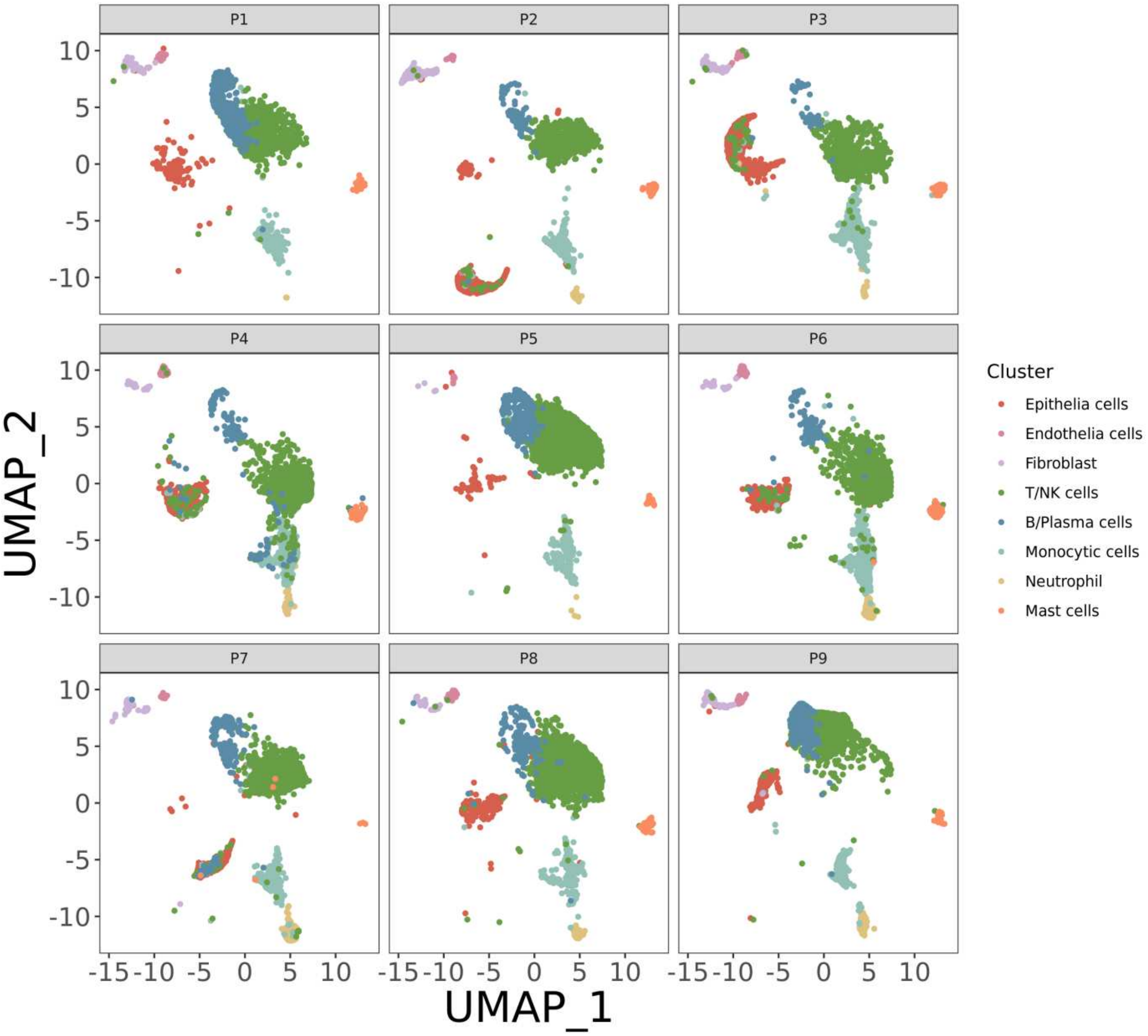
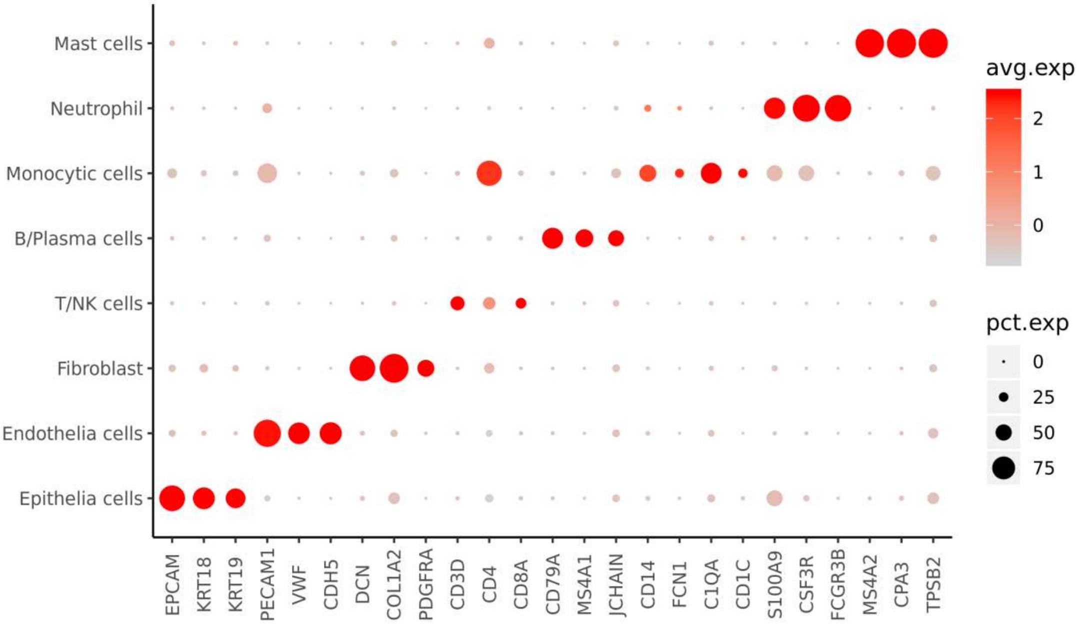
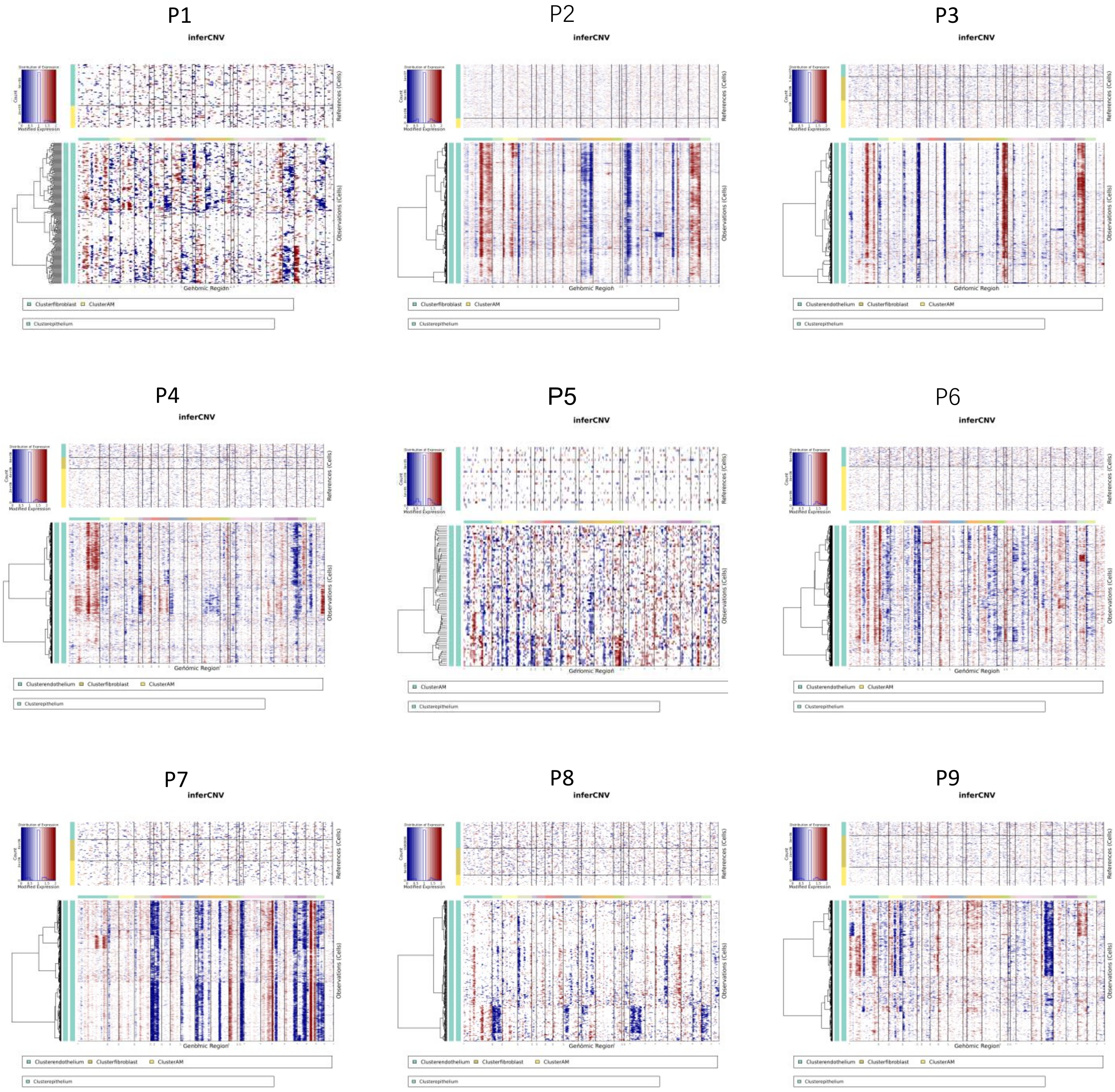
Supplementary Figure 1. Total cells in each treatment-naive LUAD sample.



Supplementary Figure 2. Bubble plot of marker genes of each cell subgroup.



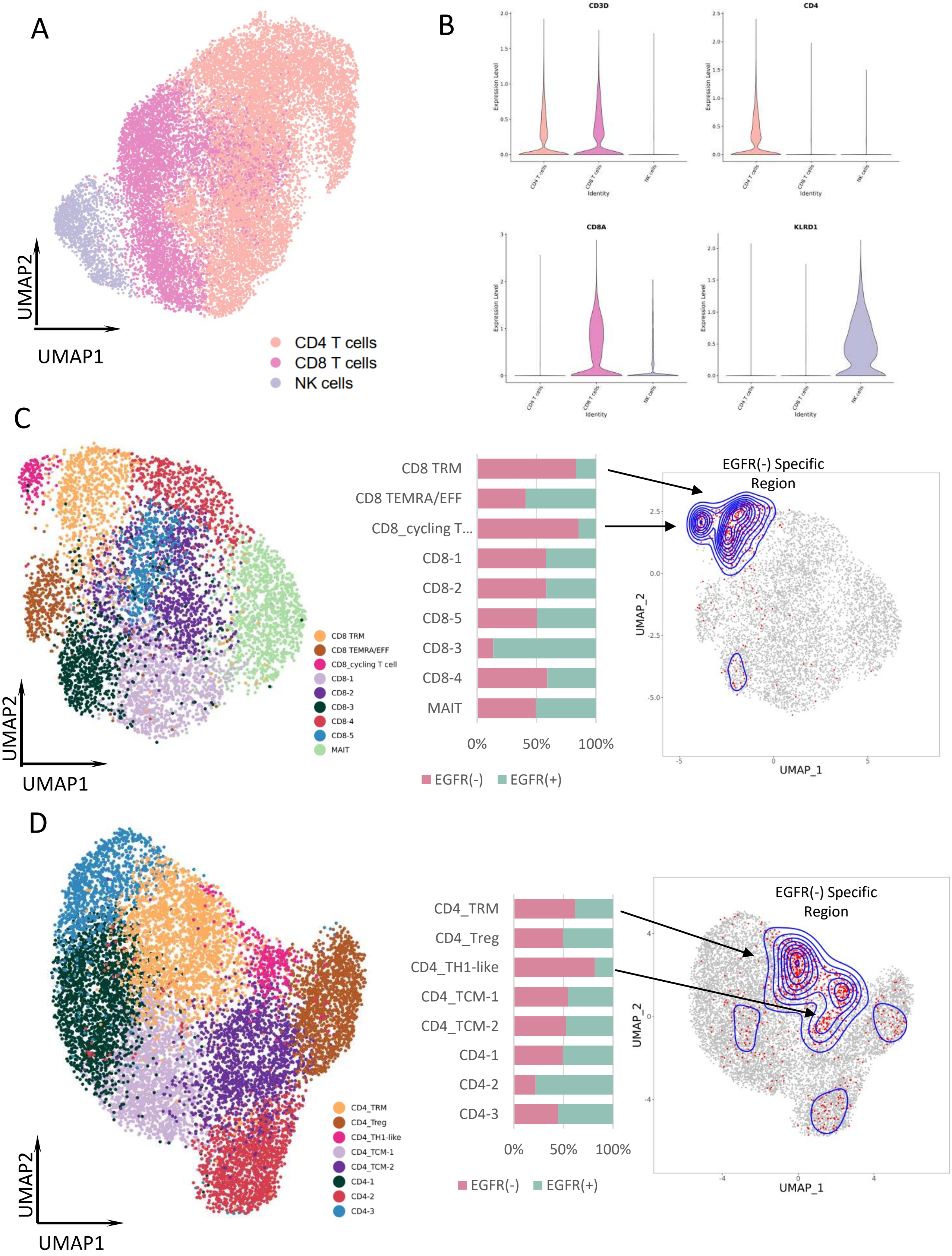
Supplementary Figure 3. Identification of tumor cells and normal cells from epithelial cells in each treatment-naïve sample.



Supplementary Figure 4. Further clustering of T and NK cells.

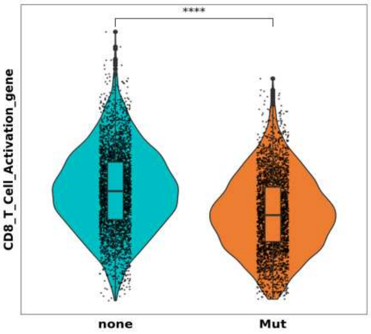
A. UMAP plot of 19,984 T/NK cells from treatment-naïve samples.
B. Violin plot of different marker genes for T/NK cell clusters.
C. UMAP plot of CD8+ T cells from treatment-naïve samples (left). The proportion of each CD8+ T cell cluster in EGFR (-) (pink) and EGFR (+) (cyan) group (middle). UMAP plot of CD8+ T cell from EGFR(-) specific region calculated by DASeq (right).
D. UMAP plot of CD4+ T cells from treatment-naïve samples (left). The proportion of each CD4+ T cell cluster in EGFR (-) (pink) and EGFR (+) (cyan) group (middle). UMAP plot of CD4+ T cell from EGFR(-) specific region calculated by DASeq (right).
E. Marker genes of active CD8+ T cell differing in EGFR status.
F. Expression of PD1, LAG3 and TIM3 protein by CD8+T cells in EGFR (-) and EGFR (+) TME.
G. Bubble plot of cytokines and interleukin expression by each cluster of CD4+ T cells.

Supplementary Figure 4 (A-D)



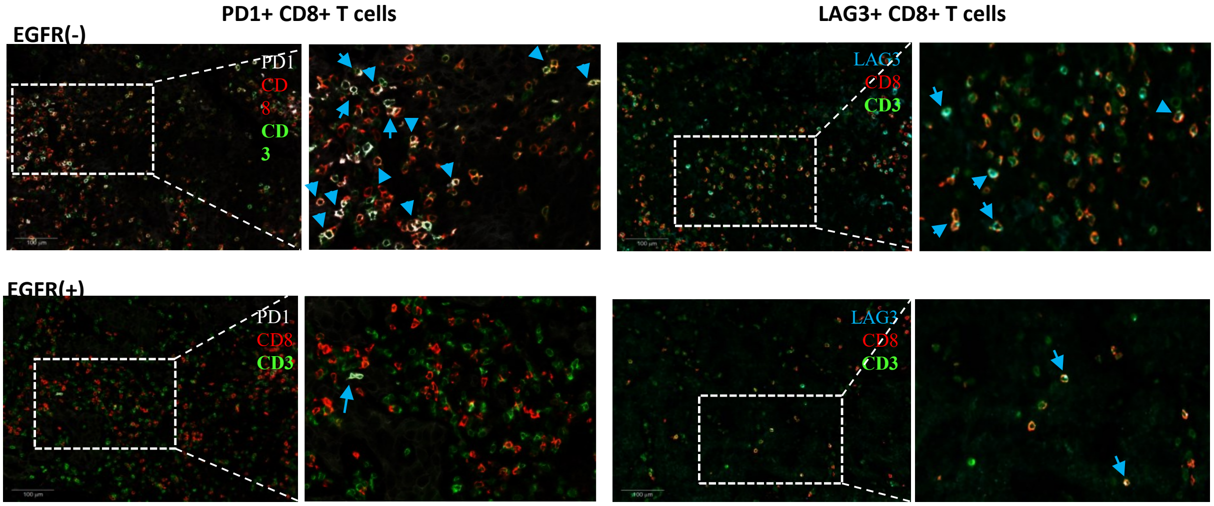
Supplementary Figure 4 (E-G)

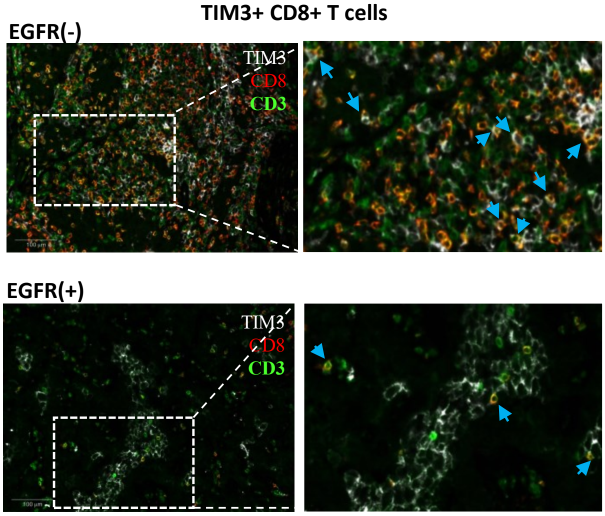
E



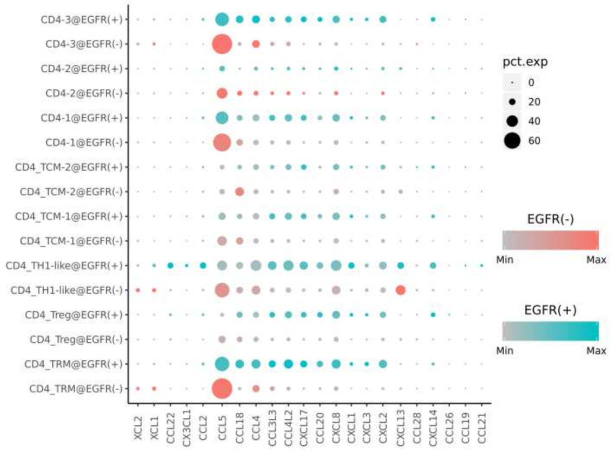
Subtype of T cells	Marker gene
Cytotoxic	CST7; GZMA; GZMB; IFNG; NKG7; PRF1
Exhaustion	CTLA4; HAVCR2; LAG3; PDCD1; TIGIT
CD8_T_Cell_Activation_gene	CD69; CCR7; CD27; BTLA; CD40LG; IL2RA; CD3E; CD47; EOMES; GNLY; GZMA; GZMB; PRF1; IFNG; CD8A; CD8B; FASLG; LAMP1; LAG3; CTLA4; HLA-DRA; TNFRSF4; ICOS; TNFRSF9; TNFRSF18
Type_I_Interferon_response_gene	IRF1; IFIH1; IFITM3; DDX58; IFI44L; IFI6; IFITM2; NAMPT; OASL; RTP4; TREX1; ADAR; FAM46C; LY6E; MCOLN2; APOBEC3G; IL15; ISG15; MX1; TLR3
Type_II_Interferon_Response_gene	IFNG; CXCL9; CXCL10; STAT1; CD274; CDKN1A; MYC; SMAD7; IRF1; HLA-A; HLA-B; HLA-C; HLA-E; HLA-F; HLA-G; HLA-K; HLA-L; HLA-L; HLA-DMA; HLA-DOA; HLA-DPA1; HLA-DQA1; HLA-DRA; HLA-DMB; HLA-DOB; HLA-DPB1; HLA-DQA2; HLA-DRB1; HLA-DQB1; HLA-DRB3; HLA-DQB2; HLA-DRB4

F



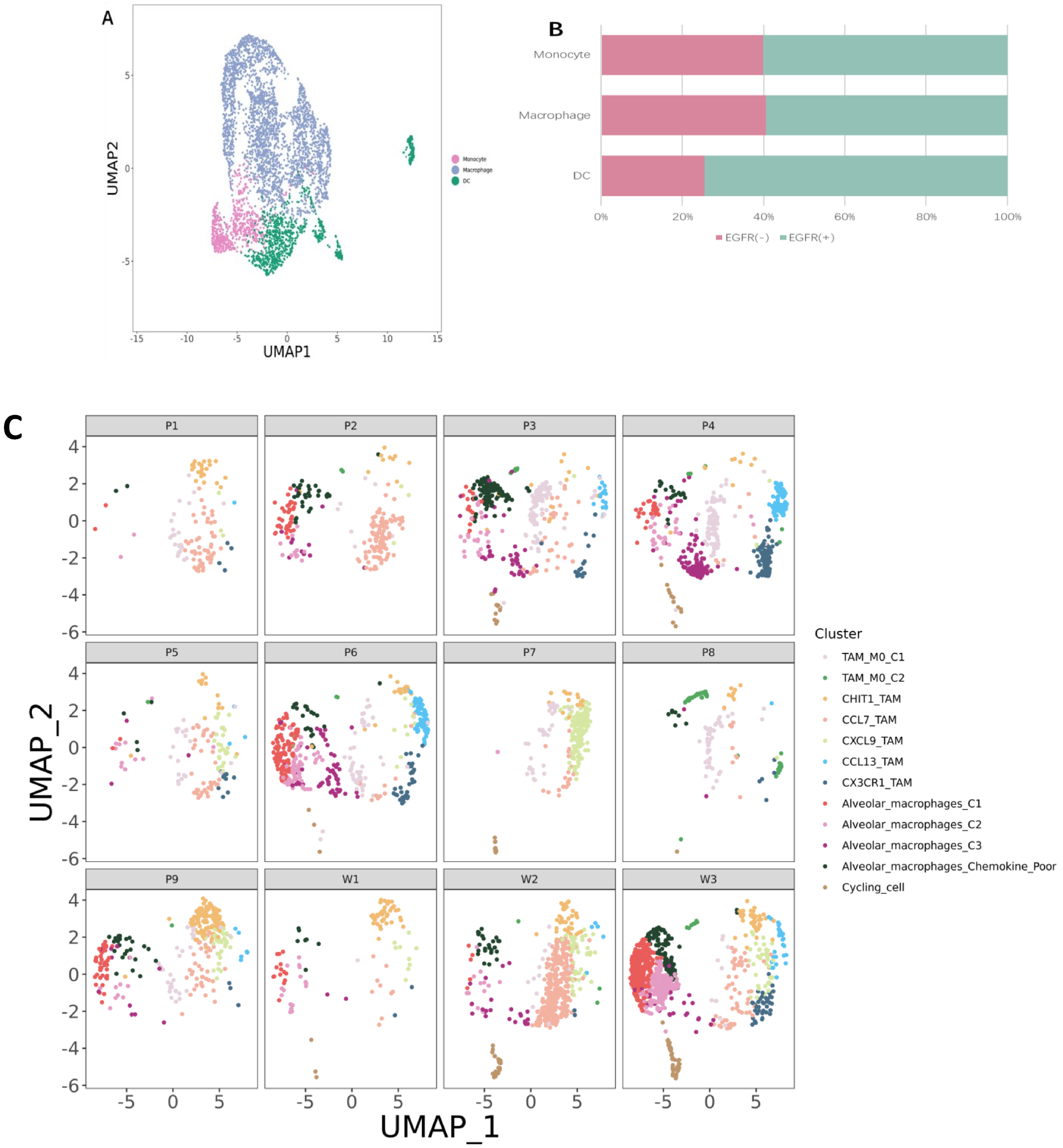


G



Supplementary Figure 5. Further clustering of monocytic cells and TAM clusters in each sample.

A. UMAP plot of 4,429 monocytic cells from treatment-naïve samples.
B. The proportion of monocytes in EGFR (-) (pink) and EGFR (+) (cyan) group.
C. TAM clusters identified in each LUAD sample.

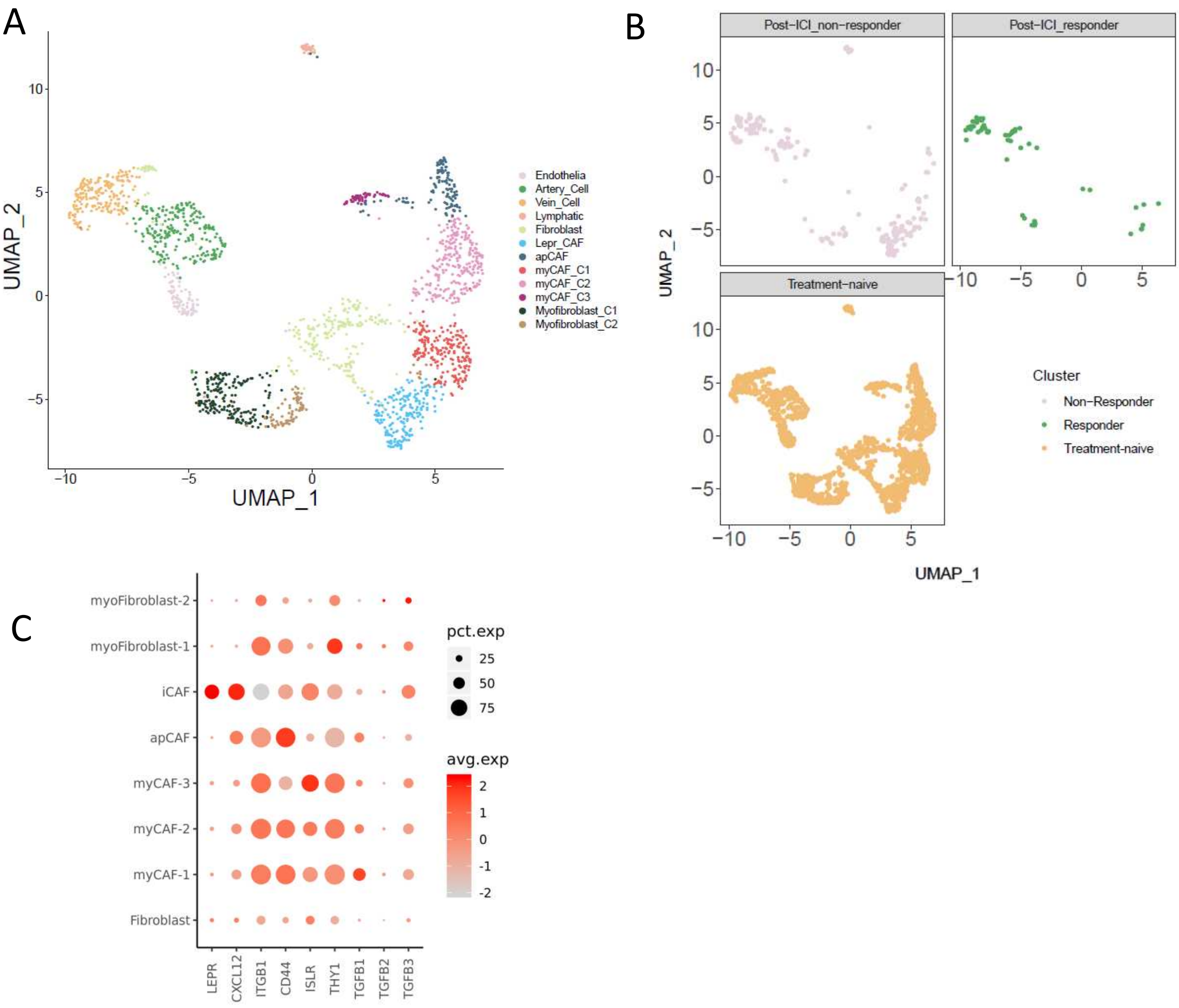


Supplementary Figure 6. CAFs identified in treatment-naïve and post-treatment samples.

A. UMAP plot of pooled fibroblast and endothelial cells in both treatment-naïve and post-treatment samples.

B. UMAP plot of pooled fibroblast and endothelial cells from post-ICI responder, post-ICI non-responder, treatment-naïve samples, respectively.

C. Bubble plot of MSC marker genes and TGF-β expressed by CAFs in treatment-naïve samples.



Supplementary Figure 7. Dendritic cells identified in the TME.

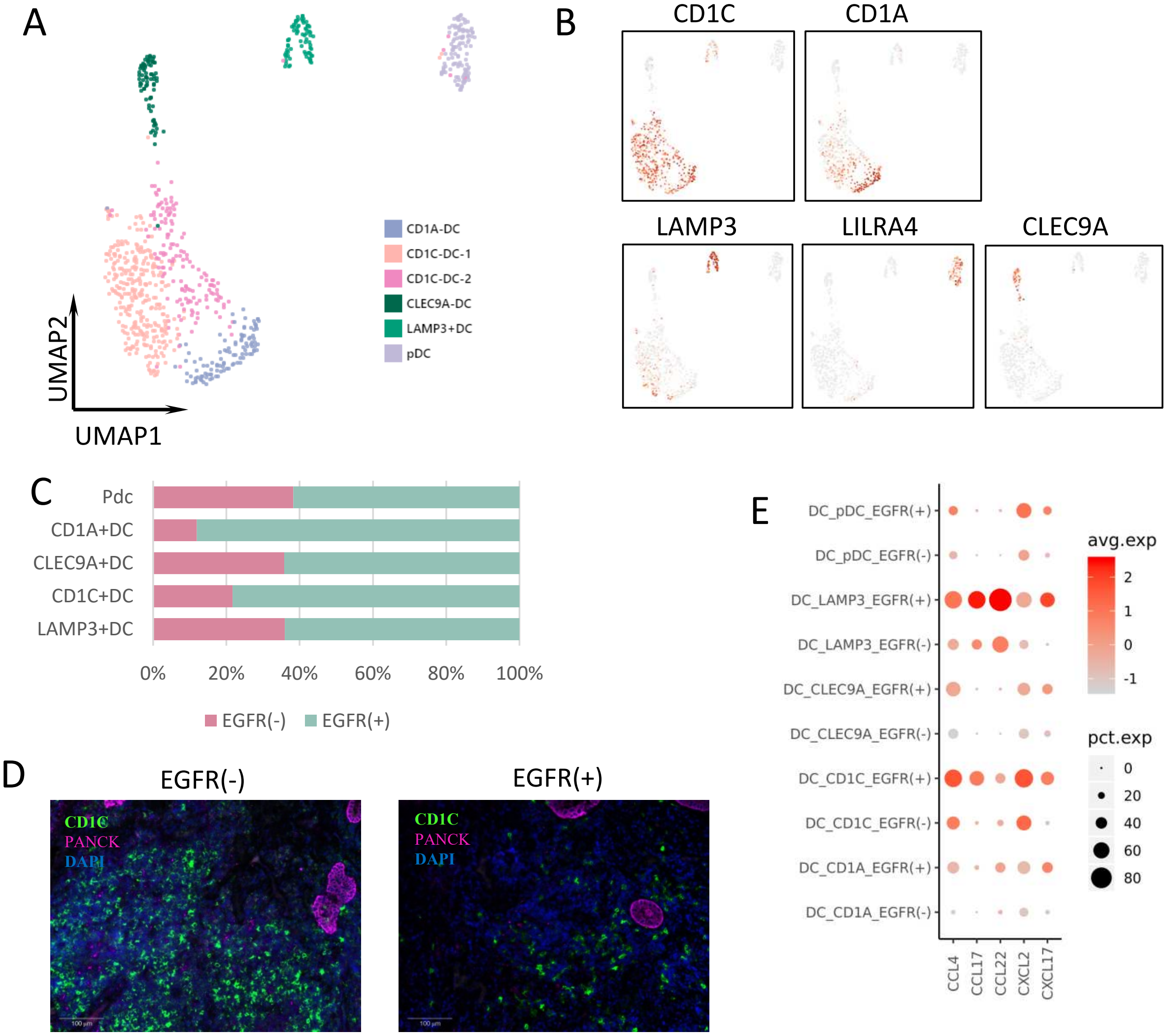
A. UMAP plot of 839 DCs from treatment-naïve samples.

B. Expression of marker genes for different DC types.

C. The proportion of each DC cluster in EGFR (-) (pink) and EGFR (+) (cyan) group.

D. The distribution of CD1C+ DCs in the tumor stromal area of EGFR (-) and EGFR (+) TME.

E. Bubble plot of cytokine expression among DCs clusters from different group.



Supplementary Figure 8. Neutrophil, endothelial and mast cells identified in the TME.

A. Volcano map of genes upregulated and downregulated in neutrophils of EGFR (+) samples.
B. UMAP plot of 491 endothelial cells from treatment-naïve samples.
C. Expression of marker genes for different endothelial clusters.
D. The proportion of each endothelial cell cluster in EGFR (-) (pink) and EGFR (+) (cyan) group.
E. Bubble plot of cytokine expression among endothelial cell clusters from different groups.
F. Bubble plot showing the most prevalent genes expressed in mast cells.