SGN-B7H4V, a novel, investigational vedotin antibody-drug conjugate directed to the T cell checkpoint ligand B7-H4, shows promising activity in preclinical models

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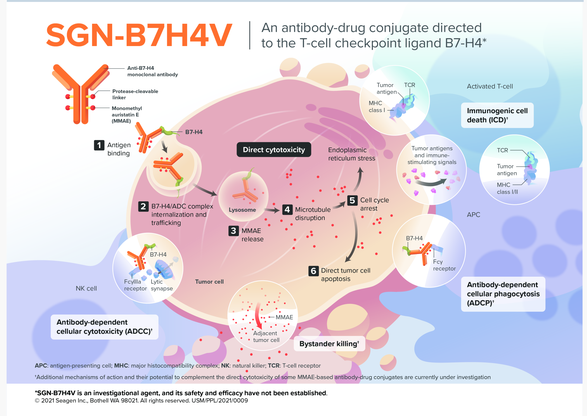
Background

- SGN-B7H4V is a novel, investigational vedotin antibody drug conjugate (ADC) directed to B7-H4, a member of the B7 family of immune checkpoint ligands.
- B7-H4 expression is elevated on a variety of solid tumors including breast, ovarian, and endometrial tumors [1,5].
- SGN-B7H4V is composed of a fully human IgG1 anti-B7-H4 monoclonal antibody (B7H41001 mAb) conjugated to the microtubule disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker that has been clinically validated in multiple vedotin ADC programs [2-4].
- SGN-B7H4V is designed to bind and internalize the immune checkpoint ligand B7-H4/ADC complex from the surface of malignant cells and release the cytotoxic payload MMAE.
- SGN-B7H4V is tolerated in rat and NHP toxicity studies at doses consistent with approved vedotin ADCs [6].
- Here, we characterize the target antigen B7-H4 and evaluate SGN-B7H4V activity in preclinical models.

Proposed Mechanism of Action



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

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Acknowledgements: We would like to thank K. Spahr for conjugation support and M. Anderson for *in vivo* biology support.

Disclosures: All authors are employees of and/or hold stock in Seagen, Inc.

Characterization of B7-H4 Expression

Expression of B7-H4 by multiple solid tumor types

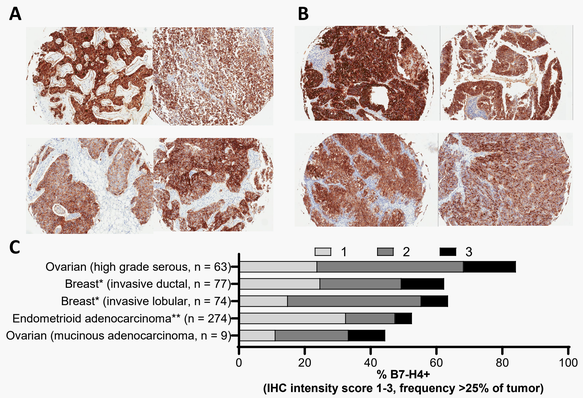


Figure 1. B7-H4 expression is elevated on multiple solid tumor types, including breast, ovarian, and endometrial tumors. B7-H4 expression (brown) is detected on breast **(A)** and ovarian **(B)** carcinoma tumor cores by immunohistochemistry (IHC) using a rabbit mAb (clone D1M8I). **(C)** Summary of B7-H4 IHC scores on ovarian, breast, and endometrial tumor cores.
*Scores based on intensity: 0 = none, 1 = weak, 2 = moderate, 3 = strong. Tumors were considered positive in panel **(C)** if membrane (M) and/or apical membrane staining was observed on > 25% of tumor cells.*
**B7-H4 expression was in all three breast subtypes (Her2+, HR +, and triple-negative breast cancer (TNBC)).*
***All indications except endometrioid, which had apical membrane staining, had uniform membrane staining.*

B7-H4 is low on immune cells

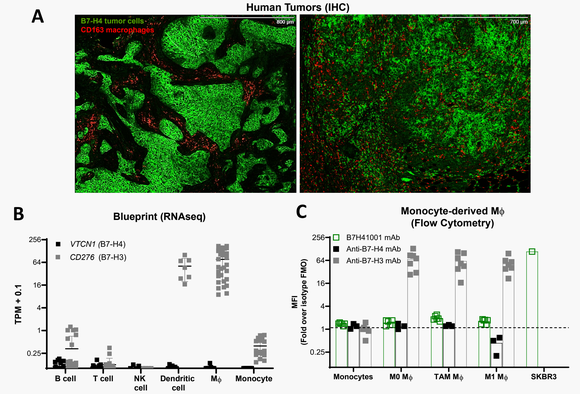
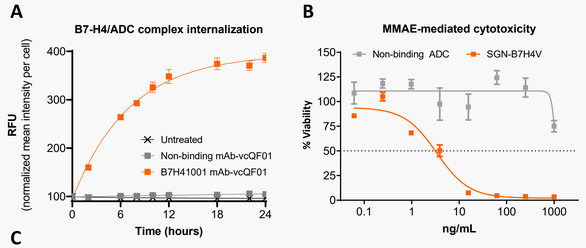


Figure 2. B7-H4 expression is low on immune cells, including tumor-associated macrophages (TAMs). (A) Expression of B7-H4 on CD163+ TAMs was not observed on 14 dual-stained solid tumor sections. Representative stained TNBC tumors are shown. **(B)** B7-H4 (*VTCN1*) RNA is very low on immune cells in BLUEPRINT compared to the B7 family member *CD276* (B7-H3). **(C)** Flow staining for surface B7-H4 protein is low on innate cells (monocytes and macrophages (MΦ)) compared to B7-H3. The breast cancer cell line SKBR3 is included as a positive control.

SGN-B7H4V Has Multimodal Cytotoxic Activity

SGN-B7H4V internalizes the checkpoint ligand B7-H4/ADC complex and kills tumor cells by MMAE-mediated cytotoxicity



C

	Cell Line (B7-H4 copy #)	MX-1 (212K)	SKBR3 (88K)	MDA-MB-468 (28K)	MDA-MB-231 (0)
Cytotoxicity x50 (ng/mL)	SGN-B7H4V	3	4	105	> 1000
	Non-binding ADC	> 1000	> 1000	> 1000	> 1000

Figure 3. Internalization of the B7-H4/ADC complex and resultant cytotoxicity. **(A)** B7-H4 is internalized upon binding to SGN-B7H4V. MX-1 cells were incubated with B7H41001 mAb (the SGN-B7H4V mAb backbone) or non-binding control mAb conjugated to a quenched fluorophore using the same vc-PAB linker used in SGN-B7H4V and unquenched fluorescence was monitored. **(B)** SGN-B7H4V kills spheroids of B7-H4$^+$ MX-1, **(C)** SKBR3, and MDA-MB-468, but not B7-H4$^-$ MDA-MB-231 cells.

SGN-B7H4V also kills tumors cells by antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP)

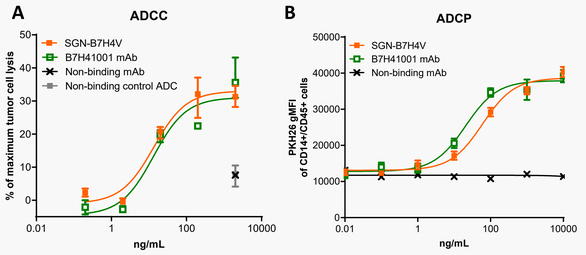


Figure 4. SGN-B7H4V kills tumor cells by ADCC and ADCP in vitro. SGN-B7H4V and the unconjugated B7H41001 mAb backbone exhibit the antibody-mediated effector functions ADCC **(A)** and ADCP **(B)**.

SGN-B7H4V Drives Robust Antitumor Activity

SGN-B7H4V demonstrates strong antitumor activity in xenograft models of TNBC and ovarian carcinoma

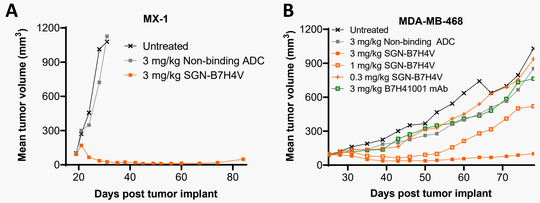
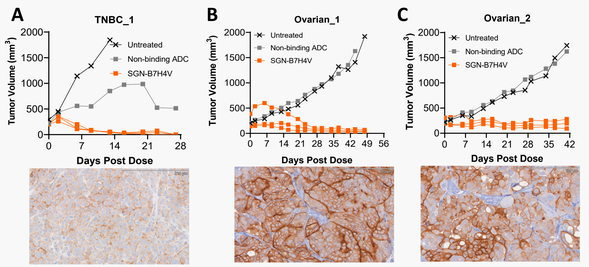


Figure 5. SGN-B7H4V elicits robust antitumor activity in CDX models of TNBC. SGN-B7H4V induces tumor regression at 1-3 mg/kg in the B7-H4$^+$ MX-1 **(A)** and MDA-MB-468 **(B)** models of TNBC; in contrast, the unconjugated B7H41001 mAb backbone has minimal antitumor activity.



D

Model	*VTCN1* mRNA (TPM)	B7-H4 IHC score (% + tumor)	Tumor Status / Histology	Treatment History
TNBC_1	44	51%	Metastatic / triple negative breast adenocarcinoma	Not Available
Ovarian_1	274	95%	Metastatic / serous ovarian carcinoma	No prior treatment
Ovarian_2	288	68%	Metastatic / serous ovarian carcinoma	Cisplatin/Docetaxel; Bevacizumab (maintenance); Carbo/Paclitaxel; Cisplatin/Paclitaxel; Paclitaxel

Figure 6. SGN-B7H4V demonstrates strong antitumor activity in PDX models of TNBC and ovarian cancer. SGN-B7H4V exhibited antitumor activity in **(A)** a PDX model of TNBC with heterogenous B7-H4 staining, **(B)** a PDX model of ovarian cancer with uniformly high B7-H4 staining, and **(C)** a heavily-pretreated PDX model of ovarian cancer with heterogenous B7-H4 staining. PDX model metadata is shown in panel **(D)**.
B7-H4 expression (brown) was detected by IHC on untreated PDX tumors.

Conclusions

- B7-H4 is a promising ADC target expressed by several solid tumor types, including breast, ovarian, and endometrial tumors, and, in contrast to other B7 family members, B7-H4 expression is low on immune cells, including TAMs.
- In vivo, SGN-B7H4V leverages a clinically validated payload and demonstrates strong antitumor activity in xenograft models with uniformly high and heterogenous expression through multiple potential mechanisms including direct MMAE-mediated cytotoxicity and bystander activity ascribed to vedotin ADCs. SGN-B7H4V also kills tumor cells by ADCC and ADCP in vitro.
- Altogether, these data support further evaluation of SGN-B7H4V in a planned, first-in-human phase 1 clinical study.

Poster No. 854
Society for Immunotherapy of Cancer, Virtual; November 10–14, 2021

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