PHASE 1 STUDY OF SEA-TGT, A HUMAN, NONFUCOSYLATED MONOCLONAL ANTIBODY DIRECTED TO TIGIT WITH ENHANCED IMMUNE EFFECTOR FUNCTION, IN PATIENTS WITH ADVANCED MALIGNANCIES (SGNTGT-001, TRIAL IN PROGRESS)

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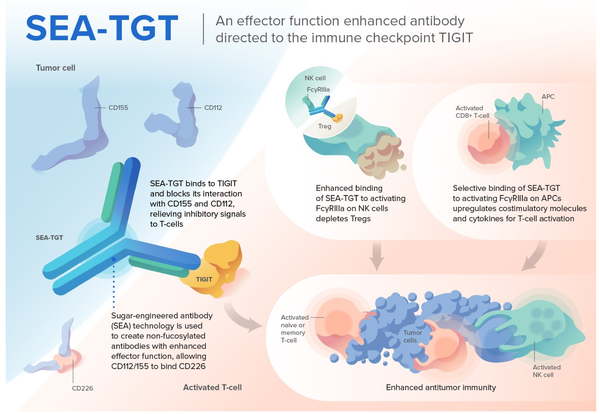
Background and Rationale

- 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.[1,2]
- TIGIT mediates its immunosuppressive effect by blocking the binding of CD226 on T cells to the CD155 and CD112 ligands, limiting T-cell proliferation and activation. Thus, relief of TIGIT blockade is a potential therapeutic target for stimulating antitumor T-cell response.
- SEA-TGT is an investigational, human, nonfucosylated monoclonal antibody (mAb) directed to TIGIT, blocking its 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.[3]
  - Binds with high affinity to the activating FcγRIIIA receptor and has decreased binding to the inhibitory FcγRIIb receptor.
- Preclinical studies with SEA-TGT supported initiation of a phase 1 study and the rationale for combining SEA-TGT with other agents:[3]
  - SEA-TGT demonstrated superior antitumor immune responses compared to other TIGIT mAbs lacking effector-enhanced backbones.
  - SEA-TGT showed antitumor activity as monotherapy and in combination with other immune modulators, including an anti–PD-1 antibody.
- Sasanlimab, an anti–PD-1 antibody, has demonstrated antitumor activity and was well tolerated in patients with advanced solid tumors, including non-small cell lung cancer and urothelial carcinoma.[4,5]
- SEA-TGT alone and in combination with an anti–PD-1 antibody, may achieve clinical responses in patients with advanced malignancies.

Proposed Mechanism of Action of SEA-TGT

- SEA-TGT elicits antitumor effects by:
  - Blockade of inhibitory checkpoint signals directed to T cells.
  - Depletion of immunosuppressive Tregs.
  - Amplification of naïve and memory T cells.

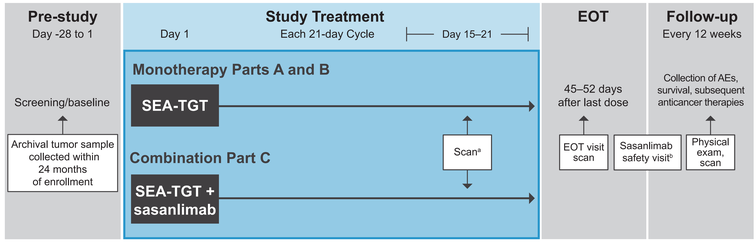


SEA-TGT is an investigational agent, and its safety and efficacy have not been established. Proposed mechanism of action based on preclinical data.

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, some of which may be 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 sasanlimab.



[a]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.
[b]Visit occurs 110 days ±2 weeks after the last dose of sasanlimab. Assessments include physical examination, complete blood count with differential, comprehensive metabolic panel including amylase, lipase, and total bilirubin.
AE=adverse event; EOT=end of treatment; SEA=sugar-engineered antibody.

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 rate, 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) 1.1 and modified RECIST 1.1 for immune-based therapeutics.
  - Lymphomas: Lugano 2014 classification criteria with the incorporation of the Lymphoma Response to Immunomodulatory Therapy Criteria.[6]

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Eligibility Criteria

Key Inclusion Criteria

≥18 years
Eastern Cooperative Oncology Group performance status score of 0 or 1
Measurable disease defined as:
- Solid tumors: Measurable disease according to RECIST 1.1
- Lymphomas: Fluorodeoxyglucose-avid disease by PET and measurable disease of ≥15 mm in the greatest transverse diameter by CT scan, as assessed by the site radiologist

Parts A and B

Histologically or cytologically confirmed advanced or metastatic malignancy:
- Unresectable locally advanced or metastatic and relapsed, refractory or progressive disease, specifically:
  - Non-small cell lung cancer
  - Gastric/gastroesophageal junction carcinoma
  - Cutaneous melanoma (excluding acral or mucosal varieties)
  - Head and neck squamous cell carcinoma
  - Bladder cancer
  - Cervical cancer
  - Ovarian cancer
  - Triple-negative breast cancer
- Lymphomas, specifically:
  - Classical Hodgkin lymphoma
  - Diffuse large B-cell lymphoma[a]
  - Peripheral T-cell, not otherwise specified

Part C

Local histologically confirmed advanced disease, specifically:
- Non-small cell lung cancer
- Head and neck squamous cell carcinoma
- Cutaneous melanoma (excluding acral or mucosal varieties)

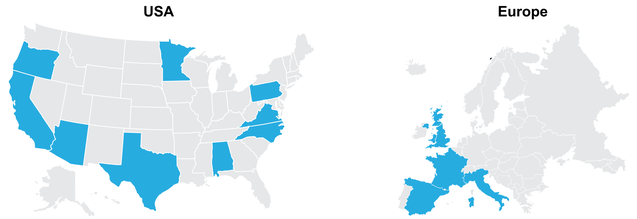
Key Exclusion Criteria

- 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
- Recent 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 monoclonal antibody
- Prior use of anti–PD-1/PD-L1 therapy (Part C only)

[a]As defined by World Health Organization criteria.
CT=computed tomography; PD-L1=programmed cell death protein-ligand 1; PET=positron emission tomography; 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.

Summary

- This study will assess the safety and antitumor activity of SEA-TGT, as monotherapy and in combination with sasanlimab, for patients with solid tumors and lymphomas.
- Enrollment is underway at 18 sites in France, Italy, Spain, the UK, and the USA.



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