CTLA-4 Overexpression Does Not Confer Response to Ipilimumab in Melanoma

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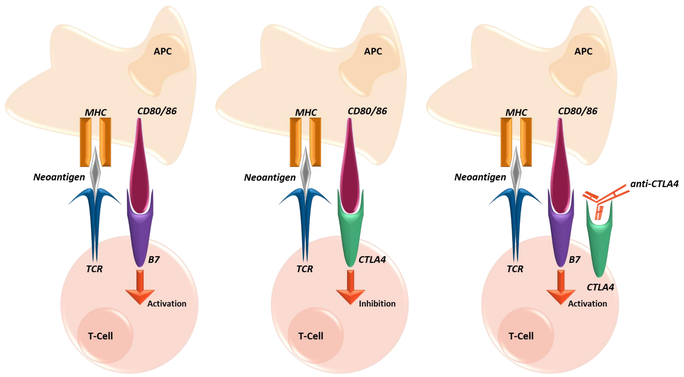
Introduction

CD8 positive tumor infiltrating lymphocytes (TILs) are under investigation as a marker of response to checkpoint inhibitors because they are highly associated with adaptive immune response. Given the growing number of trials for new indications for combination ipilimumab + nivolumab, lack of predictive markers for ipilimumab, and evidence to support therapeutic target overexpression as markers of response, we examined the role of CTLA-4 expression and the presence of CD8+ TILs in response to ipilimumab and combination ipilimumab + nivolumab in malignant melanoma



Methods

Pre-treatment formalin-fixed paraffin embedded (FFPE) melanoma tissue samples taken prior to treatment by ipilimumab (n=36), or combination ipilimumab + nivolumab (n=10), were evaluated for the abundance of 394 immune transcripts, including CD8 and CTLA4, by the RNA-Seq component of a comprehensive immune profiling panel (Figure 1). Results for all transcripts, including CTLA4 and CD8 (defined as the mean of CD8A and CD8B transcripts) were QC filtered, normalized and ranked based on a reference population of various tumor types.

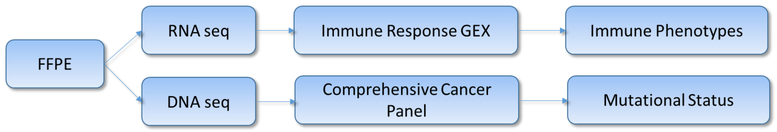
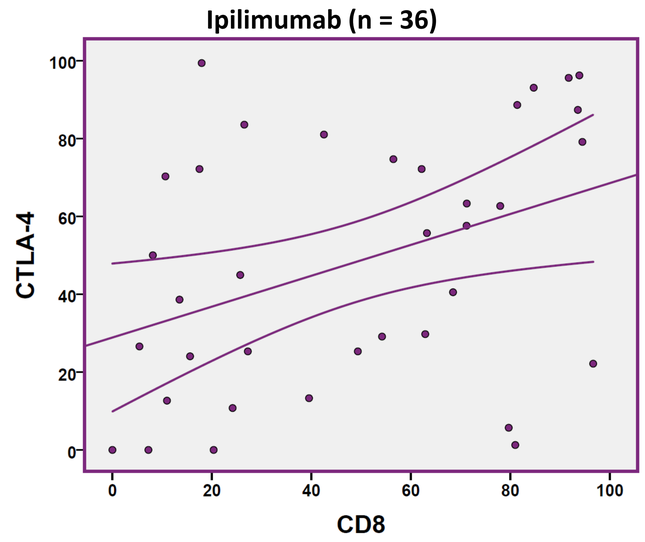
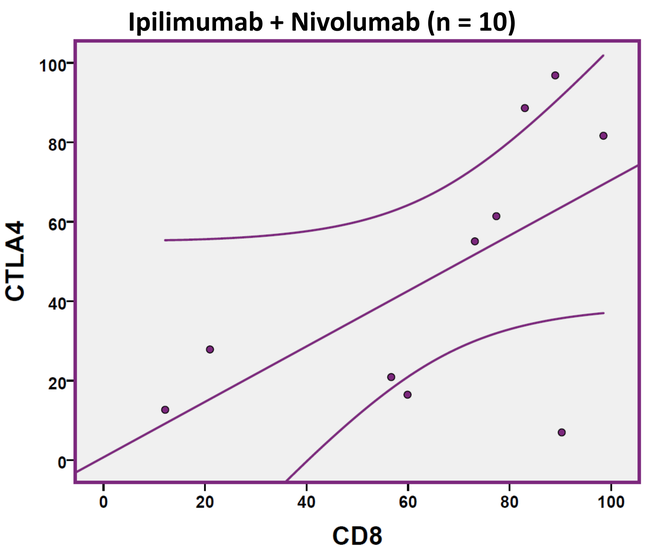


Figure 1: NGS workflow

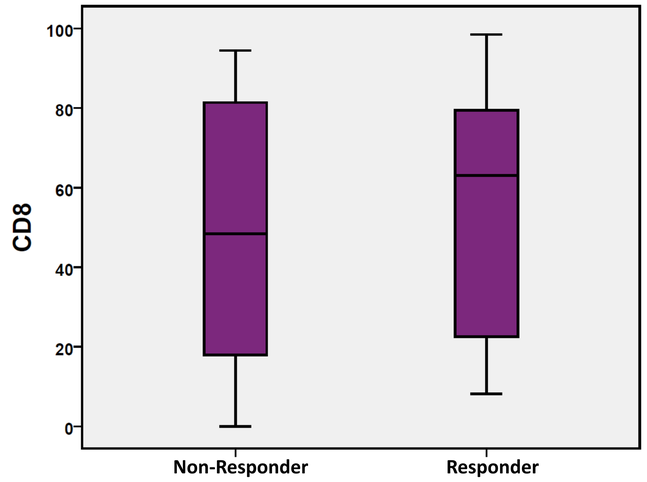
Retrospective chart review was performed to assess treatment response following RECIST v1.1. Clinical benefit (responders) were defined as having CR, PR, or SD with at least 6 months of survival from first dose. Non-responders were defined as PD or SD with less than 6 months of survival post-first dose. Pearson correlations and independent samples t-tests were performed to assess associations between CTLA-4 and CD8, and differences in expression between responders and non-responders.

Results

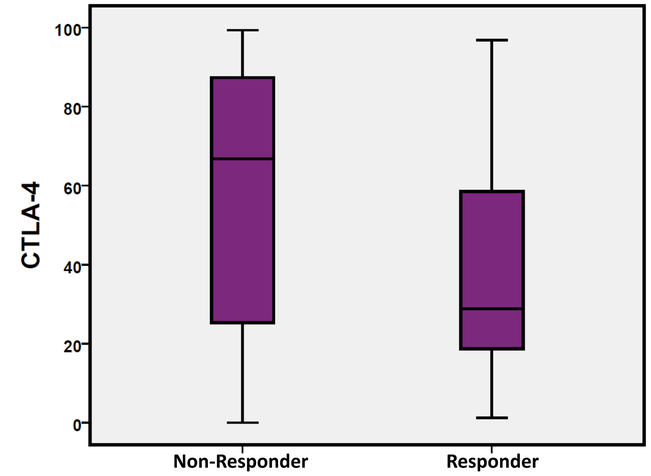




Modest positive associations between CTLA-4 and CD8 (TILs) were observed for melanoma patients treated by single agent ipilimumab ($r^2 = 0.39$, $p = 0.02$), and patients treated by dual agent ipilimumab + nivolumab ($r^2 = 0.60$, $p = 0.07$).



Higher mean levels of CD8 (TILs) were observed in responders, with no significant difference between responders (M = 57.1, SD = 30.2) and non-responders (M = 48.6, SD = 32.9); $t(44) = -0.895$, $p = 0.313$).



Lower mean levels of CTLA-4 were observed in non-responders for both regimens, with a modestly significant difference between responders (M = 54, SD = 35) and non-responders (M = 38.7, SD = 26.8); $t(44) = 1.769$, $p = 0.046$.

Conclusions

- In this small melanoma study, we confirm that decreased expression of CTLA-4 appears to be associated with increased expression of CD8 (TILs), as well as response to ipilimumab checkpoint blockade, suggesting these patients are inherently immunogenic.
- Additional biomarkers of response for patients with overexpression of CTLA-4, including CD8 should be further explored.

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