Methods BxPC-3, PANC-1, and MIA-PaCa2 were incubated alone or in combination with Tinzaparin (T) or Nab-Paclitaxel (A) and/or Gemcitabine (G) and/or Nivolumab (N), Pembrolizumab (P) and/or Ipilimumab (I). The effect of these regimens 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 were 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.

Results In a triple combinatorial scheme, N+PE+I+P+T, the protein levels of VEGFR2 were decreased (0.1 to 0.7 folds) in a dose-dependent way in mKRAS PC cell lines (PANC1 and MIAPACA2). The number of PANC-1 cells was decreased around 40% in a triple combinatorial scheme of T+P+I+N (or I+P) 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 Treg's 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 mKRAS 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, a reduction in VEGFR2 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.

References

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0202

203

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

Jae-Chul Lee,1 Woo Seok Yang,1 Hyeyoung Park,1 Hye-mi Nam,1 Hyun-Jung Cho,1 Mi-Young Oh,1 Eun-Young Kwak,1 Jinhyun Park,1 Myung Eun Jung,2 Hwaok Chung,3 Minju Kim,3 Jae-Hwan Kim,3 Byoung Chul Cho,1 Jae-Chul Lee.1 1MOGAM Institute for Biomedical Research, Yongin-si, Korea, Republic of; 2GC Pharma, Yongin-si, Korea, Republic of; 3Yonsei Cancer Center, Seoul, Korea, Republic of

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 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 hPDX 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.

References

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0203

204

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

Ju Young Lee*, Inae Park, Myungwon Nam, Christmann Low, Eugene Kim, Hansol Choi, Elena Vagia, Chant Mi Jung, Young Kwang Chae, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, Oak Park, IL, USA

Background There is a high unmet need for effective systemic treatment for patients with metastatic radioactive iodine