PHASE 1 STUDY OF SGN-ALPV, A NOVEL, INVESTIGATIONAL VEDOTIN ANTIBODY–DRUG CONJUGATE DIRECTED TO ALPP/ALPPL2 IN ADVANCED SOLID TUMORS (SGNALPV-001, TRIAL IN PROGRESS)

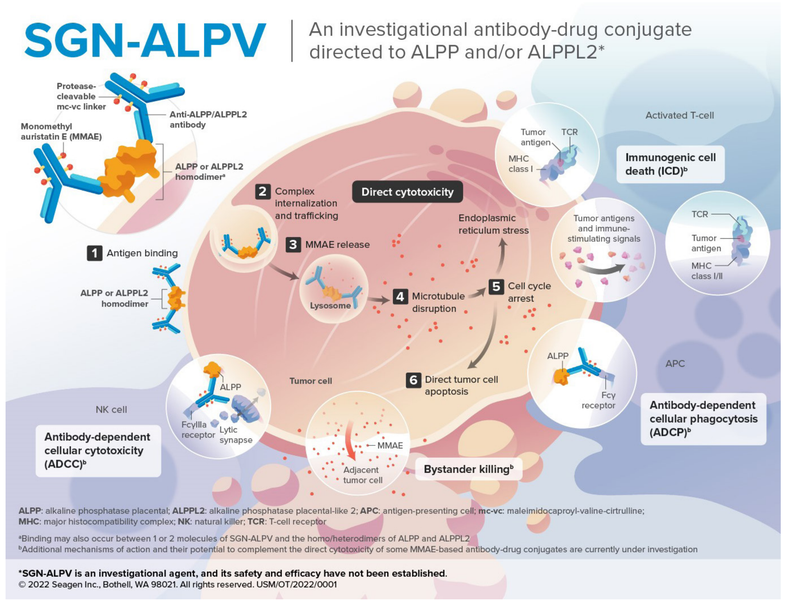
Nehal Lakhani[1], Claire Friedman[2], Cesar A. Perez[3], Allison Wehr[4], Suzanne McGoldrick[4], Patricia LoRusso[5]

[1]START Midwest, Grand Rapids, MI, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Sarah Cannon Research Institute at Florida Cancer Specialists, Orlando, FL, USA; [4]Seagen Inc., Bothell, WA, USA; [5]Yale University Medical Center, New Haven, CT, USA

BACKGROUND

- ALPP and ALPPL2 are cell-surface glycoproteins which play a key role in purinergic signal transduction and nucleotide recycling.[1] They can form homodimers or heterodimerize with one another due to 98% sequence similarity[2,3]
- ALPP and ALPPL2 are overexpressed across a broad range of solid tumors, including ovarian, endometrial, NSCLC, gastric, cervical, and testicular cancers[4–6]
- The restricted expression pattern of ALPP and ALPPL2 in normal tissue relative to cancerous tissues make them ideal molecular targets for ADCs[2,3]
- SGN-ALPV is an investigational vedotin ADC comprising 3 components: a fully human IgG1 monoclonal antibody (h12F3) that binds to ALPP and/or ALPPL2 on the cell surface, the microtubule-disrupting agent MMAE, and a protease-cleavable mc-vc linker that covalently attaches MMAE to the anti-ALPP/ALPPL2 antibody and enables preferential release of MMAE within target cells[3]
- Preclinical studies show SGN-ALPV exhibited robust antitumor activity in cell line- and patient-derived xenograft models of ovarian, lung, pancreatic, and gastric carcinoma, including models with both homogenous and heterogeneous expression of ALPP and ALPPL2 in tumors, consistent with the robust bystander activity of vedotin ADCs[3]
- SGNALPV-001 (NCT05229900) is a phase 1, first-in-human, open-label, multicenter study designed to evaluate the safety, tolerability, PK, and antitumor activity of SGN-ALPV in patients with select advanced solid tumors

SGN-ALPV PROPOSED MECHANISM OF ACTION[3,7–10]



ELIGIBILITY

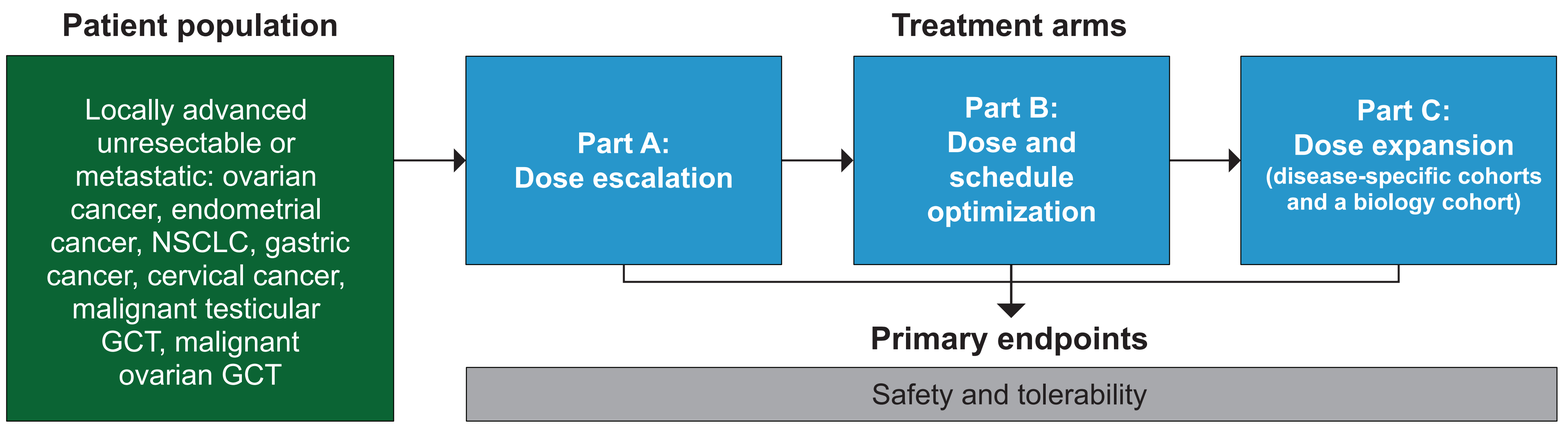
Key Inclusion Criteria

- Patients must have disease that is relapsed or refractory to approved therapies, and in the judgement of the investigator should have no appropriate standard-of-care therapeutic option
- Adults aged ≥18 years must have a histologically or cytologically confirmed unresectable or metastatic solid malignancy of the following type:
  - Ovarian cancer
  - Endometrial cancer
  - NSCLC
  - Gastric cancer
  - Cervical cancer
  - Malignant testicular germ cell tumor except for pure teratomas
  - Malignant ovarian germ cell tumor except for pure teratomas

Key Exclusion Criteria

- History of another malignancy ≤3 years before first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy, except for malignancies with a negligible risk of metastasis or death
- Patients with known active CNS metastases; patients with previously treated, stable brain metastases are eligible
- Patients who previously received MMAE-containing drugs or agents targeting ALPP or ALPPL2
- Pre-existing neuropathy Grade ≥2 per NCI CTCAE v5.0

STUDY DESIGN



- Part A (dose escalation) will estimate the MTD of SGN-ALPV through incremental dosing using the modified Toxicity Probability Interval design[11]
- Part B (dose schedule and optimization) may subsequently open to determine a recommended dose and schedule if more than 1 dose and schedule are identified as candidates from Part A
- Part C (dose expansion) will open in disease-specific cohorts and a biology cohort following determination of the recommended dose and schedule from Parts A and B
- Patients may continue treatment until progressive disease per RECIST v1.1, unacceptable toxicity, withdrawal of consent, initiation of subsequent therapy, or study termination, whichever occurs first

OBJECTIVES

Primary Objectives	Primary Endpoint
To evaluate the safety and tolerability of SGN-ALPV	• Type, incidence, severity, seriousness, and relatedness of AEs • Type, incidence, and severity of laboratory abnormalities
To identify the MTD of SGN-ALPV	• Incidence of DLTs
To identify a recommended dose and schedule for SGN-ALPV	• Incidence of DLTs and cumulative safety by dose level
Secondary Objectives	**Secondary Endpoints**
To assess the immunogenicity of SGN-ALPV	• Incidence of ADAs
To assess the PK of SGN-ALPV	• Estimates of PK parameters including AUC, C_{max}, T_{max}, $t_{½}$, and C_{trough} • Additional parameters may be evaluated as necessary
To assess the antitumor activity of SGN-ALPV	• ORR per RECIST v1.1 • DOR • PFS • OS • CA-125 response rate according to GCIG criteria in patients with ovarian cancer only • Combined RECIST/CA-125 overall response rate in patients with ovarian cancer only

ASSESSMENTS

- Safety assessments will include the monitoring and recording of AEs, concomitant medications, electrocardiograms, 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 for PK and ADA analyses will be collected at protocol-defined time points
- Safety, PK, and immunogenicity endpoints will be summarized using descriptive statistics
- For antitumor activity analyses, the ORR, CA-125 response rate (ovarian cancer only), and combined RECIST/CA-125 response rate (ovarian cancer only) will be presented along with the associated 95% exact CIs
- PFS, OS, and DOR (for patients who achieve a response) will be estimated using the Kaplan-Meier method

SUMMARY

- The SGNALPV-001 trial is investigating the safety, tolerability, PK, and antitumor activity of SGN-ALPV in patients with select advanced solid tumors
- SGN-ALPV is an investigational vedotin ADC directed to ALPP/ALPPL2, which are cell-surface proteins with elevated expression in a broad range of tumor types and restricted normal tissue expression[3]
- Enrollment for SGNALPV-001 is ongoing in the United States and is also planned across Europe

Abbreviations

ADA, antidrug antibody; ADC, antibody-drug conjugate; AE, adverse event; ALPP, alkaline phosphatase placental; ALPPL2, alkaline phosphatase placental-like 2; AUC, area under the concentration-time curve; CA-125, cancer antigen 125; C_{max}, maximum concentration; CNS, central nervous system; C_{trough}, trough concentration; DLT, dose-limiting toxicity; DOR, duration of objective response; GCIG, gynecological cancer intergroup; GCT, germ cell tumor; mc-vc, maleimidocaproyl-valine-citrulline; MMAE, monomethyl auristatin E; MTD, maximum tolerated dose; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; $t_{½}$, half-life; T_{max}, time to C_{max}.

Disclosures

- This study is sponsored by Seagen Inc., Bothell, WA, USA.
- Nehal Lakhani reports consultancy for Innovent, Ikena, and S.K. Life Sciences; also research funding from Alexion, Alexo, Alpine Bio, Alpine Immune Sciences, Apexian, Asana, Ascentage, Astellas, BeiGene, Celgene, Cerulean, Constellation, Coordination Therapeutics, CytomX, Epizyme, Formation, Forty-Seven, Genmab, Gilead, GlaxoSmithKline, Helsinn, Ikena, Incyte, InhibRx, Innovent, Jounce, LAM Therapeutics, Lilly, Livzon, Loxo, Macrogenics, Merck, Mersana, Northern Biologics, Odonate, Pfizer, Regeneron, Sapience, Seagen Inc, Servier, Shattuck Labs, Symphogen, TaiRx, Tesaro, and Tizona. Allison Wehr and Suzanne McGoldrick are employees of and report equity ownership in Seagen Inc.

References

1. Zimmerman H, et al. Purinergic Signal. 2012;8:437-502.
2. Su Y, et al. Cancer Res. 2020;80(20):4552-64.
3. Anderson S, et al. Presented at: AACR; April 8–13, 2022; New Orleans, LA.
4. Liu S, et al. Hum Pathol. 2019;86:49-56.
5. Stigbrand T, et al. Eur J Gynaecol Oncol. 1990;11(5):351-60.
6. Reiswich V, et al. J Pathol Clin Res. 2021;7(6):577-89.
7. Jain N, et al. Pharm Res. 2015;32(11):3526-40.
8. Liu BA, et al. Cancer Res. 2020;80(16 Suppl):5581.
9. Li F, et al. Cancer Res. 2016;76(9):2710-9.
10. Klussman K, et al. J Immunother Cancer. 2020;8:A654.
11. Ji Y, et al. Clin Trials. 2010;7(6):653-63.

Acknowledgements

Medical writing support was provided by Calum Suggett, MSc, and editorial support by Travis Taylor, BA, all of Scion, London, supported by Seagen Inc.

Presented at American Society for Oncology Annual Meeting, June 3–7, 2022, McCormick Place, Chicago, IL, USA.; Abstract Number for Publication: TPS3159