A phase 1, first-in-human, open-label, dose-finding and expansion study of XmAb808, a B7H3 x CD28 bispecific antibody, in combination with pembrolizumab in patients with advanced solid tumors

Abstract #764

BACKGROUND

XmAb808: B7H3-targeted CD28 Bispecific Antibody

- XmAb808 is a fully human, common light chain, B7H3 x CD28 bispecific antibody (BsAb) designed to provide targeted CD28-mediated costimulation of T cells at the interface of B7H3 expressing tumors.
- Monovalent, low-affinity CD28 binding prevents superagonism of T cells, while bivalent, high-affinity B7H3 binding with a 2+1 antibody format may direct XmAb808 to cancer cells with high levels of B7H3 expression relative to normal tissue.
- By providing “Signal 2” to T cells within the tumor microenvironment, XmAb808 is anticipated to augment anti-tumor responses when used in combination with other immunotherapies, such as CD3-directed bispecific T-cell engagers and immune checkpoint inhibitors.

TAA x CD28 Bispecific Antibodies May Expand the Utility of Checkpoint Blockade and CD3 T-cell Engagers

- T cells in the tumor microenvironment require TCR/peptide MHC (pMHC); Signal 1 and costimulatory receptor (Signal 2) engagement to achieve optimal activation.
- Tumor cells do not typically express CD28 ligands (CD80/86); this lack of costimulation may compromise the activity of CD3 engagers or anti-PD1 therapies in the clinic.
- Using Xencor’s XmAb® platforms, we have generated BsAb that conditionally provide CD28 costimulation only in the presence of tumor-associated antigen (TAA) and TCR engagement.

XmAb808 is anticipated to augment anti-tumor responses when used in combination with other immunotherapies, such as CD3-directed bispecific T-cell engagers and immune checkpoint inhibitors.

B7H3 Is Expressed in Multiple Solid Tumors

- B7H3 is broadly expressed across multiple solid tumor histologies (blue), often at higher levels than in corresponding normal tissue (red). Dot size denotes relative B7H3 transcript levels (data from The Cancer Genome Atlas).
- B7H3 protein expression was evaluated by immunohistochemistry in prostate adenocarcinoma tissue microarray samples. Selected examples of various staining patterns are shown.

METODS

Study Objectives & Key Eligibility Criteria

Primary Objectives
- Safety and tolerability
- Identify recommended dose

Secondary Objectives
- Pharmacokinetics (PK)
- Immunogenicity
- Anti-tumor activity

Inclusion Criteria
- Confirmed diagnosis of selected advanced solid tumors with disease progression on standard therapies
- Measurable disease by RECIST 1.1; or evaluable by PCWG3 criteria for subjects with prostate cancer
- Baseline tumor tissue
- ECOG 0-1
- Life expectancy >3 months

Exclusion Criteria
- Previous treatment with any agent targeting CD28
- Prior Grade 4 immuno-therapy-related AE
- Inadequate organ function
- Known hypersensitivity to pembrolizumab

Study Schema

Part A: Dose Escalation

7-week DLT Period

- Screen
- Monotherapy Lead-in (6 weeks)
- Cycle 1
- Cycle 2+

Part B: Expansion - Disease-Specific Cohorts

- Screen
- Cycle 1 (6 weeks)
- Cycle 2+ (6 weeks)

Dose Escalation Decision Table

Table 1. Modified Toxicity Probability Interval-2 (mTPI-2) Decision Table

Dose escalation will follow the mTPI-2 decision table to efficiently escalate to dose levels where pharmacologic effect is seen while minimizing the number of subjects treated at unacceptably toxic dose levels.

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