Title of Research
Evidence-Based Prescribing of Ipilimumab vs. Dacarbazine for Advanced Melanoma: Using Advanced Predictive Analytics to Integrate Treatment Effectiveness and Patient Values

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Data Sharing Agreement Date
April 17, 2018

Summary of Research
This request for CA184-024 trial dataset is for research for Hadi Beyhaghi's dissertation.

Melanoma accounts for the majority of deaths due to skin cancer and remains a global public health concern. Advanced melanoma is the most aggressive form of skin cancer and is associated with poor prognosis with median overall survival ranging from 5.1 to 24.3 months. Recent progress in the treatment of advanced melanoma, particularly with checkpoint immunotherapy, has led to some patients becoming long-term survivors with the same risk of death as those who did not have cancer. However, long-term follow-up is the ultimate way to determine whether this distinct subpopulation truly exists (in terms of survival), and the predictors of long-term survival are not yet fully understood. This apparently distinct subgroup of patients, if not distinguished, can introduce heterogeneity in clinical outcomes, such as overall survival (OS). This heterogeneity poses several challenges, which render traditional statistical analyses used to estimate treatment effects biased or insufficient. This application seeks to address three of these challenges:

1. Estimating long-term treatment effect using trial data may be difficult in situations where therapies result in some patients failing quickly and others having long survival (Aim 1)
2. Developing treatment rules based on patients characteristics can be a challenge for standard regression models in the context of heterogeneous treatment response, particularly when there are numerous potential outcome predictors and a limited sample size/short follow-up of clinical trials (Aim 2)
3. Incorporating patients' differential preferences in individualized treatment rules adds a further layer of complexity that needs to be tackled to make optimal treatment decisions (Aim 3).

This research will analyze data from the CA184-24 trial – a rich checkpoint immunotherapy trial with a long follow-up period – using novel statistical approaches to answer questions regarding outcomes prediction and selecting the best treatment option for advanced melanoma patients.

Study Design

This retrospective, longitudinal study will analyze patient-level data previously collected in the CA 184-24 clinical trial. Patients participating in this trial were followed up for more than five years and their health outcomes, including how long they lived after receiving treatment, were recorded. Access to data is 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.

We will describe, apply, and evaluate the performance of novel statistical methods to answer some of the methodologically-challenging questions regarding outcomes prediction and treatment selection for advanced melanoma. We will use data from a clinical trial that compares two drugs for patients with advanced melanoma. This research has three aims:

1. To evaluate a new statistical method to predict health outcomes using clinical trials data. This will involve evaluating the performance of recursively imputed survival trees (RIST) versus standard parametric models for projecting survival from trial data in the context of prolonged time to event.
2. To identify clinical characteristics to optimize treatment decision-making. This will involve developing individualized treatment rules based on patient characteristics to maximize overall survival in patients with advanced melanoma using outcome-weighted learning.
3. To develop a decision guide that incorporates patient preferences. This will involving integrating the heterogeneity of patients' preferences (in addition to patient characteristics) into individualized treatment rules to support the selection of advanced melanoma treatment. The goal will be to optimize individually preference-weighted outcomes using an outcome-weighted learning approach.

For the first aim, we assume that only the first two years of data are available. Using trial data from the first two years of follow up, we will use a novel statistical method to predict patients' health outcomes (in this case how long they will live after receiving the treatment) based on their characteristics and the treatment received. We will evaluate the predictive performance of the method by comparing these predictions with what was observed in reality (using the full length of the follow up data).

For the second aim, we will analyze the trial data to determine which treatment can maximize patients' survival based on features such as age, sex, and the melanoma tumor characteristics. For this aim, we will use another novel statistical method that analyzes the clinical trials data. The proposed method aims to determine what patient characteristics directly predict the success or failure of different treatment options. This should enable development of a decision guide to help select the best treatment for each patient.

For the third aim, we use a similar statistical method to that used for the second aim. We will analyze the trial data to determine what treatment works best when we consider the patient's unique preferences relating to the various health outcomes, including overall survival, treatment costs and side-effects.

Study Population
The study population comprises participants in trial CA 184-24. Among a total of 502 patients with previously untreated metastatic melanoma (250 assigned to ipilimumab plus DTIC and 252 to DTIC monotherapy), 498 patients were treated (247 to ipilimumab plus DTIC and 251 to DTIC monotherapy).

Funding Source of Research
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Requested Study
CA184-024 (NCT00324155): Dacarbazine and Ipilimumab vs. Dacarbazine With Placebo in Untreated Unresectable Stage III or IV Melanoma