SGN-PDL1V, a novel, investigational PD-L1-directed antibody-drug conjugate for the treatment of solid tumors

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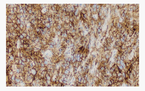
Background

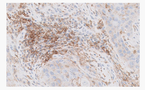
- PD-1/PD-L1 immune checkpoint inhibitors have transformed cancer therapy, but a significant unmet need persists for patients with relapsed/refractory tumors after PD-1/PD-L1 treatment.
- PD-L1 is an attractive target for antibody-drug conjugates (ADCs) in addition to its role as an immune checkpoint.
  - Tumor expression of PD-L1 is observed in patients across a broad spectrum of tumor types [1, 2].
  - Normal expression of PD-L1 is limited primarily to immune cells, particularly antigen-presenting cells [1, 2].

Examples of PD-L1 Staining in Tumor Tissue

NSCLC (20x magnification)



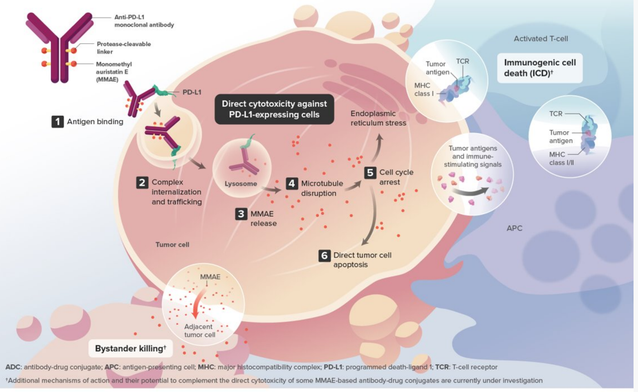
HNSCC (20x magnification)



Source: Agilent PD-L1 IHC 22C3 pharmDx Interpretation Manuals for NSCLC and HNSCC

- SGN-PDL1V is a novel, investigational PD-L1-directed ADC comprised of a fully human anti-PD-L1 monoclonal antibody (Seagen PD-L1 mAb) conjugated to the clinically validated [3-5] vedotin drug-linker.
  - The Seagen PD-L1 mAb utilizes a human IgG1 Fc backbone engineered to eliminate Fc effector functions, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).
  - The vedotin drug-linker is composed of the microtubule disrupting agent monomethyl auristatin E (MMAE) and a protease-cleavable linker.
- SGN-PDL1V proposed MOAs are distinct from other PD-L1-directed therapeutics and may benefit patients across many indications, including those with relapsed/refractory tumors after PD-1/PD-L1 treatment.
- SGN-PDL1V is tolerated in NHP toxicity studies at doses consistent with other approved vedotin ADCs [6].

SGN-PDL1V | Proposed mechanism of action of an ADC directed to the T-cell checkpoint ligand PD-L1*



ADC: antibody-drug conjugate; APC: antigen-presenting cell; MHC: major histocompatibility complex; PD-L1: programmed death-ligand 1; TCR: T-cell receptor

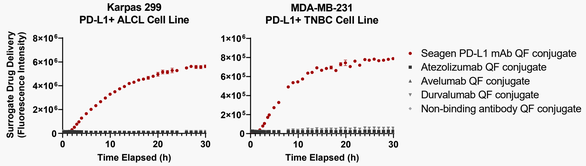
†Additional mechanisms of action and their potential to complement the direct cytotoxicity of some MMAE-based antibody-drug conjugates are currently under investigation

*SGN-PDL1V is an investigational agent, and its safety and efficacy have not been established.

SGN-PDL1V Demonstrates Internalization and Potent Cytotoxic Activity

SGN-PDL1V is engineered for rapid internalization into cells

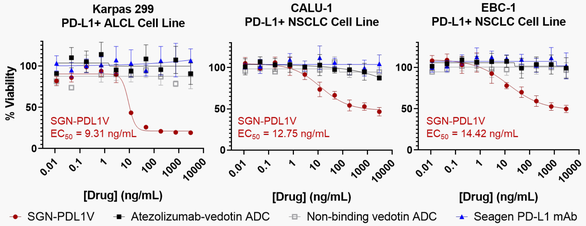
- Seagen PD-L1 mAb achieves faster internalization and proteolytic cleavage compared to other approved PD-L1 mAbs.



Quenched fluorophore (QF) conjugates incorporate a specialized fluorophore containing the same linker found in SGN-PDL1V, and only emit fluorescence upon cleavage of the linker. QF conjugates allow for quantitation of internalization and proteolytic cleavage, serving as a surrogate for drug delivery. PD-L1-expressing cell lines were incubated with indicated QF conjugates at 37°C and fluorescent signal was quantified using the Incucyte Live-Cell Analysis System.

SGN-PDL1V is cytotoxic in cancer cell lines *in vitro*

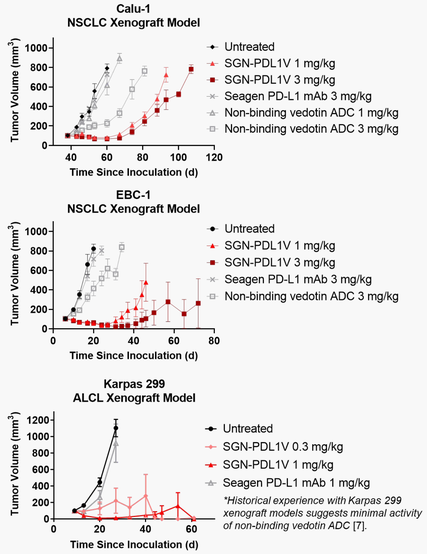
- Consistent with internalization data, SGN-PDL1V delivers drug and elicits cytotoxicity in PD-L1-expressing cancer cell lines.
- SGN-PDL1V is inactive on PD-L1-negative cell lines (data not shown).



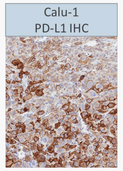
Calu-1 and EBC-1 cell lines were treated with IFNγ 24 hours prior to stimulate PD-L1 expression. All cell lines were treated as indicated for 96 hours, and cell viability was assessed by total ATP relative to untreated control.

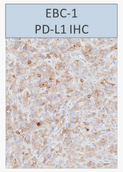
Robust antitumor activity of SGN-PDL1V in xenograft tumor models illustrates potent MMAE-driven cytotoxicity

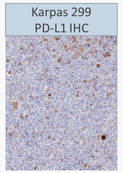
- Activity in xenograft tumor models, including those with low, heterogeneous PD-L1 expression, demonstrates direct cytotoxicity against PD-L1-expressing cells and bystander killing.



*Historical experience with Karpas 299 xenograft models suggests minimal activity of non-binding vedotin ADC [7].





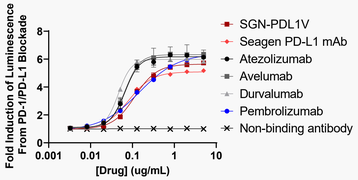


Cells were implanted subcutaneously into female nude (EBC-1) or SCID (Calu-1, Karpas 299) mice, which lack immune effectors. All test articles were administered i.p. weekly for a total of 3 doses when tumor volumes reached 100 mm^3. Five mice were included in each treatment group.

SGN-PDL1V Has PD-1/PD-L1 Immune Checkpoint Blockade Potential

SGN-PDL1V blocks the PD-1/PD-L1 checkpoint *in vitro*

- SGN-PDL1V is comparable to unconjugated Seagen PD-L1 mAb, indicating that conjugation does not affect blocking activity.

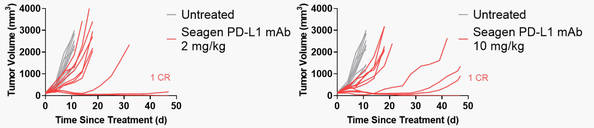


Test Article	EC_{50} (μg/mL)
SGN-PDL1V	0.114
Seagen PD-L1 mAb	0.080
Atezolizumab	0.066
Avelumab	0.066
Durvalumab	0.046
Pembrolizumab	0.147
Non-binding Ab	Not determined

An engineered CHO-K1 cell line expressing PD-L1 was incubated with an engineered Jurkat T cell reporter cell line expressing PD-1 in the presence of test article. In this assay, the absence of treatment results in inhibition of TCR mediated luminescence. However, upon disruption of the PD-1/PD-L1 interaction, TCR activation induces luminescence (shown as fold induction over background in above graph).

Antitumor activity of Seagen PD-L1 mAb *in vivo* suggests PD-1/PD-L1 checkpoint blocking activity

- Immunocompetent MC38 model expressing human PD-L1 allows assessment of PD-1/PD-L1 checkpoint blocking activity.
- Models currently being developed to assess cytotoxicity and checkpoint blockade MOAs simultaneously.

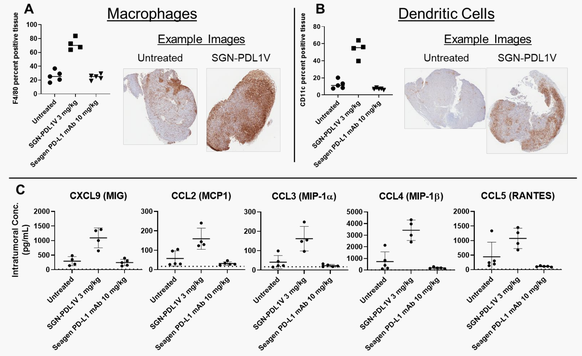


MC38 cells expressing human PD-L1 were implanted subcutaneously into female C57BL/6 mice expressing chimeric PD-1 and PD-L1 with human extracellular domains. Test articles were administered i.p. every 3 days for a total of 3 doses when tumor volumes reached 100-150 mm^3. Ten mice were included in each treatment group. CR, complete response.

SGN-PDL1V Induces MMAE-Mediated Immune Activation in a Xenograft Model

- SGN-PDL1V achieves increased infiltration of macrophages and dendritic cells (DCs) into the tumor microenvironment (TME).
- Increases in pro-inflammatory chemokines were also observed, consistent with the increase in immune infiltration.
- Immune activation observed is consistent with other vedotin ADCs and likely mediated through the MMAE payload, a known inducer of immunogenic cell death (ICD) [8].
- Activated human macrophages and DCs, which can express PD-L1 in the TME, are not negatively affected by SGN-PDL1V in a target-dependent fashion by *in vitro* cytotoxicity and functional assays (data not shown).

Karpas 299 ALCL Xenograft Model



Karpas 299 cells were implanted subcutaneously into SCID mice. Test articles were administered i.p. once when tumor volumes reached 200 mm^3 (day 0). Tumors were harvested on day 6 for IHC and cytokine analysis. (**A**, **B**) Percent (**A**) F4/80 and (**B**) CD11c positive cells in tumor sections by IHC along with representative images. (**C**) Intratumoral chemokine levels. Dotted lines represent the limit of detection.

Conclusions

- SGN-PDL1V is a PD-L1-directed ADC with multiple distinct proposed MOAs including:
  - SGN-PDL1V demonstrates direct cytotoxicity against PD-L1 expressing cells as well as bystander killing, achieving robust antitumor activity even in models with low, heterogeneous PD-L1 expression.
  - Cytotoxicity mediated by SGN-PDL1V also leads to additional immune activation due to MMAE-mediated immunogenic cell death.
- Additionally, SGN-PDL1V may inhibit the PD-1/PD-L1 immune checkpoint.
- These data support further evaluation of SGN-PDL1V in a planned first-in-human Phase 1 study.

References:

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