MHC-I SKEWING IN MUTANT CALRETICULIN-POSITIVE MYELOPROLIFERATIVE NEOPLASMS IS COUNTERED BY HETEROCLITIC PEPTIDE CANCER VACCINATION

In this study, we examine class-I major histocompatibility complex (MHC-I) allele frequency in CALR-MUT MPN patients from two independent cohorts and observed that MHC-I alleles that present CALR-MUT neoepitopes with high affinity are under-represented in CALR-MUT MPN patients. We speculate that this is due to an increased chance of immune-mediated tumor rejection by individuals expressing one of these MHC-I alleles such that the disease never clinically manifests. As a consequence of this MHC-I allele restriction, we reasoned that CALR-MUT MPN patients would not efficiently respond to cancer vaccines composed of the CALR-MUT fragment, but could so when immunized with a properly modified CALR-MUT heteroclitic peptide vaccine approach.

Results We found that heteroclitic CALR-MUT peptides specifically designed for CALR-MUT MPN patient MHC-I alleles efficiently elicited a cross-reactive CD8+ T cell response in human PBMC samples otherwise unable to respond to the matched weakly immunogenic CALR-MUT native peptides. We also modeled this effect in mice and observed that C57BL/6J mice, which are unable to mount an immune response to the human CALR-MUT fragment, can mount a cross-reactive CD8+ T cell response against a CALR-MUT-derived peptide upon heteroclitic peptide immunization and this was further amplified by combining the heteroclitic peptide vaccine with blockade of the immune checkpoint molecule PD-1.

Conclusions Together, our data underscore the therapeutic potential of heteroclitic peptide-based cancer vaccines in CALR-MUT MPN patients.

Ethics Approval Approval was obtained for the use of patient-derived specimens and access to clinical data extracted from patient charts by the Institutional Review Boards at Memorial Sloan Kettering Cancer Center, the Dana-Farber Cancer Institute and the Massachusetts General Hospital, as well as by the Danish Regional Science Ethics Committee. Mouse experiments were performed in accordance with institutional guidelines under a protocol approved by the Memorial Sloan-Kettering Cancer Center Institutional Animal Care and Use Committee.

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BLOCKADE OF THE INHIBITORY COLLAGEN RECEPTOR LAIR-1 WITH NC410, A LAIR2-FC FUSION PROTEIN, ENHANCES ANTI-TUMOR ACTIVITY OF THE BIFUNCTIONAL FUSION PROTEIN BINTRAfasP ALFA

Background LAIR-1 is an immune inhibitory receptor expressed on several immune cell types including activated T cells, B cells, NK cells, macrophages, and dendritic cells. The ligands for LAIR-1 contain collagen-like domains which are commonly found in extracellular matrix collagens and complement component C1q. In numerous cancer types, including gastric, colon, ovarian, bladder, and others, upregulation of collagens has been shown to enhance tumor growth, metastases, and invasion while actively suppressing antitumor immunity. Although humans produce a natural, soluble decoy, LAIR-2, that 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 which combined NC410, a LAIR-2-Fc fusion protein capable of blocking LAIR-1 signaling, and bintrafasp alfa, a first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor β receptor II (TGF-βRII) 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 demonstrate that the combination of NC410 and bintrafasp alfa more effectively controls in vivo tumor growth of the collagen rich MC38 colon carcinoma compared to either monotherapy. We hypothesize that this potent antitumor immune response is propagated through the synergy of activated tumor infiltrating lymphocytes and a repolarization of macrophages towards a tumoricidal phenotype. MC38 tumors treated with the combination of NC410/Bintrafasp alfa contained higher numbers of infiltrating CD4+ and CD8+ T cells and higher numbers of CD38+ and MHCII+ 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.

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Trial Registration N/A
Background Clinical data demonstrates increased antigen presentation diversity is a key factor in determining response rates to checkpoint inhibitors. In addition to tumour mutational burden/microsatellite instability, increased HLA heterozygosity and HLA evolutionary diversity are non-overlapping factors recently identified to further diversify the immunopeptidome and improve clinical response to checkpoint therapies. Endoplasmic reticulum aminopeptidase 1 (ERAP1) is an enzyme that trims peptides loaded into classical and non-classical class I MHC molecules. Ablation of mouse ERAP modifies the immunopeptidome, resulting in improved immunogenicity, generation of CD8+ T cell responses and tumor growth inhibition. Recently identified selective small molecule potently inhibit ERAP1 across key species and haplotypes. We report the further profiling of lead candidate ERAP1 inhibitors in human primary T cell in vitro assays and in vivo tumor models in mice.

Methods Human cancer cell lines treated with ERAP1 inhibitors in vitro or in vivo in xenograft mouse models were assessed by immunopeptidomics to profile peptide repertoire changes. Novel or upregulated peptides were also tested in human immunogenicity assays. FACS analysis of T cells stimulated with Tyrosinase mRNA transfected human dendritic cells ± ERAP1 inhibition was to assess T cell repertoire changes. ERAP1 inhibitor and anti PD-1 mAb combination was assessed in syngeneic mouse tumor models to investigate tumour growth inhibition and PD end-points (e.g. IHC).

Results Analysis of human cervical, lung, colorectal and melanoma cell lines carrying distinct HLA haplotypes demonstrates a consistent and profound effect of ERAP1 inhibition on the immunopeptidome. Novel and upregulated cancer associated antigens identified in association with multiple different HLA-A and B alleles stimulate IFNγ production in primary naïve human T cell immunogenicity assays. The impact of ERAP1 inhibition on the T cell repertoire to the melanoma antigen tyrosinase is ongoing. The combination of ERAP1 inhibitor and anti PD-1 mAb led to significant tumor growth inhibition in the CT26 syngeneic mouse tumor model that correlated with increased infiltration of T cells to the tumor. Further PD end-points to be analysed include immune gene array and TCR Vbeta repertoire.

Conclusions Grey Wolf ERAP1 inhibitors significantly modify the immunopeptidome both in vitro and in vivo across a broad range of HLA and tumor types. Combination of these inhibitors with anti PD-1 leads to significant T cell infiltration and tumor growth inhibition. Thus, ERAP1 mediated modulation of the immunopeptidome has the potential to drive anti tumor T cell responses and be a transformative immunotherapy.

REFERENCES