Background As tumor genomes are shaped by their interaction with the immune system, a phenomenon known as immunoeediting, it is critical to understand how immunotherapies impact this process. Checkpoint inhibitors directly influence T cells responding to neoantigens, as such, these therapies drastically affect the genomes of surviving tumor clones. Similar to the concept of immune camouflage, where genomes of pathogens evolve in a way to avoid immune detection, we hypothesized that tumor clones surviving checkpoint inhibition therapy harbor mutations more prone to immune avoidance.

Methods We analyzed a published cohort of Nivolumab-treated melanoma patients (n=41) for which tumor samples were collected from the same site prior (‘Pre’ samples) and during (‘On’ samples) Nivolumab therapy. The immunogenic and tolerance potential of mutations from the Pre and On samples were evaluated with the Ancer neoantigen screening platform, which includes the EpiMatrix algorithm to identify HLA class I and HLA class II neoepitopes and the JanusMatrix algorithm to evaluate neoepitopes for homology with the self genome. Prior work with JanusMatrix showed that neoantigens highly homologous to self might be inhibitory.

Results Tumor samples collected during Nivolumab therapy demonstrated increased homology (self-like) scores from their matched pre-therapy samples (paired t test, p=0.0475). While this increase in homology with self was significant across the cohort, the effect was more pronounced in patients exhibiting complete (CR) or partial responses (PR), compared to patients with stable (SD) or progressive disease (PD). An ANOVA analysis confirmed that increase in homology after Nivolumab therapy was significantly greater in CR/PR patients, as opposed to SD or PD patients (p=0.0005). This observation was supported by Receiver Operating Characteristic (ROC) analysis discriminating CR/PR patients from SD/PD patients based on differences in homology with self between Pre and On treatment samples (AUC=0.7484, p=0.0313). A comparative ROC analysis employing baseline patient tumor mutation burden (TMB) yielded non-conclusive results (AUC= 0.5054, p=0.9613).

Conclusions Our Ancer analysis highlights that Nivolumab therapy affects the tolerance profile of tumors in a manner that is consistent with the concepts of immunoeediting and immune camouflaging. Interestingly, tumors in patients with favorable outcomes demonstrated the greatest increase in self-like neoepitopes. This observation suggests that collecting tumor biopsies shortly after the initiation of checkpoint inhibitor therapy and evaluating their tolerance profile may be employed as a prognostic biomarker. Furthermore, this approach highlights in silico tools may distinguish effector from tolerance inducing neoepitopes, a critical feature for designing novel neoantigen-based precision immunotherapies.

REFERENCES