SINGLE CELL ANALYSIS OF PHASE II STUDY OF NIVOLUMAB AND RELATLIMAB IN METASTATIC UVEAL MELANOMA REVEALS TUMOR AND IMMUNE RESPONSE TO DUAL PD-1 AND LAG-3 INHIBITION

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**Background** Uveal melanoma (UM) is the most common intraocular malignancy in adults, often leading to incurable metastatic disease. Prognosis for metastatic UM remains poor, with limited response to CTLA4 and PD1/PDL1 checkpoint inhibition. Recently, we discovered high expression of the checkpoint molecule LAG3 on CD8+ cytotoxic T-cells in metastasizing UM. We performed a clinical trial to evaluate the effect of combined PD-1 plus LAG3 inhibition in metastatic UM with correlative analyses of the immune response to therapy.

**Methods** We treated 27 patients. Blood samples and fine needle biopsies were collected for 26 patients. Of the currently processed 21 patient samples, correlative analyses were performed on metastatic UM biopsies (n=8) and circulating T cell samples (n=31) from patients at baseline (n=21) and the end of treatment (n=10). The tumor biopsies underwent single-cell RNA sequencing (scRNA-seq) analysis, whereas T cells underwent scRNA-seq and single cell T cell receptor sequencing (scTCR-seq).

**Results** Evaluating circulating T cells at baseline versus end of treatment, we identified T cell transcriptional profiles associated with therapy response, including patients with partial response (n=2), stable disease (n=7) and progressive disease (n=12). Furthermore, scTCR-seq revealed increased clonal abundance of select T cell populations following therapy. Using deep learning algorithms, we identified clonally expanded anti-melanoma circulating T-cells, which exhibited distinctive cytokine and immune checkpoint expression profiles.

**Conclusions** These findings indicate that T cells are capable of clonal expansion against melanoma-specific antigens in metastatic UM, and that LAG3/PD1 inhibition is associated with alterations in circulating T cells that may predict treatment response. These findings provide new insights into host immunity and response to LAG3 inhibition in metastatic UM.

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