A PHASE 1 STUDY OF SGN-STNV, A NOVEL ANTIBODY–DRUG CONJUGATE TARGETING SIALYL-THOMSEN-NOUVEAU ANTIGEN (STN), IN ADULTS WITH ADVANCED SOLID TUMORS (SGNSTNV-001, TRIAL IN PROGRESS)

Nehal J. Lakhani[1], Irene Brana[2], Vi Kien Chiu[3], Afshin Dowlati[4], Elizabeth Katherine Lee[5], Anna Minchom[6], Suzanne M. McGoldrick[7], Xiaoxia Han[7], Amita Patnaik[8]

[1]START Midwest, Grand Rapids, MI, USA; [2]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]The Angeles Clinic & Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA, USA; [4]Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, OH, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Drug Development Unit, Royal Marsden Hospital, Surrey, UK; [7]Seagen Inc., Bothell, WA, USA; [8]START San Antonio, San Antonio, TX, USA

Background and Clinical Rationale

Background

- Sialyl-Thomsen-nouveau antigen (STn) is a tumor-associated carbohydrate antigen with high prevalence of expression across various solid tumor types and limited expression in normal tissue.
  - Several different tumor-associated glycoproteins, such as mucin-1 (MUC1) and mucin-16 (MUC16), present STn on the cell surface.[1,2]
  - Expression of STn has been demonstrated for non-small cell lung cancer (NSCLC), ovarian, and gastric cancers, as well as mucinous subtypes of solid tumors.[3-5]
  - STn is thought to promote cancer progression by affecting cell adhesion, migration, and propagation of invasiveness, and has been linked to immunosuppression, advanced disease, chemotherapy resistance, and decreased survival.[3,6-8]
  - The presence of STn on several different tumor-associated glycoproteins allows an STn-targeted antibody-drug conjugate (ADC) to bind to multiple proteins on the cell surface simultaneously.
- SGN-STNV is a novel investigational ADC which is designed to direct the microtubule-disrupting agent monomethyl auristatin E (MMAE) to STn-expressing cells. SGN-STNV is comprised of an anti-STn monoclonal antibody conjugated to MMAE via a protease-cleavable linker.

Preclinical studies

- Preclinical studies of SGN-STNV support the rationale to investigate SGN-STNV in patients with cancer:

Safety:

» In non-human primates, SGN-STNV was tolerated up to a dose of 4 mg/kg when given once weekly (q1wk, 4 doses total) with no severe toxicities.[4]

» The effects observed were consistent with toxicities previously reported for other MMAE ADCs.

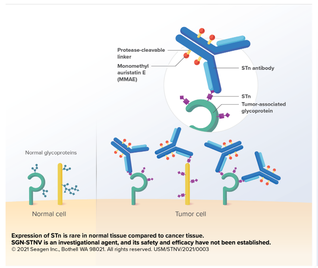
Efficacy:

» In vivo studies of SGN-STNV in mice demonstrated growth inhibition of cancer cell lines and patient-derived tumor xenograft models in tumor types for which there is a high unmet need including gastric, ovarian, esophageal, and NSCLC.[4,5]

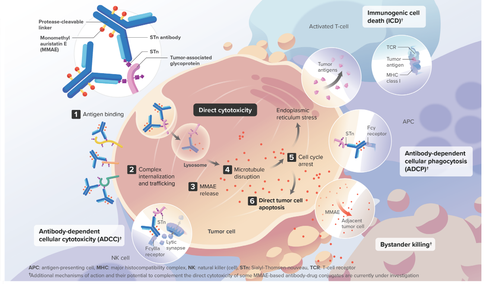
Proposed Mechanism of Action

- Once bound to STn, the SGN-STNV-STn complex is internalized and trafficked to the lysosome, where proteases cleave the linker and release MMAE into the cytoplasm. MMAE binds and disrupts microtubules, inducing cell cycle arrest and apoptosis.[5]
- In line with other MMAE-platform ADCs, SGN-STNV is proposed to drive immunogenic cell death (ICD) via an endoplasmic reticulum (ER)-stress response. The SGN-STNV antibody backbone has demonstrated preclinical evidence of changes in immune effector function, including antibody dependent cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP).[5]

SGN-STNV | An ADC directed to STn, a carbohydrate antigen present on multiple tumor-associated proteins



Expression of STn is rare in normal tissue compared to cancer tissue.
SGN-STNV is an investigational agent, and its safety and efficacy have not been established.

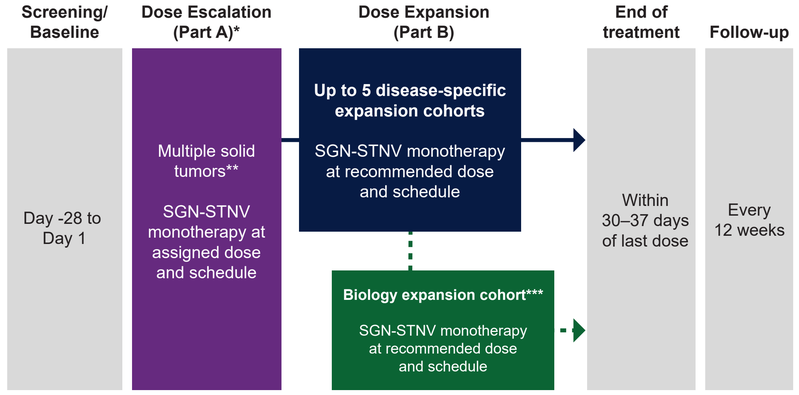


APC: antigen-presenting cell; **MHC**: major histocompatibility complex; **NK**: natural killer (cell); **STn**: Sialyl-Thomsen-nouveau; **TCR**: T-cell receptor
†Additional mechanisms of action and their potential to complement the direct cytotoxicity of some MMAE-based antibody-drug conjugates are currently under investigation

†SGN-STNV is an investigational agent, and its safety and efficacy have not been established.

Study Design

- SGNSTNV-001 (NCT04665921) is a phase 1, open-label, multicenter, dose escalation, and dose expansion study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-STNV in adults with select advanced solid tumors.



*Dose-escalation utilizes the modified toxicity probability interval (mTPI) method.[9]
**See eligibility criteria.
***The biology cohort will be gated based on data generated from other expansion cohorts and will require additional biopsies.

Objectives and Corresponding Endpoints

Primary Objectives	Corresponding Primary Endpoints
• To evaluate the safety and tolerability of SGN-STNV in patients with advanced solid tumors • To identify the maximum tolerated dose (MTD) of SGN-STNV in patients with advanced solid tumors • To identify a recommended dose and schedule for SGN-STNV	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) • Type, incidence, and severity of laboratory abnormalities • Incidence of dose limiting toxicities (DLTs)
Secondary Objectives	**Corresponding Secondary Endpoints**
• To assess the antitumor activity of SGN-STNV • To assess the PK of SGN-STNV • To assess the immunogenicity of SGN-STNV	• Objective response rate (ORR) as assessed by the investigator per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1).[10] ORR is defined as the proportion of subjects achieving a partial response (PR) or complete response (CR). • Progression-free survival (PFS) • Overall survival (OS) • Duration of objective response (DOR) • Estimates of selected PK parameters for plasma SGN-STNV antibody, antibody-conjugated MMAE, and unconjugated MMAE concentrations • Incidence of antidrug antibodies (ADAs)

Eligibility

Key Inclusion Criteria:

- Eligible patients must be ≥18 years with advanced/refractory solid tumors in any of the following cancers: NSCLC, HER2-negative breast cancer, ovarian, cervical, endometrial, esophageal, gastric/GEJ or colorectal cancer, appendiceal or exocrine pancreatic adenocarcinoma, or pseudomyxoma peritonei of unknown origin
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Measurable disease per RECIST v1.1 at baseline
- Adequate renal, hepatic, and hematologic function
- Chemotherapy, radiotherapy, immunotherapy, biologics, and/or other approved or investigational antitumor treatment completed at least 4 weeks prior to the first dose of study drug.

Key Exclusion Criteria:

- Patients with known active central nervous system metastases
- Prior treatment with MMAE-containing drugs.

Response Assessments

- Antitumor activity will be assessed by radiographic imaging at screening and every 6 weeks during treatment through documentation of progressive disease (PD).
- Tumor evaluation will be performed by computed tomography (CT) and/or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis.
- Antitumor activity will be based on objective response (OR) assessments as defined by RECIST v1.1. Treatment decisions by the investigator will be based on RECIST v1.1.

Summary

- SGN-STNV is a novel investigational ADC which is designed to direct MMAE to cells expressing the tumor-associated carbohydrate antigen STn.
- Preclinical data on STn-expression and SGN-STNV antitumor activity support the study of the SGN-STNV clinical activity in patients with solid tumors, including tumors for which there is high unmet need.
- SGNSTNV-001 (NCT04665921) is a phase 1, open-label, multicenter study designed to evaluate the safety, tolerability, PK, and antitumor activity of SGN-STNV in adults with select advanced solid tumors.
- The study includes both dose escalation (Part A) and multiple disease-specific cohorts and a biology cohort in dose expansion (Part B).
- Study accrual for Part A is ongoing in the USA and the UK, and sites are planned in Canada, Spain, Italy, and France.

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Disclosures: This study is sponsored by Seagen Inc., Bothell, WA, USA. NJL: Advisory Board: Innovent Biologics; Research Grant/Funding (Institutional, Local PI): Alpine Biosciences, ALX Therapeutics, Ascentage, Astellas, Celgene, Constellation Pharma, Forty Seven, Helsinn, Ikena, InhibRx, Jounce, Loxo/Lilly, Merck, Mersana Therapeutics, Northern Biologics, Odonate, Pfizer, Regeneron, Samumed, Sapience Therapeutics, Seagen, Shattuck Labs, Symphogen. The institutions of NJL, IB, VKC, AD, EKL, AM, and AP received research funding from Seagen Inc. SMM and XH are employees of and hold ownership interest in Seagen Inc.

Presentation No. 556TiP
European Society of Medical Oncology 2021, Virtual Congress; September 16–21, 2021

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