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 effect 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.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0694

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

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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 TNF5FR8 (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