Background Leukocyte-associated immunoglobulin-like receptor 1 (LAIR-1) is an immune inhibitory receptor that binds collagen-like domains commonly found in extracellular matrix (ECM) collagens and complement component C1q. LAIR-1 is expressed on several immune cell types including activated T cells, B cells, NK cells, dendritic cells, and macrophages. Numerous cancer types including gastric, colon, ovarian, bladder, and others, upregulate collagens which enhances tumor growth, metastases, and invasion while actively suppressing antitumor immunity. While a soluble decoy, LAIR-2, is expressed in humans and competes with LAIR-1 for binding of collagen domains, excess LAIR ligands in the tumor often result in an immune suppressive environment.

Methods Here, we report on a novel immunotherapy approach combining NC410, a novel fusion protein consisting of two LAIR-2 molecules grafted on to an IgG1 antibody backbone, capable of targeting the tumor ECM and blocking LAIR-1 signaling; and bintrafusp alfa, a first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β receptor II (TGF-β RII or TGF-β "trap") fused via a flexible linker to the C-terminus of each heavy chain of an IgG1 antibody blocking programmed death ligand 1 (anti–PD-L1).

Results We have demonstrated that the combination of NC410 and bintrafusp alfa more effectively controls in vivo tumor growth of the collagen rich MC38 colon and EMT6 mammary carcinomas compared to either monotherapy. We demonstrate that this potent anti-tumor immune response is propagated through the synergy of activated tumor infiltrating lymphocytes and a repolarization of myeloid cells in the tumor microenvironment. MC38 tumors treated with the combination of NC410 plus bintrafusp alfa contained higher numbers of infiltrating T cells, NK cells, and M1 polarized macrophages.

Conclusions This study highlights the synergy of reshaping the large suppressive myeloid cell populations often present in tumors with activation of adaptive T-cell immune responses dampened by checkpoint inhibition. The results also provide the rationale for the future evaluation of this combination therapy in the clinic.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.570