Progress Updates

SU2C Colorectal Cancer Dream Team:

"Targeting Genomic, Metabolic, and Immunological Vulnerabilities of Colorectal Cancer"

The Team's work in correlating genomic features and immune signatures in colorectal cancer has shown that a particular signaling pathway in cancer cells -- the Wnt pathway – can be a driver of resistance to immunotherapy. This suggests that the Wnt pathway is a potential target for treatment that would help immunotherapies to work better in defeating the cancer. The Team has shown the potential of aspirin as a treatment for colorectal cancer that is driven by a certain type of genetic mutation. And finally, the Team's work on cell-free DNA is showing that it can be helpful in detection and treatment of colorectal cancer.

January 2021

- The Team conducted a phase III, open label trial, treating patients with MSI-H-dMMR metastatic CRC with pembrolizumab in the first-line setting. The results of this trial have been published in *The New England Journal of Medicine*, and has resulted in the FDA approval of pembrolizumab for use in MSI-H-dMMR metastatic CRC in the first-line setting.
- The Team has continued with enrollment of patients to a Phase III Colorectal Cancer trial, with additional Dream Team site activations.
- The Team has completed enrollment and correlative analyses across Cohort B of the Vitamin C trial (Vitamin C monotherapy in KRAS/BRAF mutant colorectal cancer).
- The Team has been continuing their dose escalation studies of high dose Vitamin C with radioembolization for colorectal liver metastases.
- The Team has continued to enroll the phase II study of PI3K inhibitor copanlisib with nivolumab in advanced colorectal cancer, with completion of enrollment expected this quarter, followed by analysis of correlative specimens for translational endpoints soon thereafter.

June 2021

- The Team has data highlighting the potential for machine learning assessment of H&E-stained sections to provide robust, quantitative tumor-immune biomarkers for precision medicine.
- The Team has found that yogurt may help prevent precursors of CRC, with a potential increased benefit for men as compared to women.
- The Team has completed patient enrollment to the phase II trial of pembrolizumab in high TMB, mismatch repair proficient cancers.
- The Team has been conducting a phase II clinical trial where patients can be treated with a new drug called CB-389, in combination with a chemotherapeutic drug used in CRC treatment called capecitabine. Of the 14 patients who have completed treatment, five have not experienced disease progression after 6-months.

January 2020

- The Team has assessed various therapeutics that demonstrate the ability to induce potent neoantigens in non-immunogenic tumors. These findings are now being tested in a pre-clinical setting and being translated to a Phase II clinical trial.
- The Team has data supporting the concept of therapeutic resistance being associated with clonal diversity, which is the opposite of the current accepted dogma.
- The Team has created novel Vitamin C analogue biomarkers that are being used in preclinical imaging and being planned for use in first-in-human trials this summer.

Progress Updates

- The Team has continued defining the mechanism of action for CB-839, including the creation of a pharmacodynamic assay for elucidating CB-839/glutaminase interactions

June 2019

- The Team has continued enrollment and correlative analyses in their vitamin C and PIK3CA trials
- The Team has discovered that SMAD4 loss correlations with colorectal cancer recurrence, loss of immune infiltrate and chemoresistance.
- The Team has found a possible role of calcium in cancer immunoprevention via T cell function modulation.
- The Team has preclinical data linking high-fructose corn syrup to enhanced intestinal tumor growth in mice.

January 2019

- The team has worked to build better combinations of targeted drugs for colorectal cancer.
- Promising laboratory results have prompted a clinical trial of the B-Raf inhibitor dabrafenib + MEK inhibitor trametinib + the anti-PD1 inhibitor PDR001.
- The team has completed a Phase I clinical trial and has shown safety for combination therapy with the glutaminase inhibitor CB-839 and capecitabine for patients with PIK32CA-mutant metastatic colorectal cancer.
- The team is exploiting the vulnerability of colorectal cancers with mutant KRAS or BRAF to ascorbate. Of the subjects treated so far, two have exhibited disease stabilization.
- Initial analyses of six patients enrolled in their vitamin C trial suggest that high-dose vitamin C increases DNA damage repair pathways, as well as ROS cellular regulation pathways.
- The team designed a new clinical trial arm that will combine the DNA damage effects of vitamin C with therapeutic doses of liver directed radioembolization (Y90 therapy).

June 2018

- The team has identified two genes involved in DNA repair that are highly mutated in colorectal cancer patients.
- The team has found that activation of the WNT/β-catenin signaling pathway may help cancer cells evade the immune system. Drugs that block this pathway may help a patient respond better to immunotherapy.
- The team has opened a clinical trial testing a combination of vitamin C and phenformin (a drug that can increase the uptake of vitamin C) with the hope of inhibiting tumor growth.
- Based on promising results from its phase I study, in March 2018 the team opened a phase II clinical trial that combines a new drug called CB-839 with capecitabine, a chemotherapeutic drug used in CRC treatment.

December 2017

- The Team found potential parameters that can be used to predict how effective a patient's immune system can be in fighting cancer cells.
- The Team has developed a tool that can help tell if Vitamin C is trafficked into tumor cells. This tool would be helpful as they conduct the clinical trial with Vitamin C.
- The Team is conducting 5 clinical trials and is planning 9 clinical trials that tests different kinds of treatment strategies: chemotherapy, targeted therapy, and immunotherapy. In these trials, they are particularly paying attention to the mutations in the tumors of the patients that they treat so that they can determine which drugs can be more effective to treat different groups of patients depending on the kind of mutations that their cancer cells have.
- The Team has shown that circulating DNA in the blood can be used to identify the mutations of a patient's cancer tissue. By using DNA in the blood, the response of a patient's tumor to treatment can be more easily monitored than having to get a tumor biopsy frequently.