MHC-I skewing in mutant calreticulin-positive myeloproliferative neoplasms is countered by heteroclitic peptide cancer vaccination

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bead arrays and the peptide library generated above will be used to assess anti-cancer B and T cell responses.

Trial Registration NCT04470024

Ethics Approval The original clinical trial was approved by the Providence Portland Medical Center IRB, approval # 13-046. The proposed clinical trial has not yet been reviewed by the IRB.

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**Abstracts**

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

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Background The majority of JAK2V617F-negative myeloproliferative neoplasms (MPN) have disease-initiating frameshift mutations in calreticulin (CALR) resulting in a common novel C-terminal mutant fragment (CALRMUT), representing an attractive source of neoantigens for cancer vaccines. However, studies have shown that CALRMUT-specific T cells are rare in CALRMUT MPN patients, but the underlying reasons for this phenomenon are unknown.

Methods In this study, we examine class-I major histocompatibility complex (MHC-I) allele frequency in CALRMUT MPN patients from two independent cohorts and observed that MHC-I alleles that present CALRMUT neoepitopes with high affinity are under-represented in CALRMUT 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 CALRMUT MPN patients would not efficiently respond to cancer vaccines composed of the CALRMUT fragment, but could do so when immunized with a properly modified CALRMUT heteroclitic peptide vaccine approach.

Results We found that heteroclitic CALRMUT peptides specifically designed for CALRMUT 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 CALRMUT 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 CALRMUT fragment, can mount a cross-reactive CD8+ T cell response against a CALRMUT-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 CALRMUT MPN patients.

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

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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 LAIR2-Fc fusion protein capable of 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-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 bintrafusp 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/Bintrafusp 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