**Dr. Kimberly Komatsubara**

**Project Title:** A Phase II Study of Epacadostat (IDO inhibitor) and Pembrolizumab in Patients with Imatinib-Refractory Advanced Gastrointestinal Stromal Tumors

**Abstract:**
While targeted therapy with imatinib has significantly improved survival for patients with inoperable and metastatic gastrointestinal stromal tumors (GIST), the majority will eventually progress after a median of 20-26 months. Standard second-line treatment with sunitinib has a response rate of 7%, and third-line treatment with regorafenib has a response rate of only 5%. More effective treatments for imatinib-refractory GIST are needed. There is pre-clinical and clinical evidence that the anti-tumor mechanism of KIT inhibition in GIST is partially mediated by effects on the immune system. Indoleamine 2,3-dioxygenase (IDO) is an enzyme that metabolizes tryptophan to immunosuppressive metabolites that suppress cytotoxic T effector cells and activate inhibitory T regulatory cells. In a GIST mouse model, KIT inhibition with imatinib alters the tumor immune microenvironment by inhibiting IDO. Further, imatinib enhances the effect of anti-CTLA-4 and anti-PD-1 therapy in mice. We have also observed clinical benefit in refractory GIST patients treated on our ongoing phase I trial of dasatinib and ipilimumab. This data suggests that inhibition of IDO may be an important anti-tumor mechanism in GIST and can be combined with checkpoint inhibition to potentiate tumor control.

For Aim 1, we will assess the efficacy of combined IDO and PD-1 inhibition in a single-arm phase II study of epacadostat (IDO inhibitor) and pembrolizumab (anti-PD-1 antibody) in patients with imatinib refractory GIST (N=23 patients), with a primary endpoint of objective response rate using immune related RECIST criteria. For Aim 2, we will characterize the effects of IDO and PD-1 inhibition on the tumor immune microenvironment by analyzing baseline and post-treatment (after 6 weeks of therapy) tumor biopsies for IDO activity and expression, tumor infiltrating lymphocytes, and PD-L1 expression. We hypothesize that treatment with epacadostat and pembrolizumab will increase the response rate compared to what has been historically achieved with salvage tyrosine kinase inhibitor therapy. This trial will evaluate a novel combination of an IDO inhibitor with anti-PD-1 therapy, as well as further characterize the effects on the tumor immune microenvironment in GIST. Results of this trial may ultimately lead to a more effective treatment option for imatinib-refractory GIST patients.