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 brentuximab 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 demonstrated 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.2,3 Vedotin ADCs can elicit MMAE-mediated immunomodulatory changes to the tumor microenvironment (TME) via induction of immunogenic cell death4–7 which may position vedotin ADCs to uniquely synergize with checkpoint inhibitors. This is supported by clinically meaningful responses observed when vedotin ADCs are paired with anti-PD1 agents.8,9 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 tumor cell types and upregulation 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 in 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.