A PHASE 1 STUDY OF SGN-B6A, AN ANTIBODY–DRUG CONJUGATE TARGETING INTEGRIN BETA-6, IN PATIENTS WITH ADVANCED SOLID TUMORS (SGNB6A-001, TRIAL IN PROGRESS)

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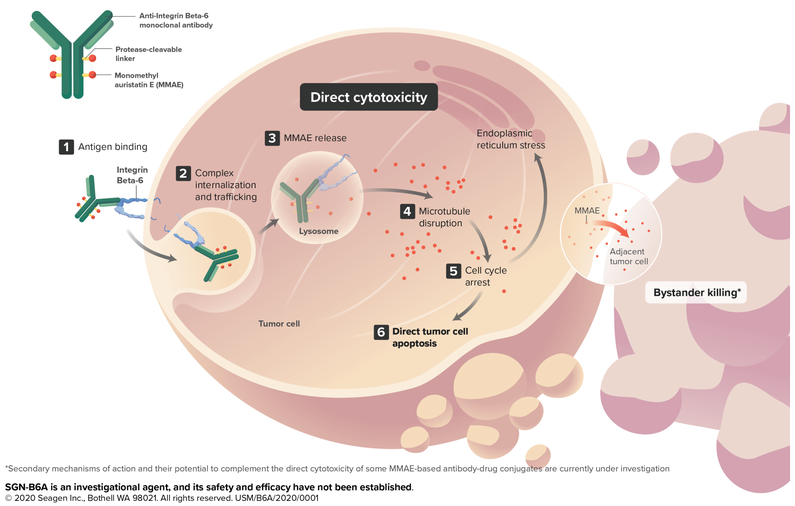
Background and Clinical Rationale

- The extracellular matrix (ECM) has received significant attention as a therapeutic target due to its recognized role in solid tumor pathogenesis.[1] Malignant cells may be able to achieve greater invasiveness into surrounding healthy tissue when the cell surface receptor integrin beta-6 is expressed[2,3]
- Integrin beta-6 promotes cellular adhesion through interactions with the ECM[3]
- Integrin beta-6 expression is prevalent in numerous solid tumors and is a negative prognostic marker in cancers including colorectal, non-small cell lung, gastric, and cervical cancers[4-8]
- SGN-B6A is an investigational antibody–drug conjugate (ADC) directed against integrin beta-6.[9,10] This ADC consists of a humanized immunoglobulin G1 anti-integrin beta-6 monoclonal antibody conjugated through a protease-cleavable valine-citrulline peptide linker to the microtubule-disrupting agent, monomethyl auristatin E (MMAE)[9,10]
- In several xenograft models, SGN-B6A treatment resulted in tumor growth delay and promoted regression in tumor volume versus a non-binding control[9,10]
- Once SGN-B6A binds to integrin beta-6, it is internalized and trafficked to lysosomes where cleavage of the drug-linker releases MMAE, leading to microtubule disruption, cell cycle arrest, and apoptosis[11]

Proposed Mechanism of Action of SGN-B6A

SGN-B6A | An antibody-drug conjugate directed to Integrin Beta-6

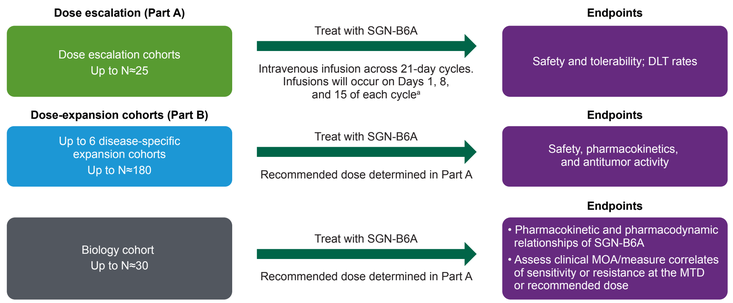


*Secondary mechanisms of action and their potential to complement the direct cytotoxicity of some MMAE-based antibody-drug conjugates are currently under investigation

SGN-B6A is an investigational agent, and its safety and efficacy have not been established.

Study Design

- SGNB6A-001 (NCT04389632) is a phase 1, first-in-human, open-label, multicenter study designed to assess the safety, tolerability, pharmacokinetics, and antitumor activity of SGN-B6A in adults with select advanced solid tumors
- The study will enroll up to 235 participants and will be closed 3 years after the final patient receives their concluding dose or when there are no patients remaining in the follow-up, whichever occurs first
- Dose escalation (Part A)
  - Patients will receive treatment to evaluate dose-limiting toxicities (DLTs) of SGN-B6A, in order to evaluate the maximum tolerated dose (MTD) and/or select a recommended dose
  - The dose-escalation portion will evaluate safety and tolerability, and identify the MTD of SGN-B6A via the modified toxicity probability interval method[12]
  - In the case the MTD is above the doses used in the study, the recommended dose and schedule will be based on safety, pharmacokinetics, and pharmacodynamic and biomarker analyses, in addition to preliminary antitumor activity
- Dose expansion (Part B)
  - *Disease-specific expansion cohorts:* Patients will be treated at the MTD or recommended dose to assess the safety, pharmacokinetics, and antitumor activity of SGN-B6A
  - *Biology Cohort:* Patients who consent to protocol-specified research biopsies may be eligible to enroll in a biology cohort. Pre- and post-treatment tumor samples from patients in the biology cohort may help to further characterize SGN-B6A activity



[a]There will be an option to limit the frequency to Days 1 and 8, or just Day 1.

DLTs, dose-limiting toxicities; MOA, mechanism of action; MTD, maximum tolerated dose.

Endpoints

Table 1: Endpoints

Primary

- Safety, tolerability; DLTs

Secondary

- Antitumor activity measured using best response per RECIST v1.1, as well as objective response rate, progression-free survival, overall survival, and duration of objective response
- Pharmacokinetics
- Anti-SGN-B6A antibody levels

Exploratory

- Pharmacodynamics
- Pharmacokinetic/pharmacodynamic relationships
- Response, toxicity, pharmacokinetics, pharmacodynamics, and resistance to SGN-B6A in relation to exploratory biomarkers
- Integrin beta-6 characterization on malignant cells

DLTs, dose-limiting toxicities; RECIST, Response Evaluation Criteria in Solid Tumors.

Assessments

DLT

- DLTs will be monitored during dose escalation over the first 21-day cycle
- Grading will be carried out per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0

Efficacy

- Response will be measured using radiographic tumor evaluation on Days 15–21 of Cycles 2, 4, 6, and every subsequent 3rd cycle until progression
- Assessment of antitumor activity will be conducted according to RECIST v1.1

Safety and tolerability

- The safety monitoring committee will track the safety of SGN-B6A across the study

Pharmacokinetic and immunogenicity assessments

- Blood samples will be collected on Days 1, 2, 8 ,4, 15, and 22 of Cycles 1 and 2, and then on Day 1 of Cycles 3, 4, 6, 8, and every subsequent 4th cycle

Pharmacodynamic and biomarker assessments

Disease-specific expansion cohorts:

- Patients 1–12 per cohort
  - Archival tumor tissue collected within 24 months of enrollment must be provided
  - There will be an optional on-treatment biopsy on Cycle 1, Day 4
- Patients 13–30 per cohort
  - Archival tumor tissue collected within 24 months of enrollment must be provided wherever possible
  - Fresh baseline tumor tissue biopsy must be provided wherever possible
  - There will be an optional on-treatment biopsy on Cycle 1, Day 4, preferably from the same tissue

Biology cohort:

- Archival tumor tissue collected within 24 months of enrollment must be provided wherever possible
- Fresh baseline biopsy must be provided
- On-treatment biopsy on Cycle 1, Day 15 must be provided, preferably from the same tissue

Eligibility Criteria

Table 2: Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Must be at least 18 years of age • Must have histologically or cytologically confirmed metastatic or unresectable solid malignancy with 1 of the following tumor types: non-small cell lung cancer, head and neck squamous cell cancer, breast cancer, esophageal cancer, ovarian cancer, cutaneous squamous cell cancer, exocrine pancreatic adenocarcinoma, bladder cancer, cervical cancer, or gastric cancer • Standard therapies must have failed, been intolerable, or be designated medically inappropriate • Must have an Eastern Cooperative Oncology Group performance status score of 0 or 1	• Presence of carcinomatous meningitis • History of another malignancy within 3 years of the first SGN-B6A dose or evidence of residual disease from a prior diagnosed malignancy, unless malignancies have a negligible risk of metastasis or death[a] • Presence of known active central nervous system metastases[b] • Prior treatments involving MMAE or directed against integrin beta-6

[a]Examples of malignancies that do not exclude participation (e.g., 5-year overall survival ≥90%), include adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.

[b]Patients who were previously treated for brain metastases may enroll if they do so after having been clinically stable for at least 4 weeks following brain metastasis treatment, they do not have new or enlarging brain metastases, and they have not received corticosteroids prescribed for brain metastases-related symptoms for at least 7 days prior to the first SGN-B6A dose.

MMAE, monomethyl auristatin E.

Summary

- SGN-B6A is an investigational ADC directed against integrin beta-6, a cell-surface receptor that is a negative prognostic marker in several solid tumors[3-8]
- The SGNB6A-001 trial is evaluating the safety, tolerability, pharmacokinetics, and antitumor activity of SGN-B6A in adults with select advanced solid tumors
- Enrollment is underway in the USA and Europe at 8 planned sites
- Study start date: June 2020
- Primary completion date: November 2023

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