Background From 2019–2022, we prospectively enrolled 1200 pan-cancer patients treated with immune checkpoint inhibitors (CPI) and identified three CPI-diabetes mellitus (DM) cases as part of the Radiohead study. Baseline and on-treatment blood samples were collected. From this longitudinal cohort, we evaluated whether islet autoantibodies and HLA typing could be used to predict a patient’s risk of developing CPI-DM.

Methods For islet autoantibody analysis, serum for 829 patients with both a baseline and early on-treatment sample were tested for GAD, IA-A, mIAA and ZnTA-8 autoantibodies using a radiobinding assay. HLA types were imputed from SNP genotypes generated using an Illumina GSAv3 array, using HIBAG and population-specific reference panels for 1029 patients. Fisher exact was used for autoantibodies and high-risk type 1 DM HLA types (DR3, DR4, DQ8, DQ2) associated with CPI-DM development. Logistic regression was used for combined HLA type and autoantibody risk prediction.

Results Of the 829-patient autoantibody subset, GAD was the most common autoantibody at 5.31%, followed by insulin at 3.74%. Two of the three (66%) CPI-DM patients had positive GAD, one prior to CPI initiation and the other emerging early on treatment. For every 35 patients with pre-treatment GAD positivity, one would be projected to develop CPI-DM; this increases to one in 19 patients if GAD positive is determined at either pre or early on treatment. The presence of GAD at baseline and/or early on treatment but not the other autoantibodies was associated with CPI-DM development (relative risk 34.84, p=0.004).

All three CPI-DM subjects were carriers of known HLA risk genotypes for T1DM, compared to 50% of patients in the remaining cohort of 1026 patients. The DR4-DQ8 risk haplotype was present in 2 out of 3 CPI-DM patients (66%), in contrast to 18% in the rest of the cohort. There was insufficient statistical power for association testing, due to the low number of cases.

In the 769-patient combined cohort, for which both HLA type and autoantibody status was determined, presence of GAD at baseline (odds ratio 21.8, p=0.01) was predictive of CPI-DM development after adjustment for HLA DR4-DQ8; results were similar with adjustment for other individual T1DM high risk HLA types.

Conclusions Pre-treatment and/or early on treatment analysis of T1DM autoantibodies and HLA types have the potential to predict development of CPI-DM and might be a critical first step in risk stratification for this rare immune-related adverse event. Given the very small number of cases, these findings must be further validated in high-risk cohorts.

Acknowledgements We would like to thank the Juvenile Diabetes Research Foundation and the Leona M. and Harry B. Helmsley Charitable Trust for their support as well as the patients who participated in our study.