Background STING is an innate immune pathway that detects intracellular DNA from foreign pathogens as well as stressed or tumor cells and activates a proinflammatory, type I interferon (IFN) response.\(^1\) STING activation is critical for mounting anti-viral immunity, and recent advances suggest this pathway can be co-opted to drive an anti-tumor immune response.\(^2\) However, STING activation requires careful and controlled agonism as dysregulated STING signaling is associated with autoinflammatory diseases including systemic lupus erythematosus (SLE), Aicardi-Goutières syndrome (AGS) and STING-associated vasculopathy with onset of infancy (SAVI).\(^3\) Balancing anti-tumor immunity against the risk of systemic immune activation has likely hindered the clinical success of systemic STING agonist small molecules.\(^4\) To date, STING agonist therapies have shown limited anti-tumor activity potentially due to their short half-life and poor retention within the tumor microenvironment (TME).\(^5\) We hypothesized that targeted delivery of a potent STING agonist to the tumor microenvironment via an antibody drug conjugate (ADC) may overcome these limitations.

Methods STING agonist ADCs were generated by conjugating novel, potent cleavable and non-cleavable drug-linkers to a tumor-targeting antibody. The potency of these STING agonist ADCs and released free drugs were evaluated on human myeloid cells in vitro. Finally, the antitumor activity of STING ADCs were evaluated in vitro in a tumor and immune cell co-culture system as well as in vivo in syngeneic murine tumor models.

Results STING agonist ADCs with both non-cleavable and cleavable drug-linkers demonstrated comparable potency in vitro – with a similar capacity to induce type I IFN signaling and elicit immune-mediated tumor cell killing. However, in vivo, STING agonist ADCs with the non-cleavable drug-linker led to superior antitumor activity compared to ADCs with cleavable drug-linkers. STING agonist ADCs with this novel, potent non-cleavable drug-linker demonstrated robust, durable antitumor activity across multiple tumor models as well as reduced systemic immune activation compared to a small molecule agonist.

Conclusions Here, we report the generation of a STING agonist ADC that elicits robust antitumor activity across multiple preclinical murine tumor models. Drug-linker design was critical for maximizing antitumor activity, as ADCs with the non-cleavable drug-linker drove enhanced antitumor activity compared to cleavable drug-linkers. This targeted ADC delivery led to antitumor activity with reduced systemic immune activation compared to a small molecule STING agonist. Altogether, these data demonstrate the potential of STING agonists as ADC payloads to drive tolerated, efficacious anti-cancer responses.

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.