SGN-PDL1V, A NOVEL, INVESTIGATIONAL PD-L1-DIRECTED ANTIBODY-DRUG CONJUGATE FOR THE TREATMENT OF SOLID TUMORS

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Background PD-1/PD-L1 immune checkpoint inhibitors have transformed oncology, but a significant unmet need persists for patients with relapsed/refractory tumors following PD-1/PD-L1 treatment. PD-L1 is expressed in patients across a broad spectrum of tumor types and displays limited normal tissue expression, highlighting the potential of PD-L1 as a target for antibody-drug conjugates (ADCs) in addition to its role as an immune checkpoint. SGN-PDL1V is a PD-L1-directed ADC currently under preclinical investigation, which is comprised of an anti-PD-L1 antibody conjugated to the vedotin drug-linker. The vedotin drug-linker, consists of the microtubule disrupting agent, monomethyl auristatin E (MMAE), and a protease-cleavable peptide linker, which has been clinically validated in multiple ADC programs including brentuximab vedotin, enfortumab vedotin and polatuzumab vedotin.¹⁻³ The proposed SGN-PDL1V primary mechanism of action is direct cytotoxicity against PD-L1-expressing malignant cells through delivery of the MMAE payload. Additionally, MMAE induces immunogenic cell death, leading to subsequent immune activation in the tumor microenvironment.⁴ Here, we characterize the preclinical activity and tolerability of SGN-PDL1V.

Methods SGN-PDL1V cytotoxicity was evaluated using PD-L1 expressing tumor cell lines in vitro and xenograft tumor models in vivo. Inhibition of the PD-1/PD-L1 immune checkpoint was assessed in a luminescent reporter system in vitro and a syngeneic tumor model in vivo. The tolerability and safety profile of SGN-PDL1V was determined in a non-human primate study.

Results In vitro, SGN-PDL1V demonstrated internalization and potent cytotoxic activity against PD-L1 expressing tumor cells. In vivo, SGN-PDL1V achieved tumor regressions in multiple tumor xenograft models at doses as low as 1 mg/kg when dosed weekly for a total of three doses. This activity was observed in immunocompromised mice, which lack responses to PD-1/PD-L1 inhibition. Notably, activity was observed even in xenograft models with low, heterogeneous PD-L1 expression, supporting the possibility to treat patients across a wide range of PD-L1 expression levels. Additionally, SGN-PDL1V exhibited potential to inhibit the PD-1/PD-L1 checkpoint in vitro and in vivo. The tolerability and safety profile of SGN-PDL1V were assessed in a non-human primate study and found to be comparable to other FDA-approved vedotin ADCs.

Conclusions SGN-PDL1V is a promising PD-L1 directed ADC with a unique cytotoxic mechanism of action among other PD-L1-targeted therapeutics. SGN-PDL1V demonstrated robust activity in multiple preclinical models and comparable tolerability and safety profile to other vedotin ADCs in non-human primates. Collectively, these data support further evaluation of SGN-PDL1V in a planned, first-in-human Phase 1 study.

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Trial Registration N/A

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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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