PHASE 1 STUDY OF SGN-B7H4V, A NOVEL INVESTIGATIONAL VEDOTIN ANTIBODY–DRUG CONJUGATE DIRECTED TO B7-H4, IN PATIENTS WITH ADVANCED SOLID TUMORS (SGNB7H4V-001, TRIAL IN PROGRESS)

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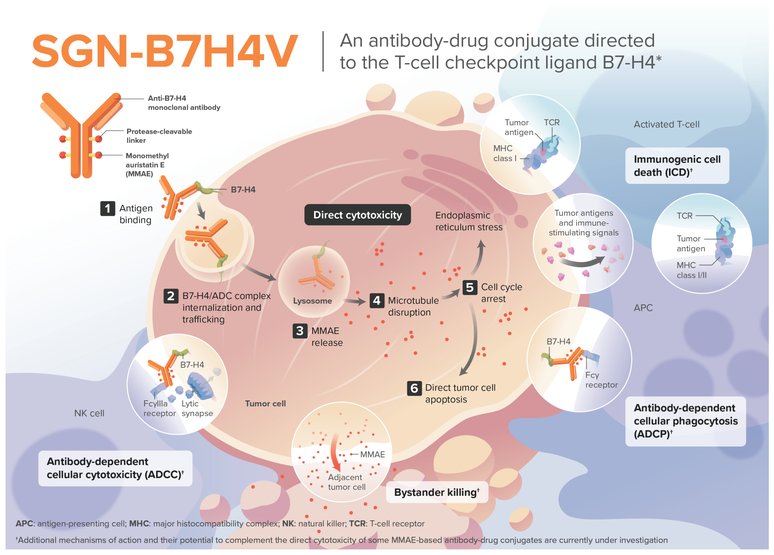
BACKGROUND

- B7-H4, a B7 immune checkpoint ligand, is expressed at low levels in normal tissue and negatively regulates T-cell function by inhibiting T-cell proliferation and cytokine production[1]
- B7-H4 protein expression is elevated across a broad range of solid tumors, including ovarian cancer, breast cancer, endometrial carcinoma, cholangiocarcinoma and gallbladder carcinoma, and sqNSCLC[2–7]
- Targeting B7-H4-expressing tumor cells may relieve B7-H4-mediated T-cell inhibition, making B7-H4 an ideal molecular target for ADCs[1–7]
- SGN-B7H4V is a novel investigational vedotin ADC comprising 3 components: a fully human IgG1 monoclonal antibody that binds to B7-H4 on the cell surface, the microtubule-disrupting agent MMAE, and a protease-cleavable mc-vc linker that covalently attaches MMAE to the anti–B7-H4 antibody and enables preferential release of MMAE within target cells[8,9]
- Preclinical studies show that SGN-B7H4V elicits robust antitumor activity in CDX models of TNBC and PDX models of TNBC and ovarian cancer[8]
- SGN-B7H4V also exhibits antitumor activity in preclinical PDX models with both heterogenous and uniformly high B7-H4 staining, consistent with the bystander activity of vedotin ADCs[8]
- SGNB7H4V-001 (NCT05194072) is a phase 1, first-in-human, multicenter, open-label trial evaluating the safety, tolerability, PK, and antitumor activity of SGN-B7H4V in patients with select advanced solid tumors

SGN-B7H4V PROPOSED MECHANISM OF ACTION



*SGN-B7H4V is an investigational agent, and its safety and efficacy have not been established.

ELIGIBILITY

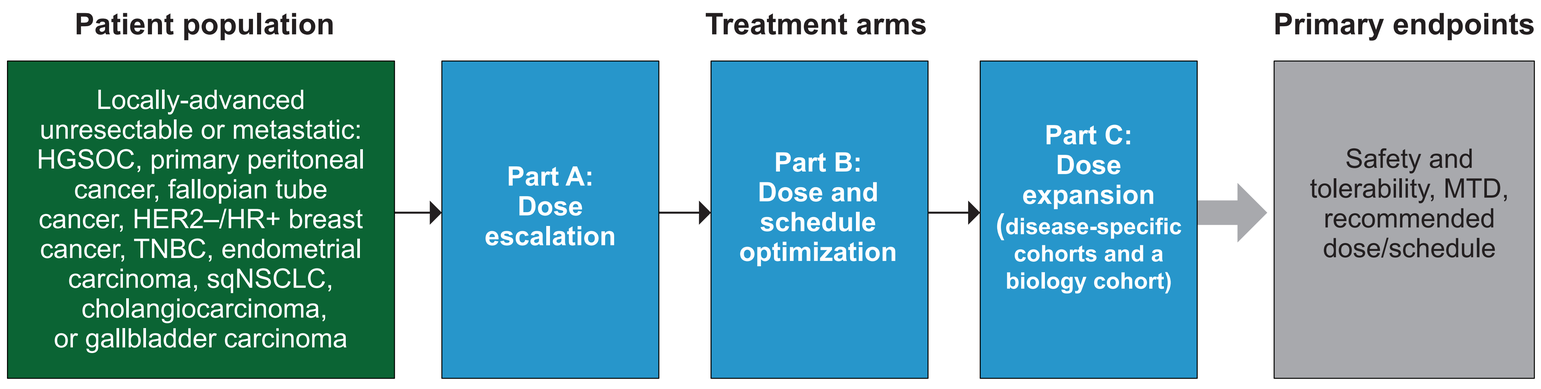
Key Inclusion Criteria

- Adults 18 years of age and older are eligible if they have 1 of the following histologically or cytologically confirmed locally-advanced unresectable or metastatic solid tumor types: HGSOC, primary peritoneal cancer, or fallopian tube cancer, HER2–/HR+ breast cancer, TNBC, endometrial carcinoma, sqNSCLC, cholangiocarcinoma, or gallbladder carcinoma
- Parts A and B: patients must have disease that is relapsed or refractory or be intolerant to SOC therapies, and, in the judgement of the investigator, should have no appropriate SOC therapeutic option
- Part C: patients must have disease that is relapsed or refractory, or be intolerant to SOC therapies, unless contraindicated
- Eligible patients must also have an ECOG performance status of 0 or 1 and measurable disease per RECIST v1.1 at baseline

Key Exclusion Criteria

- History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy
- Known active central nervous system metastases
- Carcinomatous meningitis
- Previous receipt of an MMAE-containing agent or an agent targeting B7-H4
- Pre-existing Grade ≥2 neuropathy per NCI CTCAE v5.0
- Corneal disease or injury requiring treatment or active monitoring
- Chemotherapy, immunotherapy, biologics, and/or other approved or investigational antitumor treatment not completed 4 weeks prior to study treatment initiation, or within 2 weeks prior to study treatment initiation if the underlying disease has progressed on treatment

STUDY DESIGN



- Part A (dose escalation) will evaluate the safety, tolerability, and PK of SGN-B7H4V, and identify the MTD and recommended dose for the schedule(s) evaluated
- Part B (dose and schedule optimization) will further evaluate selected doses and schedules identified in Part A in parallel randomized cohorts, to determine a recommended dosing regimen
- Part C (dose expansion) will evaluate the recommended dosing regimen in disease-specific cohorts and a biology cohort
- Patients may continue treatment until progressive disease per RECIST v1.1, unacceptable toxicity, withdrawal of consent, death, or study termination, whichever occurs first

OBJECTIVES

Primary Objectives	Corresponding Endpoints
To evaluate the safety and tolerability of SGN-B7H4V in patients with advanced solid tumors	• Type, incidence, severity, seriousness, and relatedness of AEs • Type, incidence, and severity of laboratory abnormalities
To identify the MTD of SGN-B7H4V in patients with advanced solid tumors	• Incidence of DLTs
To identify a recommended dose and schedule for SGN-B7H4V	• Incidence of DLTs and cumulative safety by dose level
Secondary Objectives	**Endpoints**
To assess the antitumor activity of SGN-B7H4V	• ORR (CR or PR) per RECIST v1.1 • CRR per RECIST v1.1 • DOR • PFS • OS
To assess the PK of SGN-B7H4V	• PK parameters to be estimated may include, but are not limited to, AUC, C_{max}, T_{max}, $t_{½}$, and C_{trough}. Additional analytes may be evaluated as necessary
To assess the immunogenicity of SGN-B7H4V	• Incidence of ADAs

ASSESSMENTS

- Safety assessments will include the monitoring and recording of AEs, concomitant medications, physical examination findings and laboratory tests
- The determination of antitumor activity will be based on objective response assessments as defined by RECIST v1.1
- Blood samples will be collected for PK and ADA analyses at protocol-defined time points
- Dose escalation and identification of MTD will be guided by the modified Toxicity Probability Interval method using the DE analysis set[10]
- Safety and efficacy (antitumor activity) endpoints will be summarized using descriptive statistics based on the all-treated-subjects analysis set
- The observed ORR per RECIST v1.1 and the 95% CIs will be presented by tumor types and doses where appropriate
- DOR, PFS, and OS will be estimated using the Kaplan-Meier method

SUMMARY

- The SGNB7H4V-001 trial (NCT05194072) will evaluate the safety, tolerability, PK, and antitumor activity of SGN-B7H4V in patients with select advanced solid tumors
- SGN-B7H4V is a novel investigational vedotin ADC directed to B7-H4, a member of the B7 family of immune checkpoint ligands that exhibits elevated expression in a broad range of solid tumors relative to normal tissue[8]
- Enrollment is ongoing in the US and is planned in sites in the EU

Abbreviations

ADA, antidrug antibody; ADCs, antibody-drug conjugates; AE, adverse event; AUC, area under the concentration time curve; CDX, cell line-derived xenograft; CI, confidence interval; C_{max}, maximum concentration; CR, complete response; CRR, complete response rate; CTCAE, Common Terminology Criteria for Adverse Events; C_{trough}, trough concentration; DE, dose-limiting toxicity evaluable; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HGSOC, high-grade serous epithelial ovarian cancer; HR, hormone receptor; IgG, immunoglobulin G; mc-vc, maleimidocaproyl valine-citrulline; MMAE, monomethyl auristatin E; MTD, maximum tolerated dose; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, pharmacodynamic; PDX, patient-derived xenograft; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; sqNSCLC, squamous non-small cell lung cancer; SOC, standard of care; $t_{½}$, apparent terminal half-life; T_{max}, time to maximum concentration; TNBC, triple-negative breast cancer.

Disclosures

- This study is sponsored by Seagen Inc., Bothell, WA, USA
- Amita Patnaik reports consultancy for Bayer, Bristol-Myers Squibb, Genentech/Roche, Merck, Novartis, Seagen, and Silverback Therapeutics; honoraria for Texas Society of Clinical Oncology; and research funding from AbbVie, Arcus Ventures, Astellas, Bolt, Corvus, Daiichi Sankyo, Exelixis, Five Prime, Fochon Pharma, Forty Seven, Infinity Pharma, Ionova, Klus Pharma, Lilly, Livzon, Merck, Pieris Pharma, Plexxikon, Pfizer, Sanofi, Seagen, Surface Oncology, Symphogen, Syndax, Tesaro, Upsher-Smith, and Viego Therapeutics. Ping Xu and Natalya Nazarenko are employees of and report equity ownership in Seagen Inc.

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