were observed in a type, frequency and degree similar to other treatment arms. After repeated dosing, 1 patient demonstrated grade 1 arthritis; 1 patient demonstrated self-limited, transient grade 2 elevated LFTs; 1 patient developed grade 3 rashes, which responded quickly to oral steroid and did not recur after re-dosing. Interestingly, two out of 10 resected patients demonstrated CAP grade 2 pathologic responses in the resected PDACs after a single neoadjuvant treatment; this was not observed with other treatment cohorts (GVAX alone or GVAX+nivolumab) in this neoadjuvant platform trial. Nine out of 10 resected patients remain disease free after a median follow up of 12 months. Immunology endpoints are being analyzed by multiplex immunohistochemistry, DNA sequencing for neoantigen loads, and RNA/TCR sequencing.

Conclusions Previous observations of liver toxicity with urelumab or other T cells agonists and severe immune-related adverse events were not observed in this trial, suggesting urelumab (8 mg) is safe as neoadjuvant/adjuvant therapy in this resectable PDAC patient population. Immune and clinical efficacy of anti-CD137 agonist-based combinations warrant further investigation.

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Trial Registration NCT02451982

Ethics Approval The study was approved by the Johns Hopkins Medical Institution Institutional Review Board, approved number IRB00050517

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Combination immunotherapies

MCLA-145 (CD137XPD-L1): A POTENT CD137 AGONIST AND IMMUNE CHECKPOINT INHIBITOR THAT DOES NOT SHOW SIGNS OF PERIPHERAL TOXICITY

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Abstract 812 Figure 1

Study Schema

Background T cell Acute Lymphoblastic Leukemia (T-ALL) is a devastating malignancy found primarily in pediatric populations. Standard of care for T-ALL has not progressed from intensive regimens of chemotherapy. Another therapeutic strategy for treating T-ALL is to harness anti-leukemia T cells by immunotherapy. Currently, whether T-ALL is sufficiently immunogenic to generate anti-leukemia T cells is unknown. Furthermore, it is unclear how differences in the immune milieu of distinct tissue types (lymphoid vs non-lymphoid) that become infiltrated by T-ALL impacts T cell interactions with leukemia.

Methods These studies utilized primary T-ALL cells from a murine model that were transplanted into immune-competent, congenic (CD45.1) recipient mice. Tissues were evaluated by flow cytometry at distinct stages of disease to help determine if T cells respond to T-ALL. In addition, frozen tissue sections were analyzed using NanoString’s GeoMX Digital Spatial Profiling platform to evaluate T cells in specific regions of varying proximity to T-ALL.

Results Drastic changes to the composition of the TME were found at distinct stages of tumor burden. Evaluation of changes to the hosts’ (CD45.1+) T cells revealed a higher frequency of CD8 T cells with an activated phenotype. Furthermore, this increase largely correlated with tumor burden (figure 1). As this may represent anti-leukemia T cell responses, we next determined if they could be harnessed with immunotherapies directed against T cell co-signaling receptors. Although PD1 and OX40 monotherapies had no discernable effect, the combination of anti-PD1 with anti-
Abstract 816 Figure 1 Increase in memory CD8+ T cells in response to T-ALL

Changes to the T cell compartment were evaluated by transplanting primary T-ALL cells (CD45.2+) into innate-competent CD45.1 congenic recipient mice. T cells were then evaluated in the spleens at distinct stages of disease. As shown below, an increase in the frequency of CD8+ T cells that are memory (CD44+) and effector memory largely correlated with tumor burden in the spleens of transplanted mice that could indicate anti-leukemia T cell responses. Data is representative of a cohort from 1 of 3 independent experiments.

OX40 led to a drastic reduction in T-ALL burden. Importantly, control of tumor growth was accompanied by a concomitant increase in cytotoxic CD8 T cells actively undergoing proliferation specifically in response to combination therapy. To gain better insight into T cell interactions with T-ALL, frozen tissue sections were used for comprehensive digital spatial profiling using NanoString’s GeoMX platform. This analysis revealed strong correlations between immune markers indicative of anti-leukemia responses as well as suppressive factors. Interestingly, regions enriched for activation markers were largely constrained to certain regions indicating the formation of ‘immunological hotspots’ in the context of T-ALL.

Conclusions The results from these studies suggest that T-ALL is recognized by T cells. As immune responses were not uniform within an organ, it will be important to specifically evaluate these ‘immunological hotspots’ in order to identify targets to activate T cells found in these regions. Ongoing studies are therefore aimed at comparing T cell interactions with T-ALL and their responses to immunotherapy between tissue types.

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