



SU2C Gynecologic Cancers Convergence Research Team:

“Connecting Immune Health and Tumor Biology in Gynecologic Cancers”



[This abstract was provided by the scientists when their application was accepted.]

Checkpoint blockade targeting PD-1 and CTLA-4 has resulted in impressive responses in many cancers. However, there have been mixed results to checkpoint blockade in gynecologic malignancies, an area of unmet clinical need. In high-grade serous ovarian cancer (HGSOC), benefit from anti-PD-1/L1 therapies in the recurrent setting has been modest. Conversely, the response rate to pembrolizumab in women with uterine cancer that demonstrate microsatellite instability (MSI^{HI}) has been robust. MSI^{HI} cancer arises in tumors that harbor somatic or germline mutations in DNA mismatch repair (MMR) genes. MSI^{HI} uterine cancer harbors large numbers of single nucleotide variations (SNVs), while HGSOC classically demonstrates genomic instability with copy number alterations but relatively few SNVs. Thus, the clinical activity of checkpoint blockade in these two diseases is consistent with previous data that tumor mutational burden plays an important role.

Our group has previously shown that tumor mutational load correlates with clinical benefit in metastatic melanoma and non-small cell lung cancer, thought to result from the increased odds of forming neoantigens. Indeed, neo-epitopes appear critical to drive T cell responses that can be re-invigorated by PD-1 pathway blockade. In melanoma, the cells re-invigorated by PD-1 blockade are exhausted CD8 T cells (T_{EX}). However, high mutational burden and re-invigoration of T_{EX} does not appear to fully explain clinical outcomes as there appears to be a threshold to the effect of mutational burden. The number of tumor mutations is

not a binary biomarker for response to checkpoint blockade and even in many MSI^{HI} patients with high mutational burden, checkpoint blockade fails. Thus, the relationship of the tumor mutational phenotype and the evolution of the tumor-immune interaction likely influence the outcome of immunotherapy.

Thus, we hypothesize that in tumors with high mutational burden (e.g. MSI^{HI}), failure to respond to checkpoint blockade is due to underlying baseline or tumor-induced immune dysfunction. We predict that T cell exhaustion and senescence will be two distinct types of immune dysfunction. Moreover, we suspect that the mechanism of MMR deficiency (germline versus somatic defects in DNA repair pathways) will differentially impact senescence versus exhaustion. Dissecting the immune defects present in patients with highly mutated tumors will provide insights into immune responsiveness and provide opportunities to predict outcomes and tailor treatment regimens,





Scientific Abstract

especially when compared to mutationally quiet HGSOc. To study our proposed aims, we will use samples from two clinical trials at MSKCC.

We also propose to study patients with MSI^H tumors treated with checkpoint blockade as standard of care. Samples from ongoing clinical trials at UPenn will serve as validation cohorts as we have done previously in melanoma.