Methods BxPC-3, PANC-1, and MIA-PaCa2 were incubated alone or in combination with Tinzaparin (T) and/or Nab-Paclitaxel (A) and/or Gemcitabine (G) and/or Nivolumab (NI), Pembrolizumab (PE) and/or Iplimumab (PI). The effect of these regimes on various signaling pathways controlling proliferation and apoptosis was identified in vitro through Western blot. Cell viability was measured with MTT assay. NOD/SCID mice will be used to generate xenografts with the PANC-1 cell line. Human peripheral blood mononuclear cells (PBMCs) from healthy donors will be injected to give mice a human-like immune system.2

Results In a triple combinatorial scheme, NE/PE+PI+T, the protein levels of VEGFR2 were decreased (0.1 to 0.7 folds) in a dose-dependent way in mtKRAS PC cell lines (PANC1 and MIAPACA2). The number of PANC-1 cells was decreased around 40% in a triple combinatorial scheme of T+PI+(NI or PE) after 48 hours. The triple combination of Gemcitabine + Nab-paclitaxel + Tinzaparin leads to a decrease in tumor size relative to control by 51% and relative to Nab-P + G by 15%. The combination of chemotherapy, immunotherapy, and Tinzaparin contributes an additional 20% Preliminary data show that the quadruple therapeutic regimen increases the percentage of CD8+ cells from 5% to 27% and decreases Tregs' percentage from 9.5% to 4% (in TILs).

Conclusions In vitro experiments show a decrease in the cell viability of PC cell lines and a reduction in the protein levels of VEGFR2 in mtKRAS cell lines. In vivo experiments with NOD/SCID mice and humanized NOD/SCID mice show a significant reduction in tumor volume in the combination therapy regimens with Tinzaparin. Possible mechanisms for these effects include an increase in CD8+ cells, a decrease in Tregs cells, a reduction in VEGFR-2 expression, and an increase in cancer cell apoptosis. This synergistic strategy can create new avenues for the treatment of patients with pancreatic cancer, achieving a better clinical outcome and greater survival.

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PRECLINICAL CHARACTERIZATION AND DEVELOPMENT OF MG1124, A NOVEL IMMUNE CHECKPOINT INHIBITOR TARGETING CEACAM1 FOR NSCLC PATIENTS

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Background CEACAM1 is the only member of CEACAM family which is expressed on lymphocytes such as T cells and NK cells that mediate suppression of inflammatory T cell response. It is known that CEACAM1-CEACAM1 homophilic interaction induces downregulation of ZAP70 phosphorylation in response to T cell receptor (TCR) stimulation. There is a wealth of research demonstrating the correlation between CEACAM1 expression and cancer progression, in a wide range of indications. We developed a fully human monoclonal antibody (mAb) MG1124 that specifically binds to CEACAM1 but not to other CEA family members, thereby exerting anti-tumor effect via triggering immune response.

Methods T cell activation of MG1124 was determined by an NFAT-luciferase reporter assay with CEACAM1 overexpressing Jurkat stable cells. In vitro efficacy of MG1124 was examined using an NK cell- or cytotoxic T cell-mediated tumor cell killing assay. The anti-tumor efficacy of MG1124 alone or in combination was studied in a humanized mouse model. As MG1124 binds to monkey CEACAM1 with high affinity, pharmacokinetics assessment of MG1124 was performed in cynomolgus monkeys.

Results An anti-CEACAM1 antibody MG1124 bound to CEACAM1 but not to other CEA family members. MG1124 blocked CEACAM1 homophilic interaction by binding to the N domain of CEACAM1. Especially the homophilic interaction induced downregulation of ZAP70 phosphorylation in response to TCR stimulation in a CEACAM1 overexpressing Jurkat stable cell line, which was rescued by MG1124 resulting in augmentation of NFAT activity and IL-2 expression. NK cell or cytotoxic T cell-mediated tumor lysis was increased by MG1124 in a CEACAM1 expression-dependent manner. MG1124 inhibited tumor growth in CEACAM1 expressing NSCLC CDX humanized mouse models. In an NSCLC PDX humanized mouse model, MG1124 dose-dependently inhibited tumor growth as monotherapy. Moreover, MG1124 showed synergistic anti-cancer activity with pembrolizumab in NSCLC huPDX models. Pharmacokinetic (PK) analysis in cynomolgus monkeys showed that the half-life (T1/2) of MG1124 was estimated to range from 14 to 17 days, and the peak plasma concentration (Cmax) and overall exposure (AUC) were found to be generally dose proportional. Following this PK study, a toxicity study in cynomolgus monkeys is ongoing.

Conclusions MG1124, a novel anti-CEACAM1 mAb, blocked CEACAM1-mediated negative regulation and restored NK or cytotoxic T cell activities. MG1124 showed effective anti-tumor activity in vivo mouse models and its combination with PD-1 blockade further enhanced treatment efficacy. The data presented herein support further advancement of MG1124 towards clinical development. MG1124 is a potential therapeutic candidate for immune checkpoint blockade in cancer therapy.

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THE ROLE OF IMMUNE CHECKPOINT INHIBITOR AS A SINGLE AGENT OR COMBINATION THERAPY IN ADVANCED THYROID CANCER

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Background There is a high unmet need for effective systemic treatment for patients with metastatic radioactive iodine
refractory (RAI-R) differentiated thyroid cancer (DTC) and anaplastic thyroid cancer (ATC). Immunotherapy may be used as an alternative option for those without targetable mutations or have become resistant to targeted therapy. Here we review the clinical trials and retrospective studies and discuss the potential role of immune checkpoint inhibitors (ICIs) in advanced thyroid cancer.

Methods The details of pertinent clinical trials were obtained from clinicaltrials.gov (NIH) using search terms including 'thyroid cancer' and 'immunologic.' The NCT numbers and search terms were used to search for published results on databases such as PubMed, American Association of Cancer Research, and American Society of Clinical Oncology. The efficacy outcome measures were determined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Results In RAI-R DTC, responses to three different regimens have been reported: pembrolizumab, nivolumab plus ipilimumab, and pembrolizumab plus lenvatinib. No CR was reported, and the overall response rates (ORRs) varied from 9% (pembrolizumab monotherapy and nivolumab plus ipilimumab) to 64% (pembrolizumab plus lenvatinib) (figure 1a).1-4

In ATC, four studies have reported favorable outcomes in the context of dabrafenib and trametinib.5 The efficacy of spartalizumab, a PD1-inhibitor, was evaluated in a phase I/II trial, rendering an ORR of 19%, with 3 CRs (7%) and 5 PRs (12%) [6]. The study of nivolumab plus ipilimumab reported an ORR of 30% in ATC, with a near CR and two without clear evidence of disease at 13 and 26 months.2 A trial that tested the combination of atezolizumab, vemurafenib, and cobimetinib in BRAFV600E-mutated patients reported an ORR of 59%.7 A retrospective study reported an ORR of 60% after adding pembrolizumab at the time of progression on lenvatinib8 (figure 1b). There are 25 ongoing trials evaluating the efficacy of ICIs in different types of thyroid cancer. Three trials are testing pembrolizumab as monotherapy, three trials are assessing ICI combination therapy, and six trials are testing the efficacy of various ICI and tyrosine kinase inhibitor (TKI) combinations (figure 2).

Conclusions The recent trials and a retrospective study have reported favorable outcomes in ATC, suggesting ICIs have a potential role in treating patients with ATC. In particular, dual ICIs or combination of TKI and ICI can be developed as treatment options for ATC. Further large scale randomized prospective studies are required to establish ICIs as standard of care.

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205 PD-1/PD-L1/CTLA-4 INHIBITOR THERAPY FOLLOWING PROGRESSION ON A DIFFERENT PD-1/PD-L1 INHIBITOR: A CASE SERIES

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Background There are increasing numbers of immune checkpoint inhibitors (CPI) targeting the PD-1/PDL-1 and CTLA-4 pathways, which are approved in a wide variety of tumor types. A case series has previously described the sequential use of first line CPI, followed by second line CPI in renal cell carcinoma and melanoma patients, and both patient populations had progressive disease. There is still a lack of data on the safety and efficacy of challenging a patient who has previously progressed on a CPI with a different class of CPI, in other tumor types.

Methods We retrospectively collected data from patients treated with a CPI, who were subsequently challenged with another CPI, at a single institution. Exclusion criteria included patients with renal cell carcinoma and melanoma. Patient characteristics, immune-related adverse effects (irAEs), cancer type, tumor proportion score if available, treatment type, treatment response/progression per RECIST v1.1, and survival data were collected.

Results We identified 11 patients with various pathologies who received sequential CPI after progressing on first line CPI (table 1). Cancer types included non-small cell lung cancer (n=5), head and neck cancer (n=2), urothelial carcinoma (n=1), Merkel cell carcinoma (n=1), poorly differentiated carcinoma (n=1), and hepatocellular carcinoma (n=1). The tumor proportion score was available in 6 patients. Out of these patients, all were metastatic at the time of second line CPI. First line CPIs were all PD(L)-1 inhibitors, second line CPIs were all PD(L)-1 inhibitors except for one patient who received a CTLA-4 inhibitor in combination with a PD-1 inhibitor. Out of these patients, 3 patients who were trialed with second line CPI had stable disease, 5 patients had progression of disease, 1 patient had an irAE leading to discontinuation of CPI, and 2 patients died from adverse events unrelated to CPI. Out of 3 patients with stable disease on second line CPI, 2 patients had stable disease for over 2 years, and 1 patient had had stable disease for over 1 year.

Conclusions Despite concerns that sequential immunotherapy may not be efficacious, 3 out of 11 patients did significantly benefit with the long-term stable disease. We need further large-scale prospective studies and research to know more about tumor characteristics, the mechanism of resistance in immuno-oncology to help us identify patients who would benefit from sequential immunotherapy.

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206 AN IMMUNE-COMPETENT TUMOR ORGANOID PLATFORM TO TEST NOVEL IMMUNE CHECKPOINT COMBINATIONS TARGETING THE RECEPTOR CD47 IN TRIPLE NEGATIVE BREAST CANCER

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Background Immune checkpoint blockade therapy targeting PD-L1 has recently been approved for metastatic triple negative breast cancer (TNBC) patients. However, a 7% response rate calls for better models and strategies to stimulate TN tumor immunogenicity to increase patient response. Overexpression of the receptor CD47 impairs innate and adaptive tumor immunosurveillance when engaged to its counter receptor SIRPα or ligand thrombospondin-1. Co-expression of CD47 and PD-L1 is implicated with disease progression in TNBC patients. We examined through murine models and tumor organoid platforms whether targeting CD47 sensitizes TNBC tumors to PD-L1 therapy, focusing on the modulation of cellular bioenergetics as a potential mechanism and potentially predict response.

Methods The effects of targeting CD47 and PD-L1 were examined through orthotopic syngenic 4T1 and EMT-6 TNBC murine models. Due to predicting patient therapeutic response challenges, tumor organoid platforms investigated mechanisms of tumor sensitization to anti-PD-L1 by targeting CD47. Organooids were constructed by embedding murine TNBC tumor tissue and AH1 CD8+ T cells in a specialized ECM mimicking hydrogel. Immunohistochemistry was performed on organoid, human and murine TNBC tumor tissue. Cellular bioenergetics was analyzed through Seahorse® bioanalyzer.

Results Staining of human TNBC biopsies found elevated CD47 expression, signifying a potential therapeutic target. Targeting CD47 or in combination with anti-PD-L1 resulted in decreased tumor volume and weight in a TNBC murine model. The decrease in tumor burden was correlated with...