Phase I dose escalation trial of STX-001, an LNP-encapsulated self-replicating mRNA expressing IL-12, in patients with advanced solid tumors

Abstract 9556

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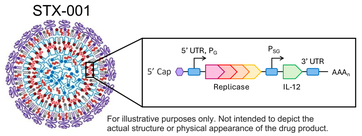
Background

- STX-001 is a novel investigational lipid nanoparticle (LNP)-encapsulated, self-replicating mRNA that encodes interleukin-12 (IL-12) (**Figure 1**).
- STX-001 is administered intratumorally to drive local IL-12 production with the goal of limiting high systemic IL-12 exposure and associated toxicities.
- STX-001 is designed to act via innate immune stimulation, immunogenic cancer cell death, and IL-12 expression[1].
- Preclinical models have demonstrated significant immune modulation and antitumor activity[2].



For illustrative purposes only. Not intended to depict the actual structure or physical appearance of the drug product.

Figure 1. Schematic of STX-001 Drug Product

STX-001's LNP and self-replicating RNA are designed to act in concert to induce an anti-tumor immune response. The intended mechanisms of action include (1) innate immune activation via pattern recognition receptor-mediated sensing of input RNA and replication intermediates; (2) LNP and replicating RNA-induced immunogenic cancer cell death; and (3) IL-12-driven T and NK cell recruitment, Th1 polarization, IFN-γ secretion, and antitumor immunity both locally and at distant sites, inducing so-called "abscopal effects."

Methods

- This is a Phase 1, open-label, multicenter, first-in-human, dose escalation trial of STX-001 in patients (pts) with advanced solid tumors.
  - The primary endpoints were safety, tolerability and the maximum tolerated dose.
  - The secondary endpoints included preliminary tumor activity and STX-001 pharmacokinetics.
- Eligible pts had treatment-refractory advanced solid tumors with ≥ 1 clinically injectable lesion(s).
- Bayesian Optimal Interval (BOIN) design was used with an initial 3 + 3 run-in for dose escalation.
- STX-001 was injected intratumorally every 3 weeks (Q3W) into (sub)cutaneous or nodal lesions at a dose of 10 µg, 30 µg, 100 µg, 300 µg, or 900 µg.
- Dose-limiting toxicities (DLTs) were assessed during the first treatment cycle (21 days).
- Response was evaluated by RECIST 1.1. Treatment beyond progression was allowed if a patient was potentially deriving clinical benefit.
- Cutoff dates were April 3, 2025 for safety and demographics, and May 1, 2025 for exploratory activity.

Demographics

Table 1. Baseline Patient Demographics and Characteristics

Demographics and Characteristics	Overall N = 22
Age (years): median (IQR), [range]	57 (49, 73) [34, 77]
Sex: n (%)	
Male	13 (59)
Female	9 (41)
Race: n (%)	
White	19 (86)
Asian	1 (4.5)
Black or African American	1 (4.5)
Other	1 (4.5)
Tumor type: n (%)	
Melanoma	16 (73)
Breast	3 (14)
Head and neck	1 (4.5)
Other	2 (9.1)
ECOG Performance Status: n (%)	
0	17 (77)
1	5 (23)
Melanoma Pts	**Overall N = 16**
Prior PD-1 inhibitor: n (%)	16 (100)
Prior PD-1 + CTLA-4 inhibitor: n (%)	12 (75)
Prior PD-1 + LAG-3 inhibitor: n (%)	5 (31)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitors, IQR, interquartile range.

Data cutoff: Apr 3, 2025

Adverse Events

Table 2. Summary of TEAEs

Event, n (%)	10 µg N = 3	30 µg N = 4	100 µg N = 4	300 µg N = 8	900 µg N = 3	Total N = 22
All TEAEs	3 (100)	4 (100)	4 (100)	8 (100)	3 (100)	22 (100)
Serious TEAEs	0 (0)	1 (25)	1 (25)	5 (63)	1 (33)	8 (36)
Treatment-related TEAEs	3 (100)	4 (100)	2 (50)	8 (100)	3 (100)	20 (91)
Occurring in ≥ 20% of all patients:						
Blood and lymphatic system disorders						
Neutropenia	0 (0)	0 (0)	0 (0)	3 (38)	2 (67)	5 (23)
Gastrointestinal disorders						
Nausea	0 (0)	2 (50)	0 (0)	2 (25)	3 (100)	7 (32)
General disorders and administration site conditions						
Injection site pain	2 (67)	4 (100)	1 (25)	3 (38)	1 (33)	11 (50)
Fatigue	2 (67)	1 (25)	1 (25)	3 (38)	3 (100)	10 (46)
Influenza like illness	1 (33)	3 (75)	2 (50)	1 (13)	1 (33)	8 (36)
Injection site erythema	0 (0)	4 (100)	1 (25)	2 (25)	0 (0)	7 (32)
Pyrexia	1 (33)	2 (50)	0 (0)	4 (50)	0 (0)	7 (32)
Chills	0 (0)	1 (25)	1 (25)	1 (13)	3 (100)	6 (27)
Immune system disorders						
CRS	0 (0)	0 (0)	1 (25)	4 (50)	1 (33)	6 (27)
Metabolism and nutrition disorders						
Decreased appetite	0 (0)	3 (75)	1 (25)	1 (13)	2 (67)	7 (32)
Nervous system disorders						
Headache	0 (0)	1 (25)	0 (0)	3 (35)	1 (33)	5 (23)

Table 3. Summary of ≥ G3 TEAEs

Event, n (%)	10 µg N = 3	30 µg N = 4	100 µg N = 4	300 µg N = 8	900 µg N = 3	Total N = 22
≥ G3 TEAEs	0 (0)	1 (25)	0 (0)	6 (75)	3 (100)	10 (46)
Serious ≥ G3 TEAEs	0 (0)	1 (25)	0 (0)	5 (63)	1 (33)	7 (32)
≥ G3 treatment-related TEAEs	0 (0)	0 (0)	0 (0)	5 (63)	3 (100)	8 (36)
Blood and lymphatic system disorders						
Febrile neutropenia	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	1 (4.5)
Lymphopenia	0 (0)	0 (0)	0 (0)	1 (13)	2 (67)	3 (14)
Neutropenia	0 (0)	0 (0)	0 (0)	2 (25)	2 (67)	4 (18)
Hepatobiliary disorders						
Hepatitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (4.5)
Immune system disorders						
CRS	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (4.5)
Investigations						
ALT increased	0 (0)	0 (0)	0 (0)	2 (25)	0 (0)	2 (9.1)
AST increased	0 (0)	0 (0)	0 (0)	2 (25)	0 (0)	2 (9.1)
Blood CK increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (4.5)
LFT increased	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	1 (4.5)
Lymphocyte count decreased	0 (0)	0 (0)	0 (0)	2 (25)	1 (33)	3 (14)
Neutrophil count decreased	0 (0)	0 (0)	0 (0)	2 (25)	0 (0)	2 (9.1)

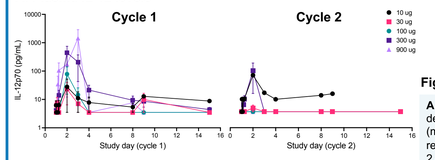
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine phosphokinase; CRS, cytokine release syndrome; G, grade; LFT, liver function test. Some pts may have experienced more than one (Serious/Treatment-related/≥ G3) TEAE.

- 1 patient experienced a DLT (G3 CRS and G4 lymphopenia in 900 µg cohort).
- 2 patients discontinued treatment due to AEs (G2 flu like illness in 30 µg cohort and G3 LFT increase in 300 µg cohort [patient had liver metastasis and adrenal insufficiency]).
- No TEAEs were fatal.

Data cutoff: Apr 3, 2025

Exploratory Pharmacodynamics

A. Plasma IL-12 levels



B. Plasma IFN-γ levels

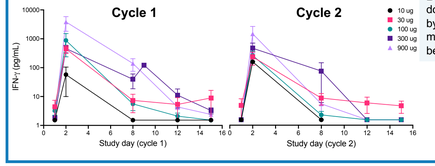


Figure 2. Plasma IL-12 and IFN-γ Levels

A. Plasma IL-12 levels increased in a dose-dependent manner, as measured by ELISA (mean ± standard error of mean [SEM]). A reduction in IL-12 levels was observed in Cycle 2 compared to Cycle 1.

B. Plasma IFN-γ levels also increased in a dose-dependent manner and were measured by Luminex assay (mean ± SEM). The magnitude of IFN-γ levels remained similar between Cycle 1 and Cycle 2.

Exploratory Activity and Translational Analyses of STX-001 Monotherapy

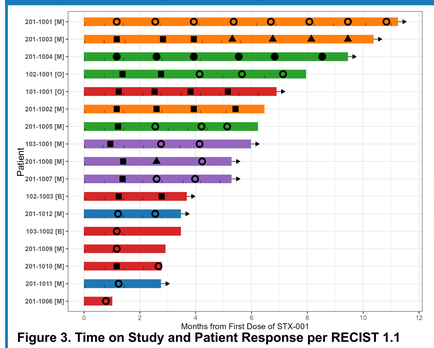


Figure 3. Time on Study and Patient Response per RECIST 1.1

Tick marks show when STX-001 dosing occurred. Arrows indicate patients still on study.
Treatment beyond progression was allowed if a patient was potentially deriving clinical benefit.

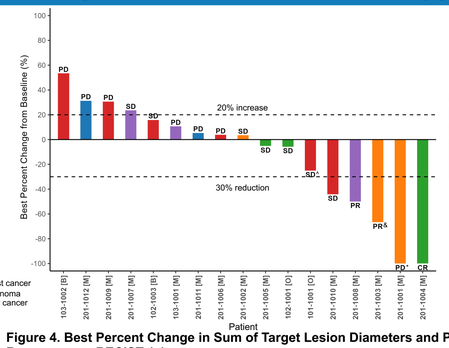


Figure 4. Best Percent Change in Sum of Target Lesion Diameters and Patient Response per RECIST 1.1

[a]Angiosarcoma patient that achieved biopsy-confirmed complete regression and molecular response by circulating tumor DNA (ctDNA). [b]Patient achieved complete metabolic response by PET. [c]Patient achieved tumor response after RECIST PD.

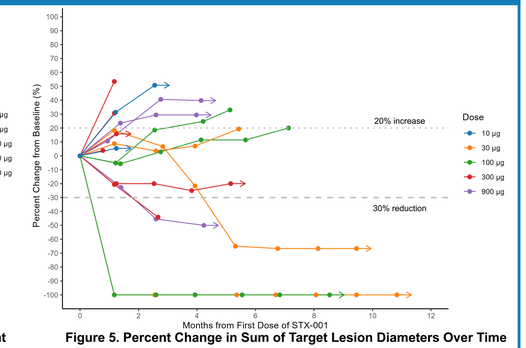


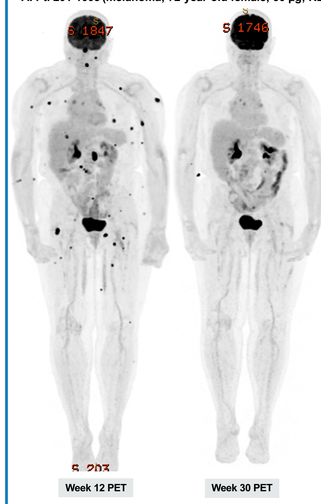
Figure 5. Percent Change in Sum of Target Lesion Diameters Over Time

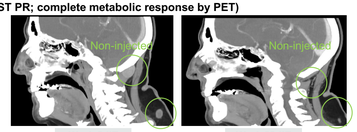
Arrows indicate patients still on study.

Data from the Response Evaluation Set (N = 17)
Data cutoff: May 1, 2025

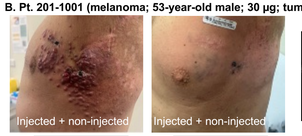
1 patient had CR, 2 had PR (1 with complete metabolic response), 7 had SD (1 with biopsy-confirmed complete regression), and 7 had PD (1 with tumor response after RECIST PD) by RECIST 1.1.

A. Pt. 201-1003 (melanoma; 72-year-old female; 30 µg; RECIST PR; complete metabolic response by PET)





B. Pt. 201-1001 (melanoma; 53-year-old male; 30 µg; tumor response after RECIST PD)



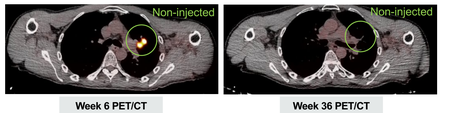
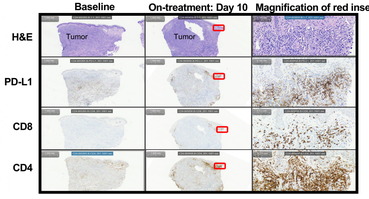


Figure 6. Clinical and Radiological Assessments

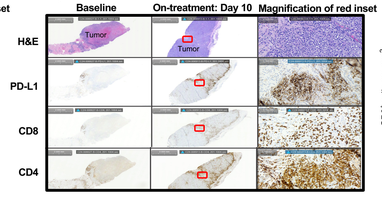
Abbreviations: CT, computer tomography; PET, positron emission tomography. Green circles indicate areas with non-injected lesions.

A. Patient received STX-001 injections into subcutaneous lesions. PET scans showed a robust metabolic response across numerous non-injected cutaneous/visceral lesions. CT scans at Week 30 demonstrated resolution of non-injected intramuscular paraspinal metastasis of the rectus capitis inferior muscle (upper lesion in image) and non-injected subcutaneous midline nodule (lower lesion in image). Patient had primary resistance to PD-1, CTLA-4, and LAG-3 inhibitors. **B.** Patient received STX-001 injections into subcutaneous and nodal lesions. Photos show robust cutaneous response of injected and non-injected lesions at Week 36. PET/CT scans show complete metabolic response in non-injected left hilar lymph node (left lesion in image) and non-injected left upper lobe lung nodule (right lesion in image) at Week 36. Response categorized as PD by RECIST 1.1 due to new lesions (which subsequently resolved). Patient had primary resistance to PD-1 and CTLA-4 inhibitors.

A. Pt. 201-1001 (melanoma; 53-year-old male; 30 µg; tumor response after RECIST PD): Non-injected lesion



B. Pt. 201-1004 (melanoma; 39-year-old male; 100 µg; RECIST CR): Non-injected lesion



C. Quantification of CD8 and CD4 T cell infiltration in injected and non-injected lesions

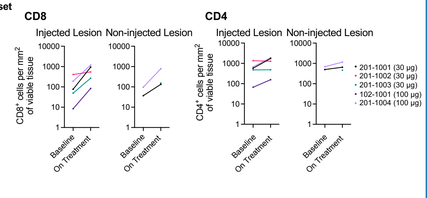
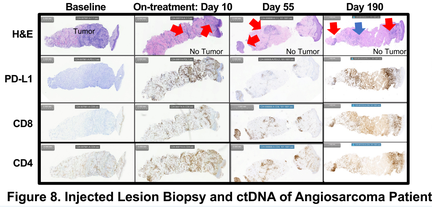


Figure 7. Assessments of Non-injected Lesion Biopsies at Baseline and 10 Days Post First Dose

Increased staining by immunohistochemistry (IHC) in the periphery of the tumor at 10 days post first dose in the non-injected (skin) lesions in **A.** Pt. 201-1001 and **B.** Pt. 201-1004 (patient received STX-001 injections into a subcutaneous lesion; prior treatments included PD-1, CTLA-4, and LAG-3 inhibitors). "Tumor" indicates presence of tumor by H&E staining. **C.** $CD8^+$ and $CD4^+$ T cell infiltration (cells/mm² of viable tissue) increased from baseline in both injected and non-injected lesions 10 days after the first dose, as quantified by immunohistochemistry. Some biopsies of non-injected lesions were not available for analysis.

A. Pt. 101-1001 (angiosarcoma; 69-year-old female; 300 µg; RECIST SD; biopsy-confirmed complete regression): Injected lesion



B. Pt. 101-1001 ctDNA levels following initiation of STX-001 treatment

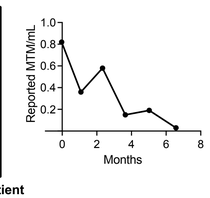


Figure 8. Injected Lesion Biopsy and ctDNA of Angiosarcoma Patient

A. Patient received STX-001 injections into a lesion on the left breast. On-treatment biopsies were characterized by intact epidermis, hypercellular areas (red arrows), and increased PD-L1 expression. Hypercellular areas were characterized by large numbers of mononuclear inflammatory cells that were mostly $CD8^+$ and $CD4^+$. On Day 190, CD8 and CD4 T cells were seen within the superficial and deep dermis along with infiltrates of foamy macrophages, many of which were PD-L1 positive (blue arrow). "Tumor" and "No Tumor" indicate presence and absence of tumor by H&E staining, respectively. **B.** Near complete reduction of ctDNA levels was observed following initiation of STX-001 treatment.

Conclusions and Future Directions

- STX-001 was well tolerated up to 300 µg, and treatment-related AEs were dose-dependent and manageable.
- Dose-dependent increases in plasma IL-12 and IFN-γ were observed, along with robust immune activation as evidenced by CD8/CD4 T cell infiltration and PD-L1 upregulation in both injected and non-injected tumors.
- Antitumor activity included 1 CR, 2 PRs by RECIST 1.1, and other tumor responses in heavily pretreated patients, including those with primary resistance to PD-1, CTLA-4, and LAG-3 ICIs.
- Abscopal effects observed by imaging/biopsies suggest systemic immune activation via local STX-001 injection.
- Findings support further development of STX-001 as monotherapy and in combination with ICIs.
- Dose optimization is ongoing with continued safety, durability, and biomarker evaluation.

References and Acknowledgements

1. Li Y, Su Z, Zhao W et al. *Nat Cancer*. 2020 Sep;1(9):882-893.
2. Sowell RT, Khurana JS, Su Z et al. *Cancer Res*. 2023;83(7):2731.

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