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**SELECTIVE DEPLETION OF TUMOR-SPECIFIC REGULATORY T CELLS IN COMBINATION WITH LOW DOSE CHEMOTHERAPY WITH OR WITHOUT PD-1 BLOCKADE IMPROVES ANTI-TUMOR T CELL RESPONSES IN SOLID TUMORS**<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0807>

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**Background** Lack of effector T cell activity in solid tumors can be attributed to suppressive mechanisms utilized by regulatory T cells (Tregs) within the tumor microenvironment. An outstanding question in the field is how to selectively deplete intratumoral Tregs to avoid the severe autoimmunity triggered by systemic depletion. CCR8 is a chemokine receptor expressed at high levels on the surface of tumor infiltrating Tregs, but not on peripheral Tregs, nor effector T cells. CCR8 targeting antibodies, which lead to rapid depletion of intratumoral Tregs in mouse models and human explant systems, are currently in the clinic as monotherapy and in combination with checkpoint inhibitors. Chemotherapy has the potential to trigger immunogenic cell death and lead to enhanced T cell priming. We hypothesized that chemotherapy treatment may combine with a Treg depleting agent such as anti-CCR8 and lead to improved outcomes. In this study, we tested the ability of an anti-CCR8 antibody to augment tumor specific effector T cell responses when paired with low doses of chemotherapy with or without an anti-PD-1 mAb in mouse syngeneic tumor models.

**Methods** The 4T1, Panc02, B16F10, and LLC mouse syngeneic tumor models were used in this study. Following implantation, mice were randomized and grouped out when tumors reached 80-120 mm<sup>3</sup>, and administered a single dose of anti-CCR8 antibody in combination with a suboptimal dose of Cisplatin, Gemcitabine, or Docetaxel with or without an anti-PD-1 mAb. Tumor growth inhibition and analysis of intratumoral lymphocyte populations were performed to assess the combination potential of Treg depletion and chemotherapy.

**Results** In multiple syngeneic tumor models with varying levels of Treg and CD8 infiltration, a single suboptimal dose of chemotherapy treatment administered at the beginning of the study did not result in meaningful tumor growth inhibition. When selective Treg depletion via CCR8 was paired with low dose chemotherapy, both 4T1 and Pano2 tumor models demonstrated significant tumor growth inhibition. Complete responses were observed in 50% of mice treated with a combination of Gemcitabine and anti-CCR8 in the Panc02 model. On the contrary, in relatively cold tumor models including B16F10 and LLC, no single agent or combination effect was observed. Finally, addition of anti-PD-1 mAb to low dose chemotherapy and Treg depletion in the LLC model led to 72% tumor growth inhibition in the triple combination group.

**Conclusions** Tumor Treg depletion demonstrates the potential to augment anti-tumor activity when paired with low dose chemotherapy in cold tumor models.

**Ethics Approval** Procedures involving the care and use of animals in the study were reviewed and approved by the Stony Brook University Institutional Animal Care and Use Committee (Protocol # 748435-3/2015-2182-NF-MI- 5.18.18) prior to conduct. During the study, the care and use of animals was conducted in accordance with the principles outlined in the Guide for the Care and Use of Laboratory Animals, 8th Edition, 2010 (National Research Council).