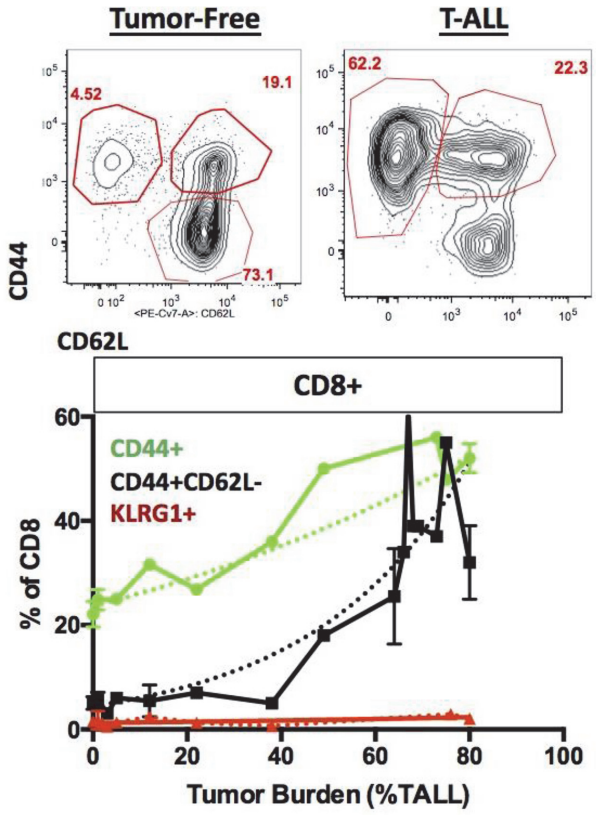

Abstract 816 Figure 1 Increase in memory CD8+ T cells in response to T-ALL
Changes to the T cell compartment were evaluated by transplanting primary T-ALL cells (CD45.2+) into immune-competent CD45.1 congenic recipient mice. T cells were then evaluated in the spleens at distinct stages of disease. As 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

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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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 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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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 booster an immune response to the malignancy.