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

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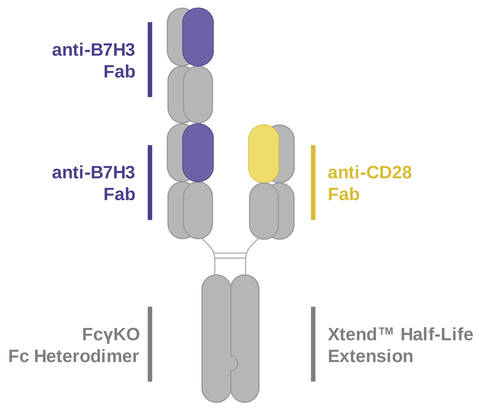
Abstract #764

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-avidity 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.

Figure 1. XmAb808 Uses Multivalency to Promote Selectivity

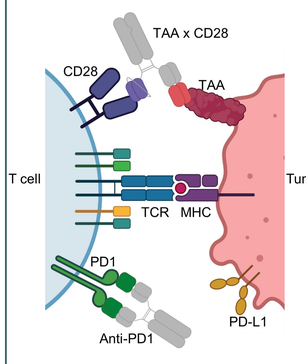


The XmAb® 2+1 format, with two B7H3 binding sites, promotes selectivity to tumor cells expressing high levels of B7H3 versus normal tissues.

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

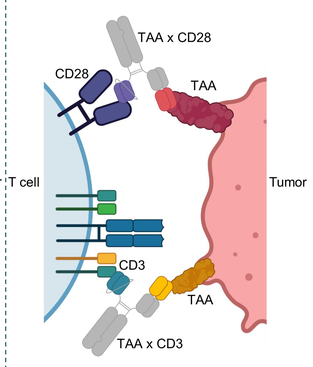
- T cells in the tumor microenvironment require TCR/peptide MHC (pMHC; Signal 1) and costimulatory receptor (Signal 2) engagement to achieve optimal activation.
- Tumor cells do not typically express CD28 ligands (CD80/86); this lack of costimulation may compromise the activity of CD3 engagers or anti-PD1 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.

Figure 2. TAA x CD28 in Combination with anti-PD1



Signal 1 by neoantigen recognition

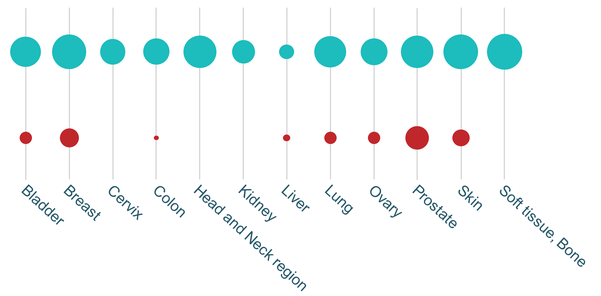
Figure 3. TAA x CD28 in Combination with T-cell Engagers



Signal 1 by TAA x CD3 BsAb

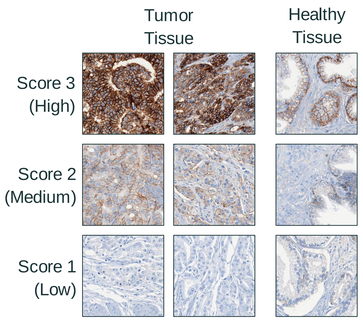
B7H3 Is Expressed in Multiple Solid Tumors

Figure 4. B7H3 RNA Expression (TCGA)



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).

Figure 5. B7H3 Protein Expression in Prostate Cancer

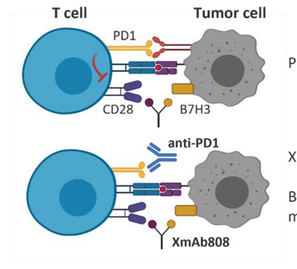


Score	Cancer (n, %)	Healthy Tissue (n, %)
3	86 (54)	5 (16)
2	69 (43)	20 (63)
1	5 (3)	7 (22)
Total	160 (100)	32 (100)

B7H3 protein expression was evaluated by immunohistochemistry in prostate adenocarcinoma tissue microarray samples. Selected examples of various staining patterns are shown.

XmAb808 in Combination with anti-PD-1 Enhances Tumor Growth Inhibition

Figure 6. XmAb808 in Combination with anti-PD1



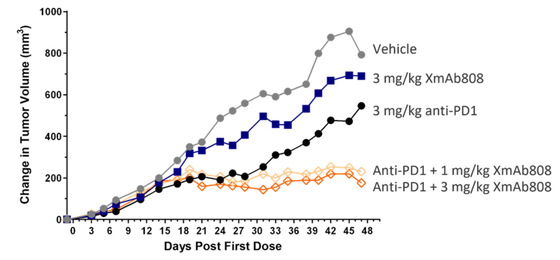
PD1 can suppress CD28 signaling

XmAb808 adds new CD28 signal

Blocking PD1 with combination should maximize activity of XmAb808

Schematic representation of XmAb808 providing a targeted costimulatory signal to T cells, in which a functional CD28 signaling pathway has been restored by an anti-PD1 checkpoint inhibitor.

Figure 7. Combination of XmAb808 and anti-PD1 in NSG Mice Engrafted with Human Breast Cancer Cell Line



Change in tumor volume over time after administration of vehicle, XmAb808, anti-PD1, or a combination of XmAb808 and anti-PD1, in NSG mice engrafted with the pp65-MDA-MB-231-GFP human breast cancer cell line.

METHODS

Study Objectives & Key Eligibility Criteria

Primary Objectives
- Safety and tolerability
- Identify recommended dose

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

Exploratory Objectives
- Intratumoral & peripheral pharmacodynamics (PD)
- ctDNA
- Association of PK/PD with clinical outcome

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 immunotherapy-related AE
- Inadequate organ function
- Known hypersensitivity to pembrolizumab

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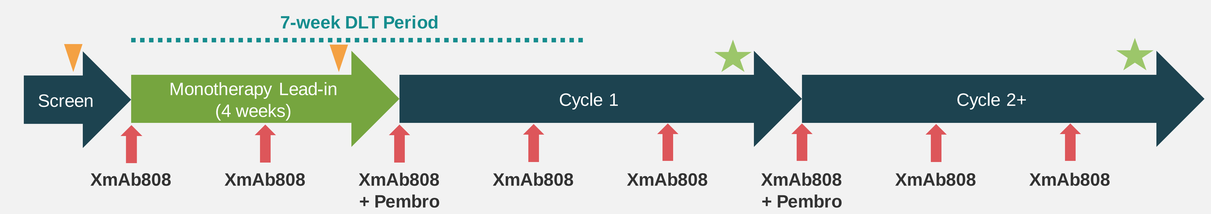
  Figure 5: Michael Hedvat, Veronica Zeng
  Figure 7: Michael Hedvat, Christine Bonzon
- Poster support: Nicholas Rinella, Charles Liles, Alex DeMerritt

Study Schema

Part A: Dose Escalation

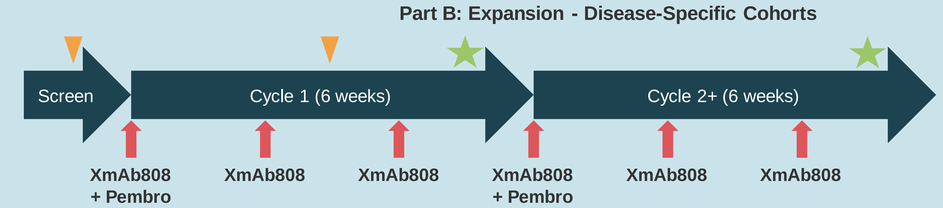


Eligible Tumor Types
Prostate Ovarian HNSCC Melanoma RCC NSCLC Urothelial CRC TNBC

6-week Cycles

Up to N=12 per cohort

Part B: Expansion - Disease-Specific Cohorts



Prostate (PD1-naïve)	HNSCC (PD1-naïve)	HNSCC (PD1-failed)	Melanoma (PD1-naïve)	Melanoma (PD1-failed)

N=20 per cohort

▼ Tumor Biopsy (Biomarker/Expansion) ▪▪▪▪ DLT Period ★ Response Assessment ▲ Dosing (IV): XmAb808 Q2W; Pembro Q6W

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.

P_T=0.3, ε_1=ε_2=0.05, overdose control 0.10												
	Sample Size											
#DLT	1	2	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	E	E	E	E	E	E	E	E
2		D	D	D	D	S	S	S	E	E	E	E
3			DU	DU	D	D	D	D	S	S	S	S
4				DU	DU	DU	D	D	D	D	D	S
5					DU	DU	DU	DU	DU	D	D	D
6						DU	DU	DU	DU	DU	DU	D
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

DLT = dose-limiting toxicity; E: Escalate to the next dose level; S: Stay at the current dose level and enroll more subjects; D: De-escalate to the next dose level; the current dose level is still eligible for escalation; DU: De-escalate to the next dose level; the current dose level is no longer eligible for escalation; Source: Guo, 2017

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