Preliminary Safety, PK/PD, and Antitumor Activity of XmAb18087, an SSTR2 x CD3 Bispecific Antibody, in Patients With Advanced Neuroendocrine Tumors

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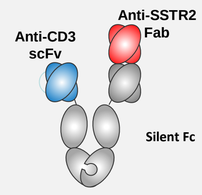
BACKGROUND

- SSTR2 is highly overexpressed in neuroendocrine tumors (NET)
- XmAb18087 (tidutamab), a humanized, anti-SSTR2 x anti-CD3 bispecific antibody, directs T-cell mediated cytotoxicity to SSTR2+ tumor cells
- Duet-1 is an ongoing, Phase 1, first-in-human study of XmAb18087 in patients with NET and GIST
- Here we report preliminary data for NET cohorts, based on a 26 August 2020 data cut

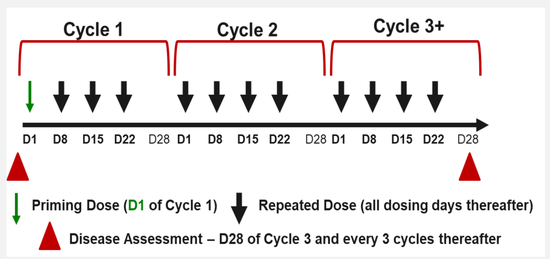


STUDY OBJECTIVES

- **Primary**
  - To determine the safety and tolerability profile of XmAb18087 in patients with advanced, well-differentiated NET of pancreatic, gastrointestinal (GI), lung, and undetermined origin
  - To identify the maximum tolerated dose (MTD) and/or recommended dose and regimen
- **Secondary**
  - To characterize pharmacokinetics (PK) and immunogenicity
  - To assess preliminary antitumor activity using RECIST 1.1 based on objective response rate, duration of response, and progression-free survival (PFS)
- **Key exploratory**
  - To assess biomarkers of cytokine release syndrome (CRS)
  - To characterize immune response in peripheral blood based on changes in lymphocyte subsets and markers of T-cell activation and exhaustion

METHODS

- Study design – 3+3 dose escalation design with cohort expansion (n ≤ 20) at MTD
- XmAb18087 is administered as a 2-hour intravenous infusion on Days 1, 8, 15, and 22 of each 28-day cycle
- Dosing includes a priming dose on Cycle 1, Day 1, followed by a higher, repeated dose on subsequent dosing days
- Patients receive prophylaxis for CRS and nausea and vomiting at least through Cycle 1
- Imaging is performed at screening and at the end of every third cycle of treatment for response assessment
- Samples are collected for evaluation of PK and pharmacodynamics in peripheral blood (T-cell activation and proliferation, cytokines) at multiple time points throughout treatment



STUDY POPULATION

- Patients with histologically or cytologically confirmed Grade 1 or 2 NET (pancreatic, GI, lung, or undetermined origin)
- Unresectable locally advanced or metastatic disease
- Progressed on/ineligible for somatostatin analogues (SSAs) and ≥ 1 other targeted therapy
  - Continuation of SSA therapy permitted if on stable dose for ≥ 3 months
- Disease progression within past 12 months
- ECOG 0 or 1
- No CNS involvement

RESULTS

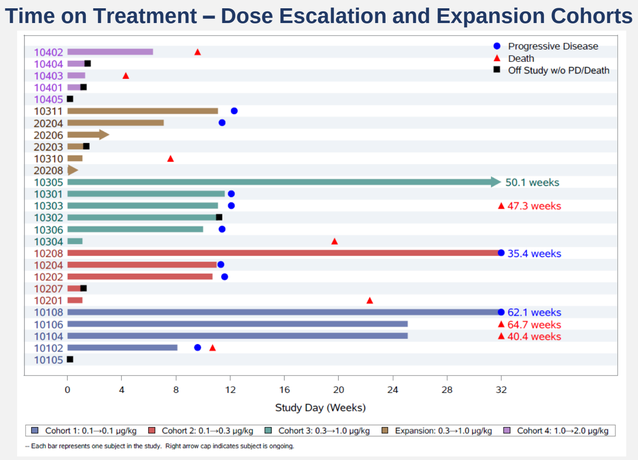
Patient Disposition	Number of Patients
Received ≥ 1 dose of XmAb18087	27
Dose escalation	21
Expansion	6
Discontinued treatment	24
Reason for discontinuation	
Disease progression	12
Withdrew consent	6
Adverse event	4
Physician decision	1
Other	1

Demographics and Baseline Characteristics	Overall (n = 27)
Age, median years (range)	61.0 (34-85)
Male	56%
Initial lesion location	
Pancreas	56%
Intestinal	15%
Pulmonary	15%
Other GEP-NET	7%
Unknown	7%
Initial lesion Grade 2	58%
Lines of prior disease-specific systemic therapies, median (range)	4 (0-10)
Prior peptide receptor radionuclide therapy	56%
Continued SSA on study	41%

XmAb18087 Cohorts and Dose Levels

Escalation Cohort	Number of Patients	Priming Dose (µg/kg)	Repeated Dose (µg/kg)
1	5	0.1	0.1
2	5	0.1	0.3
3	6 MTD	0.3	1.0
4	5	1.0	2.0

Time on Treatment – Dose Escalation and Expansion Cohorts



Treatment-Related Grade 3/4 Adverse Events Reported for ≥ 2 Patients by Dose Level

Event, n (%)	Dose Level (µg/kg) 0.1→0.1 (n = 5)	0.1→0.3 (n = 5)	0.3→1.0 (n = 12)	1.0→2.0 (n = 5)	Overall (n = 27)
Any	4 (80%)	3 (60%)	7 (58%)	3 (60%)	17 (63%)
Lymphopenia/lymphocyte count decreased	4 (80%)	3 (60%)	3 (25%)	1 (20%)	11 (41%)
GGT increased	1 (20%)	1 (20%)	3 (25%)	0	5 (19%)
Vomiting	0	0	2 (17%)	**3 (60%)**	5 (19%)
ALT/AST increased	1 (20%)	1 (20%)	2 (17%)	1 (20%)	5 (19%)
Nausea	0	0	1 (8%)	**3 (60%)**	4 (15%)
Diarrhea	0	0	2 (17%)	1 (20%)	3 (11%)
Hypophosphatemia	0	0	2 (17%)	1 (20%)	3 (11%)
Anemia	0	1 (20%)	1 (8%)	0	2 (7%)
Fatigue	0	0	0	2 (40%)	2 (7%)
Lipase increased	1 (20%)	1 (20%)	0	0	2 (7%)

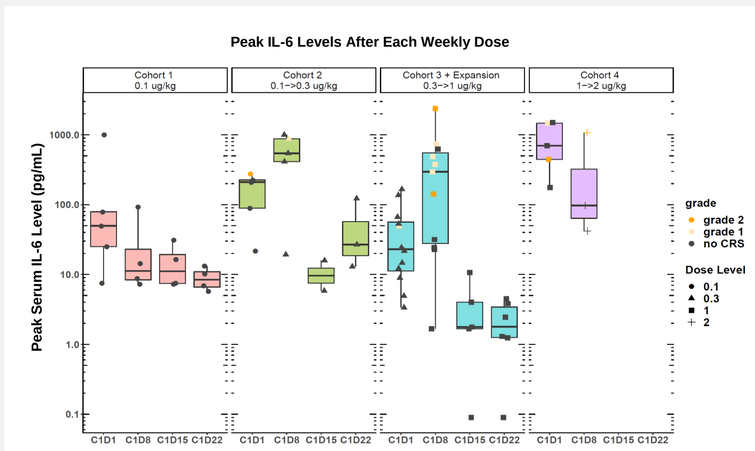
- DLT at 1.0→2.0 µg/kg – nausea and vomiting
  - May be related to engagement of SSTR2 receptors that have been identified in GI tract
- Grade 3/4 lymphopenia (41% of patients) had no apparent deleterious clinical effects
  - Transient cytopenia is characteristic of CD3 antibody therapy after the first dose
- No Grade 5 treatment-emergent adverse events were reported

Cytokine Release Syndrome by XmAb18087 Dose Level

CRS, n (%)	Dose Level (µg/kg) 0.1→0.1 (n = 5)	0.1→0.3 (n = 5)	0.3→1.0 (n = 12)	1.0→2.0 (n = 5)	Overall (n = 27)
Grade 1	0	2 (40%)	4 (33%)	0	6 (22%)
Grade 2	0	1 (20%)	2 (17%)	2 (40%)	5 (19%)

CRS was restricted to Grades 1 and 2 and limited to the first 2 doses.

Peak IL-6 and Clinical CRS Profile Supports Expansion Regimen Selection of 0.3→1.0 µg/kg

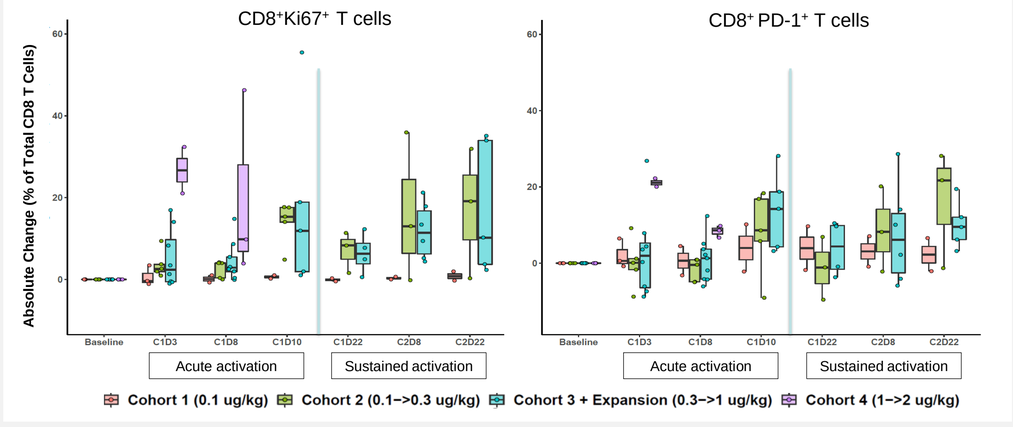


Increases in IL-6 and Grade 1/2 CRS were observed only with the first-weekly (priming) dose and the second-weekly (repeated) dose. Doses after Day 8 were not associated with IL-6 elevation or CRS events.

At 1.0→2.0 µg/kg (purple), patients had higher peak IL-6 levels and Grade 1/2 CRS (this dose exceeded the MTD due to dose-limiting GI toxicity).

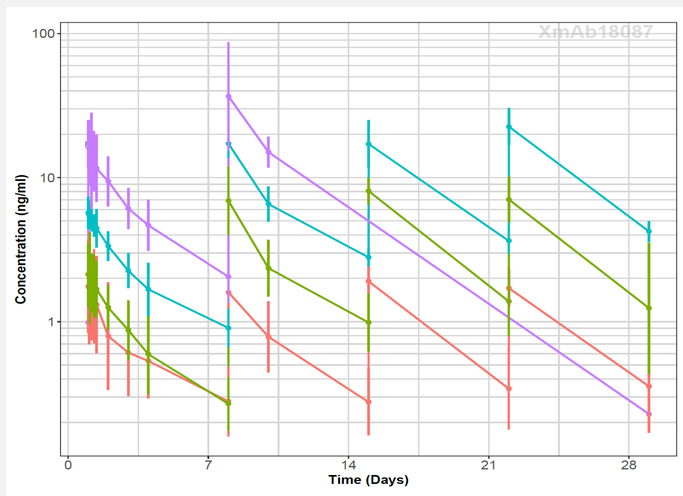
At 0.3→1.0 µg/kg (the MTD; teal), the 0.3 µg/kg priming dose (C1D1) was well-tolerated (1 Grade 1 CRS [yellow square] and IL-6 below 100 pg/mL), and several patients had Grade 1/2 CRS with the first repeated dose (C1D8).

XmAb18087 Induces Acute and Sustained T-Cell Activation and Proliferation in Peripheral Blood



Acute CD8 T-cell activation with Ki67 and PD-1 expression are noted within 48 hours after each of the first 2 doses of XmAb18087. Sustained T-cell activation is observed at trough before each weekly dose.

XmAb18087 PK Profile



PK was dose proportional at priming and repeated doses. Median half-life was 94 hours (~ 4 days).

Objective Response (RECIST 1.1)

Evaluable Patients*	Dose Level (µg/kg) 0.1→0.1 (n = 4)	0.1→0.3 (n = 3)	0.3→1.0 (n = 7)	Overall (n = 14)
Best overall response, n (%)				
CR	0	0	0	0
PR	0	0	0	0
SD	3 (75%)	1 (33%)	2 (29%)	6 (43%)
PD	1 (25%)	2 (67%)	5 (71%)	8 (57%)
Disease control rate, n (%)	3 (75%)	1 (33%)	2 (29%)	6 (43%)

- 14/27 patients met criteria for inclusion in analysis of antitumor activity (evaluable patients), including 2/6 expansion cohort patients
- Best overall response was stable disease, with a disease control rate of 43%
  - Median treatment duration – ~ 7 months

CONCLUSIONS

- Preliminary data from this ongoing, Phase 1 study in patients with low- and intermediate-grade NET indicate XmAb18087
  - Was generally well tolerated at the expansion dose (0.3→1.0 µg/kg)
    - DLT – nausea and vomiting
    - CRS limited to Grades 1 and 2
  - Demonstrated dose-proportional PK with a half-life that supports weekly dosing
  - Induced acute and sustained T-cell activation in peripheral blood
  - Was associated with stable disease in 43% of patients across dose levels
- Completion of enrollment in the expansion cohort and longer follow-up are required to evaluate PFS and the clinical utility of XmAb18087 in this patient population

ACKNOWLEDGEMENTS

Many thanks for support in the conduct of this research to the patients, their families, and caregivers, and the XmAb18087-01 investigational study teams.