SGN-B7H4V induces immunomodulatory changes to the tumor microenvironment and pairs well with an anti-PD1 agent in a preclinical model

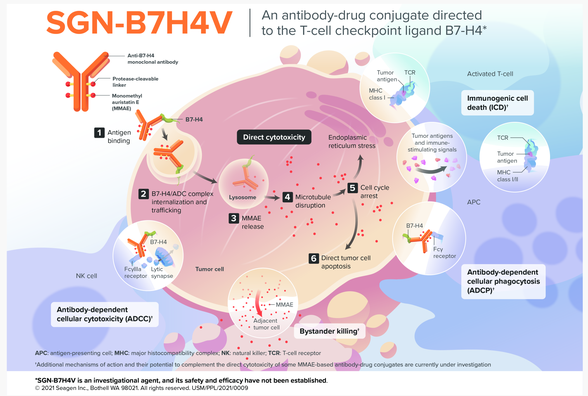
Michelle Ulrich[1], Angela Epp, Kelly Hensley[1], Li-Ya Huang[1], Julie Hahn[1], Sean Allred[1], John J. Gosink[1], Piper M. Treuting[1], John Hernandez Villanueva[1], Sarah Anderson[1], Alyson J. Smith[1], Jason P. Schrum[1], Natalya Nazarenko[1], Shyra J. Gardai[1], and Elizabeth E. Gray[1]

[1]Seagen Inc., Bothell, WA

Background

- SGN-B7H4V is a novel, investigational vedotin antibody-drug conjugate (ADC) directed to B7-H4, an immune checkpoint ligand with elevated expression on multiple solid tumor types, including breast, ovarian, and endometrial tumors [1].
- SGN-B7H4V is composed of an anti-B7-H4 human IgG1 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 B7-H4/ADC complex from the surface of B7-H4+ cells and release the cytotoxic payload MMAE which has shown strong antitumor activity in preclinical models [1].
- Vedotin ADCs elicit MMAE-mediated immunogenic cell death which results in immune changes in the tumor microenvironment [2-4]. This immune modulation positions vedotin ADCs to uniquely combine with checkpoint inhibitors, a benefit observed clinically with meaningful responses observed when vedotin ADCs are administered with anti-PD1 agents [5,6].
- Here, we characterize SGN-B7H4V-mediated immunomodulatory activity along with antitumor activity and induction of immune memory in combination with an anti-PD1 agent.

Proposed Mechanism of Action



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

References

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Statistics- Log transformed unpaired t test for RNAseq data *p≤ 0.05; ** p ≤ 0.001 ***p ≤ 0.0001 ; For IHC analysis unpaired t tests were used

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

SGN-B7H4V Drives Antitumor Activity Accompanied by Immunomodulatory Changes in the TME

SGN-B7H4V antitumor activity in B7-H4 syngeneic model

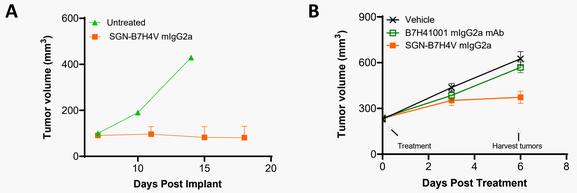
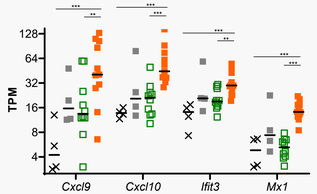


Figure 1. SGN-B7H4V drives antitumor activity in an immunocompetent tumor model. Treatment of mice bearing Renca tumors expressing murine B7-H4 with 3 weekly doses of SGN-B7H4V mIgG2a* elicited tumor regression **(A).** Immunomodulatory activity was assessed in mice treated with a single 3 mg/kg dose of SGN-B7H4V, non-binding control ADC, the B7H41001 mAb, and/or vehicle control. Tumors were harvested 6-7 days post-treatment for RNAseq or IHC **(B)**.
**ADCs and mAbs with a mIgG2a Fc backbone were used in all syngeneic models to avoid anti-drug antibody responses*

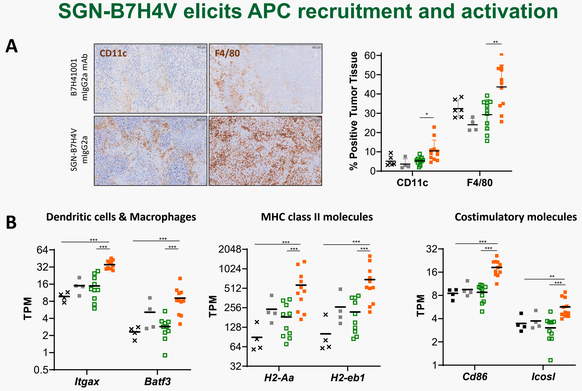
SGN-B7H4V drives cytokine and type I IFN response genes

Figure 2. SGN-B7H4V upregulates cytokines and type I interferon response genes. RNAseq analysis of tumors treated as in **Figure 1** revealed an increase in transcripts encoding cytokines and type I IFN response genes cells following treatment with SGN-B7H4V compared to the unconjugated mAb B7H41001.



× Vehicle ▪ Non-binding mIgG2a ADC ▫ B7H41001 mIgG2a mAb ▪ SGN-B7H4V mIgG2a

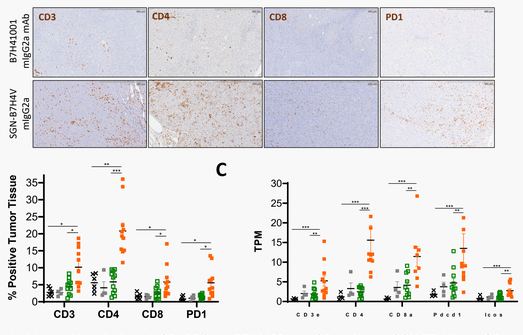
SGN-B7H4V elicits APC recruitment and activation



× Vehicle ▪ Non-binding mIgG2a ADC ▫ B7H41001 mIgG2a mAb ▪ SGN-B7H4V mIgG2a

Figure 3. SGN-B7H4V elicits recruitment of APCs and upregulation of MHC class II and costimulatory molecules. (A) IHC analysis of tumors treated as in **Figure 1** revealed that SGN-B7H4V increased CD11c+ dendritic cells (DCs), and F4/80+ macrophages compared to B7H41001 mAb. **(B)** This was corroborated by RNAseq analysis revealing an increase in *Itgax* (CD11c), *Batf3* (BatF3, which is involved in antigen cross-presentation), *H2-Aa & H2-eb1* (encode MHC class II molecules), and*Cd86*, & *Icosl* (encode costimulatory molecules).

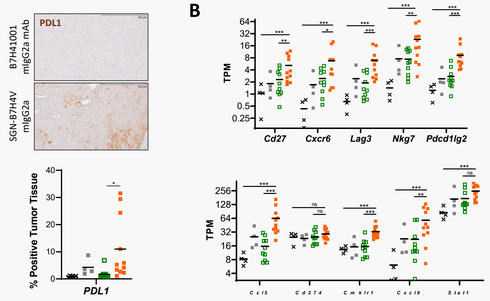
SGN-B7H4V recruits CD4 and CD8+ T cells to the TME



× Vehicle ▪ Non-binding mIgG2a ADC ▫ B7H41001 mIgG2a mAb ▪ SGN-B7H4V mIgG2a

Figure 4. SGN-B7H4V recruits CD4 and CD8+ T cells to murine B7-H4-expressing Renca tumors and upregulates markers associated with early T cell activation. (A,B) By IHC analysis SGN-B7H4 increased CD4+ and CD8+ T cells. Increase in PD-1+ cells, a marker of newly activated T cells, also occurred. **(C)** RNAseq corroborated the analysis with an increase in *Cd3e*, *Cd4*, and *Cd8a* and markers of early T cell activation including *Pdcd1* (PD-1) and *Icos*.

SGN-B7H4V upregulates genes clinically associated with anti-PD(L)1 agent responses



× Vehicle ▪ Non-binding mIgG2a ADC ▫ B7H41001 mIgG2a mAb ▪ SGN-B7H4V mIgG2a

Figure 5. SGN-B7H4V upregulates genes associated with response to anti-PD(L)1 agents. (A) IHC analysis of tumors treated as in **Figure 1** revealed an increase PD-L1+ cells following treatment with SGN-B7H4V. **(B)** RNAseq analysis revealed an increase in multiple "T cell-inflamed" genes that have been associated clinically with response to PD-1 blockade [7].

SGN-B7H4V Shows Combination Anti-Tumor Activity With an Anti-PD1 mAb

SGN-B7H4V plus anti-PD-1 mAb enhances antitumor activity

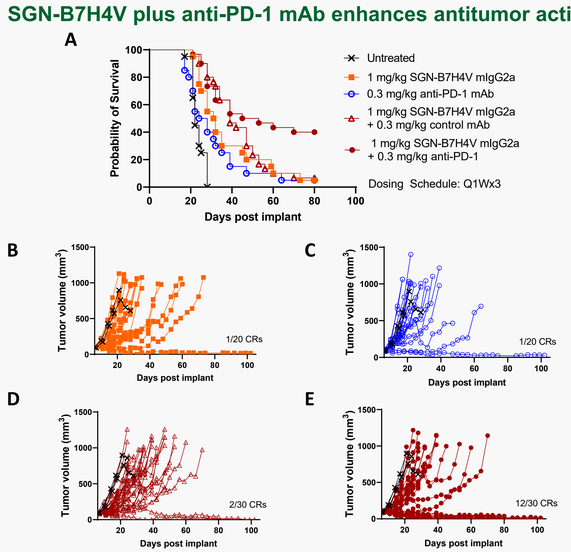


Figure 6. SGN-B7H4V in combination with an anti-PD-1 mAb elicits enhanced antitumor activity. Sub-therapeutic treatment of mB7-H4-Renca tumor-bearing mice with SGN-B7H4V in combination with anti-PD-1 mAb led to improved survival* **(A)** and enhanced antitumor activity** **(E)** compared to SGN-B7H4V alone **(B)**, anti-PD-1 mAb alone **(C)**, or SGN-B7H4V in combination with a control mAb **(D)**.
*Survival = tumor outgrowth to ~1000 mm³; **Complete response (CR) = tumor volume <50 mm³ for the final 7 days.

SGN-B7H4V plus anti-PD-1 elicits robust immune memory

Mice with complete responses (CR) being rechallenged	Tumor cells used for rechallenge	% Protection from tumor rechallenge
3 mg/kg SGN-B7H4V mIgG2a	Parental Renca	30% (3/10 mice)
1 mg/kg SGN-B7H4V mIgG2a + 0.3 mg/kg anti-PD-1 mAb	Parental Renca	58% (7/12 mice)

Figure 7. SGN-B7H4V in combination with an anti-PD-1 mAb elicits robust immune memory. Seven of the twelve (58%) mice from **Figure 6** that achieved a CR after treatment with SGN-B7H4V in combination with an anti-PD-1 mAb were protected from rechallenge with parental Renca tumor cells compared to 30% of mice that achieved a CR after treatment with 3 mg/kg SGN-B7H4V alone (**Figure 1**).

Conclusions

- SGN-B7H4V elicits immunomodulatory changes in the TME consistent with innate and adaptive anti-tumor immune responses, including: (1) Antigen-presenting cell recruitment and upregulation of costimulatory molecules; (2) Recruitment of CD4+ and CD8+ T cells and upregulation of genes associated with early T cell activation; and (3) Upregulation of genes that have been associated clinically with response to anti-PD1 agents.
- SGN-B7H4V plus an anti-PD1 agent led to improved antitumor activity and more robust immune memory compared to SGN-B7H4V alone.
- Anti-tumor activity has led to the initiation of a phase 1 trial. Additional nonclinical data further support the evaluation of SGN-B7H4V as a monotherapy in ongoing Phase 1 Study of SGN-B7H4V in Advanced Solid Tumors (NCT05194072) and potential future clinical combinations with immunotherapies.

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