immune function is unclear, with both costimulatory and proapoptotic roles described. CD30 is transiently upregulated following activation of T cell and expression has been linked to highly activated/suppressive IRF4+ effector Tregs.

Methods Here we evaluated the activity of BV on CD30-expressing T cell subsets in vitro and in vivo.

Results Treatment of enriched T cell subsets with clinically relevant concentrations of BV drove selective depletion of CD30-expressing Tregs > CD30-expressing CD4+ T memory cells, with minimal effects on CD30-expressing CD8+ T memory cells. In a humanized xenogeneic mouse model, treatment with BV selectively depleted Tregs resulting in accelerated wasting and robust T cell expansion. The observed differential activity on Tregs is likely attributable to significant increases in CD30 expression and reduced efflux pump activity relative to other T cell subsets. Interestingly, blockade of CD25 signaling prevents CD30 expression on T cell subsets without impacting proliferation, suggesting a link between CD25, the high affinity IL-2 receptor, and CD30 expression.

Conclusions Together, these data suggest that BV may have an immunomodulatory effect through selective depletion of highly suppressive CD30-expressing Tregs.

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Ethics Approval Animals studies were approved by and conducted in accordance with Seattle Genetics Institutional Care and Use Committee protocol #SGE-024.

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698 TARGETING HLA-G-MEDIATED IMMUNOSUPPRESSION WITH A FIRST-IN-CLASS ANTAGONIST ANTIBODY


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Background Human leukocyte antigen-G (HLA-G) is an immune checkpoint molecule that belongs to the non-classical HLA-class I family of receptors. HLA-G restrains immune cell activation and effector function by engaging with inhibitory receptors ILT2 and ILT4. While expression of HLA-G is highly restricted under normal healthy conditions, we have demonstrated that its expression in cancer is aberrantly upregulated and broadly detected across a variety of tumor types. Tizona Therapeutics has generated a novel, fully human antibody that specifically targets HLA-G and reverses HLA-G-mediated immunosuppression. Here we present in vivo and in vitro data demonstrating the functional impact of HLA-G blockade on immune cells and evidence to support the use of TTX-080 in the clinic to treat patients with advanced solid tumors.

Methods Evaluation of HLA-G expression in cancer was performed using immunohistochemistry, flow cytometry, and gene profiling. Expression of ILT2 and ILT4 was assessed on tumor infiltrating leukocytes by flow cytometry. To demonstrate the suppressive function of HLA-G, primary human NK cells, T cells, and monocyte-derived macrophages were cultured with target cells expressing HLA-G. TTX-080 was then evaluated for its ability to reverse this suppression. In addition, TTX-080 was investigated in vivo using a disseminated xenograft tumor model.

Results Expression of HLA-G was detected on tumor cells and tumor infiltrating leukocytes across a variety of solid tumor types. TTX-080 blocked interaction of HLA-G with both ILT2 and ILT4 and restored cytotoxicity in multiple assays using either primary NK cells or NKL cell lines. Monocyte-derived macrophages expressing ILT2 and ILT4 exhibited decreased phagocytosis of HLA-G+ target cells; this inhibition was reversed with an antigen-binding fragment of TTX-080. TTX-