number back to the baseline. Consistent with an effect of IL-8 blockade on the increase of CD15+CD14- myeloid cells, single nuclear RNA sequencing analysis of the tumor tissues showed that the innate immune response and cytokine response pathways in the myeloid cell cluster were activated by IL-8 blockade.

Conclusions This result suggested that IL-8 blockade did not simply inhibit myeloid cells as previously anticipated, but potentiated myeloid cells for the innate immune response and concomitant production of type I cytokines. Such immune responses may subsequently activate the effector T cells as the single nuclear RNA sequencing analysis demonstrated enhanced activation signals in the T cell cluster from the tumors treated by anti-IL-8 antibodies. Taken together, this study supports further testing of anti-IL-8 antibodies including B108-IL8 and HuMax-IL8 in combination with anti-PD-1 antibodies for PDAC treatment.

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P08.02 CCR2/CCR5 DUAL-ANTAGONIST 'LICENSES' THE RADIATION-INDUCED EFFECTOR T-CELL INFILTRATION IN THE ANTI-PD-1 ANTIBODY-TREATED PANCREATIC ADENOCARCINOMA

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Background The resistance of pancreatic ductal adenocarcinoma (PDAC) to immune checkpoint inhibitors (ICIs) is mainly attributed to the immune-quiet nature of its tumor microenvironment (TME). Radiotherapy (RT) activates innate responses including the RAGE and TLR2/4 pathways and subsequently modifies the TME by promoting the release of chemokines that recruit inflammatory cells into the TME. In this preclinical study, we examined the PDAC vaccine or RT as a T-cell priming mechanism together with BMS-687681, a small molecule dual-antagonist of CCR2 and CCR5 (CCR2/5i) as an immunosuppressive TME-targeting agent, in combination with the anti-PD-1 antibody (α PD-1) as a new treatment.

Materials and Methods The hemi-spleen and Orthotopic mice model were used to investigate both GVAX and RT as T-cell priming agents in combination regimens that included α PD-1 and CCR2/5i. Dissected orthotopic pancreatic tumors were collected for analysis of tumor-infiltrating immune cells by

flow cytometry. RNA from tumor-infiltrating immune cell pellets and whole-exome RNA sequencing was performed for further mechanism research.

Results CCR2 and CCR5 are associated with the immunosuppressive TME of PDAC patients and their expression were induced after treatment with GVAX+nivolumab. Using a mouse model of PDAC, we demonstrated that the addition of GVAX to CCR2/5i+ α PD-1 combination therapy did not significantly improve antitumor activity. However, RT followed by α PD-1 and prolonged treatment with CCR2/5i conferred significantly better antitumor efficacy compared to the other combination treatments we studied. The combination of RT, α PD-1, and CCR2/5i enhanced intratumoral effector and memory T-cell infiltration. This combination suppressed Treg, M2-like TAM, and M-MDSC infiltration, but not M1-like TAM and PMN-MDSC infiltration. Finally, RNA sequencing showed that CCR2/5i partially inhibited RT-induced TLR2/4&RAGE signaling, which would have otherwise led to the release of immunosuppressive cytokines including CCL2 and CCL5. The inhibition of TLR2/4&RAGE signaling permitted the expression of effector T-cell chemokines such as CCL17 and CCL22.

Conclusions This study thus supports the clinical development of CCR2/5i in combination with RT and ICIs for PDAC treatment.

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P08.03 NEOANTIGEN CANCER VACCINE AUGMENTS ANTI CTLA-4 EFFICACY

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Background Immunotherapy based on anti CTLA-4 (α CTLA-4) and anti PD1 (α PD1) is being tested in combination with different therapeutic approaches including other immunotherapy approaches such as neoantigen cancer vaccines (NCV). Here we explored, in two cancer murine models, different therapeutic combinations of α CTLA-4 and/or α PD1 with a plasmid DNA vaccine expressing neoantigens and delivered by electroporation (EP).

Materials and Methods To evaluate the impact of NCV in the MC38 and in the CT26 tumor model three plasmid vaccines were generated with or without CD4 epitopes. Therapeutic DNA vaccines were delivered by EP in different therapeutic protocols including large tumors. Flow cytometry was utilized to measure CD8, CD4, T-reg, and B cells as well as neoantigen-specific immune responses, which were also measured by IFN- γ ELISpot.

Results Immune responses were augmented in combination with α CTLA4 but not with α PD1 in the MC38 tumor model with significantly impacting tumor growth. Similarly, neoantigen-specific T cell immune responses were observed in the CT26 tumor model where large tumors regressed in all mice treated with α CTLA-4 and NCV. In line with previous evidence, we observed an increased switched memory B cells in the spleen of mice treated with α CTLA-4 alone or in combination with NCV.