

# Pan-cancer associations of B7-H3 (CD276) transcriptional expression across human malignancies

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## Abstract

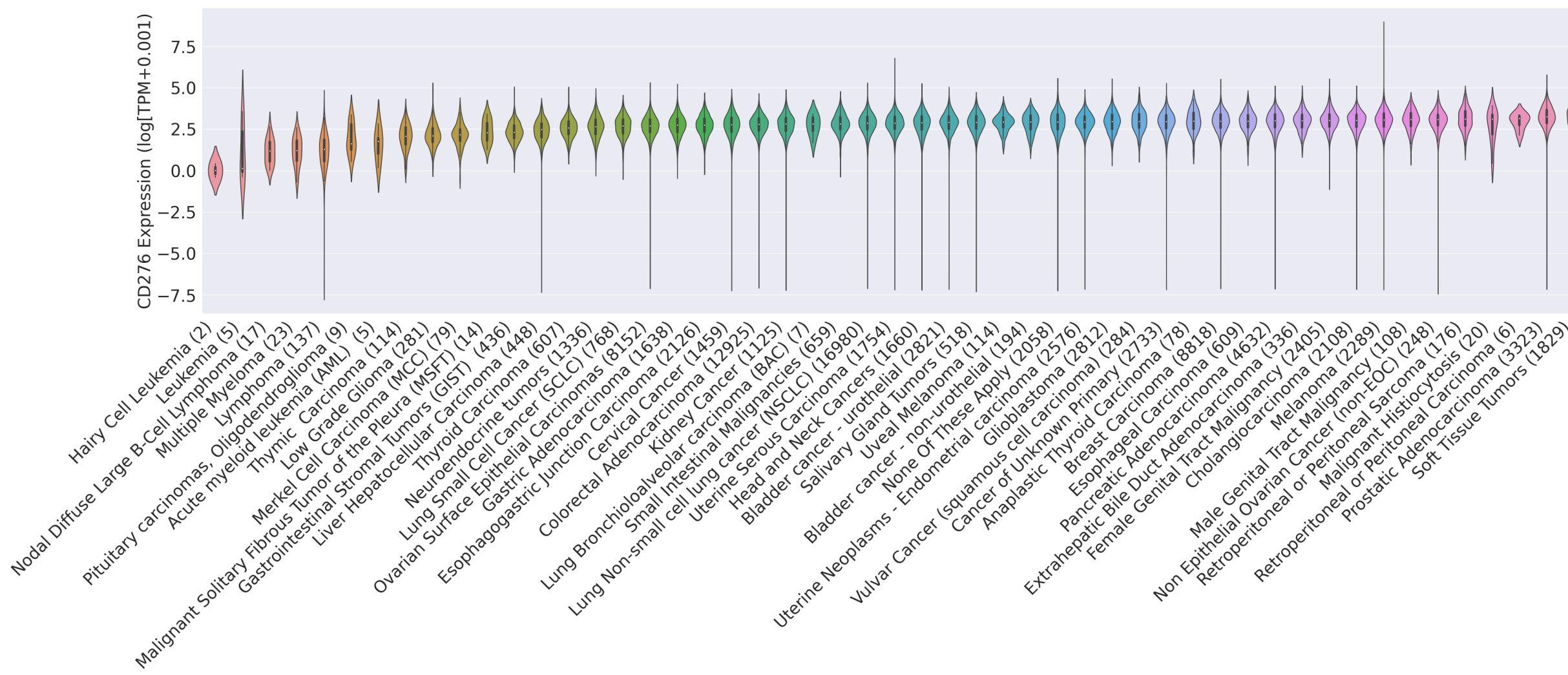
**Background:** B7-H3 (CD276) is a transmembrane glycoprotein of the B7 superfamily that includes PD-L1 and CTLA-4. B7-H3 targeted therapeutics have demonstrated promising results in both solid tumors and hematologic cancers. To understand the applicability of B7-H3 targeted therapies, we characterized the landscape of clinical outcomes, genomic, transcriptomic, and immunological features associated with B7-H3 mRNA expression in over 93,861 samples across >45 cancer types from a large real-world clinico-genomics database.

**Methods:** DNA (592-gene/whole-exome) and RNA (whole-transcriptome) sequencing was performed for samples submitted to Caris Life Sciences (Phoenix, AZ). Differential expression of individual genes was analyzed, with pathway enrichment assessed by Gene Set Enrichment Analyses (GSEA). RNA deconvolution was used to estimate immune cell infiltration of tumor microenvironments using quanTIseq (Finotello, 2019). Real-world overall survival (OS) was determined from insurance claims data and Kaplan-Meier estimates were calculated. Statistical significance was determined using  $\chi^2$  and Mann-Whitney U tests with Benjamini-Hochberg corrections for multiple hypothesis testing where appropriate.

**Results:** B7-H3 mRNA displayed robust expression in many prevalent cancer types, including prostate, pancreatic, breast, colorectal, ovarian, and lung cancers. High B7-H3 expression predicted worse OS in head & neck cancers (1.291 HR, 95% CI 1.096-1.52, p=0.002) and lung adenocarcinoma (1.247 HR, 95% CI 1.16-1.34, p<0.0001). Notably, high B7-H3 was associated with differential rates of alterations in *TP53*, *RB1*, and *KRAS* in several cancer types. When examining Hallmark gene signatures, we found that B7-H3-high samples demonstrated consistent enrichment for pathways involved in epithelial to mesenchymal transition (EMT), WNT, TGF-Beta, and Notch signaling (FDR<0.05) across cancer types. Additionally, we found high B7-H3 expression to be correlated with PD-L1 expression, as well as greater proportions of pro-inflammatory M1 macrophages but lower fractions of effector CD8+ T cells.

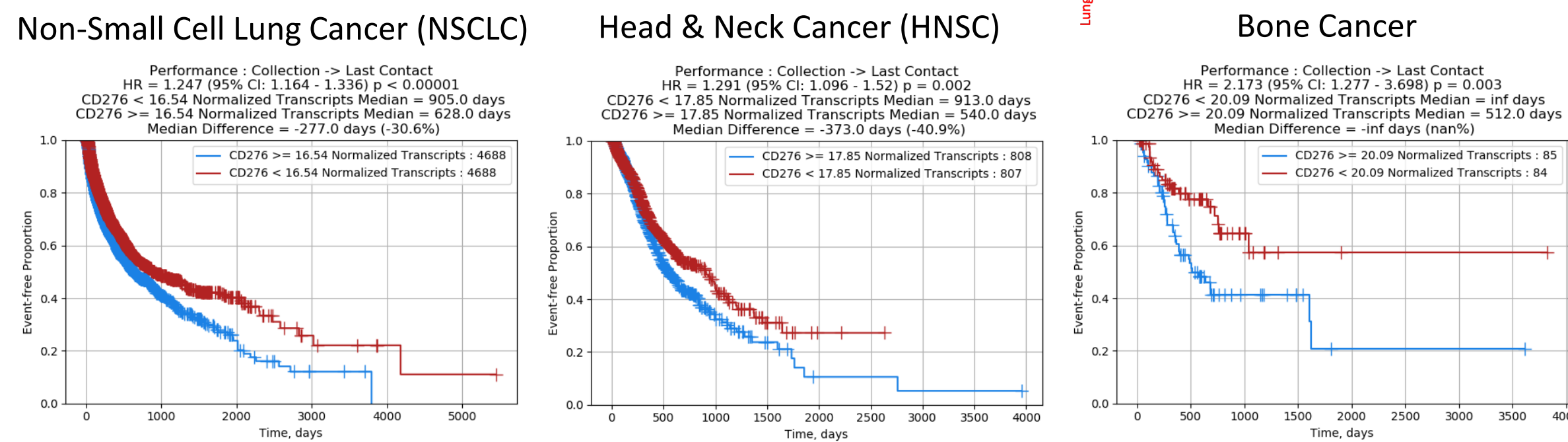
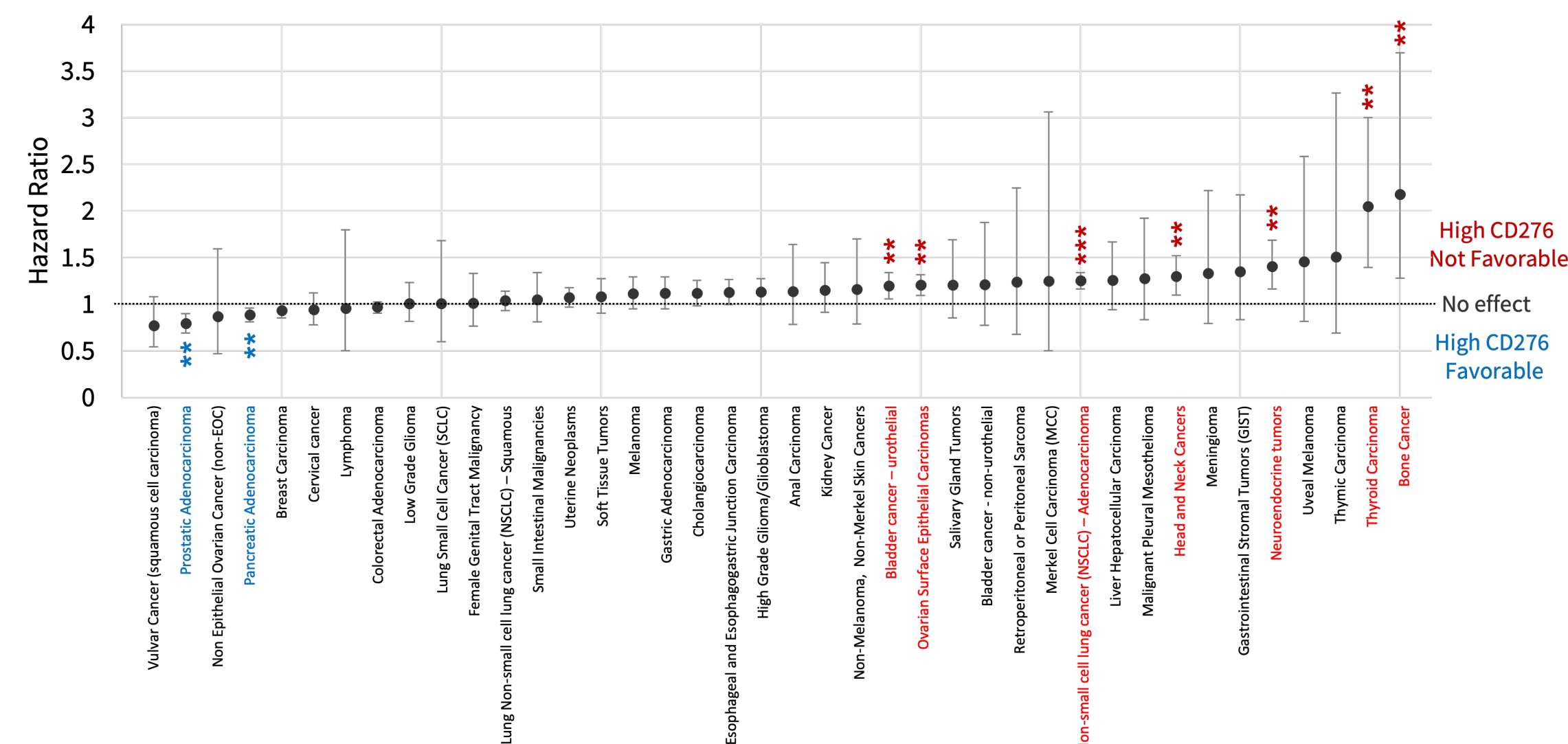
**Conclusion:** We demonstrate B7-H3 to be a promising pan-tumor target, with most solid tumors showing robust expression that is often associated with worse OS. In several major cancers, high B7-H3 expression was associated with mutational and transcriptomic repertoires not easily targeted by current precision therapies. We find B7-H3-high tumors to have increased potential for myeloid-driven immune induction, making them potentially more amenable to immunomodulatory therapies, in particular, those targeting B7-H3. Further work is warranted to elucidate different mechanistic interactions of B7-H3 with specific oncogenic pathways in each cancer type.

## The spectrum of B7-H3 (CD276) expression across human cancers



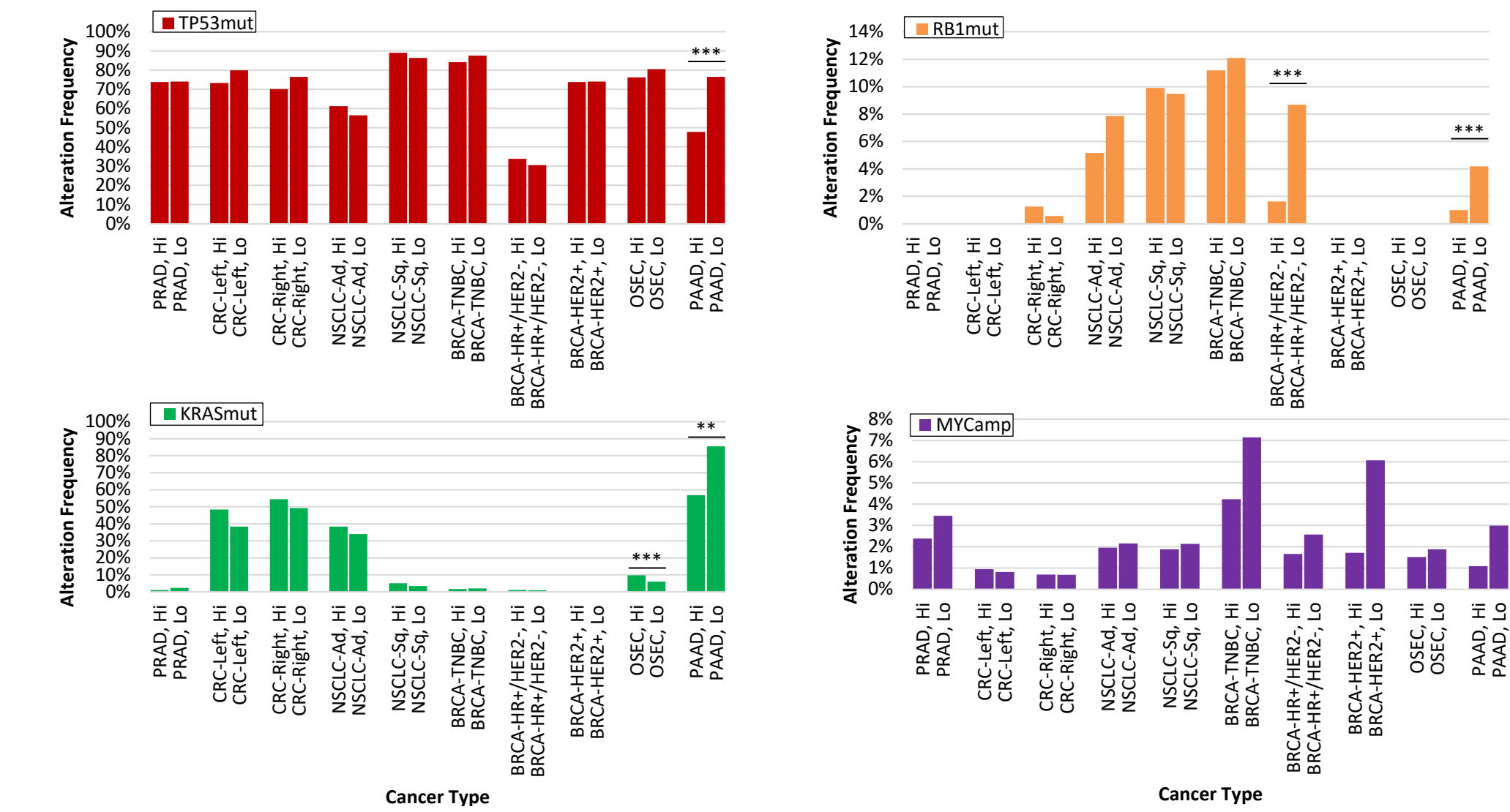
**Figure 1.** B7-H3 expression was determined in 93,861 tumors in over 45 cancer types, Transcripts Per Million (TPM) is depicted after log normalization.

## B7-H3 expression is associated with clinical outcomes



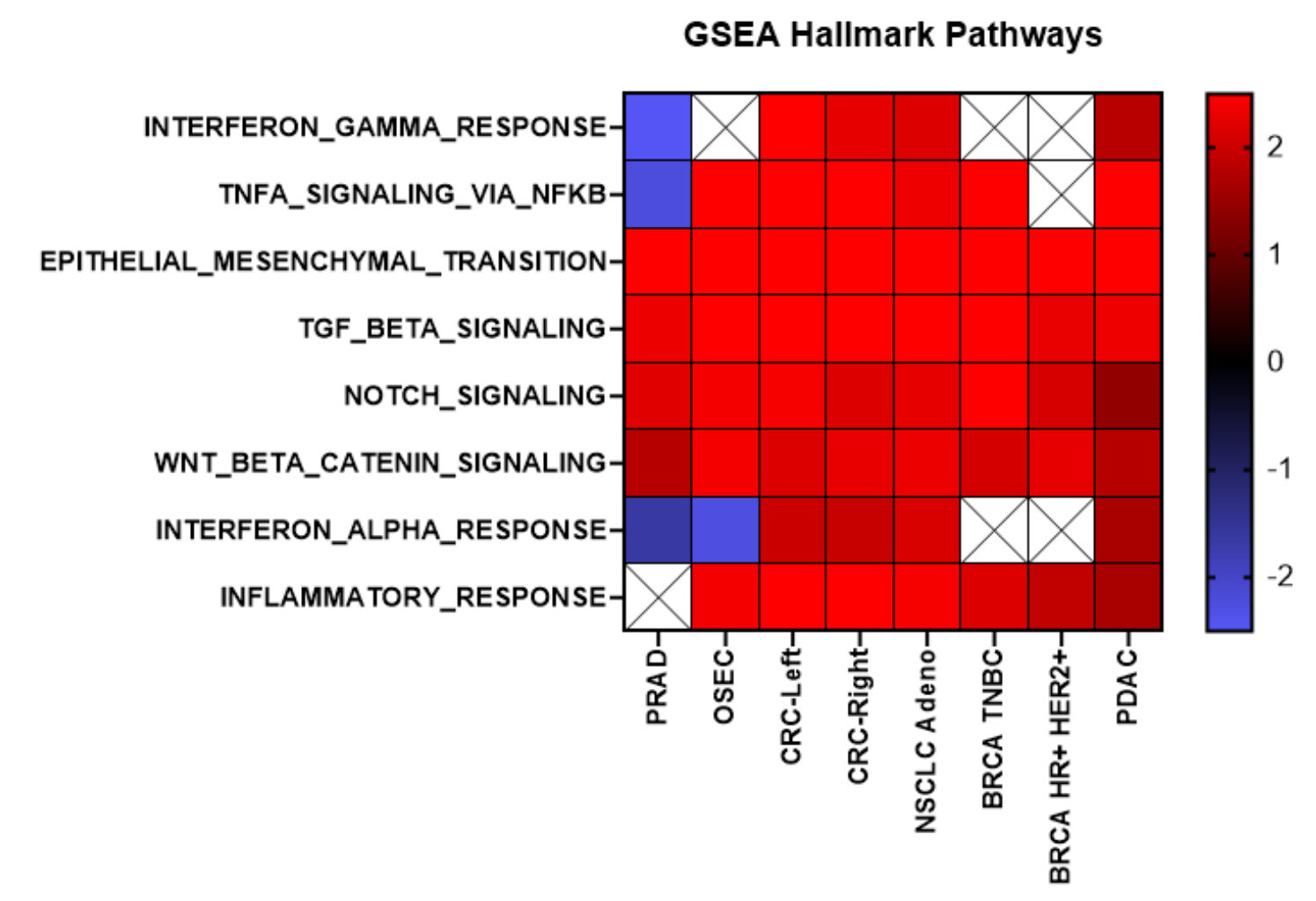
**Figure 2.** Top – The association of high B7-H3 expression with overall survival across cancers. Bottom – Kaplan-Meier curves for select cancer types displaying significant associations between B7-H3 expression and overall survival. OS data was collected from insurance claims.

## B7-H3 is expressed alongside driver mutations lacking effective precision therapies



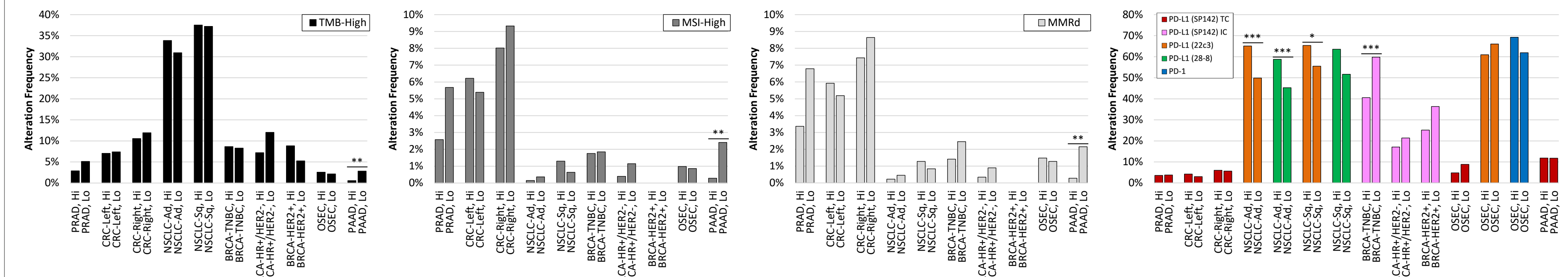
**Figure 3.** B7-H3 expression is associated with altered mutational repertoires in several cancer types. PRAD – prostate adenocarcinoma, CRC – colorectal cancer, NSCLC – non-small cell lung cancer, BRCA – breast cancer, TNBC – triple negative breast cancer, OSEC – ovarian surface epithelial carcinoma, PAAD – pancreatic adenocarcinoma

## B7-H3 expression is associated with common Hallmark Signatures



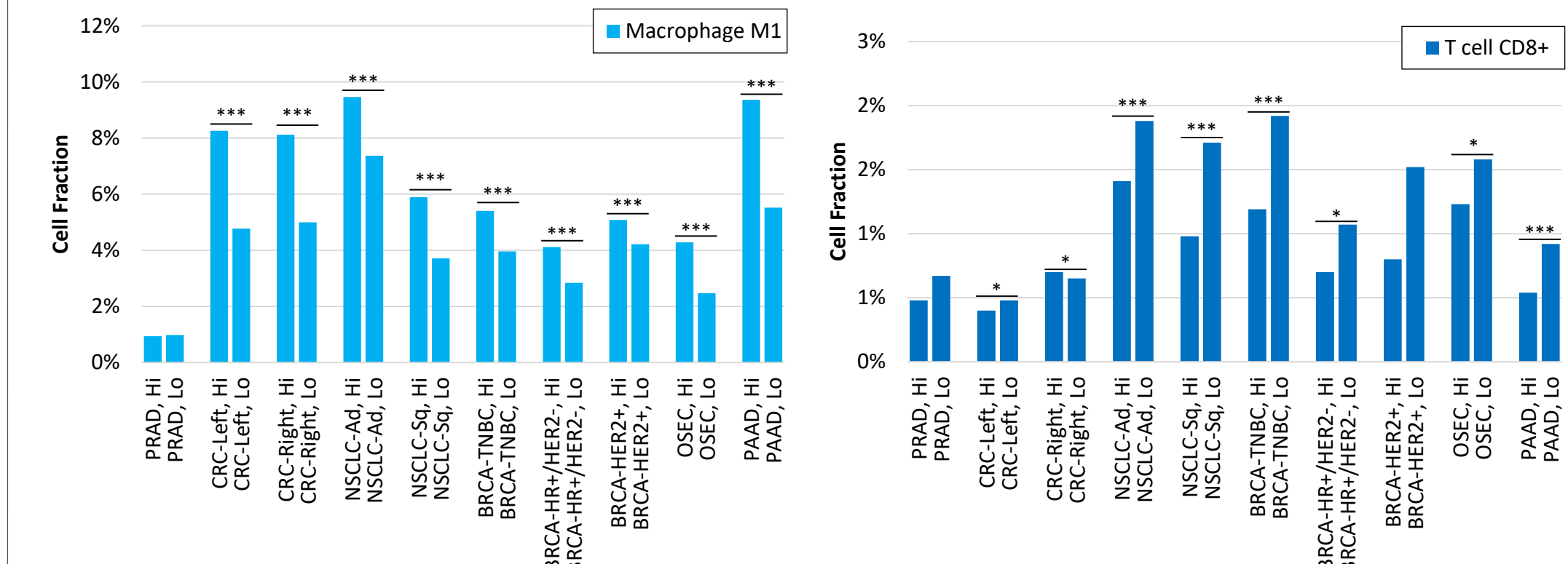
**Figure 4.** GSEA analysis with functional oncogenic pathways on B7-H3-high vs -low tumors. Normalized enrichment scores (NES) are displayed.

## B7-H3 expression status is independent of immunotherapy biomarkers



**Figure 5.** Association of B7-H3 expression with well-established predictors of immunotherapy response across selected cancer types.

## B7-H3 expression and the immune cell landscape



**Figure 6.** B7-H3-high tumors display altered immune repertoires based on immune fraction estimations using quanTIseq.

## Study Highlights

- B7-H3 is highly expressed in cancers with genomic and transcriptomic alterations that are challenging to drug.
- B7-H3 expression is independent of current immunotherapy biomarkers, but is associated with distinct immune landscapes
- In major cancer types, B7-H3 is consistently associated with signaling pathways including EMT, TGF-Beta, and Notch Signaling.

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