SGN-B7H4 INDUCES IMMUNOMODULATORY CHANGES TO THE TUMOR MICROENVIRONMENT AND PAIRS WELL WITH ANTI-PD1 AGENT IN A PRECLINICAL MODEL

Michelle Ulrich, Angela Epp, Kelly Hensley, Julie Hahn, Sean Allred, John Gosink, Piper Treuting, John Hernandez Villanueva, Sarah Anderson, Alyson Smith, Jason Schrum, Natalya Nazarenko, Shyra Gardai, Elizabeth Gray, Seagen, Bothell, WA, USA

Background SGN-B7H4V is an 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 monoclonal antibody conjugated to the microtubule disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker. This vedotin drug linker system has been clinically validated in multiple ADC programs, including brenruiximab vedotin, enfortumab vedotin, and tisotumab vedotin. SGN-B7H4V is designed to bind the immune checkpoint ligand B7-H4, internalize the ligand/ADC complex from the surface of B7-H4-expressing tumor cells and release the cytotoxic payload, MMAE, within the cell. SGN-B7H4V demonstrates strong antitumor activity in preclinical models through multiple potential mechanisms including direct MMAE-mediated cytotoxicity as well as antibody-mediated functions including antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP) in vitro.1 Vedotin ADCs can elicit MMAE-mediated immunomodulatory changes to the tumor microenvironment (TME) via induction of immunogenic cell death 2–4 which may position vedotin ADCs to uniquely synergize with checkpoint inhibitors.5 Here, we use an immunocompetent mouse model to characterize SGN-B7H4V-mediated immunomodulatory activity along with antitumor activity and induction of immune memory in combination with an anti-PD1 agent.

Methods Immunomodulatory changes in SGN-B7H4V-treated tumors were characterized by RNAseq and immunohistochemistry. The antitumor activity of SGN-B7H4V as a monotherapy and in combination with an anti-PD1 agent was evaluated using a murine B7-H4-expressing Renca syngeneic tumor model. Finally, tumor rechallenge experiments were performed to evaluate immune memory.

Results Treatment of B7-H4-expressing syngeneic tumors with SGN-B7H4V led to immunomodulatory changes in the TME, including recruitment of multiple immune cell types and up-regulation of immune-related genes that have been previously associated with response to anti-PD(L)1 agents. Moreover, SGN-B7H4V drove robust antitumor activity as well as durable immune memory as a monotherapy and in combination with an anti-PD1 agent.

Conclusions In preclinical models, SGN-B7H4V demonstrates robust antitumor activity accompanied by immunomodulatory changes in the TME. Moreover, SGN-B7H4V in combination with an anti-PD1 agent led to improved antitumor activity and elicited durable immune memory. Altogether, these nonclinical data further support the evaluation of SGN-B7H4V as a monotherapy in the ongoing Phase 1 Study of SGN-B7H4V in Advanced Solid Tumors (NCT05194072) and potential future clinical combinations with immunotherapies.

REFERENCES

Ethics Approval All animal studies were conducted in accordance with protocols reviewed and approved by the Institutional Animal Care and Use Committee at Seagen or the external testing facility that conducted the studies.