Safety, Pharmacodynamic, and Antitumor Activity of Tidutamab, an SSTR2 x CD3 Bispecific Antibody, in Subjects With Advanced Neuroendocrine Tumors

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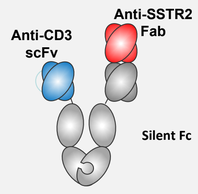
BACKGROUND

- Somatostatin receptor 2 (SSTR2) is overexpressed in neuroendocrine tumors (NETs), gastrointestinal stromal tumors (GIST), and other cancers
- Tidutamab (XmAb18087) is a humanized, anti-SSTR2 x anti-CD3 bispecific antibody that directs T–cell-mediated cytotoxicity to SSTR2+ cells
- This is an ongoing, Phase 1, first-in-human study of tidutamab in patients with NET and GIST
- We report updated preliminary data for NET cohorts, based on a 26 August 2021 data cut

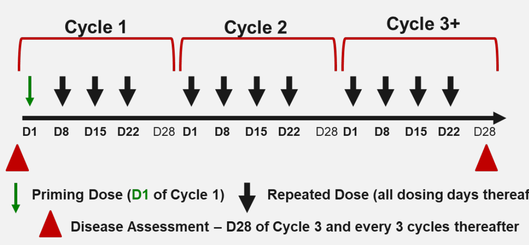


STUDY OBJECTIVES

- **Primary Objectives**
  - To assess the safety and tolerability profile of tidutamab 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 schedule of tidutamab administered by intravenous (IV) dosing on Days 1, 8, 15, and 22 of each 28-day cycle
- **Secondary Objectives**
  - To characterize pharmacokinetics (PK) and immunogenicity
  - To assess preliminary antitumor activity using RECIST 1.1 based on overall response rate (ORR) and progression-free survival (PFS)
- **Key Exploratory Objectives**
  - 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

- Tidutamab is administered as a 2-hour IV 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 3rd 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
- Tumor biopsies are performed at screening and between 1 and 3 weeks after first dose



KEY INCLUSION CRITERIA

- Patients with histologically or cytologically confirmed Grade 1 or 2 NET of pancreatic, GI, lung, or undetermined origin that is locally advanced or metastatic and has progressed within the past 12 months
- Progressed on/ineligible for somatostatin analogues (SSAs) and ≥ 1 other targeted therapy
  - Continuation of SSA therapy permitted if on stable dose for ≥ 3 months
- Subjects must have disease measurable by RECIST 1.1 using either CT or MRI
- ECOG 0 or 1
- No CNS involvement

RESULTS

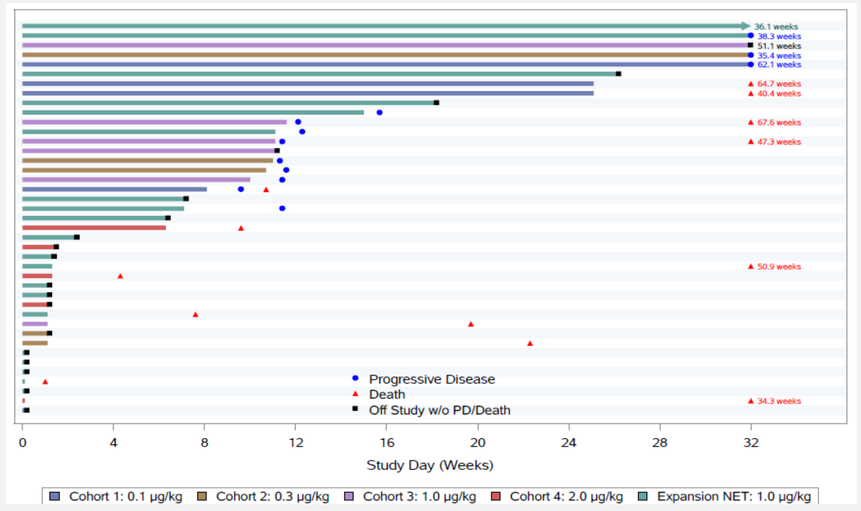
Patient Disposition	Number of NET Patients
Enrolled population	42
Received ≥ 1 dose of tidutamab	41
Dose escalation	21
Expansion	20
Discontinued treatment	40
Reason for discontinuation	
Disease progression	17
Withdrew consent	7
Adverse event	13
Physician decision	1
Lost to follow-up	1
Other	1

Demographics and Baseline Characteristics	Overall (N = 41)
Age, median years (range)	64 (34 - 85)
Male	46.3%
Initial lesion location	
Pancreas	46.3%
Intestinal	22.0%
Pulmonary	19.5%
Other GEP-NET	7.3%
Unknown	4.9%
Initial lesion Grade 2	57.9%
Lines of prior disease-specific systemic therapies, median (range)	4 (0 - 11)
Prior peptide receptor radionuclide therapy	50.0%
Continued SSA (octreotide, lanreotide) on study	41.5%

Tidutamab Cohorts and Dose Levels

Cohort	Number of Patients	Priming Dose (µg/kg)	Repeated Dose (µg/kg)
1	6	0.1	0.1
2	5	0.1	0.3
3	6	0.3	1.0
4	5	1.0	2.0
Expansion	20	0.3	1.0

Time on Treatment* (N = 41)



-Each bar represents one subject in the study. Right arrow cap indicates subject is ongoing.
*In patients who received at least 1 dose.

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

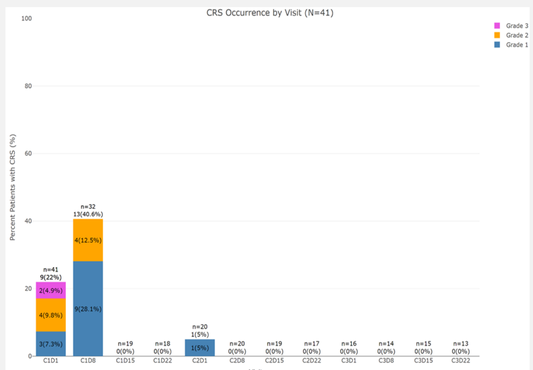
Adverse Event, n (%)	Cohort 1 0.1 µg/kg N = 5 (%)	Cohort 2 0.3 µg/kg N = 5 (%)	Cohort 3 1.0 µg/kg N = 6 (%)	Cohort 4 2.0 µg/kg N = 5 (%)	Expansion 1.0 µg/kg N = 20 (%)	Overall N = 41 (%)
Number of subjects with at least one event	3 (60.0)	3 (60.0)	4 (67.0)	3 (60.0)	14 (70.0)	27 (65.9)
Lymphopenia/lymphocyte count decreased	3 (60.0)	3 (60.0)	3 (50.0)	1 (20.0)	2 (10.0)	12 (29.0)
GGT increased	1 (20.0)	2 (40.0)	1 (16.7)	0	4 (20.0)	8 (19.5)
ALT/AST Increase	1 (20.0)	1 (20.0)	1 (16.7)	1 (20.0)	4 (20.0)	8 (19.5)
Vomiting	0	0	2 (33.3)	3 (60.0)	2 (10.0)	7 (17.1)
Diarrhea	0	0	1 (16.7)	1 (20.0)	2 (10.0)	4 (9.8)
Hypophosphatemia	0	0	2 (33.3)	1 (20.0)	1 (5.0)	4 (9.8)
Anemia	0	1 (20.0)	1 (16.7)	0	1 (5.0)	3 (7.3)
Esophageal motility disorder*	0	0	0	2 (40.0)	1 (15.0)	3 (7.3)
Fatigue	0	0	0	2 (40.0)	1 (5.0)	3 (7.3)
Lipase increased	1 (20.0)	1 (20.0)	0	0	1 (5.0)	3 (7.3)
Cytokine release syndrome	0	0	0	0	2 (10.0)	2 (4.9)
Malnutrition	0	0	0	0	2 (10.0)	2 (4.9)
Neutropenia/neutrophil count decreased	0	0	1 (16.7)	1 (20.0)	0	2 (4.9)
Esophagitis	0	0	0	1 (20.0)	1 (5.0)	2 (4.9)

*Includes Preferred terms Dysphagia and Oesophageal achalasia. 3 subjects' AEs were not resolved at the time of current data cutoff.

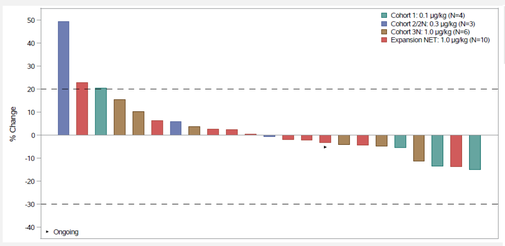
CRS Subject Counts and Percentage by Cohort and Visit

CRS, n (%)	Cohort 1 0.1 µg/kg (N = 5)	Cohort 2 0.3 µg/kg (N = 5)	Cohort 3 1.0 µg/kg (N = 6)	Cohort 4 2.0 µg/kg (N = 5)	Expansion 1.0 µg/kg (N = 20)	Overall (N = 41)
Grade 1	0	2 (40.0%)	2 (33.3%)	0	5 (25.0%)	9 (22.0%)
Grade 2	0	1 (20.0%)	1 (16.7%)	2 (40.0%)	2 (10.0%)	6 (14.6%)
Grade 3	0	0	0	0	2 (10.0%)	2 (4.9%)

A total of 23 CRS events occurred in 17 out of 41 treated subjects. Of the 23 CRS events, 14 were Grade 1, 7 were Grade 2 and 2 were Grade 3. 18 events (78%) occurred on the day of infusion, 4 (17%) on Day 1 post-infusion and 1 (4%) on Day 2 post-infusion. No CRS was observed beyond C2D1. The most common CRS symptoms (≥ 5% events) included pyrexia 61%, hypotension 48%, rigors/chills 35%, tachycardia 30%, nausea 26%, headache 26%, fatigue 17%, hypertension 17%, diarrhea 8.7%, dizziness 8.7%, hypoxia 8.7%, myalgia 8.7%, neutrophil count decreased 8.7%, tachypnea 8.7%, transaminitis 8.7%, and vomiting 8.7% (data not shown).



Best Percent Change from Baseline in Sum of Diameters by Cohort*

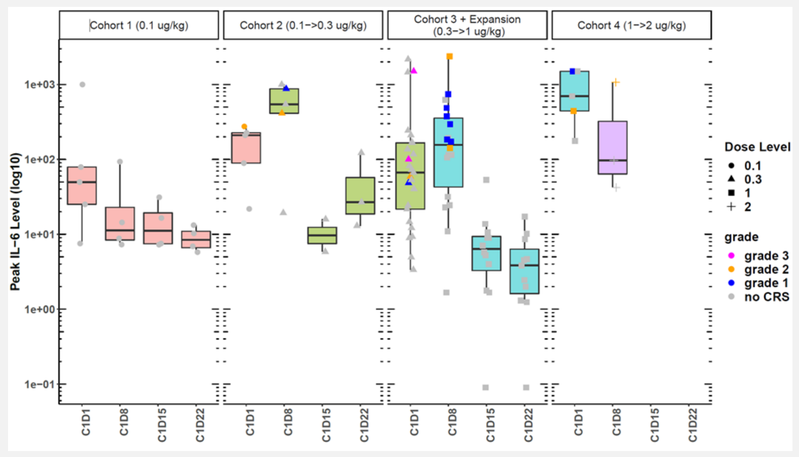


Best Overall Response and Objective Response Rate by RECIST 1.1*

Best overall response, n (%)	Cohort 1 0.1 µg/kg (N = 5)	Cohort 2 0.3 µg/kg (N = 5)	Cohort 3 1.0 µg/kg (N = 6)	Cohort 4 2.0 µg/kg (N = 5)	Expansion 1.0 µg/kg (N = 20)	Overall (N = 41)
ORR	0	0	0	0	0	0
SD	3 (60.0)	1 (20.0)	2 (33.3)	0	5 (25.0)	11 (26.8)
PD	1 (20.0)	2 (40.0)	3 (50.0)	0	3 (15.0)	9 (22.0)
NE/Not Done	1 (20.0)	2 (40.0)	1 (16.7)	5 (100.0)	12 (60.0)	21 (51.2)
Duration of Stable Disease (days)	85 (85, 273)	169 (169, 169)	99 (1, 197)	0	84 (1, 164)	85 (1, 273)

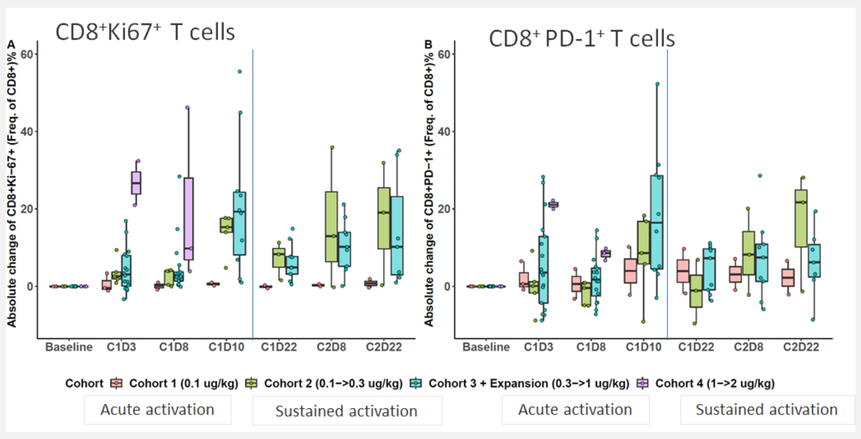
*In patients who received at least 1 dose who had at least 1 post-baseline RECIST 1.1 assessment

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



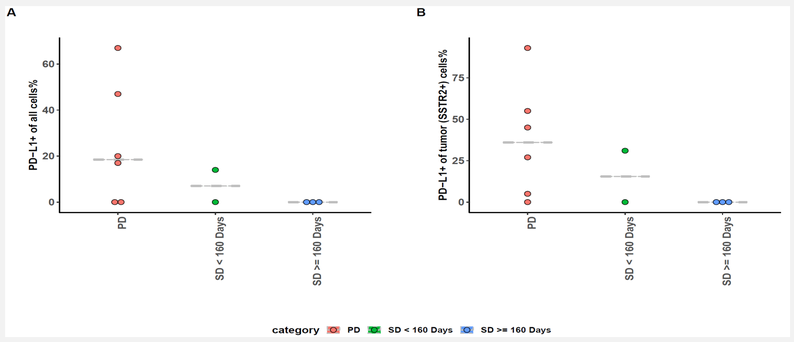
Increases in IL-6 were observed only with the first weekly (priming) dose and the second weekly (repeated) dose, and not subsequently. At 1.0→2.0 µg/kg (purple), patients had higher peak IL-6 levels; this dose exceeded the MTD due to dose-limiting GI toxicity. At 0.3→1.0 µg/kg (the MTD; teal), the 0.3 µg/kg priming dose (C1D1) was generally well-tolerated with IL-6 levels below 100 pg/mL, although 1 Grade 1 CRS (blue triangle) and 2 Grade 3 CRS (red triangle) events were observed. Several patients had Grade 1/2 CRS events with the first repeated dose (C1D8 [blue squares]). Doses after Day 8 were not associated with CRS events or IL-6 elevation.

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



Acute CD8 proliferation and activation with Ki67 and PD-1 expression were noted within 48 hours after each of the first 2 doses of tidutamab. Sustained T-cell activation was observed at trough before each weekly dose. While PD-1 increases on treatment were observed in most patients, they were generally lower in 3 patients who had stable disease ≥ 160 days.

Higher Tumor PD-L1 Expression Is Associated with Shorter Time on Study



Tumor PD-L1 was measured on FFPE archival (n = 7) and fresh (n = 4) biopsies using an RUO FIHC assay (PD-L1 clone E1L3N®, CST). In the 3 patients that achieved stable disease (SD) ≥ 160 days, PD-L1 levels were low/not detected. Progressive disease (PD) and SD patients on study < 160 days showed a range of PD-L1 levels with higher PD-L1 expression observed overall in all tumor (A) and SSTR2+ (B) tumor cells. These data provide additional support for evaluation of checkpoint inhibitor combinations with tidutamab. Overall T-cell infiltrate was low (measured by CD3 FIHC; generally ranging from not detected to 6%; data not shown). Insufficient paired biopsies were available to evaluate tumor pharmacodynamic changes on treatment.

CONCLUSIONS

- Tidutamab was generally well tolerated; safety findings include CRS and esophageal dysmotility
  - The majority of CRS events were Grade 1/2, and patients fully recovered; onset typically occurred during the first 2 infusions, and all occurred ≤ 2 days after infusion
  - Esophageal dysmotility (based on selected groups of preferred terms) was observed; most events were Grade 1/2
- The best overall response was stable disease, which was achieved by 26.8% of patients who received at least 1 dose of tidutamab and who had at least 1 post-baseline RECIST 1.1 assessment
- Biomarker analysis showed tidutamab induced acute and sustained T-cell activation/proliferation and cytokine release
- Higher baseline intratumoral PD-L1 and on-treatment increases were associated with shorter time on study
  - Increases in peripheral T-cell PD-1 expression were also observed on treatment
- Tidutamab monotherapy showed an active immune profile
  - Additional studies in other tumors that express SSTR2 are warranted, and given poor outcomes in patients with higher PD(L)-1 expression, combinations with checkpoint inhibitors should be considered

ACKNOWLEDGEMENTS

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