SGNTGT-001: A PHASE 1 STUDY OF SEA-TGT (SGN-TGT), AN EFFECTOR-FUNCTION ENHANCED MONOCLONAL ANTIBODY (MAB), IN ADVANCED MALIGNANCIES (TRIAL IN PROGRESS)

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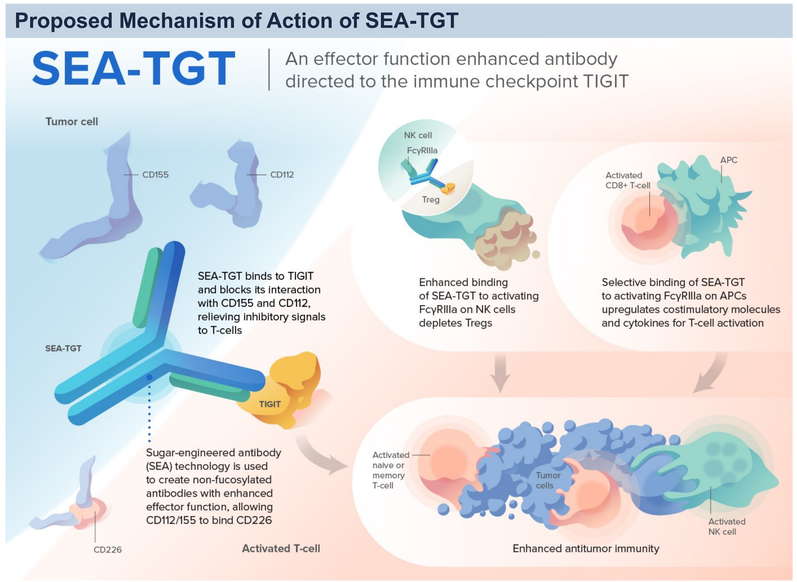
Background and Clinical Rationale

- T cell immunoreceptor with immunoglobulin (Ig) and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (TIGIT) is an inhibitory immune checkpoint receptor expressed on subsets of T cells and natural killer (NK) cells[1]
- TIGIT inhibits T and NK cell function by binding CD155 and CD112, which are upregulated on tumor cells[1]
- TIGIT mediates its immunosuppressive effect by blocking the binding of CD226 on T cells to the CD155 and CD112 ligands, which then limit T cell proliferation and activation. Thus, relief of TIGIT blockade is a potential therapeutic target for stimulating antitumor T cell response
- SEA-TGT (also known as SGN-TGT) is an investigational, humanized, non-fucosylated mAB directed against TIGIT, that blocks TIGIT's interaction with CD155 and CD112
- SEA-TGT utilizes a proprietary sugar-engineered antibody (SEA) backbone to engage both the innate and adaptive arms of the immune system[2]
  - Binds with high affinity to the activating FcγRIIIA receptor and has decreased binding to the inhibitory FcYRIIb receptor
- SEA-TGT binds TIGIT and activating FcγRIIIa leading to:
  - Relief of inhibitory checkpoint signals directed at T cells
  - Depletion of immunosuppressive T-regulatory (Treg) cells
  - Amplification of naïve and memory T cells
- In preclinical studies, SEA-TGT has demonstrated:[2]
  - Superior antitumor immune responses compared to other TIGIT mABs without effector-enhanced backbones
  - Antitumor activity as monotherapy and in combination with other immune modulators
- Based on the multiple mechanisms of action, SEA-TGT may be an active therapy in a variety of malignancies

Proposed Mechanism of Action of SEA-TGT

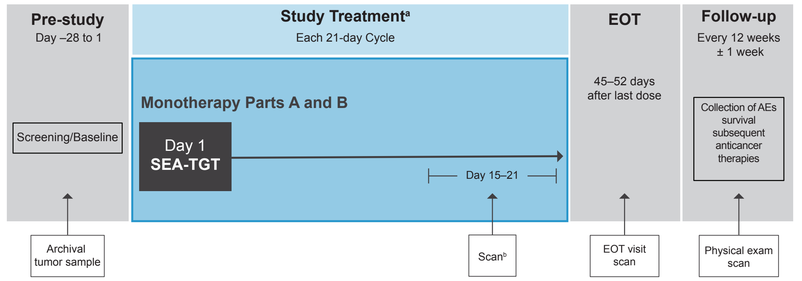


SEA-TGT is an investigational agent, and its safety and efficacy have not been established. Proposed mechanism of action based on preclinical data.

APC, antigen-presenting cell; CD, cluster of differentiation; NK, natural killer; SEA, sugar-engineered antibody; TIGIT, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif; Treg, T-regulatory.

Study Design

- SGNTGT-001 (NCT04254107, EudraCT 2019-004748-31), a first-in-human clinical study with SEA-TGT, includes patients with selected advanced malignancies, with specific malignancies considered for expansion cohorts
- This phase 1, open-label, dose-escalation and dose-expansion study will assess the safety and tolerability of SEA-TGT monotherapy and in combination with the standard, approved dose of pembrolizumab



[a]Part C will evaluate SEA-TGT in combination with pembrolizumab.
[b]Response will be assessed by radiographic tumor evaluation every 9 weeks (calculated from Cycle 1 Day 1) for the first 12 months, then every 12 weeks, regardless of dose delays.
AE, adverse event; EOT, end of treatment; SEA, sugar-engineered antibody

Endpoints

Table 1: Endpoints

Primary
- Safety and tolerability
  - AEs
  - Laboratory abnormalities
- Maximum tolerated dose, maximum administered dose, or recommended dose and schedule of SEA-TGT
  - Dose-limiting toxicities
  - Dose-level safety and activity

Secondary
- Antitumor activity
  - Objective response rate, complete response rates, duration of objective and complete responses, progression-free survival and overall survival
- PK
- Immunogenicity
  - Antidrug antibodies

Exploratory
- Biomarkers of SEA-TGT-mediated PD effects
- PK-PD correlations
- Correlative analyses of PD measurements and response, toxicity and resistance

AE, adverse event; PD, pharmacodynamic; PK, pharmacokinetics; SEA, sugar-engineered antibody.

Assessments

- Safety
  - Surveillance of AEs, laboratory test measures, physical examination findings, vital signs, electrocardiograms, and concomitant medication records
  - Monitoring for infusion-related or hypersensitivity reactions
- Response
  - Solid tumors: Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 and modified RECIST V1.1 for immune-based therapeutics
  - Lymphomas: Lugano 2014 classification criteria with the incorporation of the Lymphoma Response to Immunomodulatory Therapy Criteria

Eligibility Criteria

Table 2: Eligibility Criteria

Key Inclusion Criteria

Histologically or cytologically confirmed advanced or metastatic malignancy:
- Unresectable locally-advanced or metastatic NSCLC, gastric/GE junction carcinoma, cutaneous melanoma, HNSCC, bladder cancer, ovarian cancer or TNBC
- Lymphoma, including classical Hodgkin lymphoma, diffuse large B-cell lymphoma[a], peripheral T cell lymphoma, not otherwise specified
- Relapsed, refractory, or progressive disease, specifically:
  - Cutaneous melanoma: Patients must have received at least 1 PD-1-targeted therapy and 1 therapy directed to a targetable mutation (e.g. *BRAF*), if available and not clinically contraindicated
  - HNSCC: Patients must have received prior therapy with a platinum-based regimen, a PD-1 or PD-L1 inhibitor, and an anti-EGFR therapy, if eligible
  - Bladder cancer: Patients in Part A and B must have received platinum-based chemotherapy, enfortumab vedotin, and an anti-PD-1/PD-L1, if indicated and eligible
  - Ovarian cancer: Patients in Part A and B must have received platinum-based chemotherapy and be considered by the investigator ineligible for retreatment. If eligible and indicated, patients must have received a bevacizumab-containing regimen and a PARP inhibitor
  - TNBC: Patients must have received 1 or more prior lines of therapy for locally advanced or metastatic disease, including a taxane and PD-1/PD-L1 inhibitor
- Measurable disease defined as:
  - Solid tumors: Measurable disease according to RECIST V1.1
  - Lymphomas: Fluorodeoxyglucose-avid disease by positron emission tomography and measurable disease of ≥15 mm in the greatest transverse diameter by computed tomography scan, as assessed by the site radiologist
- ≥18 years
- Eastern Cooperative Oncology Group Performance Status score of 0 or 1

Key Exclusion Criteria
- History of another malignancy within 2 years except those with a negligible risk of metastasis or death
- Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment that has not been completed before the first dose of study drug
- Known active central nervous system metastases
- Previous or serious ongoing infection
- Previous allogeneic SCT
- History of cardiovascular event 6 months prior to first dose of SEA-TGT
- Prior use of any anti-TIGIT mAb
- Prior use of anti-PD-L1 therapy (Part C only)

[a]As defined by World Health Organization criteria.
EGFR, epidermal growth factor receptor; GE, gastroesophageal; HNSCC, head and neck squamous cell carcinoma; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; PARP, poly (ADP-ribose) polymerase; PD-L, programmed cell death protein-ligand; RECIST, Response Evaluation Criteria in Solid Tumors; SCT, stem cell transplant; SEA, sugar-engineered antibody; TIGIT, T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif; TNBC, triple negative breast cancer

Summary

- This study will assess the safety and antitumor activity of SEA-TGT, as monotherapy and in combination with pembrolizumab, for patients with solid tumors and lymphomas
- Enrollment is underway in 9 sites across Europe and North America
- Study start date: May 2020
- Estimated study completion date: March 2023

References

1. Chauvin J, Zarour HM. (2020). J Immunother Cancer 8:e000957.
2. Smith A, et al. (2021). American Association of Cancer Research 2021.

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