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 Ipilimumab (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 donors will be injected to give mice a human-like immune system.2

Results In a triple combinatorial scheme, N/PE+IPI+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+IPI+(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 leads to a reduction in tumor size compared to control by up to 60%. 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 2.5 days 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