immune dysfunction, and provide a target for cancer therapeutics. Collagens are a primary component of the extracellular matrix. Abnormal levels of collagen and of the collagen-domain containing complement component 1q (C1q) in tumor microenvironments has been proposed to disrupt anti-tumor immunity. LAIR-1 is an adhesion molecule and inhibitory receptor expressed on the cell surface of several immune cell subsets. LAIR-1 binding to collagen-like domains present in collagens and C1q inhibit immune cell function. LAIR-2 is a soluble homolog of LAIR-1 that binds to and outcompetes LAIR-1 binding to collagens and C1q and serves as a natural decoy to promote immune function.

Methods Taking advantage of a natural decoy system, we designed a protein biologic, NC410, composed of LAIR-2 fused with a functional IgG1 Fc domain to target collagen-rich tumors and promote immune activation, infiltration and effector function.

Results NC410 has increased avidity due to Fc mediated dimerization, and blocks LAIR-1 interactions with ligands, and LAIR-1 signaling. In vivo administration of NC410 in humanized tumor models reduced tumor growth in a dose dependent fashion. NC410 increased the numbers of infiltrating human CD8+ and CD4+ T cells in the tumor, which is associated with increased levels of chemokines in the local tumor environment. Effector function was also enhanced, as denoted by increased levels of IFN-gamma and Granzyme B in the local tumor environment. In addition, NC410 increased specific collagen degradative products in the serum of humanized tumor-bearing mice, suggesting NC410 may promote tumor microenvironment remodeling and immune accessibility to further promote anti-tumor immunity.

Conclusions These data support NC410 as a novel therapeutic for targeting collagen-rich tumors and enabling normalization of the tumor-immune microenvironment. FIH studies have recently been initiated with NC410.

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ORAL DELIVERY OF A MICROBIAL EXTRACELLULAR VESICLE INDUCES POTENT ANTI-TUMOR IMMUNITY IN MICE

Loise Francisco-Anderson, Loise Francisco-Anderson, Mary Abdou, Michael Goldberg, Erin Troy, Alicia Ballok, Fabian Romano Chernac, Maria Sizova, Krutika Invally, Shubhra Kashyap, Audrey McBride, Jessica Tsang, Shannon Argueta, Kristie Barth, Valeria Kravitz, Holly Ponichtera, Tyler Rommel, Kevin Huynh, Tanmoy Ganguly, Mark Bodmer*, Mark Bodmer. *Evelo Biosciences, Cambridge, MA, USA*

Background The small intestinal axis (SINTAX) is a network of anatomic and functional connections between the small intestine and the rest of the body. It acts as an immunosurveillance system, integrating signals from the environment that affect physiological processes throughout the body. The impact of events in the gut in the control of tumor immunity is beginning to be appreciated. We have previously shown that an orally delivered single strain of commensal bacteria induces anti-tumor immunity preclinically via pattern recognition receptor-mediated activation of innate and adaptive immunity. Some bacteria produce extracellular vesicles (EVs) that share molecular content with the parent bacterium in a particle that is roughly 1/1000th the volume in a non-replicating form. We report here an orally-delivered and gut-restricted bacterial EV which potently attenuates tumor growth to a greater extent than whole bacteria or checkpoint inhibition.

Methods EDP1908 is a preparation of extracellular vesicles produced by a gram-stain negative strain of bacterium of the Oscillospiraceae family isolated from a human donor. EDP1908 was selected for its immunostimulatory profile in a screen of EVs from a range of distinct microbial strains. Its mechanism of action was determined by ex vivo analysis of the tumor microenvironment (TME) and by in vitro functional studies with murine and human cells.

Results Oral treatment of tumor-bearing mice with EDP1908 shows superior control of tumor growth compared to checkpoint inhibition (anti-PD-1) or an intact microbe. EDP1908 significantly increased the percentage of IFN γ and TNF producing CD8+ CTLs, NK cells, NKT cells and CD4+ cells in the tumor microenvironment (TME). EDP1908 also increased tumor-infiltrating dendritic cells (DC1 and DC2). Analysis of cytokines in the TME showed significant increases in IP-10 and IFN γ production in mice treated with EDP1908, creating an environment conducive to the recruitment and activation of anti-tumor lymphocytes.

Conclusions This is the first report of striking anti-tumor effects of an orally delivered microbial extracellular vesicle. These data point to oral EVs as a new class of immunotherapeutic drugs. They are particularly effective at harnessing the biology of the small intestinal axis, acting locally on host cells in the gut to control distal immune responses within the TME. EDP1908 is in preclinical development for the treatment of cancer.

Ethics Approval Preclinical murine studies were conducted under the approval of the Avastus Preclinical Services' Ethics Board. Human in vitro samples were attained by approval of the IntegReview Ethics Board; informed consent was obtained from all subjects.

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BRENTUXIMAB VEDOTIN, A CD30-DIRECTED ANTIBODY-DRUG CONJUGATE, SELECTIVELY DEPLETES ACTIVATED TREGS IN VITRO AND IN VIVO

Bryan Grogan*, Reice James, Michelle Ulrich, Shyra Gardai, Ryan Heiser, Reice James. *Seattle Genetics, Inc., Bothell, WA, USA*

Background Regulatory T cells (Tregs) play an important role in maintaining immune homeostasis, preventing excessive inflammation in normal tissues. In cancer, Tregs hamper anti-tumor immunosurveillance and facilitate immune evasion. Selective targeting of intratumoral Tregs is a potentially promising treatment approach. Orthogonal evaluation of tumor-infiltrating lymphocytes (TILs) in solid tumors in mice and humans have identified CCR8, and several tumor necrosis family receptors (TNFRs), including TNFSFR8 (CD30), as receptors differentially upregulated on intratumoral Tregs compared to normal tissue Tregs and other intratumoral T cells, making these intriguing therapeutic targets. Brentuximab vedotin (BV) is approved for classical Hodgkin lymphoma (cHL) across multiple lines of therapy including frontline use in stage III/IV cHL in combination with doxorubicin, vinblastine, and dacarbazine. BV is also approved for certain CD30-expressing T-cell lymphomas. BV is comprised of a CD30-directed monoclonal antibody conjugated to the highly potent microtubule-disrupting agent monomethyl auristatin E (MMAE). The activity of BV in lymphomas is thought to primarily result from tumor directed intracellular MMAE release, leading to mitotic arrest and apoptotic cell death. The role CD30 plays in normal