



SU2C Endometrial Cancers Convergence Research Team:

“Responders and Nonresponders to Endometrial Cancers with Mismatch Repair Deficiencies”



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

About one-fourth of endometrial cancers (ie, the most common gynecologic malignancy with approximately 61,380 new cases and 10,920 estimated deaths related to the disease in the United States in 2017), 10-15% of advanced colorectal cancers, and a small but significant percentage of tumors arising from a variety of human organs including but not limited to stomach, small intestine, cervix, prostate, bile duct and liver, as well as neuroendocrine tumors, uterine sarcomas and ovarian cancers are characterized by mismatch repair (MMR) deficiency leading to microsatellite instability-high (MSI-H) phenotype, a high tumor mutational burden (ie, TMB) and lymphocytic infiltration.

Pembrolizumab is a monoclonal anti-PD-1 antibody blocking the interaction between PD-1 and its ligand PD-L1 and PD-L2. Recently published clinical trials with pembrolizumab have provided strong clinical evidence that patients with progressive MMR-deficient metastatic colorectal and non-colorectal **cancers**, may be highly responsive to PD-1 blockade, with up to 53% experiencing complete or partial response to treatment . Unfortunately, it currently remains unknown why only 50% of patients harboring MMR-deficient, MSI-H metastatic/recurrent tumors respond to anti-PD1 treatment.

Due to the high prevalence of MMR-deficiency and high clinical response rate to anti-PD-1 blockade , endometrial cancer patients may represent an ideal population to study per SU2C grant guidelines data and computation-intensive collaborations that will advance our understanding of the human immune system and cancer immunotherapy.^[1,2] Accordingly, we are planning to take advantage of the reagents (ie, tumor tissue and peripheral blood and serum) prospectively/longitudinally collected within an investigator initiated study (IIT) currently in progress at Yale University (PI: Alessandro Santin MD) entitled “A phase II evaluation of pembrolizumab, a humanized antibody against PD-1, in the treatment of persistent or recurrent hypermutated/ultramutated endometrial cancer identified by next generation sequencing (NGS) and comprehensive genomic profiling (CGP)” ClinicalTrials.gov Identifier: <https://clinicaltrials.gov/ct2/show/NCT02899793> (clinical study component supported by Merck, total enrollment 25 pts) to answer the following questions:

- *How can we predict responders from non-responders to checkpoint inhibitors?*
- *Can we predict patients that will develop side effects to these therapies? How can we relate the peptide sequence of antigens to the nucleic acid sequence of T-cell receptor variable regions?*
- *Can we predict peptide antigens from T cell receptor sequences? Can we determine with*





Scientific Abstract

some confidence the neoantigens that are expressed by tumors that are recognized by the immune system in an HLA dependent fashion?

