P100

Pretreatment gene expression signature correlation with clinical response to pembrolizumab or nivolumab in metastatic melanoma

Abstract

Background
PD-1 checkpoint blockade with the therapeutic antibodies, pembrolizumab or nivolumab, improves survival in patients with metastatic melanoma. However, not all patients experience clinical benefit. The NanoString® Tumor Inflammation Signature (TIS) measures genes associated with CD8+ T cells, natural killer cells, IFN signaling, and antigen presentation that are reflective of a pre-existing, PD-1-suppressed adaptive immune response within the tumor and associated with positive treatment outcomes in pembrolizumab in advanced-stage melanoma and other solid tumors. Here, we evaluate the TIS in pre-treatment tumor biospecimens obtained from patients receiving either nivolumab or pembrolizumab. We also assess differential gene expression in PD-1-responsive vs. non-responsive melanomas to identify potential resistance mechanisms which could be targets for further therapeutic intervention.

Results
The TIS predicted clinical benefit from pembrolizumab (n=56), but was not predictive for nivolumab (n=20), although the small sample size may limit statistical power. Additionally, the TIS was more predictive of PD-1/L1 IHC, as assessed by ROC curves. Clinical response to either therapeutic antibody was associated with an enrichment of immune gene signatures, and in depth transcriptional profiling reveal potential secondary mechanisms of immune evasion.

PD-1 Checkpoint Blockade

- Nivolumab and pembrolizumab block the negative regulatory receptor PD-1 on T cells from binding to its ligands PD-L1, expressed on tumor cells or antigen presenting cells, and PD-L2 on antigen presenting cells.
- Despite similar clinical efficacies, nivolumab and pembrolizumab are not identical, and these differences could result in as-yet-unknown differences in molecular activity or likelihood of individual patient response.

Tumor Inflammation Signature

- Biomarker classifier that measures a suppressed adaptive immune response within the tumor developed for use on the NanoString nCounter® platform.
- The signature is a weighted linear algorithm that measures 18 genes associated with presence of antigen presenting cells, T/NK cells, interferon 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 (4).

Sample Processing
Formalin-fixed, paraffin-embedded pre-treatment tumor biopsies from patients receiving either nivolumab or pembrolizumab in the community setting were profiled with NanoString’s nCounter gene expression codesets. A total of 76 patients were included from two independent cohorts. Clinical benefit to PD-1 therapy was defined as an immune-related complete or partial response. PD-1/L1 expression on tumor cells was evaluated by immunohistochemistry in 36 samples from the pembrolizumab-treated cohort using the 22C3 anti-PD-L1 antibody clone, and staining was scored by two independent pathologists.

Methods

Conclusions

- The TIS predicted clinical response to pembrolizumab, but limited numbers of nivolumab treated patients hinder interpretation. The current data suggests that TIS is not predictive for nivolumab, but validation and further studies will determine if this observation holds true in larger cohorts, and if it relates to differences between the two agents.
- TIS has superior predictive performance to PD-L1 IHC in this dataset, which confirms previous reports.
- Transcriptional profiling identifies other mechanism of immune evasion in patients where TIS score did not predict clinical performance. This could lead to the development of next generation diagnostics for immune oncology.