SITC 2022 Poster #: 740

A first-in human trial of hSTC810 (anti-BTN1A1 monoclonal antibody), targeting a novel immune checkpoint with a mutually exclusive expression with PD-1/PD-L1 in patients with relapsed/refractory solid tumors

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Background

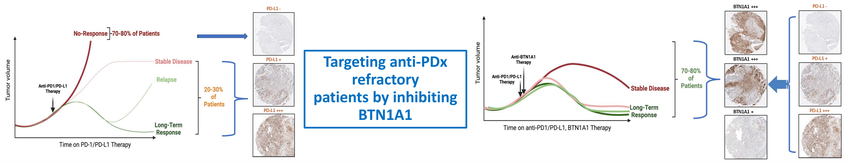
BTN1A1 is a novel immune checkpoint for cancer immunotherapy

- Butyrophilin (BTN) proteins are members of the B7 immunoglobulin superfamily and exhibit immunomodulatory functions in mammals. We have recently identified BTN1A1 as an immune checkpoint protein prominently upregulated in response to acute inflammatory insults.
- Further *in vitro* and *in vivo* assays have validated BTN1A1 as an immune checkpoint target, potentially for patients whose tumors are refractory to or relapsed after anti-PD-1/PD-L1 antibody treatment.
- We developed hSTC810, a humanized monoclonal antibody targeting BTN1A1, which entered into Phase I clinical trials in April 2022.

Hallmarks of Immune Checkpoint BTN1A1

- ✓ Discovered and proven to be an immune checkpoint
- ✓ Inhibition of T cell proliferation and activation
- ✓ Inhibition of cancer cells death by activated T cells
- ✓ Mainly expressed in cancer cells with concomitant expression in immune cells
- ✓ Exclusive expression to PD-L1

Rationale



BTN1A1 is expressed in various solid tumors and mutually exclusive with PD-L1

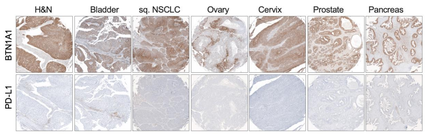


Figure 1. An immunohistochemistry-based analysis of BTN1A1 and PD-L1 expression in various tumors

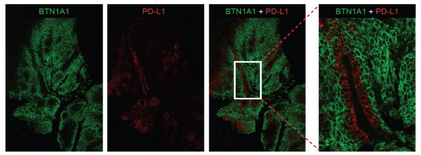


Figure 2. BTN1A1 and PD-L1 is mutually exclusive in their expression. Fluorescent multiplexed IHC (OPAL) data in squamous cell carcinoma of hypopharynx (head and neck) samples stained with anti-BTN1A1 (green), anti-PD-L1 (red).

Anatomic Site	Pathology Diagnosis	# of Cores	BTN1A1 Expression ≥ 50%	1-49%	≤ 1%
	Small cell carcinoma	6	-	-	100%
Lung, Primary	Squamous cell carcinoma	17	82%	-	18%
	Adenocarcinoma	17	82%	6%	12%
	Small cell carcinoma	6	-	-	100%
Lung, Lymph node met	Squamous cell carcinoma	17	70%	18%	12%
	Adenocarcinoma	17	41%	6%	53%
Bladder	Urothelial carincoma	38	87%	-	13%
Stomach	Adenocarcinoma	72	51%	3%	46%
Head and neck	Squamous cell carcinoma	60	88%	5%	7%
Ovary	Serous mucinous, adenocarcinoma	54	61%	17%	22%
Pancreas	Duct adenocarcinoma	50	58%	10%	32%
Breast	Carcinoma	67	48%	3%	49%
Esophagus	Squamous cell carcinoma	68	68%	13%	19%
Colon	Adenocarcinoma	40	73%	-	27%
Prostate	Adenocarcinoma	35	60%	-	40%
Gastroesophageal	Carcinoma	30	83%	7%	10%
Liver	Hepato/cholangiocellular carcinoma	40	100%	-	-
	Plasma cell myeloma	20	100%	-	-
Bone	Primitive neuroectodermal tumor	2	100%	-	-
	Ewing's sarcoma	2	100%	-	-

Table 1. BTN1A1 expression in tumor cells

Development of anti-human BTN1A1 antibody, STC810

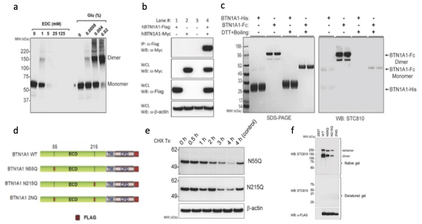


Figure 3. Characterization of the dimer- and glyco-specific anti-human BTN1A1 antibody

a-c, BTN1A1 exists as a dimeric form. a, Analysis of cross-linked hBTN1A1-Flag full length proteins obtained from hBTN1A1-Flag overexpressing HEK293T stable cell lines. b, Cell lysates from HEK293T cells co-transfected with BTN1A1-Myc and BTN1A1-Flag were immunoprecipitated with anti-Flag magnetic beads. The associated proteins were subjected to immunoblotting with anti-Flag and anti-Myc antibodies
c, STC810 preferentially recognized the dimerized Fc fusion protein, but not the monomeric His-tagged BTN1A1 ECD.
d-f, d and e, BTN1A1 glycosylation site mutants and their stability in PC3 cells. f, STC810 recognizes a native dimeric and glycosylated form of BTN1A1 in cells.

- Dissociation constant (KD) of STC810 binding to:
  - BTN1A1-His (monomer) : 7.8×10^{-9}
  - BTN1A1-Fc (dimer) : 3.3×10^{-10}

Efficacy of humanized anti-BTN1A1 monoclonal antibody, hSTC810

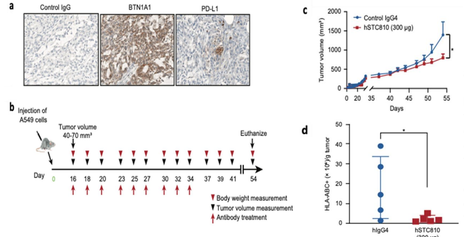


Figure 4. Therapeutic efficacy of humanized STC810 (hSTC810) in A549 humanized mouse model.

a. Representative IHC images of A549 tumors from a humanized mouse model.
b. A549 tumor growth curves in control human IgG4- or hSTC810-treated female NOD/Shi-scid/IL-2Rγnull humanized with human cord blood CD34⁺ hematopoietic stem cells. A549 cells (5 x 10^6 were engrafted (s.c.) in humanized mice (n = 6) that were then treated with hSTC810 (300 ug) 3 times per week for 3 weeks beginning day 16 post-engraftment.
c. Tumor volumes are shown as averages with the SEM.
d. mCD45⁻ hCD45⁻ HLA-ABC⁺ tumor cells per gram of tumor tissue in the indicated groups.

Clinical Study Design

- A first-in-human, phase 1, multicenter, open-label study to investigate the safety, tolerability, pharmacokinetics, and preliminary efficacy of hSTC810 monotherapy in subjects with advanced solid tumors (NCT05231746).
- This 3 + 3 dose escalation study is administered intravenously at doses of 0.3, 1, 3, 6, 10, and 15mg/kg every 2 weeks (Q2W).
- Backfill cohorts are recruited to further characterize pharmacokinetics, pharmacodynamics, and toxicity.

Eligibility

- **Key inclusion criteria**
  - Patients with advanced solid tumors ≥ 18 years
  - ECOG PS ≤ 1
  - Measurable disease per RECIST v1.1
- **Key exclusion criteria**
  - Anti-cancer treatment within 4 weeks of first dose
  - Radiotherapy or major surgery within 4 weeks of screening
  - Known severe hypersensitivity to any checkpoint inhibitor
  - History of autoimmune disease

Study Endpoint

- **Primary endpoint**
  - Maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
  - Safety and tolerability
- **Secondary endpoint**
  - Assessment of pharmacokinetics
  - Assessment of immunogenicity
  - Anti-cancer activity and potential indications of hSTC810
- **Exploratory endpoint**
  - Assessment of pharmacodynamics

Study Design

- Dose escalation: 3+3 design
- hSTC810 administrated IV every 2 weeks
- DLT period of 28 days
- Backfill enrollment in cleared dose level of 1-15 mg/kg

Study Design Schema

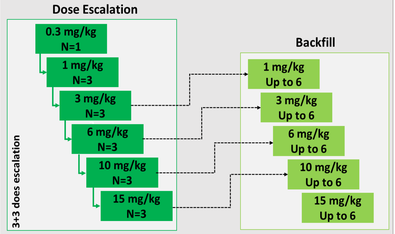


Table 2. Study Design

Study Progress as of 18 Oct 2022

Patient Characteristics	Number (n=22)	Patient Characteristics	Number (n=22)
Median age, years (range)	63 (38-75)	Tumor type, n (%)	
Gender, n (%)		Colon	12 (55%)
Male	12 (55%)	Lung	2 (9%)
Female	10 (45%)	Melanoma	2 (9%)
Average prior anti-cancer therapy, n (range)	4.5 (2-9)	Pancreatic	2 (9%)
		Bladder	1 (5%)
		Hypopharyngeal	1 (5%)
Prior immunotherapy, n (%)	7 (32%)	Cholangiocarcinoma	1 (5%)
		Esophageal	1 (5%)

Table 3. Baseline Demographics

Study Results

- **Currently, no dose-limiting toxicities (DLT) were reported up to 6 mg/kg**
- All TRAEs were Grade 1
- Common TRAEs include fatigue, somnolence, dyspepsia, and headache
- One partial response (PR) observed to date in Cohort C (3mg/kg)
  - Patient with MSI-high metastatic colorectal cancer had a 32% reduction in target lesions after 4 cycles of hSTC810
- 8 out of 18 patients continued with stable disease (SD)

Adverse Event	Grade	Event	Patient
Headache	1	7	1
Fatigue	1	6	5
Somnolence	1	2	2
Dyspepsia	1	2	2
Nausea	1	2	2
Brittle nails	1	2	2
Pyrexia	1	1	1
Dizziness	1	1	1
Vomiting	1	1	1
Peripheral neuropathy	1	1	1
Creatinine increased	1	1	1

Table 4. Treatment Related Adverse Events (TRAE) as of 18 Oct 2022

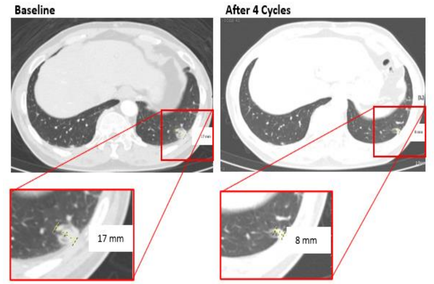


Figure 5. Partial Response in Colorectal Cancer

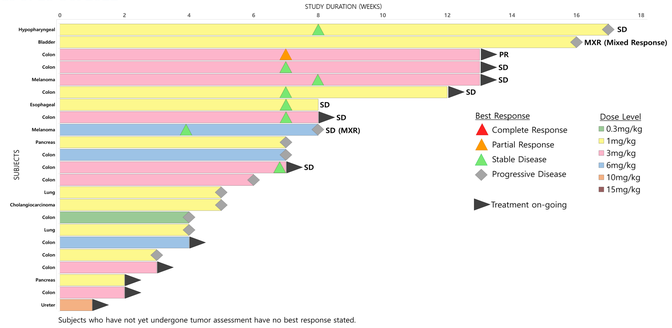


Figure 6. Summary of Best Tumor Response Evaluation as of 24 Oct 2022

Summary

- hSTC810 is safe and well-tolerated up to 6 mg/kg Q2W. No DLT was observed and MTD has not yet been reached.
- Despite treatment at low dose levels, there is evidence of early efficacy (1 PR, 8 SD, 2 MXR).
  - MSI-high metastatic colorectal cancer showed early response at 3 mg/kg.
- Further evaluation on the safety and efficacy of hSTC810 at 10, and 15 mg/kg will be conducted.
- Final study results, PK results, and the relationship between BTN1A1 tumor expression and efficacy will be announced in 2Q 2023.

Figure 7. Study Timeline