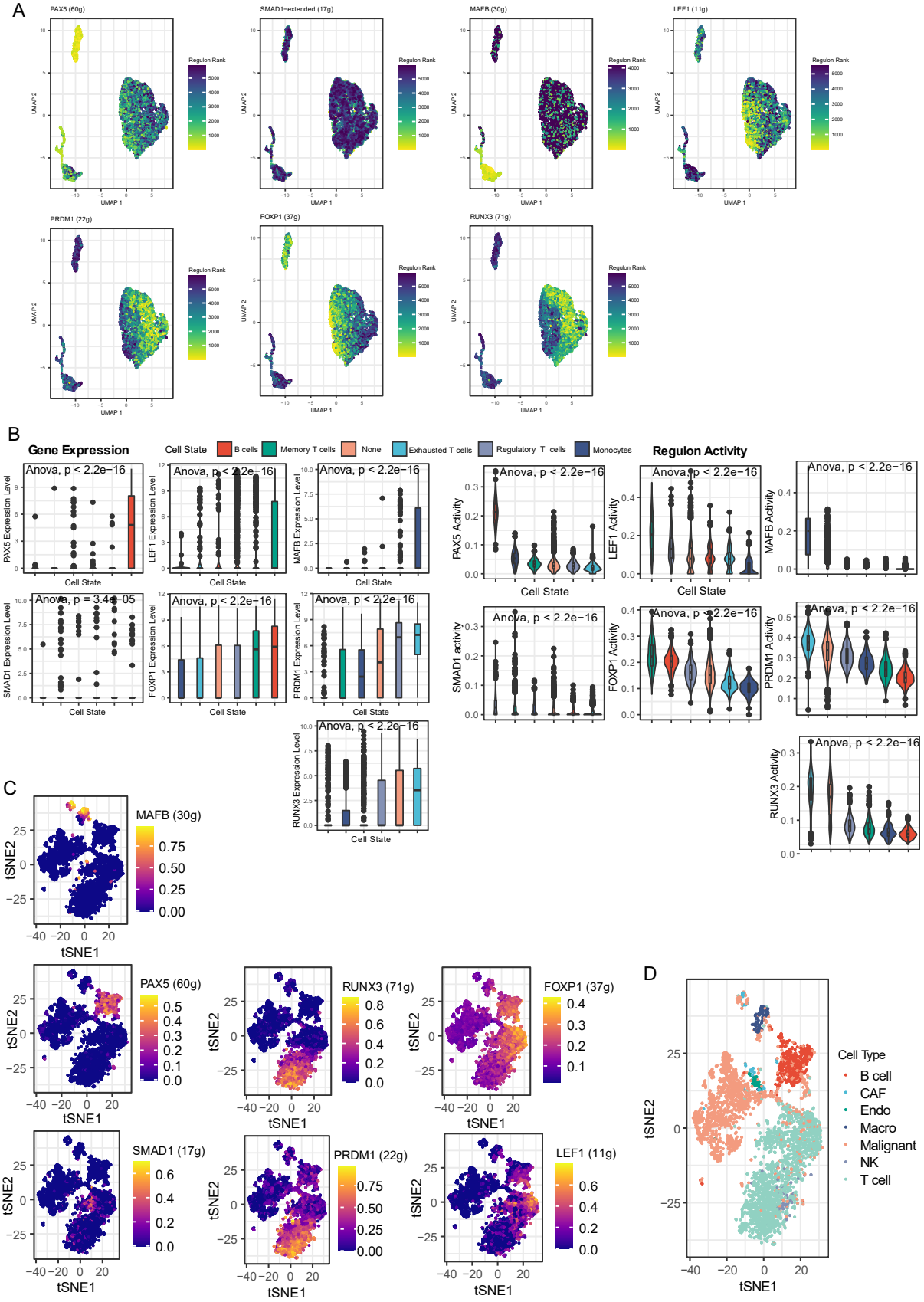
Supplementary Figure 1



Supplementary Figure S1. Regulon activity and upstream TF expression in the tumor microenvironment.

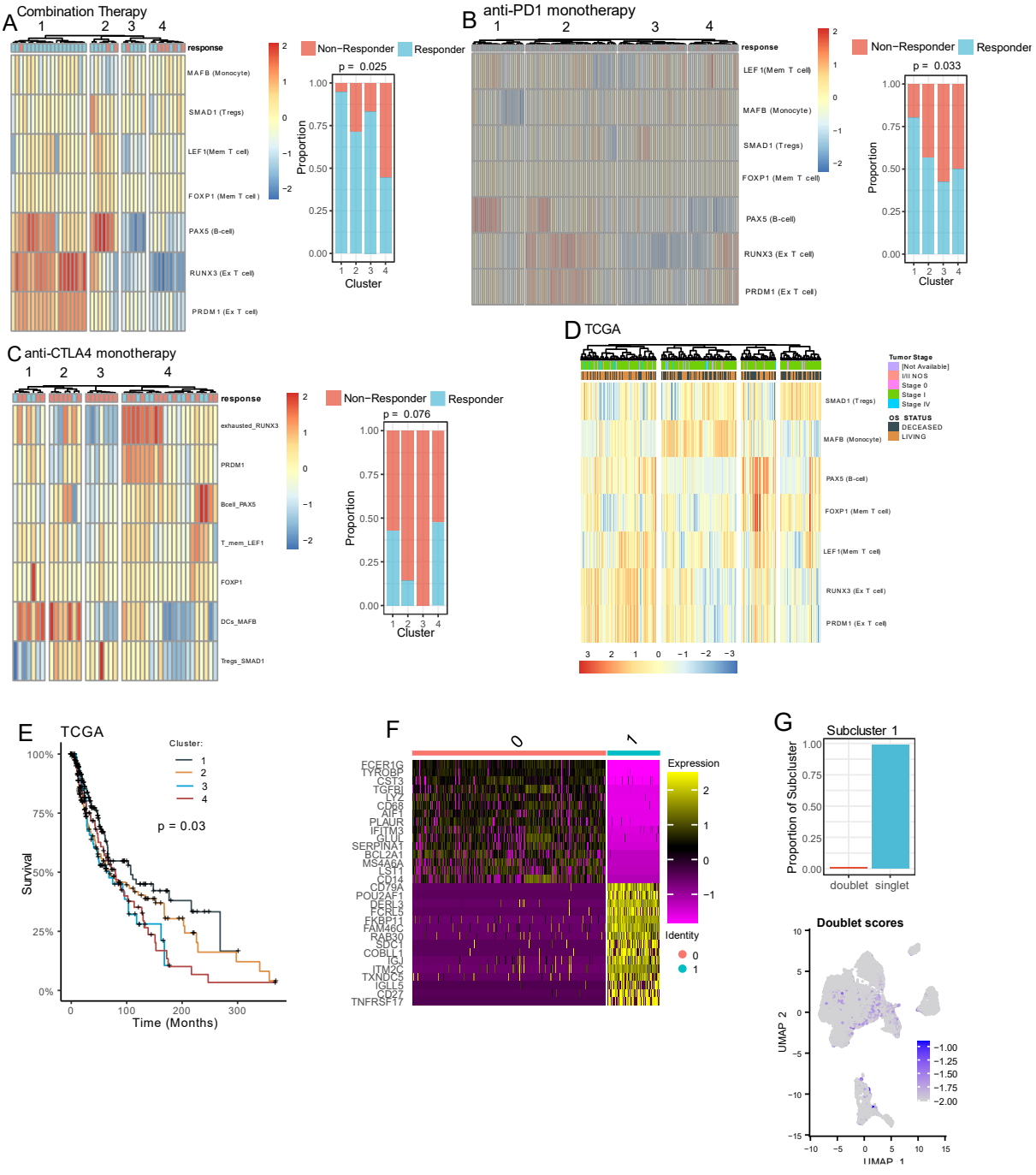
A) UMAP embeddings of pre-treatment cells, colored using a quantitative scale of the relative rank of each regulon across the population of cells.

B) Left panel: the expression levels (log TPM) of the representative TF for each regulon in the DAseq-identified cell states. Right panel: regulon activity levels in each DAseq-identified cell state.

C) T-SNE plots of malignant and non-malignant cells, colored according to the relative activity of the regulons across the population of cells. he associated annotations of the cells represented in the t-SNE plots.

D) The associated annotations of the cells represented in the t-SNE plots.

Supplementary Figure 2



Supplementary Figure S2. The predictive and prognostic value of regulons.

A, B, C) Left panels: Hierarchical clustering of patients from the bulk RNA-seq validation dataset according to their ssGSEA inferred regulon scores, which are represented by the color scale bar. Pearson correlation was used as the distance metric. Right Panels: The proportion

of responders and non-responders in each cluster. The p-value was calculated with a chi-squared test. Patients were stratified by treatment received (denoted in figure).

D) Hierarchical clustering of patients from TCGA according to their ssGSEA inferred regulon scores.

E) Kaplan Meier survival curves for each cluster identified from TCGA dataset, compared using a log rank test.

F) Heatmap displaying scaled expression values of DEGs per MLC subcluster.

G) Top panel: The proportion of doublets and singlets in subcluster 1 from the MLC state. Bottom panel: UMAP embedding of pre- and post-treatment cells from the discovery melanoma dataset (n = 16,291). The cells are colored according to their doublet prediction scores from the Chord algorithm. A high score (purple) denotes a doublet and a low score (grey) denotes a singlet.