Background Checkpoint inhibitor (CPI) antibodies induce blockade of CTLA-4 and PD-1 to reinvigorate the immune system to induce tumor cell clearance. Despite the success of CPI in cancer treatment, CPIs often result in toxicity due to immune related adverse events (irAEs). Both mechanistic understanding and predictive biomarkers for irAEs is lacking. It is necessary to characterize the effect of CPI on the immune system to reduce therapeutic toxicity and improve patient outcomes.

CD4 T follicular helper cells (Tfh) strongly express PD-1 and CTLA-4, yet little is known about the effects of CPI on these cells. Tfh provide help to antibody producing B cells within germinal centers in lymphoid tissue. Although this is an essential mechanism of adaptive immunity, several groups have shown hyperactivity in Tfh drives germinal center activity, resulting in increased help to autoreactive B cells and the generation of disease-causing autoantibodies. In the context of CPI, Tfh dysfunction may also drive the induction of autoantibodies and associated irAEs.

Methods Using flow cytometry and scRNAseq, we are analyzing PBMC samples from the Checkmate-238 clinical trial in which patients with resected stage III or IV melanoma received either αPD-1 or αCTLA-4 monotherapy. Patients have blood drawn on the same day as the first immunotherapy infusion (baseline) and two weeks post-baseline.

Tfh may be key to understanding irAE, but the study of Tfh in humans is challenging as these cells are commonly found in germinal centers of lymph nodes. To overcome this, our group has shown that circulating Tfh cells (cTfh) are recent emigrants from the lymph node and can be used to study cellular dynamics.

Results In this study, αCTLA-4-treated patients developed irAE at higher rates than αPD1-treated patients, with 46% of αCTLA-4 patients developing Grade 3 or 4 irAE compared to 14% of αPD-1 patients. We are interested in determining if the higher rate of irAE associated with αCTLA-4 was correlated to cTfh responses. Indeed, in flow cytometry studies, our lab identified a dramatic induction of activated cTfh following αCTLA-4 but not αPD-1 therapy, with a median fold-change of 7.5 within two weeks after baseline in αCTLA-4 patients but no difference in αPD-1 patients (figure 1).

Conclusions The greater influx of cTfh and higher incidence of severe irAEs suggest that αCTLA-4 therapy may predispose patients to dysregulated Tfh proliferation and induction of autoantibody responses.

REFERENCES

Ethics Approval These samples were obtained through a collaboration with Jeffrey Weber, MD, PhD at NYU Langone Health. As we are blinded and not provided details on samples this study is exempt from IRB approval.

Abstract 616 Figure 1 αCTLA-4 Induces Robust cTfh Response Compared to αPD-1
(A) Flow cytometry analysis illustrates robust induction of cTfh following αCTLA-4 monotherapy at 2 weeks post baseline (B) 7.5 fold change within two weeks after baseline of cTfh for ipilimumab (αCTLA-4) treated patients and no fold change for nivolumab (αPD-1) treated patients