NEUTROPHIL EXTRACELLULAR TRAPS (NETS) CAN BE MEASURED NON-INVASIVELY WITH CPA9-HNE – BIOMARKER POTENTIAL ACROSS DIFFERENT SOLID TUMOR TYPES IN THE IMMUNO-ONCOLOGY SETTING

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Background Serological predictive biomarkers to anti-PD-1 therapy across different solid tumor types represent an unmet medical need. High neutrophil activity is associated with poor response to immune checkpoint inhibitor therapy, amongst others due to the release of neutrophil extracellular traps (NETs) that have been shown to protect tumor cells against cytotoxic attacks. Human neutrophil elastase (HNE) and calprotectin are the major NETs constituents. We have previously shown that high levels of a serum calprotectin assay, which quantifies a specific HNE generated calprotectin fragment (CPa9-HNE), as a measure of neutrophil activity, associate with poor response to anti-PD-1 therapy in metastatic melanoma patients. The aim of this study was to investigate the performance of CPa9-HNE in serum from patients with other solid tumor types.

Methods HNE mediated degradation of calprotectin (CPa9-HNE) was measured in pretreatment serum from 223 patients with bladder cancer (n=20), breast cancer (n=20), colorectal cancer (n=20), head and neck cancer (n=20), kidney cancer (n=20), liver cancer (n=3), lung cancer (n=20), melanoma (n=20), ovarian cancer (n=20), pancreatic cancer (n=20), prostate cancer (n=20), and stomach cancer (n=20), and compared to age-matched healthy controls (n=33). Statistical differences were analyzed using the Kruskal-Wallis test adjusted for Dunn's multiple comparisons test.

Results CPa9-HNE serum levels were significantly elevated in patients with bladder cancer ($p<0.0001$), breast cancer ($p<0.0001$), colorectal cancer ($p<0.0001$), head and neck cancer ($p<0.0001$), kidney cancer ($p<0.0001$), lung cancer ($p<0.0001$), melanoma ($p=0.0001$), ovarian cancer ($p<0.0001$), pancreatic cancer ($p<0.0001$), prostate cancer ($p=0.0009$), and stomach cancer ($p<0.0001$) compared to healthy controls. In all solid tumor types, a large patient-to-patient variation was observed. CPa9-HNE was also significantly elevated in stage IV cancer patients compared to stage I cancer patients ($p=0.044$).

Conclusions The novel serological biomarker CPa9-HNE measuring HNE mediated degradation of calprotectin is significantly elevated in patients with different solid tumor types suggesting that these patients have high neutrophil activity. As high neutrophil activity is associated with poor response to anti-PD-1 therapy, CPa9-HNE may be used as a biomarker for anti-PD-1 therapy across different solid tumor types.

Ethics Approval The serum samples in this study was obtained from the commercial vendor Proteogenex and BioIVT, and according to the vendors, sample collection was approved by an Institutional Review Board or Independent Ethical Committee and patients gave their informed consent (Protocol numbers PG-ONC 2003/1 and WIRB® Protocol #20161665). All investigations were carried out according to the Helsinki Declaration.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.021>