SGN-B6A INDUCES IMMUNOGENIC CELL DEATH AS A SECONDARY MECHANISM OF ACTION

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Background SGN-B6A is a novel investigational antibody-drug conjugate (ADC) directed to integrin beta-6 and uses the clinically validated vedotin drug-linker platform that delivers the microtubule disrupting agent, monomethyl auristatin E (MMAE).1 SGN-B6A is designed to bind and internalize the integrin beta-6/ADC complex from the surface of malignant cells and release the cytotoxic payload MMAE. We have previously demonstrated the antitumor activity of SGN-B6A in cell line-derived xenograft models originating from multiple carcinomas as well as patient-derived xenograft models of non-small cell lung cancer (NSCLC).2 Other ADCs delivering the MMAE payload (including vedotin ADCs using the antibodies brentuximab, enfortumab, ladiratuzumab, and tisotumab) have been shown to induce immunogenic cell death (ICD) in preclinical models3-7 and have demonstrated promising clinical activity in combination with immunotherapies.8-10 Since the induction of ICD appeared to be a consequence of the activity of MMAE, and is independent of the antibody that delivers it, we hypothesized that this mechanism of action may also apply to SGN-B6A.

Methods In vitro and in vivo assessment of ICD was performed in cell lines derived from pancreatic carcinoma. Induction of ICD markers were assessed using plate-based assays, flow cytometry, and immunoblotting. ICD was also assessed in vivo using RNA sequencing and immunohistochemistry (IHC) on cell line-derived xenografts.

Results Consistent with this hypothesis we observed that tumor cells treated with SGN-B6A in vitro showed key hallmarks of immunogenic cell death, including markers of endoplasmic reticulum (ER) stress, exposure of calreticulin, and release of ATP and high mobility group protein B1 (HMGB1). Further, in vivo studies demonstrated that treatment with SGN-B6A led to immune activation and recruitment of immune cells to the tumor environment.

Conclusions Preclinical models suggest that, like other vedotin ADCs, SGN-B6A induces immunogenic cell death which then promotes activation and recruitment of immune cells to the tumor. These data provide a strong rationale for the combination of SGN-B6A with immunotherapies, which may further lead to enhanced antitumor activity and can be utilized as a potential treatment for integrin-beta-6-expressing tumors including NSCLC, head and neck squamous cell carcinoma, and esophageal carcinoma. Altogether, our preclinical results support the current evaluation of SGN-B6A in an ongoing phase 1 study (NCT04389632).

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.