Background: Effective cancer treatment requires durable elimination of malignant cells. Cytotoxic chemotherapeutic agents used to treat cancer often show initial anti-tumor efficacy, but fail to produce long-term durable responses in patients. The elicitation of durable responses and improved survival in response to cytotoxic agents may be associated with the induction of innate and adaptive immune responses to the cancer. For example, tumor cells undergoing apoptosis following exposure to some cytotoxic agents emit immunostimulatory damage-associated molecular patterns (DAMPs), this form of cell death is termed immunogenic cell death (ICD). ICD can promote the recruitment and activation of both the innate and adaptive immune system, providing an additional mechanism to drive an anti-tumor response.

Methods: Vedotin-based antibody drug conjugates (ADCs) drive cytotoxicity in tumor cells by engaging tumor antigens on the cell surface, internalizing with the cell surface antigen, and delivering monomethyl auristatin E (MMAE) payload. Following intracellular delivery, MMAE induces mitotic arrest, as well as an endoplasmic reticulum (ER) stress response resulting from microtubule disruption. Following tumor cell treatment, indicators of the ER stress response are observed with vedotin-based ADCs including induction of phospho-JNK and CHOP. This mechanism of MMAE-induced ER stress results in emission of hallmark ICD DAMPs including cell-surface calreticulin, extracellular release of HMGB1 and ATP. In this presentation we highlight the ability of MMAE to induce the hallmarks of ICD in multiple cancers across different tissue origins using distinct valine-citrulline-MMAE (vedotin)-based ADCs.

Results: The culmination of these ICD hallmarks resulted in innate immune cell activation in vitro and in vivo in mouse xenograft models. Tumor bearing mice treated with vedotin-based ADCs resulted in the promotion of immune cell recruitment and activation in tumors. Analysis of immune activation by vedotin-based ADCs included production of innate cytokines and upregulation of HLA/MHC-Class II expression, which supports a role in activating both the innate and adaptive immune response. To further our understanding of the potent and broad ability of vedotin ADCs to induce ICD, we have also begun to examine the ICD potential of different classes of ADC payloads including other microtubule inhibitors (auristatins and maytansines), and DNA damaging agents (DNA alkylators or topoisomerase inhibitors). Initial data indicate differences in ICD induction by these agents.

Conclusions: These results help build the rationale for vedotin-based ADCs as preferred partners for immune checkpoint blockade agents.

Ethics Approval: Studies with human samples were performed according to institutional ethics standards. Animal studies were approved by and conducted in accordance with Seattle Genetics Institutional Care and Use Committee protocol #SGE-029.