number back to the baseline. Consistent with an effect of IL-8 blockade on the increase of CD15+CD14- myeloid cells, single nucleic 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.

Disclosure Information P. Li: None. N. Rozich: None. J. Wang: None. J. Gai: None. J. Wang: None. Y. Xu: None. B. Herbst: None. R. Yu: Employment (full or part-time); Significant; NovaRock. S. Muth: None. N. Niu: None. K. Li: None. V. Fune: None. A. Osipov: None. C. Wolfgang: None. M. Lei: Employment (full or part-time); Significant; NovaRock. T. Liang: None. L. Zheng: B. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received); Significant; Bristol-Meyer Squibb, Merck, iTeos, Amgen, NovaRock, Inxmed, Halozyme. E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Alphamab, Mingruzhiyao. F. Consultant/Advisory Board; Significant; Biosion, Alphamab, NovaRock, Akrevia/Xilio, Ambrx, Novagenesis, Datarevive, Snow Lake Capitals, Mingruzhiyao. Other; Significant; Aduro Biotech.

**PO08.02 CCR2/CCR5 DUAL-ANTAGONIST 'LICENSES' THE RADIATION-INDUCED EFFECTOR T-CELL INFILTRATION IN THE ANTI-PD-1 ANTIBODY-TREATED Pancreatic adenocarcinoma**

1,2J Wang*, 2M Tun Saung, 2K Fujiwara, 2N Niu, 1A Narang, 1J He, 2L Zheng. 1The first affiliated hospital of Zhengiang University, Hangzhou, China; 2Jonhs Hopkins university, school of medicine, Baltimore, MD, USA

**Background** The resistance of pancreatic ductal adenocarcinoma (PDAC) to immune checkpoint inhibitors (ICIs) is mainly attributed to the immune-quiescent 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 (αPD-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 αPD-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+αPD-1 combination therapy did not significantly improve antitumor activity. However, RT followed by αPD-1 and prolonged treatment with CCR2/5i conferred significantly better antitumor efficacy compared to the other combination treatments we studied. The combination of RT, αPD-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.