

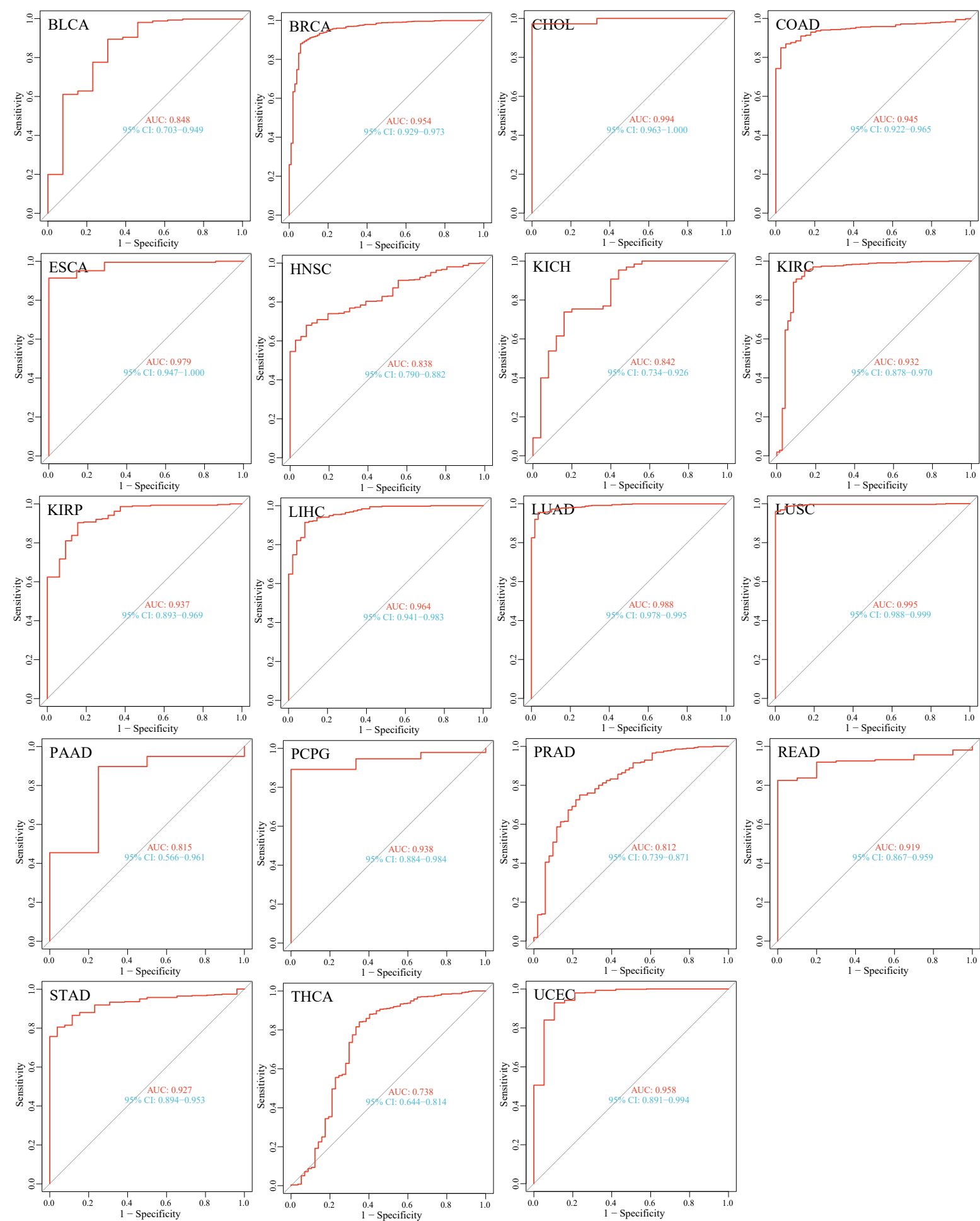


Figure S1. Pan-cancer diagnostic performance of *TOP2A* mRNA expression. ROC curves evaluating the discriminatory capacity of *TOP2A* for distinguishing tumor from normal tissues across pan-cancer, with AUC values and 95% CI indicated.

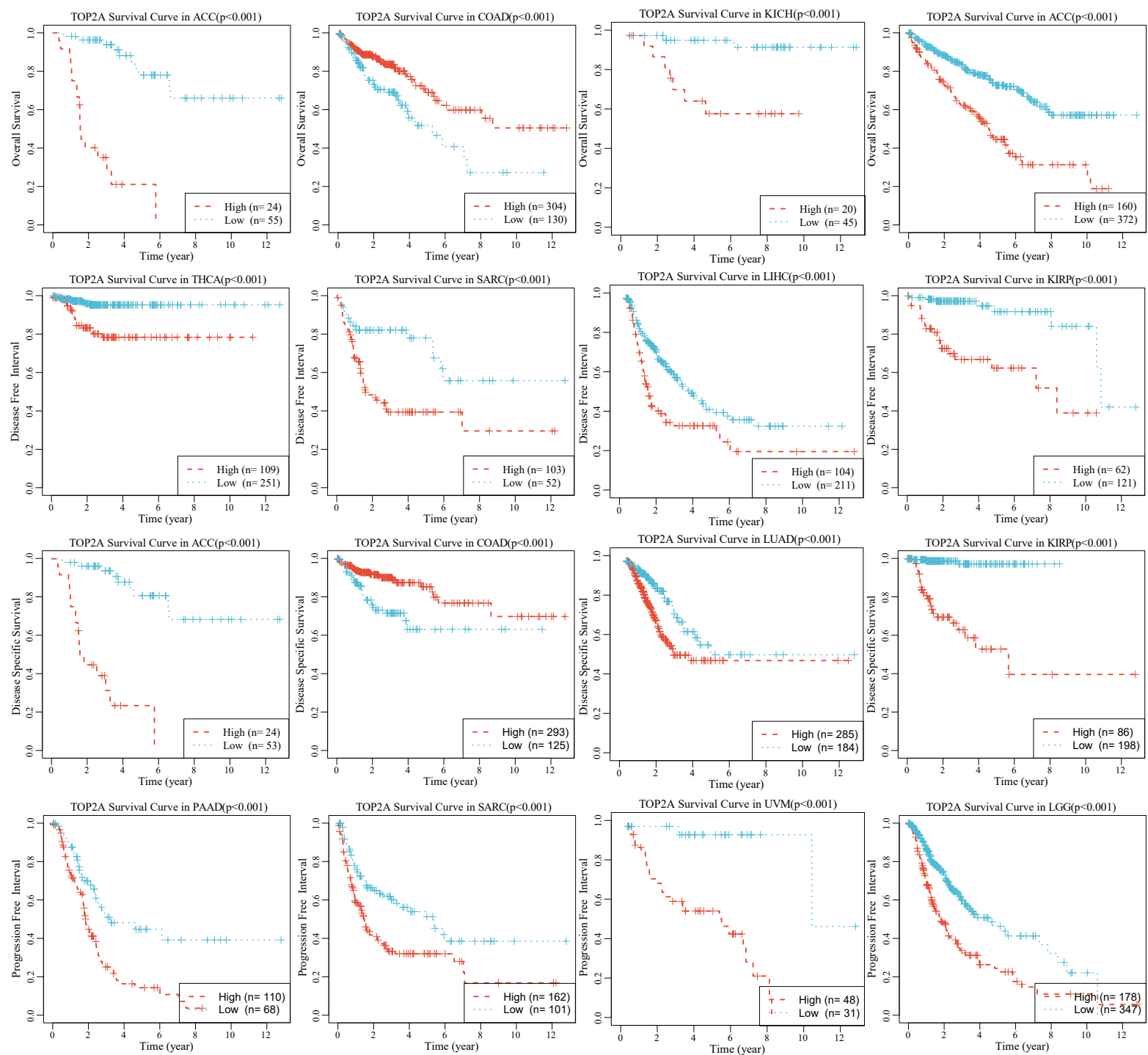


Figure S2. Prognostic value of *TOP2A* across four clinical survival endpoints in representative cancers. Kaplan-Meier survival curves comparing overall survival (OS), disease-specific survival (DSS), disease-free interval (DFI), and progression-free interval (PFI) between *TOP2A*-high and *TOP2A*-low subgroups in representative cancer types.

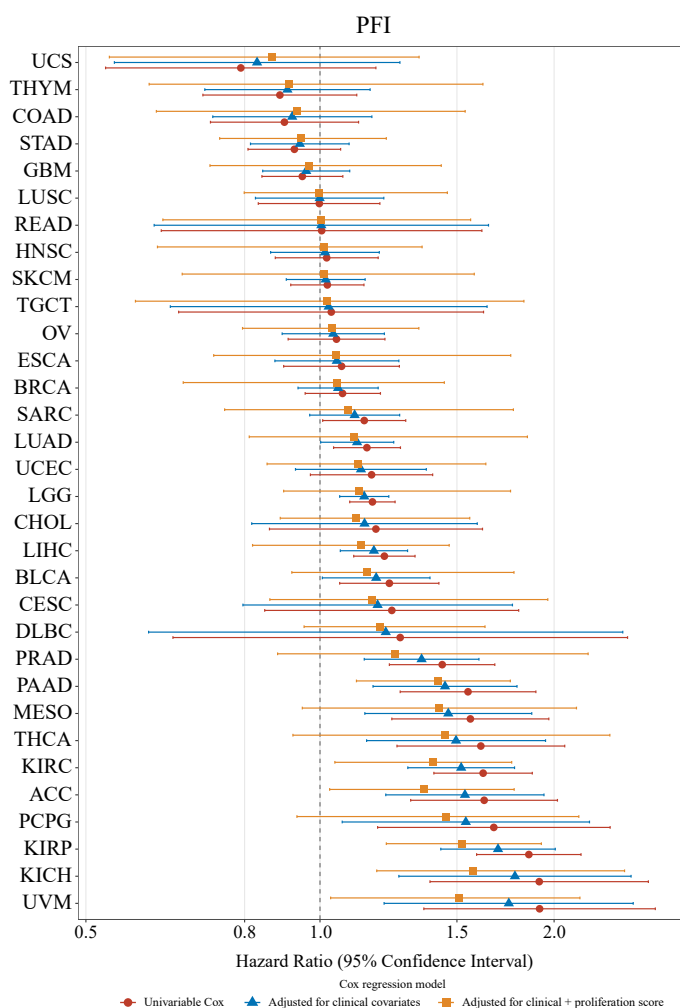
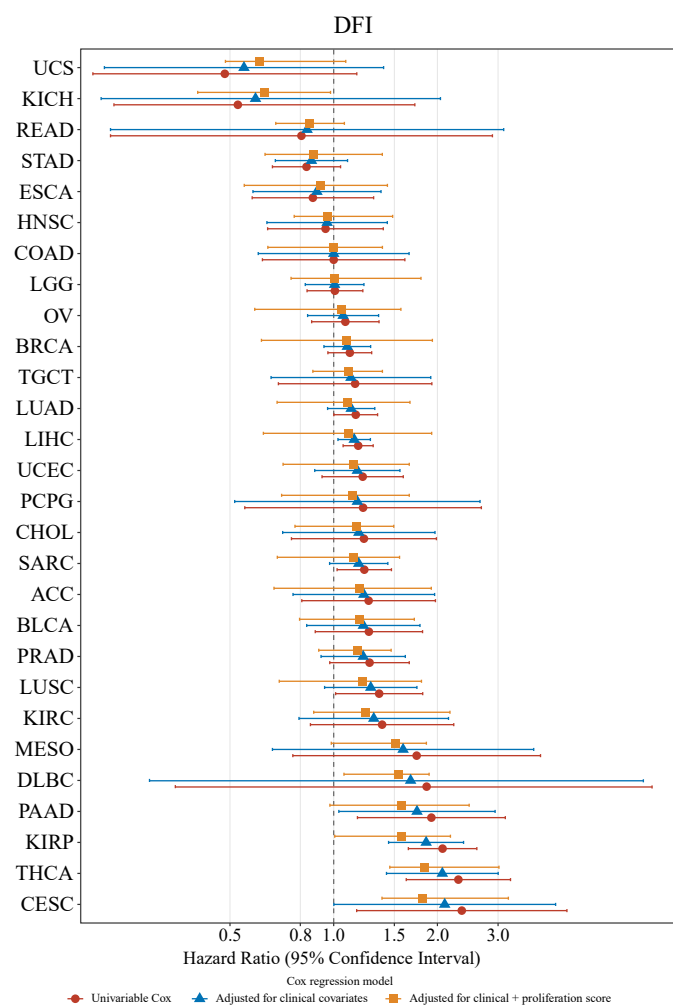
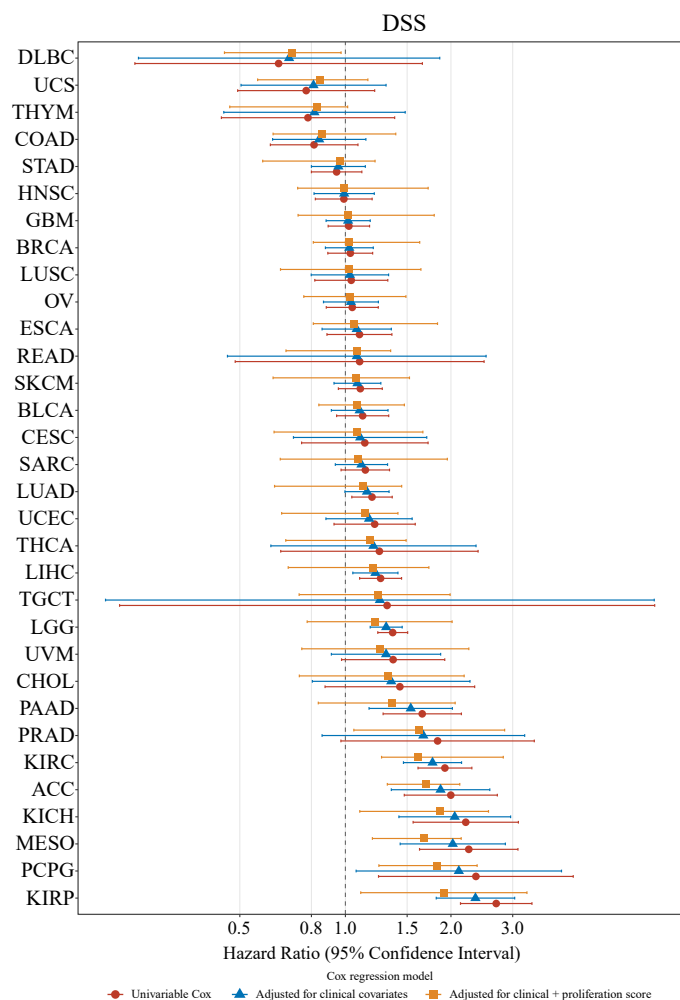
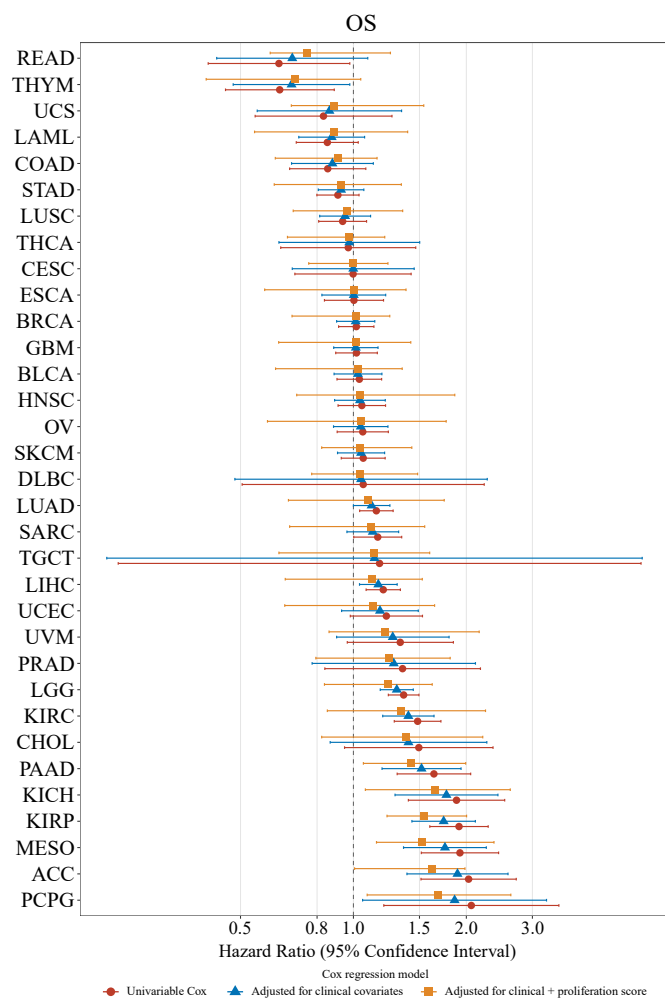


Figure S3. Forest plots of multivariable Cox regression for OS, DSS, DFI, and PFI.

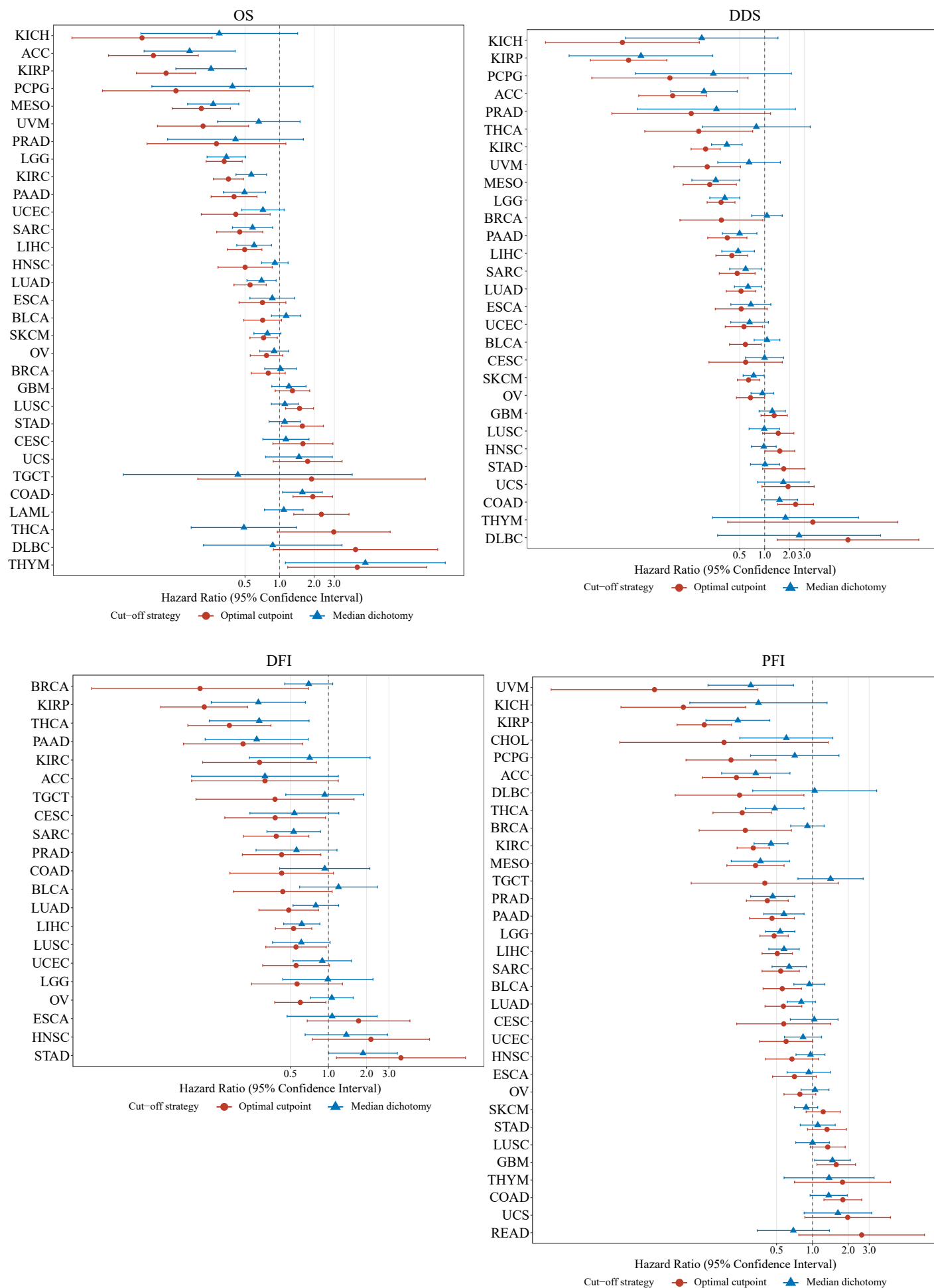


Figure S4. Cut-off sensitivity analysis comparing optimal cutpoint and median dichotomization for each survival endpoint.

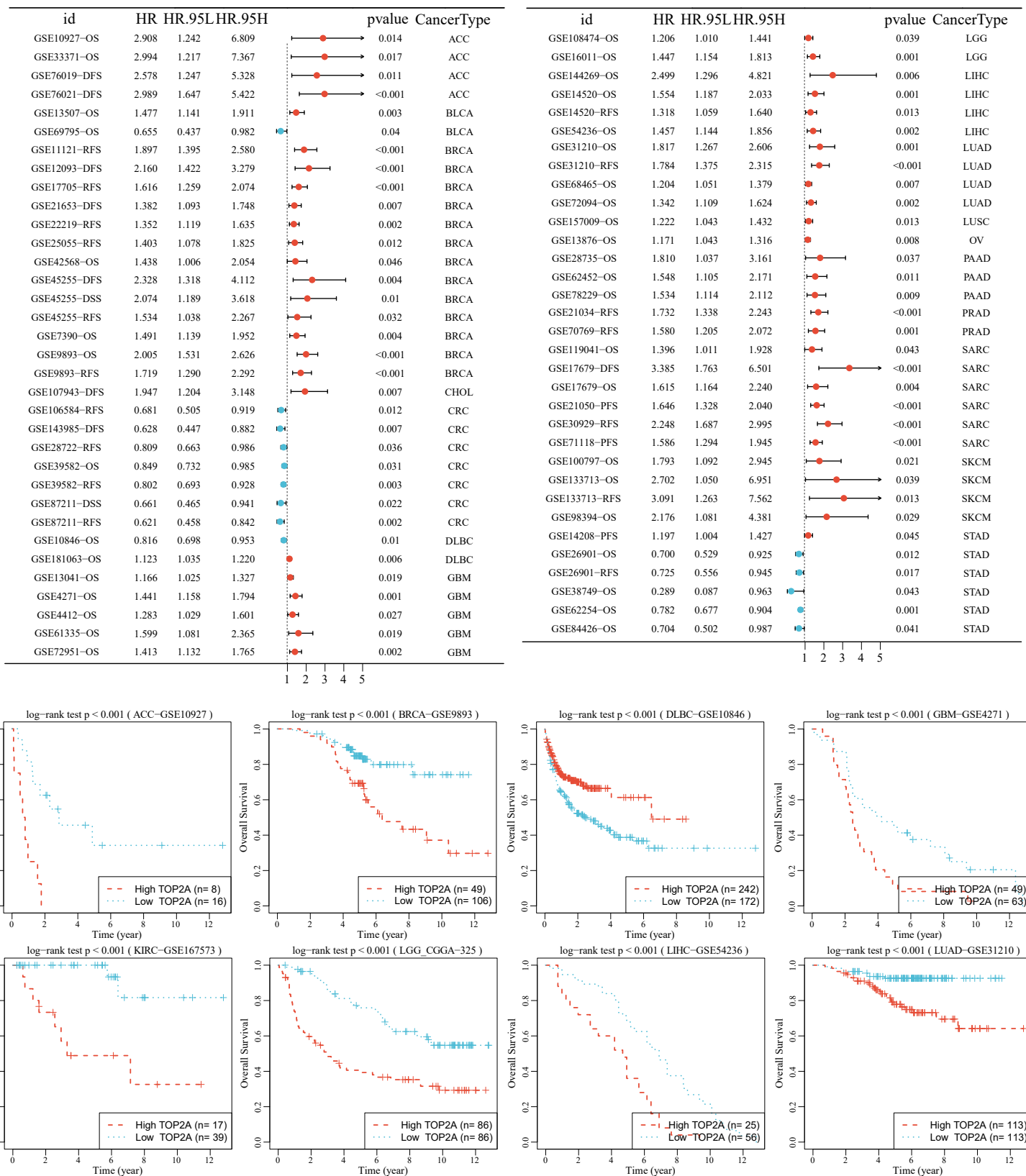


Figure S5. External multi-cohort validation confirms the robust pan-cancer prognostic value of *TOP2A*. (A) Forest plot visualizes pooled hazard ratios (HR) and 95% confidence intervals (CI) for the association between high *TOP2A* expression and four clinical survival endpoints (OS, DFS, RFS, PFS) across 59 independent GEO validation cohorts. (B) Kaplan-Meier survival curves for OS in representative cancer types that exhibited statistically significant prognostic associations in panel A.

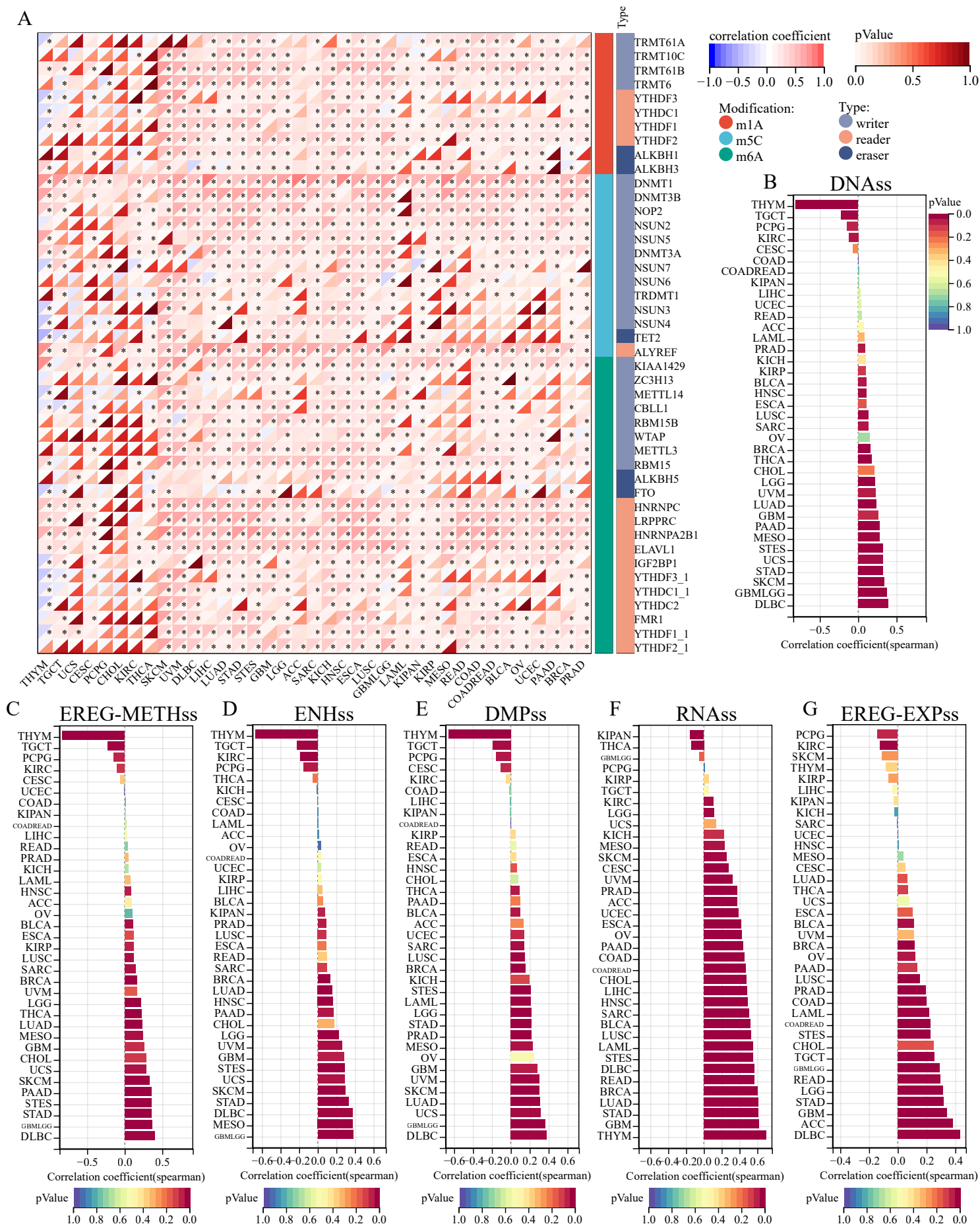


Figure S7. Association between *TOP2A* expression, epitranscriptomic regulation, and tumor stemness across pan-cancer. (A) Heatmap showing the Spearman correlation between *TOP2A* mRNA expression and core RNA epitranscriptomic modification regulators (m¹A, m⁵C, m⁶A) across pan-cancer. (B-E) Bar plots showing the Spearman correlation between *TOP2A* mRNA expression and DNA methylation-based stemness indices: (B) DNAss, (C) EREG-METHss, (D) DMPss, (E) ENHss. (F-G) Scatter plots showing the Spearman correlation between *TOP2A* mRNA expression and RNA-based stemness indices: (F) RNAss, (G) EREG.EXPss. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.



Figure S8. PPI network and functional enrichment of *TOP2A* co-expressed genes. (A) Experimentally validated *TOP2A* PPI network (STRING database, confidence score > 0.7). (B) Bar plot showing the top enriched Gene Ontology (GO) biological process terms for the top 100 *TOP2A* co-expressed genes, with adjusted p values indicated. (C) GSEA of KEGG pathways in *TOP2A*-high vs. *TOP2A*-low groups, with normalized enrichment score (NES) and false discovery rate (FDR) indicated. FDR < 0.05 was considered statistically significant for enrichment analyses.

A

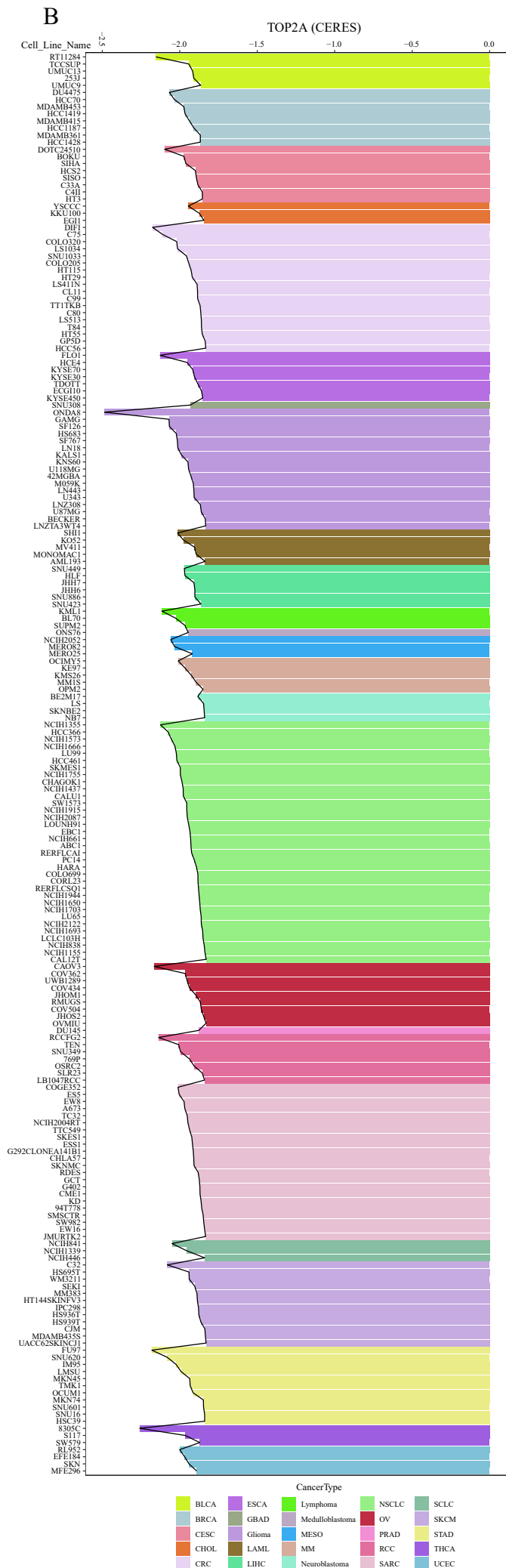
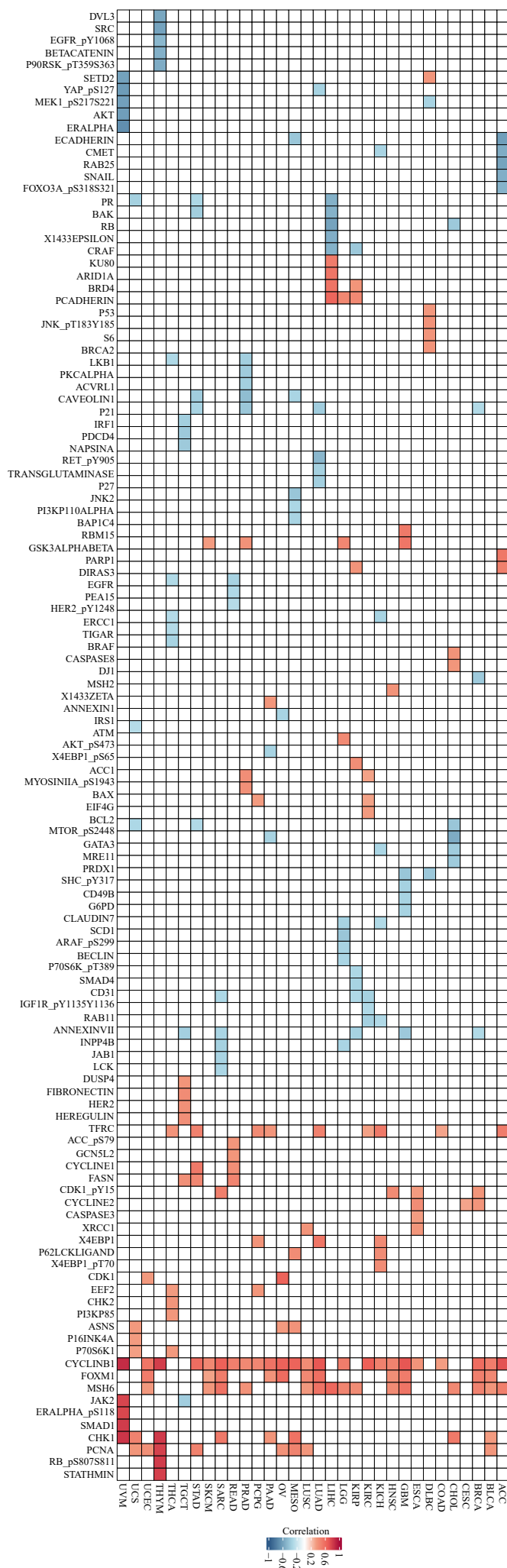


Figure S9. Protein-level validation and tumor cell dependency of *TOP2A*. (A) Heatmap showing the Spearman correlation between TOP2A protein expression and core proliferation/DNA repair pathway proteins from the TCPA RPPA cohort. (B) Bar plot showing the CERES dependency scores of TOP2A across the top 200 tumor cell lines from the Cancer Dependency Map (DepMap) portal. Scores < -1 indicate stronger tumor cell dependency on TOP2A for growth.

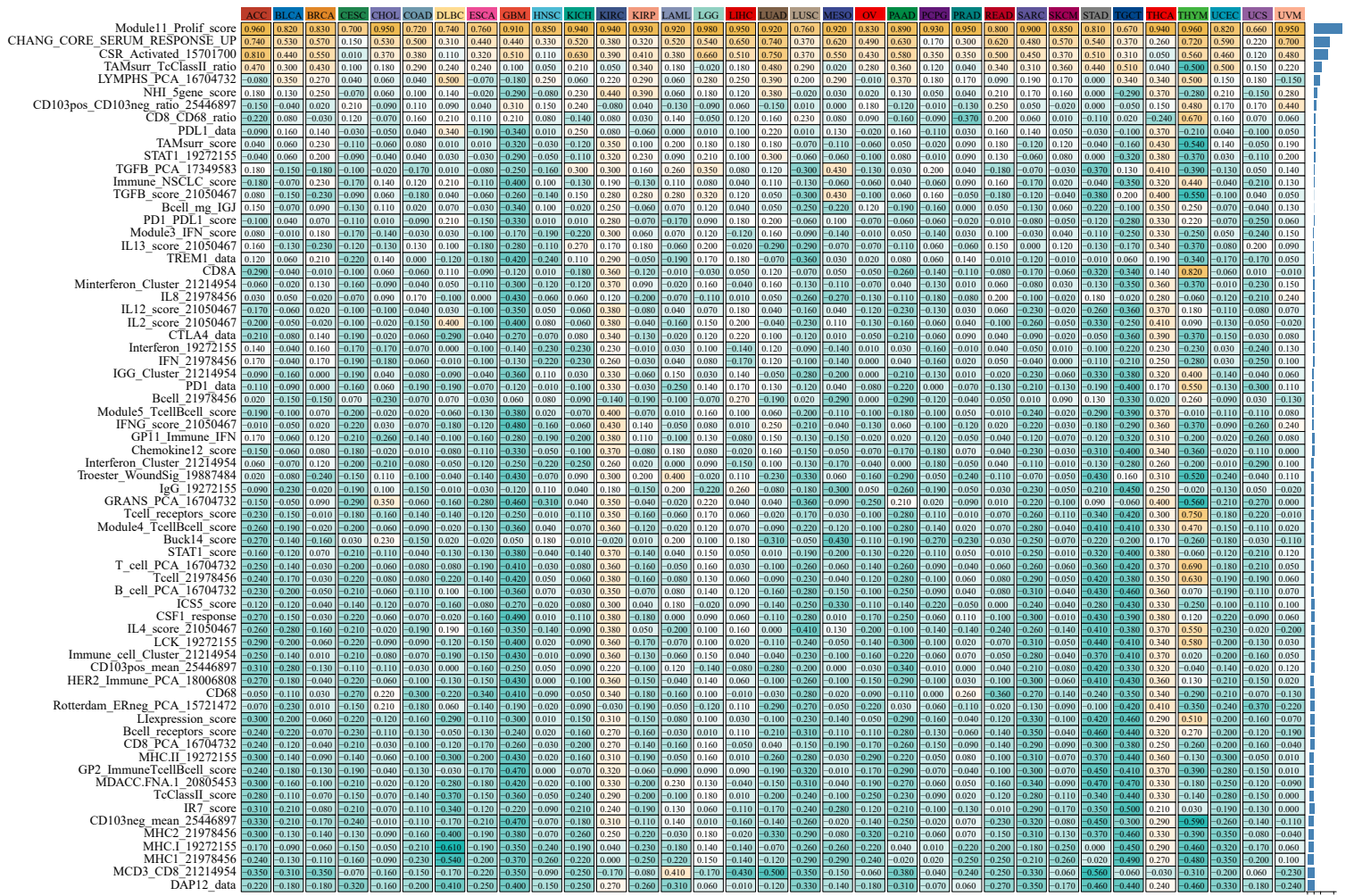


Figure S10. Pan-cancer correlation between *TOP2A* and 68 immune-related signatures. Heatmap displays Spearman correlation coefficients between *TOP2A* mRNA expression and immune response pathways, cytolytic activity, inflammatory response, and immune cell infiltration signatures across 33 cancer types. Significance indicators reflect FDR-adjusted P values; *FDR < 0.05, **FDR < 0.01, ***FDR < 0.001.

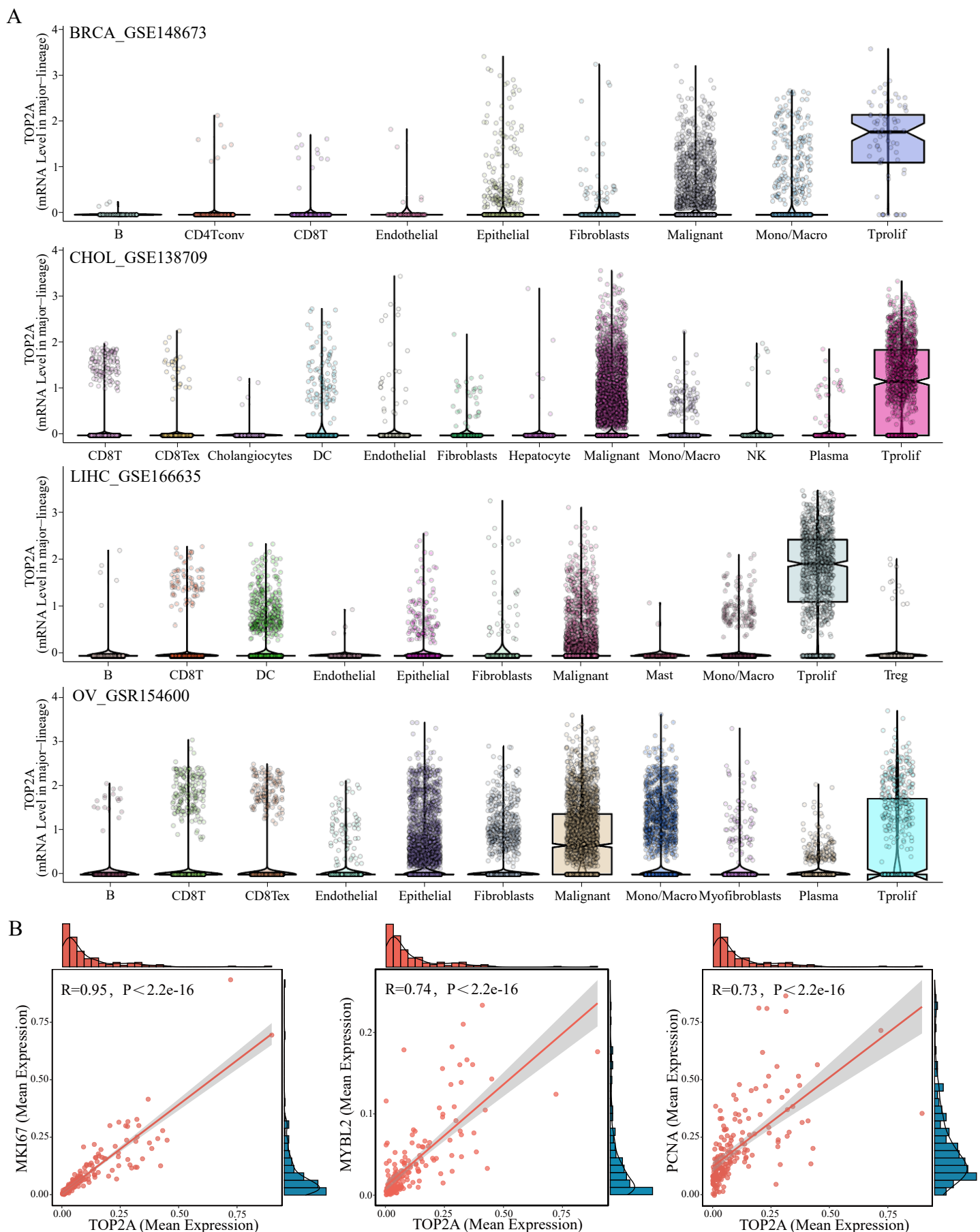
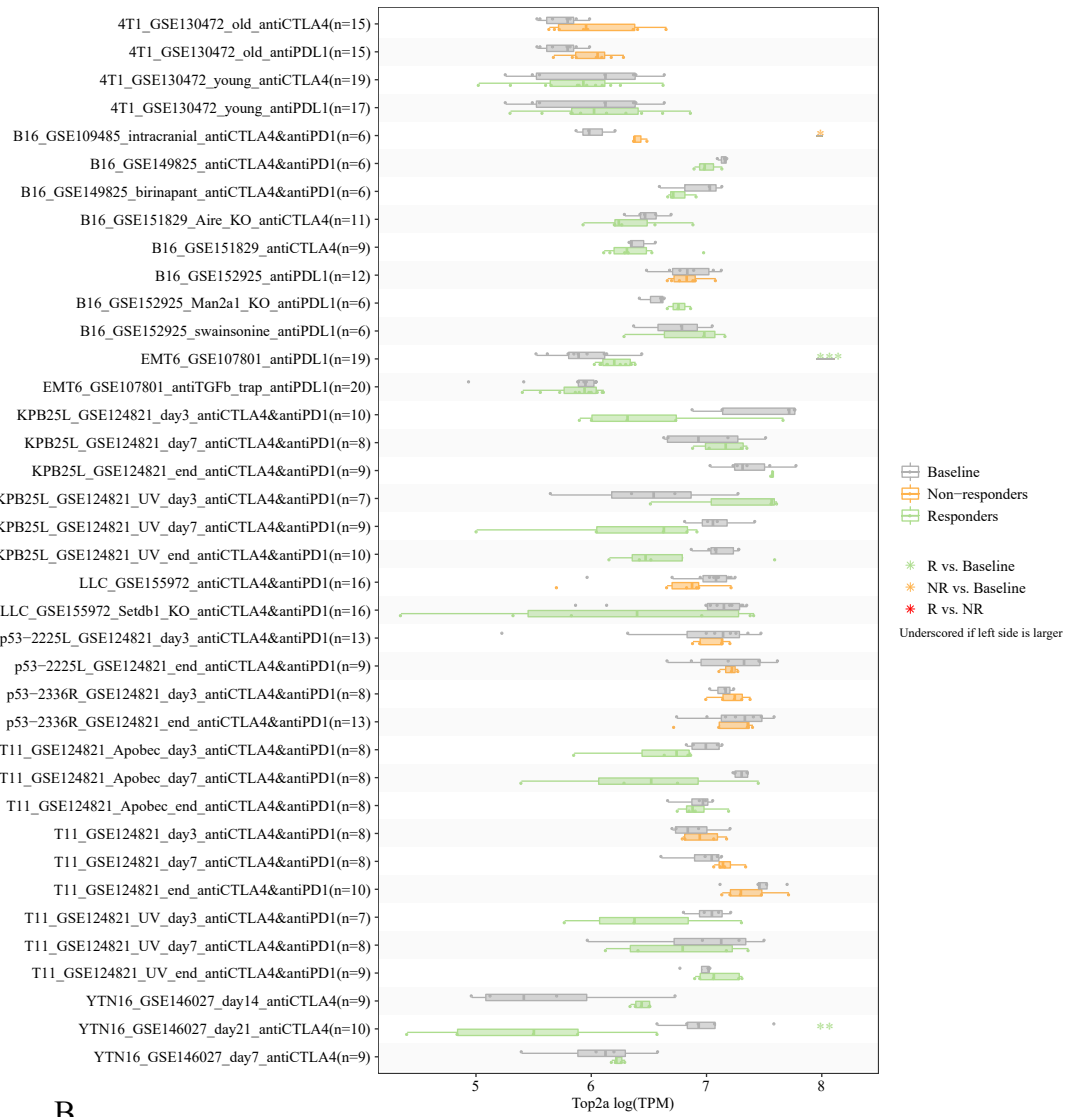


Figure S12. Supplementary validation of the proliferation-specific expression pattern of *TOP2A* across single-cell and pan-cancer bulk datasets. (A) Violin plots comparing *TOP2A* expression levels across major cell lineages in the four representative single-cell datasets presented in Figure 7B. **(B)** Scatter plots showing the Spearman rank correlation between mean *TOP2A* expression and mean expression of proliferation markers (MKI67, MYBL2, PCNA) across the TCGA pan-cancer.

A



B

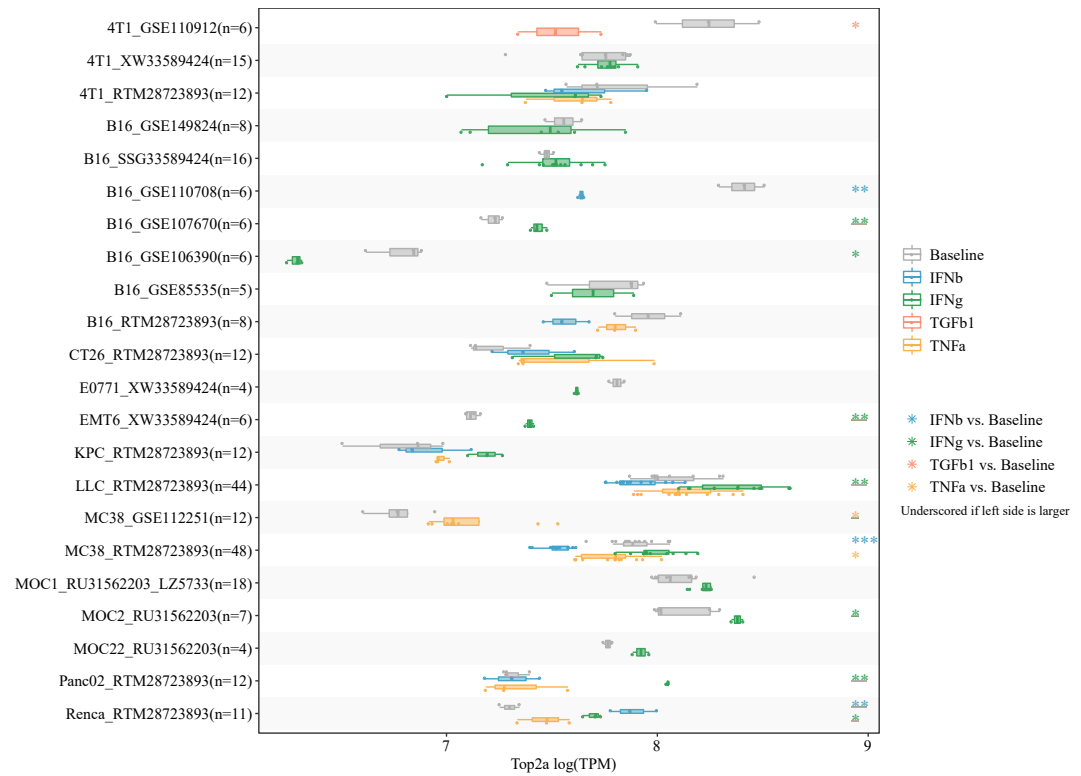


Figure S13. *TOP2A* expression is associated with immune checkpoint blockade (ICB) therapy response. (A) Box plot comparing *TOP2A* mRNA expression levels before and after IFN- γ /TNF- α cytokine stimulation from the TISMO database. **(B)** Box plot comparing *TOP2A* mRNA expression levels between ICB therapy responders and non-responders from the TISMO database. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

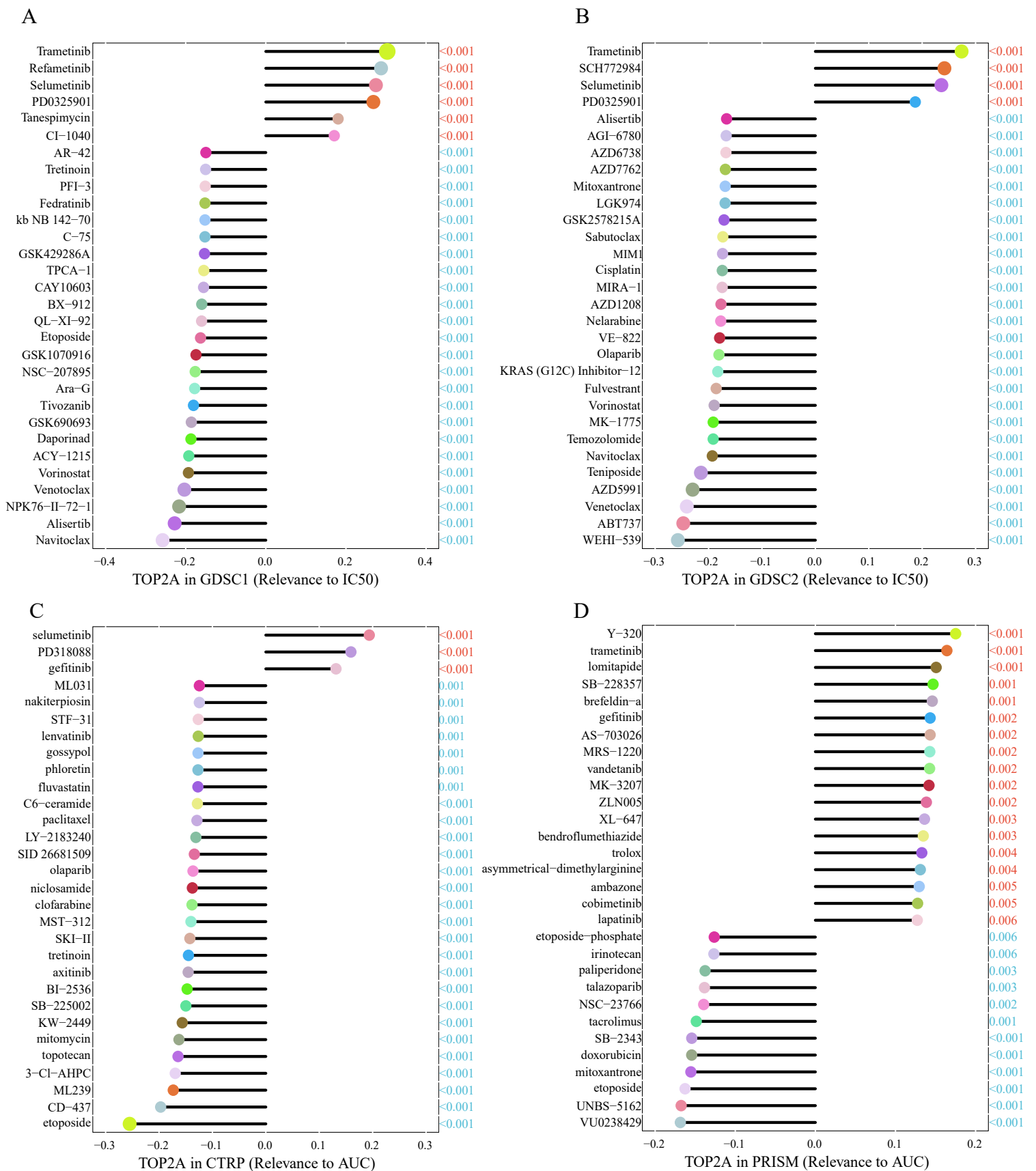


Figure S14. Multi-database validation of the association between *TOP2A* expression and pan-cancer drug sensitivity. Lollipop plots showing the Spearman correlation between *TOP2A* mRNA expression and drug sensitivity metrics across four independent pharmacogenomic databases: (A) GDSC1, (B) GDSC2, (C) CTRP, (D) PRISM. Negative correlation indicates enhanced drug sensitivity in *TOP2A*-high tumors, while positive correlation indicates intrinsic resistance.