melanoma and other skin tumours

1090PD GENETIC DETERMINANTS OF IPILIMUMAB OUTCOMES FOR ADVANCED MELANOMA

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Aim: Ipilimumab has substantially increased survival for patients with advanced melanoma, however, the benefit is only observed in a small portion of treated patients. Clearly there are yet unknown factors that affect response. Unlike host immunity and tumor microenvironment, the underlying genetic factors, as putative markers of response, have been sparsely studied. To date, the role of germline genetic variants in the modulation of immunotherapy response has been almost completely unexplored. To this end, we have performed whole-exome sequencing (WES) to discover novel germline determinants of response to ipilimumab therapy for metastatic melanoma.

Methods: Blood samples were collected from 80 metastatic melanoma patients treated with ipilimumab at the New York University Cancer Center. WES was performed on objective responders (OR) and non-responders (NR), defined by immune-related response criteria, using the Nextera platform (Illumina) at average 30x coverage. Patient and tumor characteristics were obtained from a well-annotated institutional database. A novel method for testing the association between OR and NR by variant and gene/molecular network enrichment was implemented. Gene-Set Enrichment Analysis and Pathway Studio were used to test the pathway associations.

Results: The preliminary analysis evaluating the first 30 OR and 30 NR identified significant associations with ipilimumab response for several loci including RPS6KB1 (p = 0.001) and LNX2 (0.001). In addition, the pathway analysis showed significant associations for SMAD 3 (p = 0.04) and interleukin 1 (p = 0.04) related pathways.

Conclusions: The preliminary findings on a subset of 60 patients provide promising evidence for the presence of germline genetic factors associated with response to ipilimumab therapy. While several novel genetic loci (RPS6KB1, LNX2) and molecular pathways (SMAD3, interleukin 1) have been identified in our preliminary scan, the study is currently undergoing a larger expansion involving >80 patients, anticipating the final analysis to be complete by September 2014. This expanded analysis will not only provide a validation of the current novel findings but, due to a substantial increase of power, will also have a greater ability to display the true effect of additional novel germline genetic factors modulating immunotherapy response.

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