Abstract No. 1766

SGN-ALPV a novel, investigational vedotin ADC demonstrates highly effective targeting of oncofetal phosphatases ALPP and ALPPL2 in preclinical models

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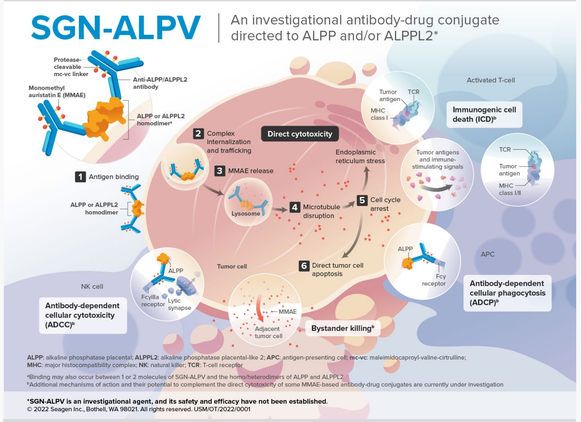
Background

- SGN-ALPV is a novel, investigational vedotin antibody drug conjugate (ADC) directed to the placental phosphatases, ALPP and ALPPL2.
- ALPP and ALPPL2 share high similarity and form homo- and heterodimers with a highly restricted normal tissue profile.
- ALPP/ALPPL2 expression is elevated on a variety of solid tumors including ovarian, endometrial, germ cell, non-small cell lung (adenocarcinoma), bladder, and gastric [1-2].
- h12F3 is a humanized IgG1 anti-ALPP/ALPPL2 antibody selected for target specificity and cytotoxic potency from a pool of ~1000 antibody clones.
- SGN-ALPV is composed of the h12F3 antibody conjugated to 4 molecules of the microtubule disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker that has been clinically validated in multiple vedotin ADC programs [3-5].
- SGN-ALPV is designed to bind and internalize both homo- and heterodimers of ALPP and ALPPL2 from the surface of malignant cells and release the cytotoxic payload MMAE.
- In nonhuman primate toxicity studies, SGN-ALPV is tolerated at doses consistent with other vedotin ADCs [7].

Proposed Mechanisms of Action



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

References

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Characterization of ALPP/ALPPL2 Expression

Expression of ALPP/ALPPL2 on multiple solid tumor types

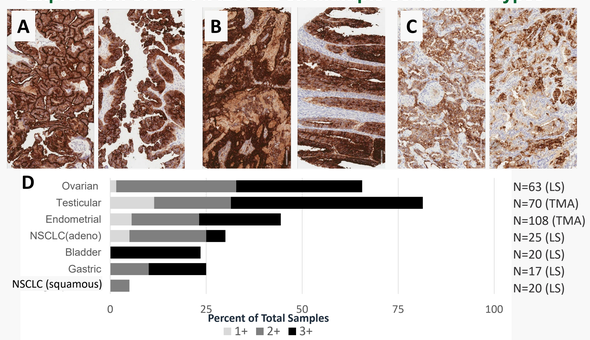


Figure 1. ALPP/ALPPL2 expression is elevated on multiple solid tumor types, including ovarian, endometrial, germ cell, lung and gastric. ALPP/ALPPL2 expression (brown) is detected on ovarian **(A)**, endometrial **(B)**, and non-small cell lung (adenocarcinoma) **(C)** tumor cores by immunohistochemistry (IHC). **(D)** Histopathology summary of ALPP/ALPPL2 IHC scores on large tissue sections (LS) or tumor microarrays (TMA) from different tumor types. N= sample number *Scores based on intensity: 0 = none, 1 = weak, 2 = moderate, 3 = strong. Tumors were considered positive in panel **(E)** if membrane (M) and/or apical membrane staining was observed on > 25% of tumor cells.*

ALPP/ALPPL2 has a highly restricted normal tissue expression

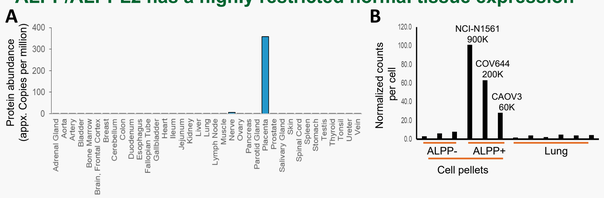
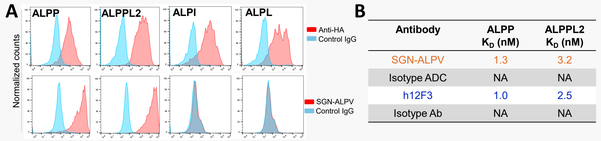


Figure 2. ALPP/ALPPL2 main normal tissue expression is in placenta. (A) Liquid chromatography tandem mass spectrometry (LC-MS/MS) on a panel of human tissues detected limited expression in normal tissue. **(B)** Low protein expression was detected in lung and reproductive tissues by IHC. In follow up analysis using Nanostring DSP, lung expression was significantly lower than cancer cell lines with ALPP expression similar to ovarian cancer.

SGN-ALPV targets ALPP and ALPPL2

SGN-ALPV binds ALPP/ALPPL2 with high specificity and affinity

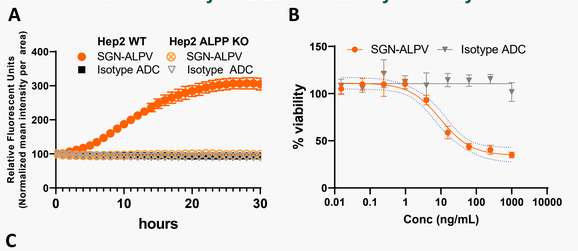


Antibody	ALPP K_D (nM)	ALPPL2 K_D (nM)
SGN-ALPV	1.3	3.2
Isotype ADC	NA	NA
h12F3	1.0	2.5
Isotype Ab	NA	NA

Figure 3. SGN-ALPV specifically binds to ALPP/ALPPL2 (A) Flow cytometry histograms showing SGN-ALPV specificity to HEK293 cells expressing HA-tagged ALPP and ALPPL2, but not ALPI (GI expression) and ALPL (ubiquitously expressed). **(B)** Dissociation constants (K_D) showing that SGN-ALPV retains high affinity of parental antibody (h12F3).

SGN-ALPV Has Multimodal Cytotoxic Activity

SGN-ALPV internalizes ALPP/ALPPL2/ADC complex and kills tumor cells by MMAE-mediated cytotoxicity



C

		Cell Line (ALPP/ALPPL2 copy #)	NCI-H1651 (900K)	RMUGS (480K)	NCI-N87 (130K)	CAOV3 (60K)
Cytotoxicity IC_{50} (ng/mL)	2D	SGN-ALPV	33.3	11.7	9.7	74
		Non-binding ADC	>1000	>1000	>1000	>1000
	3D	SGN-ALPV	ND	1.6	19.4	147
		Non-binding ADC	ND	>1000	>1000	>1000

Figure 4. Internalization of target/ADC complex and resultant cytotoxicity. (A) SGN-ALPV is internalized upon binding to ALPP/ALPPL2. Parental and ALPP knock-out (KO) Hep2 cells were incubated with SGN-ALPV or non-binding ADC and detected with a pH sensor-conjugated anti-human IgG Fab. Fluorescence was monitored using an IncuCyte. **(B)** Unlike ADC control, SGN-ALPV kills ALPP/ALPPL2-expressing NCI-N87 cells **(C)**. Summary of in vitro cytotoxicity by SGN-ALPV on ovarian (RMUGS and CAOV3), lung (NCI-H1651), and gastric cell lines (NCI-N87) in 2D and spheroid (3D) cultures.

SGN-ALPV mediates antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP)

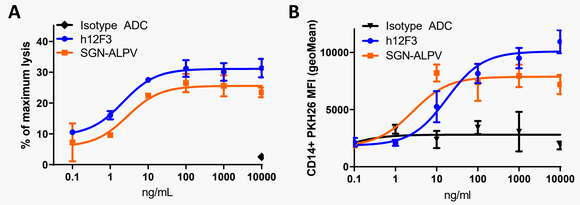


Figure 5. SGN-ALPV kills tumor cells by ADCC and ADCP in vitro. SGN-ALPV and the unconjugated h12F3 Ab backbone exhibit both antibody-mediated effector functions ADCC **(A)** and ADCP **(B)**.

SGN-ALPV Drives Robust Antitumor Activity

SGN-ALPV demonstrates strong antitumor activity

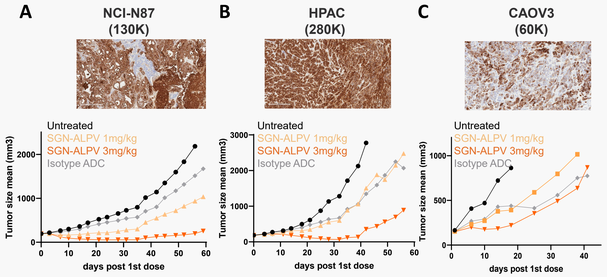


Figure 6. SGN-ALPV elicits robust antitumor activity in cell-derived xenografts SGN-ALPV induces tumor growth delays and regressions at 1-3 mg/kg (QWx3) in gastric –NCI-N87- **(A)**, pancreatic –HPAC- **(B)**, and ovarian –CAOV3- **(C)** models expressing ALPP/ALPPL2 (IHC image).

SGN-ALPV efficacy in patient-derived xenograft (PDX) models

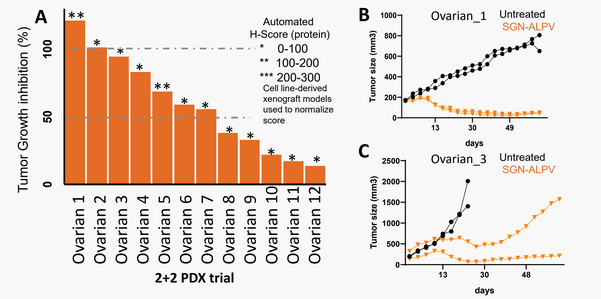


Figure 7. SGN-ALPV demonstrates strong antitumor activity in PDX models of ovarian cancer. (A) SGN-ALPV shows antitumor activity in 58% (7/12) of PDX models with heterogenous target expression. Tumor growth inhibition ranged from 55% to >100% at doses of 5mg/kg (QWx3). ALPP/ALPPL2 expression on PDX models was obtained by IHC on untreated PDX tumors and H-score was determined via HALO (confirmed by pathologist). Antitumor activity was seen in PDX models from both chemotherapy-pretreated **(B)** and naïve **(C)** patients.

Conclusions

- ALPP and ALPPL2 are promising ADC targets expressed by several solid tumor types, including ovarian, endometrial, germ cell, and smaller fractions of gastric and lung cancer. Importantly, these phosphatases exhibit a restricted normal tissue expression which may potentially enable a favorable safety profile.
- *In vivo*, SGN-ALPV leverages a clinically validated payload and demonstrates strong antitumor activity in xenograft models with uniform or heterogenous target expression through multiple mechanisms of action including direct MMAE-mediated cytotoxicity and bystander activity ascribed to vedotin ADCs [6]. Additionally, *in vitro* studies indicate SGN-ALPV also kills tumor cells by ADCC and ADCP.
- Altogether, these data support the evaluation of SGN-ALPV in the currently enrolling first-in-human phase 1 clinical study NCT05229900.

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