764 **A PHASE 1, FIRST-IN-HUMAN (FIH), 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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Background B7H3 is preferentially expressed by many solid tumors, making it an attractive therapeutic target. XmAb808 is a fully human B7H3 x CD28 bispecific antibody 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. 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. This Phase 1, FIH study of XmAb808 is designed to evaluate its safety/tolerability, pharmacokinetics (PK), and preliminarily assess anti-tumor and pharmacodynamic (PD) activity in combination with pembrolizumab in patients with selected advanced solid tumors.

Methods The study will be conducted at approximately 15 sites in the United States and consists of Part A (dose escalation) and Part B (expansion). In Part A, subjects will receive XmAb808 every 2 weeks (Q2W) during a 4-week monotherapy lead-in period to evaluate safety and PK/PD. After the lead-in, subjects will continue XmAb808 Q2W in combination with pembrolizumab, 400 mg every 6 weeks (Q6W). Dose escalation of XmAb808 will use a modified toxicity probability interval (mTPI)-2 design with a maximum of 12 subjects in each dose-level cohort. The dose-limiting toxicity (DLT) period is 49 days and includes the lead-in plus 3 weeks post-initiation of pembrolizumab. Additional biomarker cohorts (12 subjects each) may be enrolled at safety-cleared dose levels for further dose optimization and to study intratumoral PD. Recommended dose(s) will be evaluated for safety with concurrent-start dosing of XmAb808 and pembrolizumab and used in Part B for further characterization. Disease-specific cohorts (20 subjects each) will be enrolled in Part B, including prostate cancer, head and neck squamous cell carcinoma and melanoma, with separate cohorts for subjects who are naïve to or failed prior anti-PD1 therapy. Response assessments (RECIST 1.1) will occur Q6W. Primary objectives are to evaluate safety/tolerability by adverse events/DLTs and to identify a recommended dose/schedule of XmAb808 in combination with pembrolizumab. Secondary objectives include analysis of PK, immunogenicity and anti-tumor activity. Exploratory objectives include analysis of intratumoral and peripheral PD, including markers of T-cell activation; expression of tumor/immune markers; ctDNA levels; and association of PK and/or PD with clinical outcome. Enrollment has begun.

Ethics Approval The study was approved by each institution's IRB.

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