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 SGN-B7H4V is composed of a fully human IgG1 anti-B7-H4 monoclonal antibody (mAb) conjugated to the microtubule disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker. 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. This "vedotin" drug linker system has been clinically validated by multiple ADC programs, including brentuximab vedotin, enfortumab vedotin, and polatuzumab vedotin.²⁻⁴ Here, we characterize the target antigen B7-H4 and evaluate SGN-B7H4V activity in preclinical models.

Methods B7-H4 expression was characterized by RNA expression and immunohistochemistry across multiple solid tumor types. The ability of SGN-B7H4V to kill B7-H4-expressing tumor cells in vitro and in vivo in a variety of xenograft tumor models was also evaluated. Finally, the tolerability of SGN-B7H4V was assessed in rodent and non-human primate toxicology studies.

Results Immunohistochemistry confirmed expression of B7-H4 across multiple solid tumor types, including ovarian and breast tumors. In vitro, upon binding to SGN-B7H4V, the immune checkpoint ligand B7-H4 was rapidly internalized and delivered the cytotoxic payload MMAE. Moreover, SGN-B7H4V killed B7-H4-expressing tumor cells in vitro by MMAE-mediated cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). In vivo, SGN-B7H4V demonstrated strong anti-tumor activity in multiple xenograft models, including ovarian and breast cancer models. Activity was observed in models with both uniformly high and heterogeneous expression of B7-H4, consistent with robust bystander activity of vedotin ADCs. Finally, SGN-B7H4V was tolerated in both rat and non-human primate (NHP) toxicology studies at doses consistent with approved vedotin ADCs.

Conclusions B7-H4 is a promising ADC target expressed by several solid tumor types. SGN-B7H4V demonstrates robust anti-tumor activity in preclinical models through multiple potential mechanisms and is tolerated in rat and NHP toxicity studies. Altogether, these data support further evaluation of SGN-B7H4V in a planned, first-in-human phase 1 clinical study.

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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.

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