cohorts with higher dosing," said Allen Yang, M.D., Ph.D., senior vice president and chief medical officer at Xencor.

"We tuned XmAb20717's affinities for PD-1 and CTLA-4 for selective engagement of T cells expressing both targets, and we see pharmacodynamic activity consistent with blockade of both receptors. This design is different from combination therapy and most bispecific checkpoint inhibitors, and we hope to drive improved tolerability at higher doses," said Bassil Dahiyat, Ph.D., president and chief executive officer at Xencor. "We look forward to sharing continued progress from the XmAb20717 program, as well as our other tumor microenvironment targeting bispecific antibody programs, XmAb22841 and XmAb23104, each of which is enrolling patients in Phase 1 dose-escalation studies."

The Phase 1 study is currently enrolling patients with advanced non-small cell lung cancer, renal cell carcinoma, prostate cancer and other cancers without approved checkpoint therapies to expansion cohorts, as well as enrolling patients in additional dose-escalation cohorts. An expansion cohort for patients with melanoma is fully enrolled.

Initial Dose-Escalation Data

The dose-escalation portion of the Phase 1 study has used a standard 3+3 design, with intravenous infusions on days 1 and 15 of each 28-day cycle, to evaluate the safety and tolerability of XmAb20717 and to establish a recommended dose or maximum tolerated dose (MTD) for further investigation. Secondary objectives of the study include assessments of pharmacokinetics, pharmacodynamics and preliminary anti-tumor activity.

At the data cut off on May 1, 2020, 34 patients had been treated in six dose-escalation cohorts escalating from 0.15 to 10 mg/kg. Patients were a median of 57 years old and were heavily pretreated, having a median of four prior systemic therapies. 74% of patients had received at least one prior checkpoint therapy. Two additional dose-escalation cohorts were added. The study is currently enrolling patients at the 15 mg/kg dose level, and a 20 mg/kg dose cohort is planned.

Table 1: Patient Population

Diagnosis	Cohort 6 (10 mg/kg)	Cohorts 1-5 (0.15-6 mg/kg)	Total
Melanoma, including uveal melanoma	3	4	7
Gastric cancer	1	4	5
Triple negative breast cancer	1	3	4
Non-small cell lung cancer	1	2	3
Cervical cancer	1	--	1
Head and neck squamous cell carcinoma	--	7	7
Renal cell carcinoma	--	4	4

Other cancers*	--	3	3
Total	7	27	34

* One patient each with colorectal cancer, urothelial carcinoma and hepatocellular carcinoma

Clinical Activity Highlights

A patient with melanoma, who had progressed after treatment with pembrolizumab, achieved a confirmed complete response (CR) at the 10 mg/kg dose level, the highest completed dose-escalation cohort (cohort 6). The response rate in cohort 6 was 15% (n=1/7).

A patient with microsatellite instability-high (MSI-H) colorectal cancer, who had progressive disease after 10 months of treatment with pembrolizumab, and prior treatment with both nivolumab and ipilimumab, achieved stable disease, and continues on treatment at the 6 mg/kg dose level (cohort 5) at cycle 14 (392 days).

Safety and Tolerability

Safety was evaluated in all 34 patients. XmAb20717 was generally well tolerated through the highest dose cohort. An MTD has not been reached. The most frequent treatment-emergent adverse events (AEs) include those occurring in more than 15% of patients.

Table 2: Frequent Treatment Emergent Adverse Events

Adverse Event (AE)	Any Grade (%)	Grade 3/4 (%)
Any AE	100	74
Rash	50	15
Anemia	41	9
Fatigue	32	--
AST increase	21	12
Pain in extremity	21	6
Pruritus	21	3
ALT increase	18	6
Back pain	18	--
Constipation	18	--
Hypoalbuminemia	18	3
Lipase increase	18	9

Grade 3 or Grade 4 immune related adverse reaction (irARs) include rash (12%), transaminase elevations (12%), lipase increase (6%), and amylase increase, arthritis, colitis, hyperglycemia and pruritis (each 3%). Each Grade 3/4 irAR was manageable and reversible.

Biomarker Analysis

Checkpoint therapy induces T cell proliferation in a patient's peripheral blood, which is evaluated by quantifying the change in the number of T cells expressing the protein Ki67. Measurements were taken at baseline (cycle 1 day 1) and compared to the peak value throughout the first two cycles of treatment with XmAb20717. Proliferation of peripheral T cells began at the 3 mg/kg dose level and increased through the 10 mg/kg level. At the 10 mg/kg level, a consistent proliferation of both CD8+ cytotoxic T cells and CD4+ helper T cells was observed, which is consistent with dual PD-1 and CTLA-4 checkpoint inhibition. The biomarker analysis excludes patients where baseline or subsequent samples are missing.

Table 3: T Cell Proliferation

Mean Change in Percentage of Ki67+ T Cells from Baseline During First Two Cycles (± Standard Deviation)

Dose (mg/kg)	Patients (n)	CD8+ T Cells	CD4+ T Cells
0.15	2	5.6 ± 0.1	1.8 ± 1.6
0.3	3	1.7 ± 1.4	1.6 ± 1.9
1.0	5	8.9 ± 3.9	5.2 ± 2.0
3.0	5	16.0 ± 18.5	9.1 ± 10.1
6.0	7	13.6 ± 12.8	6.8 ± 6.8
10.0	7	21.4 ± 25.6	11.5 ± 11.7

About XmAb®20717

XmAb20717 is a 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 XmAb ® bispecific Fc domain serves as the scaffold for these two antigen binding domains and confers long circulating half-life, stability and ease of manufacture. XmAb bispecific Fc domains have been engineered to eliminate Fc gamma receptor (FcγR) binding, with the intent to prevent activation and/or depletion of T cells via engagement by FcγR-expressing cells. XmAb20717 is being evaluated in an ongoing Phase 1 study, which is enrolling patients with advanced solid tumors to expansion cohorts and additional dose-escalation cohorts.

About Xencor, Inc.

Xencor is a clinical-stage biopharmaceutical company developing engineered monoclonal antibodies for the treatment of cancer and autoimmune

diseases. Currently, 17 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 president and chief executive officer and Xencor's chief medical officer and any expectations relating to the timing and success of clinical trials, 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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