Immunological profiling of baseline and resected biopsies from locally/regionally advanced/recurrent melanoma treated with neoadjuvant combination ipilimumab (3mg/kg or 10mg/kg) and high dose IFN-α2B
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Abstract
Background
Melanomas are the most responsive tumor type to immune checkpoint blockade, but clinical response rates remain suboptimal. Gene expression profiling of the pretreatment tumor biopsies is an attractive approach to developing predictive biomarkers of response because it is able to directly measure the activity of the immune system within the tumor. Furthermore, characterization of the transcriptional changes induced by treatment allows insights into the mechanism of action of the therapy. UPCI 11-063 is a clinical trial to assess the safety of two doses of ipilimumab combined with high dose IFN-α2B (HDIF) in the neoadjuvant setting. Both treatment regimens induce clinical responses, with reduced toxicity observed in the low dose ipilimumab arm. This study is a follow on biomarker analysis to investigate gene expression in pretreatment and post treatment biopsies.

Results
Transcriptional profiling of tumor biopsies collected prior to treatment or at the time of surgery was performed in order to find patterns of gene expression that correlated with pathological response (pCR), radiological response (RR) or recurrence-free survival (RFS). In the baseline tumor biopsies, a number of genes were positively associated with pCR, including several members of the WNT signaling pathway. The Tumor Inflammation Signature (TIS), a signature of a perioperatively suppressed immune response in the tumor, was associated with longer RFS. Differential gene expression of paired pre- and post-treatment biopsies identified a number of genes upregulated in response to ipilimumab/IFN treatment, including signatures of multiple immune cell populations, including T cells and macrophages, which were associated with pCR.

Methods
This was a Phase II trial of 30 patients with locally/regionally advanced/recurrent melanoma who received either high (10 mg/kg) or low (3 mg/kg) dose ipilimumab plus HDIF. Tumor biopsies collected prior to treatment and at the time of surgery (6-8 weeks after the initiation of neoadjuvant therapy). RNA was transcriptionally characterized with the NanoString PanCancer Immune Profiling, Pathways, and Progression panels and custom gene content. Gene expression analysis was performed on single genes and well as gene signatures, including the Tumor Inflammation Signature, which characterizes a pre-existing adaptive immune response and was developed as a predictor for response to immune checkpoint blockade.

Tumor Inflammation Signature
- Biomarker classifier that measures a suppressed adaptive immune response within the tumor
- The signature is a weighted linear algorithm that measures 18 genes associated with presence of antigen presenting cells, T/NK cells, T cell receptor activity, and T cell exhaustion markers and normalizes their expression to 10 housekeeper genes.
- Developed as a pan-cancer predictor for clinical response to PD-1 checkpoint blockade (Ayers 2017, JCI)

Baseline TIS Predicts pCR

Performance of Tumor Inflammation Signature
Baseline TIS Predicts pCR

Conclusions
- Samples from 28 melanoma patients treated with neoadjuvant ipilimumab/IFN were profiled with NanoString gene expression panels
- Expression profiling of pre and post treatment samples suggested a mobilization of immune cells to the tumor, consistent with activation of local immunity
- The TIS, which predicts response to immune checkpoint blockade in a variety of solid tumors, may also be useful in the setting of ipilimumab/IFN.
- In depth profiling with NanoString platform identifies potential hypotheses that may be tested in future studies

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