A FIRST-IN-HUMAN TRIAL OF THE INTEGRIN BETA-6-TARGETED ANTIBODY–DRUG CONJUGATE, SGN-B6A, IN PATIENTS WITH ADVANCED SOLID TUMORS (SGNB6A-001, TRIAL IN PROGRESS)

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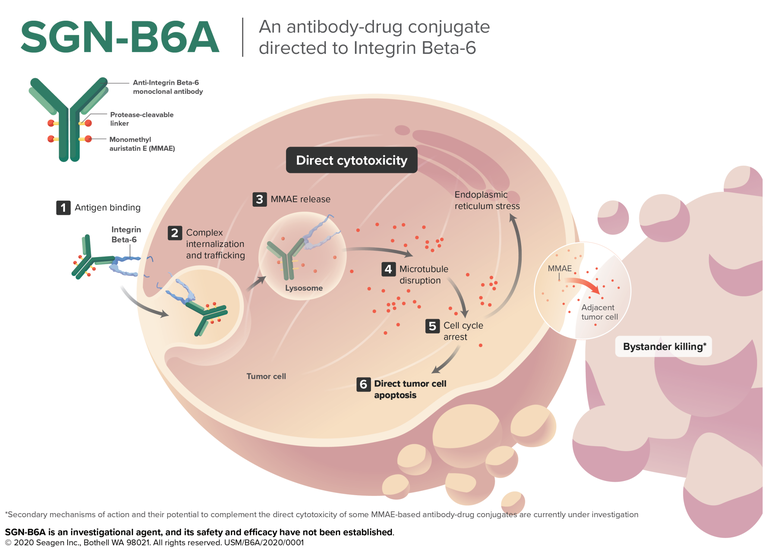
Background and Rationale

- Integrin beta-6 is a cell surface receptor that promotes cellular adhesion through interactions with the extracellular matrix (ECM), which plays a major role in solid tumor pathogenesis and invasiveness.[1–3]
- Integrin beta-6 is highly expressed in several solid tumors including head and neck squamous cell cancer (HNSCC), esophageal squamous cell carcinoma (ESCC), non-small cell lung cancer (NSCLC), and cutaneous squamous cell cancer (cSCC).[4–7]
- Integrin beta-6 expression is a negative prognostic marker making it an attractive target for anticancer therapies.[8–11]
- SGN-B6A is an investigational antibody–drug conjugate (ADC) directed against integrin beta-6.[12] 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).[13]
- In tumor xenograft models, SGN-B6A administration led to delayed tumor growth and decreased tumor volume, providing support for initiation of a phase 1 study.[12,13]

Proposed Mechanism of Action of SGN-B6A

- Once SGN-B6A binds to integrin beta-6, the complex is internalized and trafficked to the lysosome where cleavage of the linker releases MMAE, leading to microtubule disruption which induces cell cycle arrest and apoptosis.[12,13]



*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.

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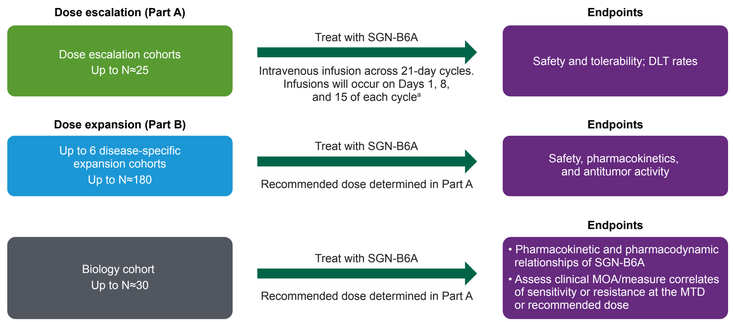
Study Design

- 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.[14]
  - If 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

Primary

- Safety, tolerability, DLTs

Secondary

- Antitumor activity measured using best response per RECIST 1.1, 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 1.1.

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 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 (in selected patients only).
- 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

Key Inclusion Criteria

- ≥18 years of age
- Histologically or cytologically confirmed metastatic or unresectable solid malignancy with 1 of the following tumor types: HNSCC, ESCC, NSCLC, cSCC, breast cancer, ovarian cancer, exocrine pancreatic adenocarcinoma, bladder cancer, cervical cancer, or gastric cancer
- Standard therapies must have failed, been intolerable, or be designated medically inappropriate
- ECOG performance status of 0 or 1

Key Exclusion Criteria

- 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 CNS 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.

CNS=central nervous system; cSCC=cutaneous squamous cell carcinoma; ECOG=Eastern Cooperative Oncology Group; ESCC=esophageal squamous cell carcinoma; HNSCC=head and neck squamous cell carcinoma; MMAE=monomethyl auristatin E; NSCLC=non-small cell lung cancer.

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.
- 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 France, Spain, Switzerland, the UK, and the USA.

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