Impact of Concomitant Statin Use on Efficacy and Toxicity of Ipilimumab

SECTION 1: PROPOSED RESEARCH PLAN

Requestor: Conry, Robert Martin
Title of the Proposed Research: Impact of Concomitant Statin Use on Efficacy and Toxicity of Ipilimumab

Summary of the Proposed Research: For background information regarding the T cell immunosuppressive and anti-inflammatory effects of statins with references, please see Section 5 (Additional Supporting Information) below.

I believe it is essential that we examine the effects of concomitant statin use on the efficacy of ipilimumab to ensure that continuation of statins does not impair immune activation and melanoma control. Likewise, the impact of statin use on the incidence of immune-related toxicities should also be examined as the anti-inflammatory effects of statins may reduce toxicity. Published results of a phase 3 trial of ipilimumab (MDX 010-20) have indicated that approximately 20% of patients took concomitant lipid-lowering agents, predominantly statins, although no analysis was undertaken to evaluate their impact on efficacy or toxicity(1). Thus, most large-scale trials of ipilimumab should contain a sufficient number of patients on statins to address the questions. I believe this issue demands immediate attention due to potential far reaching implications for concomitant use of this very prevalent drug class, statins, with all forms of immune checkpoint inhibition in multiple malignancies.

I propose to query data sets from the three phase III trials of ipilimumab listed above to determine the percentage of patients with concomitant statin use and to compare previously reported endpoints of efficacy and toxicity with statin non-users as a screen for any differences without necessarily needing to pre-define statistical parameters. If differences are identified, their statistical significance could then be examined and could provide a rationale for querying other data sets. It would be nonproductive to attempt to pre-define statistical parameters without first determining the number of patients in each trial with and without concomitant statin use.
Study Design: One or more of the phase III trials of ipilimumab cited above will be examined to determine the percentage of patients in each treatment arm with vs. without concomitant statin use. Once the sample sizes of the different treatment groups with or without statin use are known, the University of Alabama at Birmingham (UAB) Biostatistics Unit will provide a statistical analysis plan to compare efficacy endpoints previously defined in the trials such as overall response rate, progression-free survival and landmark survival between statin users vs. non-users within each treatment group. Similarly, the incidence of grade 3 or 4 toxicities will likewise be compared between statin users and non-users within the same treatment group. Although Dr. Conry is prepared to perform this analysis without assistance from BMS, he would certainly welcome the opportunity for this question to be addressed as a collaborative effort with BMS.

It would certainly seem to be in the interest of BMS to have this analysis performed. If statins prove to reduce ipilimumab efficacy, future trials could restrict concomitant statin use (which can typically be eliminated or substituted) and thereby improve response. If statins diminish ipilimumab toxicity without affecting efficacy, then they may add an important new drug class for managing immune related AEs. Furthermore, the impact of statins on ipilimumab would have important implications for optimizing trials of nivolumab as well. It would not be too surprising to find that statins impair immune recognition of cancer analogous to steroids. If so, this needs to be recognized so that future checkpoint inhibitor trials control for their use. I have discussed this issue with Joseph Ritchie, the BMS MSL for my area, and he recommended that I request access to the above cited trial data to answer this important question.

Study Population(s): Patients with stage III or IV melanoma participating in one of the three cited phase III trials of ipilimumab

Primary and Secondary Endpoints: The same primary and secondary efficacy endpoints previously reported in each trial will be analyzed to compare statins users vs. non-users. Likewise, the incidence of grade 3 and 4 toxicities will be compared between statin users and non-users.

Statistical Analysis Plan: To formulate a useful statistical plan, it will first be necessary to determine the number of statin users and non-users in each treatment cohort from each trial. The Biostatistics Unit of the UAB Comprehensive Cancer Center will then be consulted to derive a plan for statistical comparisons of efficacy and toxicity.

Publication/Communication Plan: Dr. Robert M. Conry will inform representatives of BMS of any statistically significant differences between statin users vs. non-users regarding ipilimumab efficacy or toxicity as this may influence design and interpretation of future trials of ipilimumab and perhaps nivolumab. Dr. Conry also plans to publish any statistically significant impacts of statins on ipilimumab efficacy or tolerability in a peer-reviewed journal. In fact, a sufficiently powered negative result showing no apparent impact of statins on toxicity or efficacy of ipilimumab would likely also be worthy of publication given the growing body of evidence supporting immune modulation by statins.

SECTION II: PROPOSED RESEARCH TEAM

Proposed Research Team: Robert M. Conry, M.D.
Associate Professor of Medicine
Melanoma Program Director
University of Alabama at Birmingham and Biostatistics Unit, UAB Comprehensive Cancer Center

SECTION V: ADDITIONAL SUPPORTING INFORMATION
A number of recent studies have indicated that statins have pleotropic effects on immune responses, and statins have proven effective in the treatment of autoimmune diseases in animal models. Mechanisms responsible for the immunosuppressive effects of statins in mouse models include increased generation of Foxp3(+) T regulatory cells(2) as well as increased production of immune regulatory cytokines IL-10 and TGF-beta which promote immune tolerance during tumor development(3). Retrospective analysis of 567 patients with hematologic malignancies who had hematopoietic cell transplantation revealed statin use by the donor was associated with decreased risk of grade 3-4 acute GVHD (HR 0.28) and statin use by both donor and recipient eliminated grade 3-4 acute GVHD in all patients studied(4). Similar retrospective analysis of 1206 patients undergoing hematopoietic transplantation for hematologic malignancies revealed recipient statin treatment at the time of transplant significantly decreased the risk of chronic GVHD, but also compromised the graft-versus-tumor effect(5). Statins have also been shown to reduce pulmonary inflammation in patients with community-acquired pneumonia(6) and to reduce C-reactive protein serum levels as a marker for inflammation in a case-control study of over 300 statin users(7). The above cited publications represent only a small portion of the mounting body of evidence that statins are immunosuppressive and anti-inflammatory.

References

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