Background Immune checkpoint inhibitor (ICI)-induced hepatitis is a relatively common immune-related adverse event (irAE). Understanding the underlying genetic factors contributing to the development of irAEs is crucial for identifying individuals at higher risk and possibly implementing personalized interventions. Previous studies showed that common genetic variants play a role in determining the levels of biomarkers used to assess liver injury such as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP). We therefore aimed to investigate whether polygenic risk scores (PRS), which are aggregates of genetic variants tested in large-scale genetic association studies, contribute to the risk of hepatitis irAEs during treatment with atezolizumab, a PD-L1 inhibitor.

Methods We used 16 previously published liver-injury related PRS models from the PGS catalog: 4 for ALT, 3 for AST, 4 for GGT, 4 for ALP, and 1 for cirrhosis of liver, in order to determine if genetic variants associated with susceptibility to liver injury could identify patients at risk for ICI-induced hepatitis. Since most of these PRS models were developed based on genome-wide association studies (GWAS) of individuals with European ancestry, we defined a cohort of 4,917 patients of European ancestry who had available germline whole-genome sequencing data from fifteen atezolizumab clinical trials. Among the selected patients, 2,860 received atezolizumab in combination or as monotherapy across various tumor types, and 432 of them (15.1%) developed hepatitis, determined on genome-wide association studies (GWAS) of individuals with European ancestry, we defined a cohort of 4,917 patients of European ancestry who had available germline whole-genome sequencing data from fifteen atezolizumab clinical trials. Among the selected patients, 2,860 received atezolizumab in combination or as monotherapy across various tumor types, and 432 of them (15.1%) developed hepatitis, determined on clinical diagnosis, or lab abnormalities (table 1). To test for association between hepatitis irAE risk and PRSs, we used a mixed effect Cox model allowing for a different baseline hazard per trial arm and controlling for 5 genetic principal components.

Results We observed significant associations (FDR <0.05) between hepatitis irAE risk and four ALT PRSs as well as three AST PRSs (table 2). Conversely, no significant associations were found in the control arms of the studies (N=2,057). These findings suggest that the genetic mechanisms regulating ALT and AST levels partially contribute to the risk of developing hepatitis irAEs in individuals treated with atezolizumab. Notably, the risk of hepatitis gradually increased with the quantiles of the significantly associated liver-damage PRSs (figure 1).

Conclusions Our study demonstrated a statistically significant association between genetic markers, as represented by ALT and AST PRSs, and the risk of atezolizumab-associated hepatitis and further work is warranted to characterize the potential clinical impact.

References
Abstract 449 Figure 1  Relationship between the proportion of individuals developing hepatitis (y-axis, cyan colored) and PRS quantiles (x-axis) for each of the seven significantly associated PRS (rows), categorized by whether patients were treated with atezolizumab (right) or not (left).

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