## 94 CYTOF AND SERUM PROTEOMICS SHOW DISTINCT DIFFERENCES IN IMMUNE RESPONSES BETWEEN MYCOSIS FUNGOIDES AND SEZARY SYNDROME TO MONO- AND COMBINATION ANTI-PD-1 IMMUNOTHERAPY

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**Background** Cutaneous T cell Lymphoma (CTCL) is a rare malignancy of CD4+ T cells that has few treatment options. Mycosis Fungoides (MF) and Sezary Syndrome (SS) are the most common subtypes of CTCL, with MF confined to the skin and SS a leukemic variant. The PD-1 checkpoint inhibitor, Pembrolizumab, used as a single agent or in combination with Interferon Gamma (IFNg) to treat CTCL in two Cancer Immunotherapy Trials Network (CITN) studies produced positive clinical outcomes of ~38% in each trial. Additional therapeutic approaches are needed to treat patients refractory to therapy, and informative biomarkers are essential to predict patient response. Here we describe findings from multi-omic studies conducted in the two CITN trials that were designed to elucidate such biomarkers.

**Methods** A mass cytometry (CyTOF) antibody panel targeting phenotypic, metabolic, and functional proteins expressed by reactive and neoplastic human T cells was developed. This panel was used to interrogate PBMC at several longitudinal timepoints. The serum proteome was also evaluated at these time-points using the Olink platform.

**Results** CyTOF revealed that the neoplastic T cells, while having patient-specific phenotypic profiles, tended to overexpress checkpoint and exhaustion molecules as compared to reactive T cells. IFNg therapy induced robust activation of innate immune cells, while anti-PD-1 preferentially activated CD8+ T cells. Neither therapy had significant effect on the activation state of neoplastic T cells. PD-1 expression dropped dramatically across most T cell subsets, including neoplastic T cells, following anti-PD-1 therapy. Serum proteomic evaluation revealed that high levels of the chemokines CXCL9, CXCL10 and CXCL11 at baseline were associated with negative and positive clinical outcomes in MF and SS subjects respectively following anti-PD-1 therapy as a single agent. Though not statistically significant, treatment with exogenous IFNg may have reversed this trend.

**Conclusions** We describe features of the immune response as seen in MF and SS subjects following anti-PD-1 monotherapy and in combination with IFNg and emphasize that these subtypes behave as two distinct diseases in response to therapy. It is therefore important to analyze biomarkers in SS separately from MF as combining the diseases may cloud putative signatures.

**Ethics Approval** These studies were approved Fred Hutch IRB; CITN-10 (anti-PD-1 monotherapy) approval number 8268 and CITN-13 (anti-PD-1 plus IFNg combination therapy) approval number 8588.

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