Highlights from ASCO-SITC 2019

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Upcoming Biomarkers Predictive of Response to Immunotherapy

Checkpoint inhibition has achieved significant success in the treatment of various tumor types. However, only a subset of patients achieve clinical benefit making it important to understand determinants of response. Three studies of interest at the recently concluded ASCO-SITC 2019 presented investigations around biomarkers predictive of response to immunotherapy – although early, these are steps towards improving outcomes with patient-centered approaches, and if validated have practice changing potential in the future.

Plasma proteomic profiling of patients with melanoma treated with anti–PD-1 therapy found 38 proteins differentially expressed between responders and nonresponders

- CD1c, CXCL13, CLEC5a, IL8, IGF1R, AREG and MIA are differently expressed in responders and non-responders
- A majority of these proteins are enriched within dendritic cells and monocytes/ macrophages, thus addressing a high unmet need for peripheral biomarkers
- Next steps include validation in an expanded cohort, determining the predictive value of these biomarkers toward response relative to intratumoral biomarkers such as IFNγ, PD-L1, TMB and possibilities of moving these into the treatment prediction setting

Mehta A et al, J Clin Oncol 37, 2019 (suppl 8; abstract 130, ASCO-SITC 2019)

A targeted gene sequencing approach covering 36 genetic alterations using plasma circulating tumor DNA (ctDNA) could help predict treatment responses to PD-1 blockade in advanced NSCLC

- Patients with STK11 or PTEN alteration are considered as immune inert and are associated with low response to immunotherapies; these patients should not be treated with immunotherapy
- Those with presence of KRAS and/or p53 transversion mutation constitute a highly immune cohort, amenable to PD-1 inhibition
- Also, early variations in ctDNA can accurately discriminate responders from nonresponders to anti-PD-1 therapy - patients who had a decrease in ctDNA at 1 month had significantly better outcomes than those who had no decrease
- Next steps involve prospective validation in larger and unselected patient populations, as well as determining if the performance characteristics of these plasma ctDNA tests will be adequate to alter therapy at early time points

Guibert N et al, J Clin Oncol 37, 2019 (suppl 8; abstract 103, ASCO-SITC 2019)

T-cell receptor diversity on an RNA basis may help predict the efficacy of the immune response to premalignancy of squamous cell carcinoma, potentially leading to intervention

- The diversity of TCRs was found to be negatively associated with a transcriptional signature of T-cell mediated immune activation ($p < 0.001$) - TCR diversity decreased in PMLs that regressed, compared to the PMLs that progressed or were stable ($p = 0.045$)
- The study has several limitations - bulk RNA-Seq can capture only a fraction of the T-cell receptors and the lack of functional data; limited mutational data was available, making it difficult to decipher which antigens were driving an immune response
- Despite the limitations, these studies are beginning to reveal the role of the immune response in regulating the course of events in the very earliest stages of pulmonary premalignancy and are anticipated to facilitate early interception, and prevent progression into invasive disease

Maoz A et al, J Clin Oncol 37, 2019 (suppl 8; abstract 102, ASCO-SITC 2019)