antibody and an immune checkpoint blockade. KN026 is a novel bispecific antibody that simultaneously binds to two distinct HER2 epitopes. KN046 is a novel bispecific antibody that blocks both PD-L1 interaction with PD-1/CD80 and CTLA-4 interaction with CD80/CD86. Here we reported the interim results from an ongoing phase Ib dose escalation and expansion study assessing the safety, tolerability and preliminary efficacy for KN026 in combination with KN046 in Patients with HER2 aberrated solid tumors.

Methods This study enrolled pts with solid tumors who failed available standard of care, HER2 aberration status confirmed locally (HER2 mutation, HER2 amplification and/or HER2 overexpression). Eligible pts received combination of KN026 and KN046 at three dose levels until disease progression, unacceptable toxicity or withdrawal of informed consent (DL1: KN026 20 mg/kg Q2W + KN046 3 mg/kg Q2W; DL2: KN026 20 mg/kg Q2W with loading on Days 1, 8 of Cycle 1 + KN046 5 mg/kg Q3W; DL3: KN026 30 mg/kg Q3W with loading on Days 1, 8 of Cycle 1 + KN046 5 mg/kg Q3W). Tumor response was evaluated Q8W per RECIST 1.1. Primary endpoint was DLT and key secondary endpoints were efficacy parameters (ORR, DOR, PFS).

Results As of the Sep. 08, 2020, 25 pts were enrolled into DL1 (n = 20, 3 for dose escalation), DL2 (n = 3) and DL3 (n = 2) (mGC/GEJ 15 pts; mCRC 8 pts; other solid tumors 2 pts). 15 pts remained on the study treatment and 10 pts discontinued treatment due to disease progression (n=5), death (n=2) and other reasons (n=3). 18 pts had HER2-positive status (12 of 18 failed previous trastuzumab therapy), 2 pts had HER2 mutation and 5 pts had HER2 low expression (without FISH amplification). No DLTs were observed. No pts experienced LVEF decreased or other clinically meaningful cardiac AEs. Treatment-related TEAEs occurred in 23 (92%) pts, of which 6 (24%) pts experienced grade 3 or above treatment-related TEAEs. 11 (44%) pts experienced irAEs, majority were of grade 1 or 2 except that 1 patient experienced grade 3 immune-mediated endocrinopathy. The most common (frequency $\geq 15\%$) KN026 or KN046 related TEAEs were infusion related reaction (n=11, 44.0%), anaemia (n=9, 36.0%), white blood cell count decreased (n=6, 24.0%), diarrhea (n=5, 20.0%), AST increased (n=5, 20.0%), platelet count decreased (n=5, 20.0%), rash (n=5, 20.0%) and ALT increased (n=4, 16.0%). The objective response rate in pts with HER2-positive tumors (n = 14 efficacy evaluable pts) was 9/14 (64.3%, 95% CI 35.1~87.2%) and disease control rate 13/14 (92.9%, 95% CI 66.1~99.8%). 4 out of 5 pts with HER2 mutation or low expression achieved SD including one patient with SD for more than 24 weeks. 2 death cases due to disease progression were reported, both only received one cycle of KN026 plus KN046 due to COVID-19 restriction.

Conclusions KN026 combined with KN046 is well tolerated and has demonstrated preliminary albeit profound anti-tumor activity in HER2-positive solid tumors.

Trial Registration Clinical trial information: NCT04040699

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URELUMAB (ANTI-CD137 AGONIST) IN COMBINATION WITH VACCINE AND NIVOLUMAB TREATMENTS IS SAFE AND ASSOCIATED WITH PATHOLOGIC RESPONSE AS NEOADJUVANT AND ADJUVANT THERAPY FOR RESECTABLE PANCREATIC CANCER

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Background Data analysis of specimens from prior clinical trials identified the immune co-simulatory molecule CD137 within the tumor microenvironment(TME) of pancreatic ductal adenocarcinoma(PDAC) that remain to be activated following vaccine induced T cell and PD-1 inhibitory treatments. The requirement of CD137 was subsequently supported by preclinical studies. Therefore, we conducted a clinical trial of combining anti-CD137 agonist antibody urelumab, anti-PD-1 antagonist antibody nivolumab and a GM-CSF-secreting allogeneic tumor cell vaccine(GVAX) as neoadjuvant and adjuvant therapy for resectable PDAC.

Methods Patients of ≥ 18 years old with radiographic evidence of resectable PDACs were eligible for Arm C of this trial (NCT02451982) with an accrual goal of 10 evaluable subjects. The primary objective was to evaluate changes in numbers of tumor infiltrating CD137+CD8+ T cells. Secondary objectives were safety, overall survival, disease free survival, and other immune parameters. Patients who underwent R0/R1 resection were considered evaluable. All subjects received 480mg nivolumab and 8 mg urelumab both intravenously one day prior to receiving GVAX intradermally and two weeks before surgical resection (figure 1). After surgery, eligible patients continued to receive 5 combination immunotherapy cycles in addition to standard of care chemotherapy. Treatment-related toxicity and perioperative complications are monitored.

Results Between February 2019 and August 2020, we completed planned enrollment and treated 10 evaluable patients, who underwent R0 surgical resection of their PDACs. Nausea is the most common adverse event attributed to urelumab (table 1). Other adverse events and perioperative complication

Abstract 812 Table 1
Adverse Events

Adverse Event - CTCAE Term	Grade	N (%)
Abdominal pain	2	1 (10%)
Anorexia	2	1 (10%)
Diarrhea	2	1 (10%)
Nausea	1/2	7 (70%)
Vomiting	1	2 (20%)
Fatigue	1	4 (40%)
Flu-like symptoms (fever, chills, myalgia)	1	2 (20%)
Arthritis	1	1 (10%)
Thyroiditis	2	1 (10%)
Pruritus	2	3 (30%)
Rash	3	2 (20%)
Periorbital edema (w/ pruritus around eyes)	1/2	1 (10%)
Peripheral sensory neuropathy	2	1 (10%)
LFTs increased (ALT, AST, Alk Phos)	2	1 (10%)

Abstract 812 Figure 1
Study Schema

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

814 MCLA-145 (CD137XPD-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 costimulatory 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 CD137xPD-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 potentially 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 IFN γ 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 of 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 HARNESSING 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-