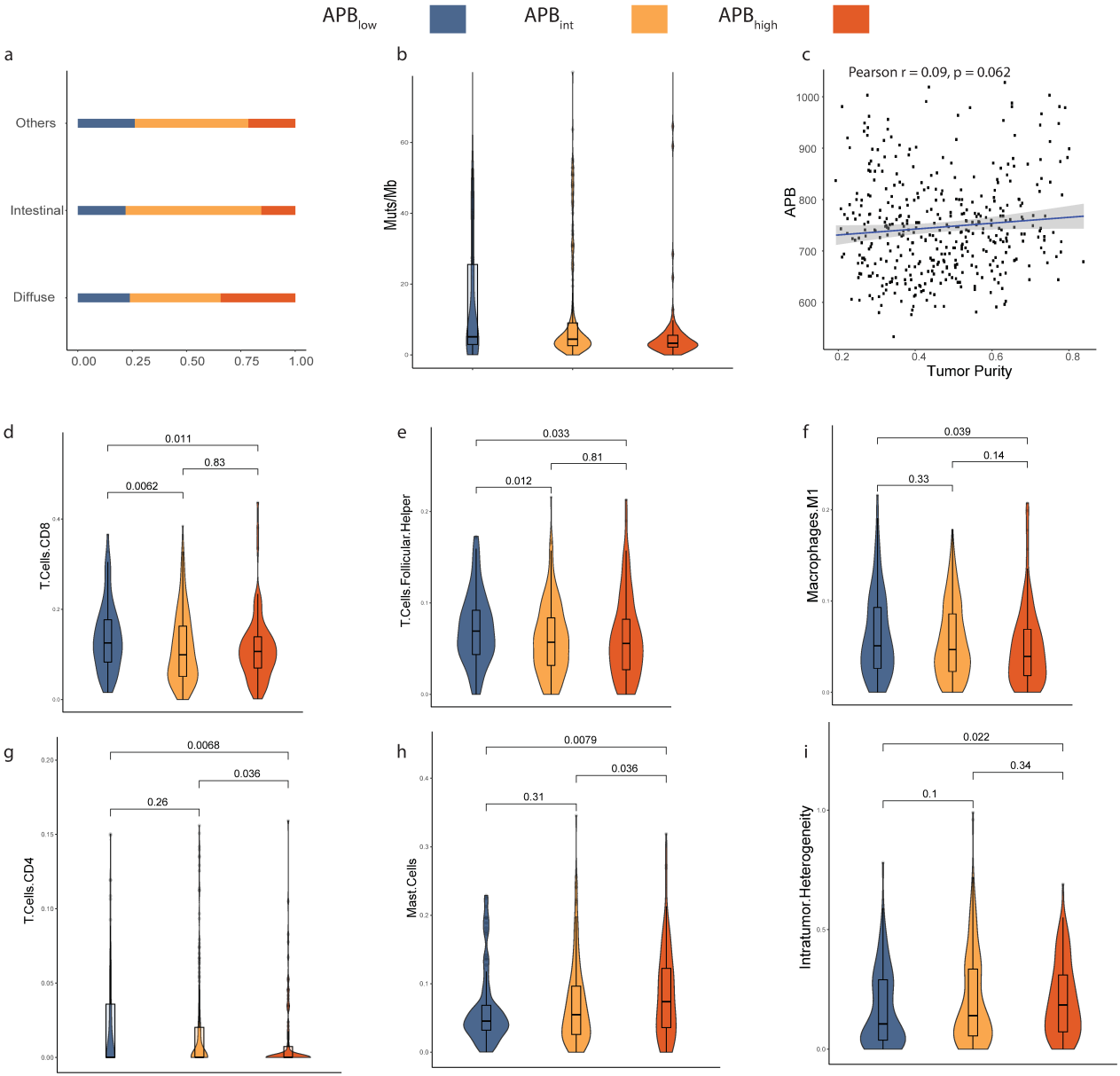
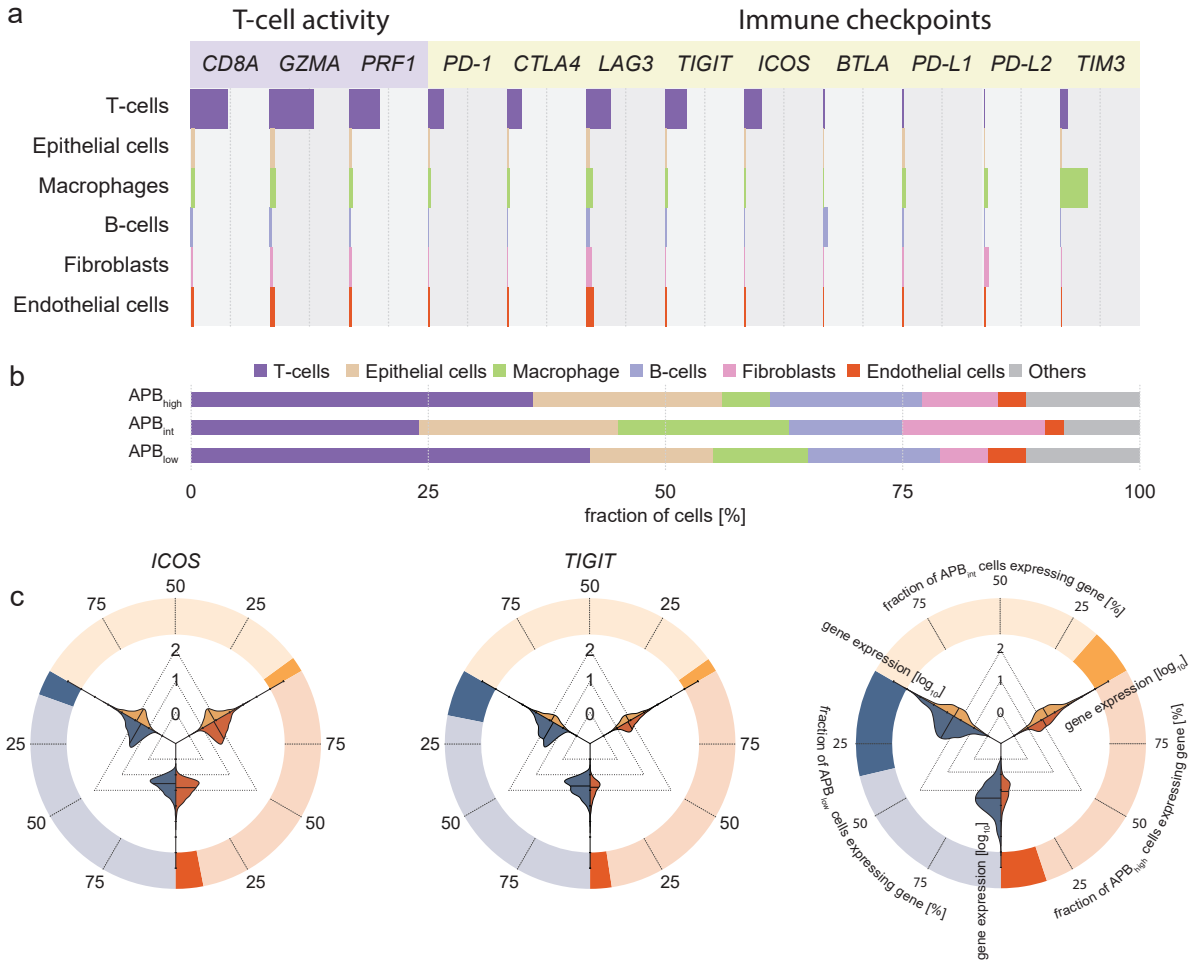
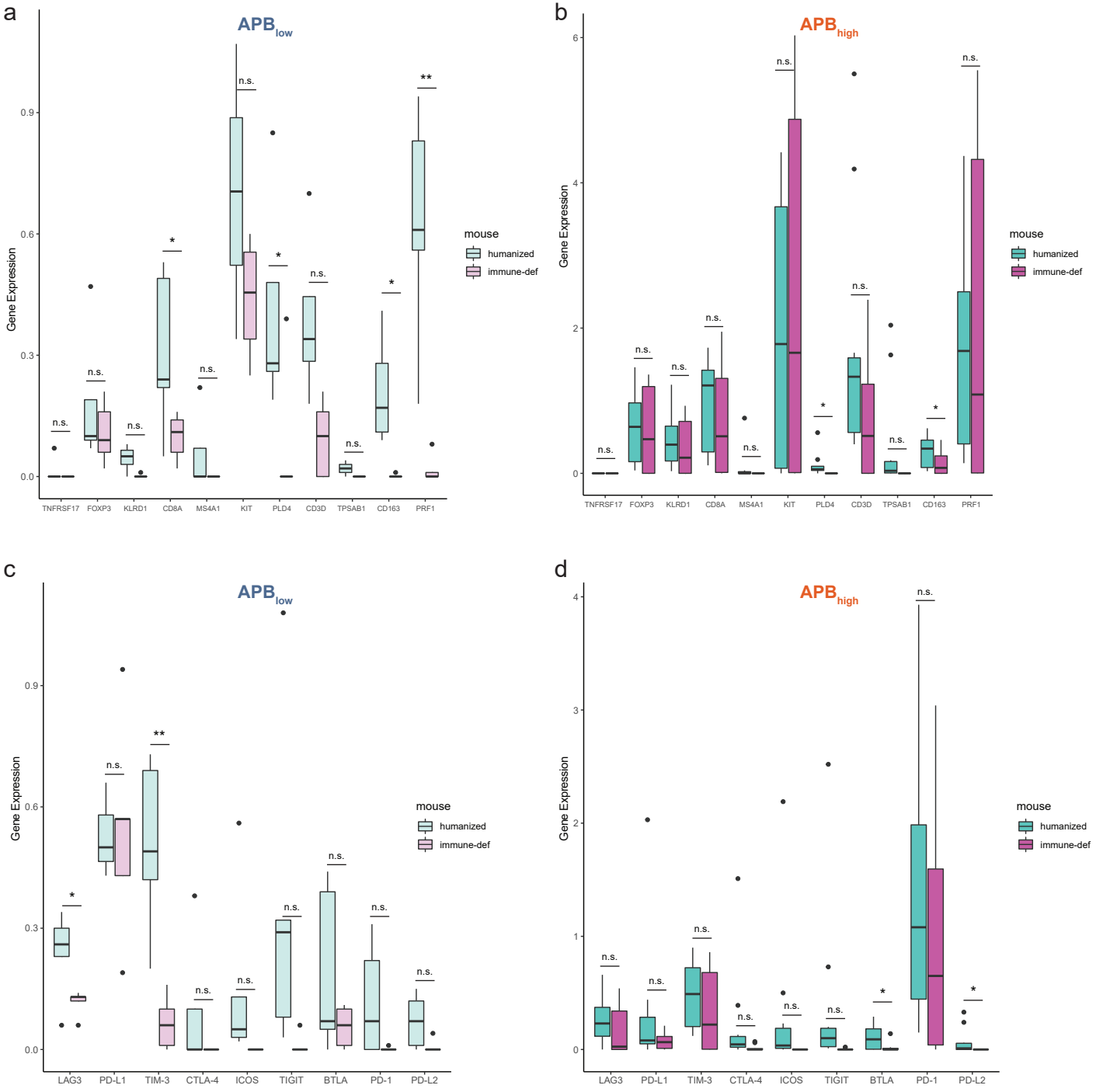
Supplementary Figure 1



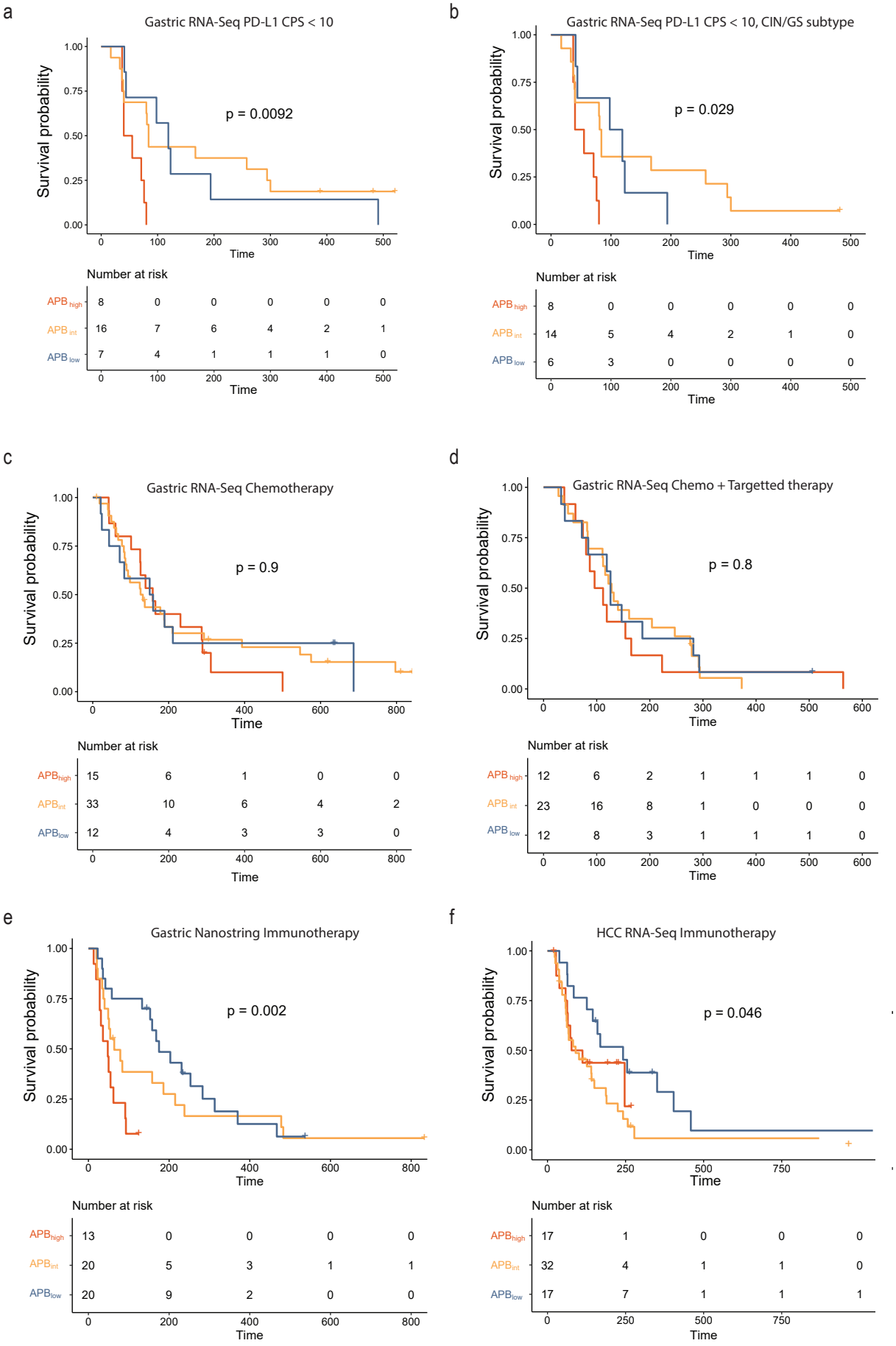
Supplementary Figure 2



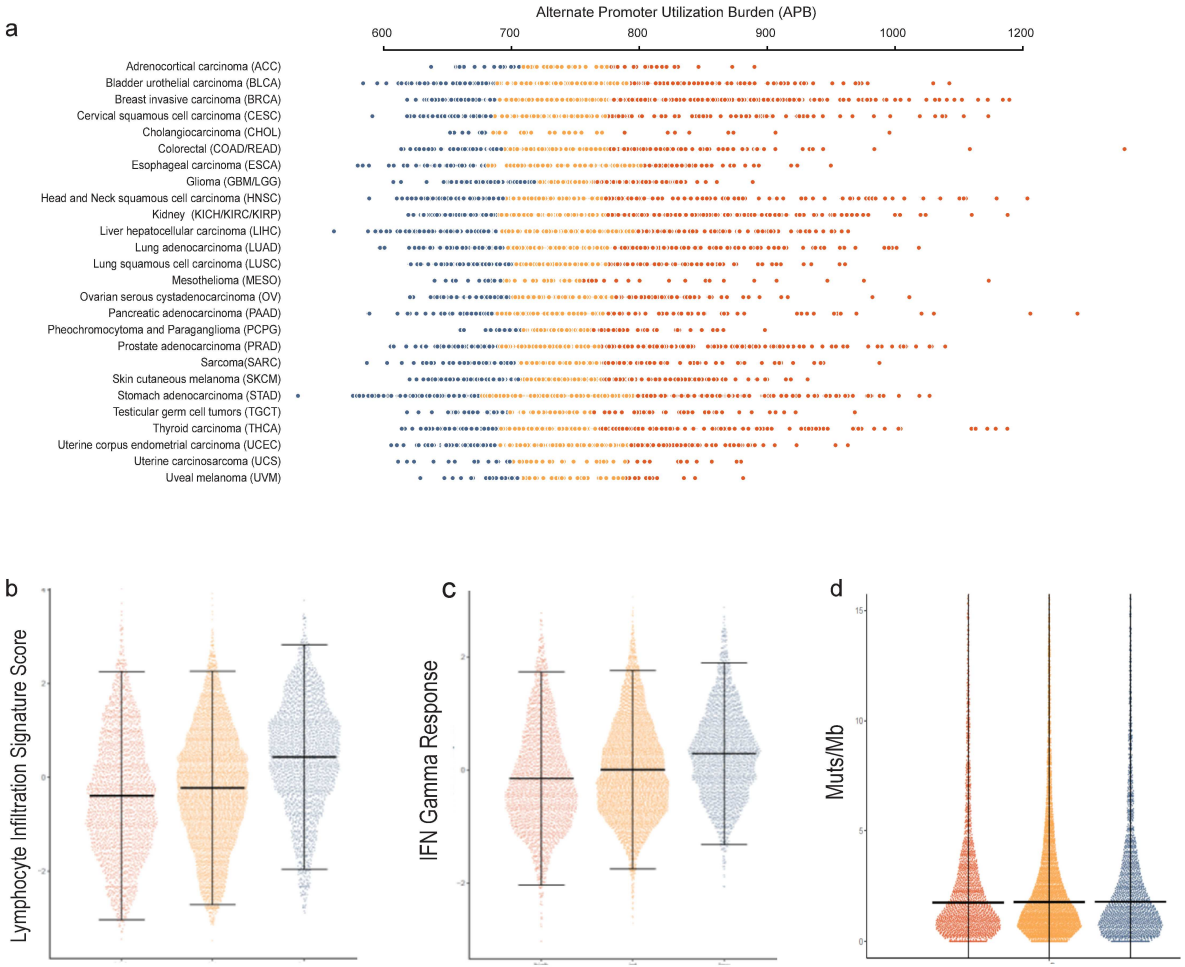
Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure Legends

Supplementary Figure 1. APB in STAD

a. STAD Histological subtype by APB group

Distribution of STAD histological subtypes by APB group. Histological subtypes included: Diffuse, intestinal and others (mucinous, papillary, signet ring, tubular and not-otherwise-specified). There were no significant differences between APB groups when categorized by histological subtype.

b. APB and tumor mutational burden in STAD

Association of APB groups in STAD with tumor mutational burden (TMB). APB_{high} group is denoted in red, APB_{int} in yellow and APB_{low} in blue. APB_{low} tumors had a modestly higher median mutation rates compared to APB_{high} tumors. However, this difference was largely driven by MSI tumors which were predominantly APB_{low}

c. Correlation between APB and tumor purity

APB was correlated with tumor purity obtained from a consensus estimation method. There is a weak positive correlation between tumor content and APB (Pearson r = 0.09, p = 0.062)

d-h. APB and correlation with immune cell types

APB groups were correlated with CD8 (d), follicular helper T cells (e), M1 macrophages (f), CD4 (g) and mast cells (h). APB_{low} tumors had higher abundance of these cell types compared to APB_{high} tumors, except for mast cells, where the converse was true. APB groups were also correlated with other cell types including B cells, dendritic cells, eosinophils, M2 macrophages, neutrophils, but no correlation was seen with APB groups (data not shown).

i. APB and correlation with intra-tumoral heterogeneity

APB groups correlated with intratumor heterogeneity scores calculated by ABSOLUTE. APB_{high} tumors appeared to have higher intratumor heterogeneity than the APB_{low} tumors (p = 0.022).

Supplementary Figure 2. scRNA-Seq in STAD by APB

a. Expression of immune correlate genes used in bulk RNA-Seq analysis (*CD8A, GZMA, PRF1* and immune checkpoints *PD-1, PD-L1, PD-L2, CTLA4, LAG3, TIGIT, TIM3, ICOS, BTLA*) within specific cell types in scRNA-Seq. *CD8A, GZMA* and *PRF1* were expressed almost exclusively within T-cells (40 to 50% of T-cells) validating the expression of *CD8A, GZMA* and *PRF1* in bulk RNA-Seq as appropriate surrogates for T-cell cytolytic activity. Similarly, several checkpoints are expressed predominantly in T-cells (*PD-1, CTLA4, LAG3, TIGIT and ICOS*). *PD-L1* and *PD-L2* (ligands of PD-1) are expressed equally on several cell types such as epithelial cells, macrophages and fibroblasts.

b. Proportion of cellular subtypes (T-cells, B-cells, macrophages, epithelial cells, endothelial cells and fibroblasts) per APB group. Quantitative data of this graph are presented in **supplementary Table 3**.

c. Circle-violin plots of expression of *TIGIT* and *ICOS* by APB group in scRNA-Seq. The outer circle demonstrates the proportion of cells within the APB group which express the gene. Three comparisons are made: APB_{low}(blue) *vs.* ABP_{int}(yellow); APB_{int} *vs.* APB_{high}(red) and APB_{low} *vs.* APB_{high}.

Supplementary Figure 3. Gene expression of tumors in *in vivo* experiment

a. Expression of genes marking specific cellular subtypes in APB_{low} cell line. Comparison made between humanized (green) and immune-deficient (pink) tumors. Levels of *CD8A* and *PRF1* (markers of cytolytic T-cells, adaptive immunity) and *PLD4* and *CD163* (markers of dendritic cells and macrophages respectively, innate immunity) were found to be higher in humanized mice compared to immune deficient mice. * : $p < 0.05$, ** : $p < 0.01$

b. Expression of genes marking specific cellular subtypes in APB_{high} cell line. Comparison made between humanized (dark green) and immune-deficient (dark pink) tumors. Only levels of *PLD4* and *CD163* (markers of dendritic cells and macrophages respectively, innate immunity) were found to be higher in humanized mice compared to immune deficient mice. * : $p < 0.05$

c. Expression of select immune checkpoints in APB_{low} cell line. Comparison made between humanized (green) and immune-deficient (pink) tumors. Levels of *LAG3* and *TIM-3* were found to be higher in humanized mice compared to immune deficient mice. * : $p < 0.05$, ** : $p < 0.01$

d. Expression of select immune checkpoints in APB_{high} cell line. Comparison made between humanized (green) and immune-deficient (pink) tumors.

Supplementary Figure 4. Survival curves of APB in gastro-intestinal cancers

a. Kaplan–Meier plot of subgroup of gastric cancer samples treated with immunotherapy presented in **Figure 4A** and **B**, with PD-L1 CPS < 10 (n = 31)

b. Kaplan–Meier plot of subgroup of gastric cancer samples treated with immunotherapy presented in **Figure 4A** and **B**, with PD-L1 CPS < 10 and CIN/GS subtype (n = 28)

c. Kaplan–Meier plot of gastric cancer samples treated with chemotherapy (SOX or SP) (n = 60)

d. Kaplan–Meier plot of gastric cancer samples treated with combination chemotherapy and targeted therapy (paclitaxel and ramucirumab) (n = 47)

e. Kaplan–Meier plot of gastric cancer samples treated with immunotherapy, analysed by NanoString (n = 53)

f. Kaplan–Meier plot of hepatocellular carcinoma samples treated with ICI (n = 66)

All Kaplan–Meier curves are of progression-free survival comparing APB_{high} (red) *vs.* APB_{int} (yellow) *vs.* APB_{low} (blue). P value is according to two-sided log-rank test.

Supplementary Figure 5. Alternate promoter utilization burden – pan cancer analysis

a. Alternate promoter utilization burden score across 26 tumor types. Within each tumor type, samples are divided into APB_{high} (red, top quartile), APB_{int} (yellow, middle quartiles) and APB_{low} (blue, bottom quartile) of APB.

b. Lymphocyte infiltration signature score and correlation with APB group

Lymphocyte infiltration signature defined by Thorsson *et al*. dichotomized by APB groups. The APB_{low} group has a statistically higher score compared to APB_{high} (Wilcoxon test $p < 0.0001$)

c. IFN-γ response signature and correlation with APB group

IFN-γ response signature as defined by Thorsson *et al*. dichotomized by APB groups. The APB_{low} group has a statistically higher score compared to APB_{high} (Wilcoxon test $p < 0.0001$)

d. Correlation between APB groups and TMB in Pan-TCGA analysis

Association of APB groups in Pan-Cancer analysis of 7,919 samples with tumor mutational burden (TMB). APB_{high} group is denoted in red, APB_{int} in yellow and APB_{low} in blue. There was no correlation between APB and TMB (median APB_{low} 1.8 *vs.* APB_{int} 1.8 *vs.* APB_{int} 1.8 muts/Mb, $p = 0.64$)