Background Immune checkpoint inhibitors (ICIs) have made significant improvements in the treatment of cancer patients (pts), but many continue to experience primary or secondary resistance. Here, we leveraged clinical and genomic data to identify prognostic biomarkers in pts treated with ICIs utilizing a pan-cancer approach.

Methods Patients were enrolled to the Total Cancer Care protocol (NCT03977402) across 18 cancer centers within the Oncology Research Information Exchange Network® (ORIEN). All included subjects provided an IRB-approved written informed consent at their participating institutions. RNA-seq was performed on tumors following the RSEM pipeline and gene expressions were quantified as Transcript Per Million (TPM) and were logarithmically normalized. A graphical neural network (GNN) architecture was developed based on the prior knowledge of genes and pathways. For comparison, immunoscore for each patient was calculated based on the estimated densities of tumor CD3+ and CD8+ T cells (Galon et. al., 2020) utilizing CIBERSORTx. The quality of overall survival (OS) predictions was assessed using Harrell’s concordance index (C-index). Log-rank test was used to assess stratified group differences (by ICI or cancer histology) along with Kaplan-Meier (KM) survival analysis of GNN and immunoscore.

Results Patients (n=522) with 4 cancer types including melanoma (n=125), renal cell carcinoma (n=149), non-small cell lung cancer (n=128) and head and neck cancer (n=120) treated with 6 ICI regimens were included in this analysis. ICI regimens were nivolumab (n=219), pembrolizumab (n=202), ipilimumab+nivolumab (n=69), ipilimumab (n=30), avelumab (n=1) and cemiplimab (n=1). Table 1 summarizes the overall C-index and associated 95% CIs and log-rank P values for the entire cohort (regardless of histology) resulting from our proposed GNN and the separate estimated immunoscore categorization. The corresponding KM plots showed significantly wider separations of the survival curves in favor of our proposed GNN relative to the immunoscore with more than 30% improvement in prediction power. Table 2 presents the summary of GNN top selected pathways alongside their hazard rate and their univariate Cox p-value.

Conclusions GNN analysis is a promising tool to identify relevant prognostic biomarkers in cancer patients treated with ICI. This may lead to novel therapeutic predictive signatures and identification of mechanisms of ICI resistance. Our GNN gene expression signature was significantly prognostic and outperformed the estimated CD3+, CD8+ T Cell immunoscore. Further refinements to our prediction power are ongoing along with more advanced neural network architectures to elucidate related functional pathways. Validation and functional studies will follow.

Acknowledgements We are grateful to the participating patients and their family members as well as all research staff supporting the conduct of the Total Cancer Care protocol.

Trial Registration NCT03977402

Ethics Approval Patients were enrolled to the Total Cancer Care protocol (NCT03977402) across 18 cancer centers within the Oncology Research Information Exchange Network® (ORIEN). All included subjects provided an IRB-approved written informed consent at their participating institutions.