Title of Research
Correlation of Medications and Medical Comorbidities with Clinical Response and Toxicity during Treatment with Ipilimumab

Lead Researcher
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Summary of Research
Cancer treatment is being revolutionized by checkpoint inhibitors, which help to stimulate the patient's immune system to fight their cancer. These medications can be very effective, but can also cause the immune system to attack otherwise healthy cells and organs, resulting in dangerous side effects. Though many projects have provided insight into the activity of these drugs, it is still difficult to predict which patients will respond or experience toxicities.

In addition to receiving checkpoint inhibitors, cancer patients are often being treated for other common medical conditions, such as heart disease or diabetes. Published studies suggest that many diseases, medications and environmental factors may impact the functioning of the immune system. For example, smoking, a history of psychological stress/depression, low levels of vitamin D and elevated neutrophil levels have been linked to the development of inflammatory disorders of the colon in patients not receiving checkpoint inhibitors. Such features may serve as modifiers of risk and benefit, as classifiers of response probability, or as signifiers of novel mechanisms for response and toxicity. Considering these features in aggregate may define immunologic subtypes with greater predictive power for response and toxicity than they would have in isolation.

The researchers have initiated a clinical review of patients with various underlying malignancies who received checkpoint blockade as part of their treatment at the Dana-Farber Cancer Institute (a total of 100 to date). They identified several novel clinical features associated with response and toxicity, including improved overall survival in patients treated with aspirin and decreased overall survival in patients with type II diabetes. There was a trend towards increased survival and increased frequency of toxicity requiring systemic steroids in patients taking vitamin D. These findings are supported by preclinical data.

This study will examine multiple studies that treated cancer patients with checkpoint inhibitors, to see if medications or medical conditions might predispose patients to respond or develop toxicity. This is believed to be the first study of its kind, and could identify new avenues for research to improve outcomes for patients.

Study Design
The researchers will first evenly divide all pooled patients into "exploratory" and "confirmatory" data sets, to decrease the risk that findings are the result of chance. They will use multiple analytic techniques to determine whether particular medications, medical conditions, or other clinical factors predict response or toxicity. These analyses will look at these variables alone and in combination with one another in the exploratory data set and then confirm them in the confirmatory data set. Primary endpoints for the analysis are: overall survival two years following initiation of study drug; and incidence of certain levels of toxicity that were attributed to study drug or coded as "immune-related" toxicities. Secondary endpoints for the analysis include: progression-free survival; clinical benefit (defined as a complete response, a partial response or stable disease for six months or more); and incidence of other levels of toxicity.

Access to clinical trial data was requested in several areas: demographic data including basic demographics, melanoma subtype, tumor staging, smoking status, and prior therapies; known genetic or histologic modifiers such as BRAF or PD-L1 status; treatment response and survival; adverse events; concomitant medications; medical comorbidities; and baseline laboratory data including complete blood counts, complete metabolic panels, hemoglobin A1c, 25-hydroxy vitamin D levels, and cytokine levels, if available.

Study Population
The study population will comprise all patients enrolled in the clinical trials listed below who received ipilimumab as a single-agent or in combination with peptide vaccines. All of these patients will be considered in toxicity analyses. Only studies enrolling patients with measurable disease will be considered in efficacy analyses.

Funding Source of Research
This project is funded by the Center for Immuno-oncology at the Dana-Farber Cancer Institute.

Requested Study
CA184-013 (NCT00050102): Comparison Study of MDX-010 (CTLA-4) Alone and Combined With DTIC in the Treatment of Metastatic Melanoma

CA184-002 (NCT00094653): MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients With Unresectable or Metastatic Melanoma

CA184-025 (NCT00162123): A Companion Study for Patients Enrolled in Prior/Parent Ipilimumab Studies

CA184-004 (NCT00261365): Phase II Study to Determine Predictive Markers of Response to BMS-734016 (MDX-010)

CA184-042 (NCT00623766): Evaluation of Tumor Response to Ipilimumab in the Treatment of Melanoma With Brain Metastases

CA184-078 (NCT00796991): Drug-Drug Interaction - 3 Arm - Carboplatin/Paclitaxel, Dacarbazine

CA184-087 (NCT00920907): Comparison of Ipilimumab Manufactured by 2 Different Processes in Participants With Advanced Melanoma

CA184-396 (NCT01990859): Phase 2 Study of Ipilimumab in Japanese Advanced Melanoma Patients

CA184-016 (NCT00084656): Monoclonal Antibody Therapy and Vaccine Therapy in Treating Patients With Resected Stage III or Stage IV Melanoma

CA184-022 (NCT00289640): Study of Ipilimumab (MDX-010) Monotherapy in Patients With Previously Treated Unresectable Stage III or IV Melanoma