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/adjutant 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

**814** MCLA-145 (CD137XP-L1): A POTENT CD137 AGONIST AND IMMUNE CHECKPOINT INHIBITOR THAT DOES NOT SHOW SIGNS OF PERIPHERAL TOXICITY

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**Background** Only a fraction of cancer patients benefit from currently available immune checkpoint inhibitors (ICI). Attempts to improve efficacy of ICI by combining with co-stimulatory receptor agonists such as CD137 (4-1BB) have led to greater anti-tumor activity preclinically but have shown systemic toxicity in the clinic. MCLA-145 is a human CD137×PD-L1 bispecific common light chain antibody (bAb), identified through functional screening of agonist and ICI bAb combinations. Further, MCLA-145 can overcome Treg and macrophage suppression to potently activate T cells in these immune suppressive conditions. In two ICI insensitive xenograft models, MCLA-145 demonstrated good anti-tumor activity and CD8+ T cells were enriched in tumors post treatment (indicative of intratumor expansion and recruitment). No signs of GvHD were observed in mice following treatment with MCLA-145 in contrast to that seen in animals treated with other ICI mAbs.

**Methods** The EC30 from an in vitro T cell transactivation assay based on IFNg was used as an estimate of the MABEL for MCLA-145. A 2 compartment PK model coupled to a target-mediated drug disposition component was generated based on the available cynomolgus monkey PK data.

**Results** Repeated doses of MCLA-145 up to 100 mg/kg/wk in cynomolgus monkeys were well tolerated without major adverse effects, and dose-dependent increases in serum MCLA-145 concentrations were observed. Following allometric scaling, the model was used to predict exposure in humans following MCLA-145 IV given over 2-hours every 2 weeks, including the starting dose for the FIH trial.

**Conclusions** Conditional activation of CD137 signaling by MCLA-145, triggered by a neighboring target cell expressing PD-L1, may provide both improved efficacy and safety. MCLA-145 is currently undergoing clinical investigation (NCT03922204).

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**816** EVALUATING THE POTENTIAL OF HARNESING ANTI-LEUKEMIA T CELLS FOR THE TREATMENT OF T CELL ACUTE LYMPHOBLASTIC LEUKEMIAS (T-ALL)

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**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-
Background Elevated levels of Prostaglandin E2 (PGE2), an eicosanoid notably synthesized by the cyclooxygenase-2 (COX-2), exert strong immunosuppressive effects in the tumor microenvironment. COX-2-positive solid tumors have the ability to use this pathway as a resistance mechanism, especially to escape from the host immune system, thus limiting the anti-tumor effects of immune checkpoint inhibitors (ICI). These immunosuppressive effects are largely mediated by the EP4 receptor, expressed on multiple immune cells.

Methods A novel series of EP4 receptor antagonists has been developed, with improved pharmacokinetic properties when compared to the EP4 receptor antagonists currently being evaluated in clinical trials. An intensive lead optimization program led to the identification of DT095895, a small molecule development candidate with a ‘best-in-class’ potential. DT095895 was assessed in multiple syngeneic mouse tumor models selected for their COX-2 expression profile.

Results DT095895 preclinical package will be presented in the poster. Efficacy was seen both in a monotherapy setting, as well as in combination with an ICI. Additionally, a specific biomarker program was implemented and validated in order to show target engagement. A phospho-flow murine whole blood assay was set-up to assess the ability of DT095895 to inhibit CREB phosphorylation induced by a selective EP4 receptor agonist in CD3+ cells. This biomarker was further developed for human whole blood to support Phase 1 and clinical trials studies.

Conclusions DT095895 is a selective EP4 receptor antagonist and demonstrates strong anti-tumor effects in multiple syngeneic mouse tumor models, both as a monotherapy and in combination with ICI, through the inhibition of the PGE2-induced immunosuppression. DT095895 progresses in regulatory development.

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Abstract 818

Synergistic cancer immunotherapy using tumor tissue-derived exosomes and artificially produced bacterial outer membrane vesicles

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Background Checkpoint inhibitors work only in cancers that host inflammatory cells, and ‘cold’ tumors normally do not respond. Therefore, making ‘cold’ tumors ‘hot’ is required to increase the response rate to immunooncology therapies in general. Bacteria and bacterial products have been utilized for cancer immunotherapy for more than 100 years, but currently no such treatment is available because of the severe side effects that are observed. In this study, we produced artificial outer membrane vesicles (aOMVs) from Escherichia coli outer membrane, and injected them together with cancer tissue-derived exosomes to boost an immune response to the malignancy.

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Abstract 817

DT095895, a selective EP4 receptor antagonist with monotherapy efficacy in syngeneic mouse model(s) and best-in-class properties

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Background Increased levels of Prostaglandin E2 (PGE2), an eicosanoid notably synthesized by the cyclooxygenase-2 (COX-2), exert strong immunosuppressive effects in the tumor microenvironment. COX-2-positive solid tumors have the ability to use this pathway as a resistance mechanism, especially to escape from the host immune system, thus limiting the anti-tumor effects of immune checkpoint inhibitors (ICI). These immunosuppressive effects are largely mediated by the EP4 receptor, expressed on multiple immune cells.

Methods A novel series of EP4 receptor antagonists has been developed, with improved pharmacokinetic properties when compared to the EP4 receptor antagonists currently being evaluated in clinical trials. An intensive lead optimization program led to the identification of DT095895, a small molecule development candidate with a ‘best-in class’ potential. DT095895 was assessed in multiple syngeneic mouse tumor models selected for their COX-2 expression profile.

Results DT095895 preclinical package will be presented in the poster. Efficacy was seen both in a monotherapy setting, as well as in combination with an ICI. Additionally, a specific biomarker program was implemented and validated in order to show target engagement. A phospho-flow murine whole blood assay was set-up to assess the ability of DT095895 to inhibit CREB phosphorylation induced by a selective EP4 receptor agonist in CD3+ cells. This biomarker was further developed for human whole blood to support Phase 1 and clinical trials studies.

Conclusions DT095895 is a selective EP4 receptor antagonist and demonstrates strong anti-tumor effects in multiple syngeneic mouse tumor models, both as a monotherapy and in combination with ICI, through the inhibition of the PGE2-induced immunosuppression. DT095895 progresses in regulatory development.

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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 immune-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.