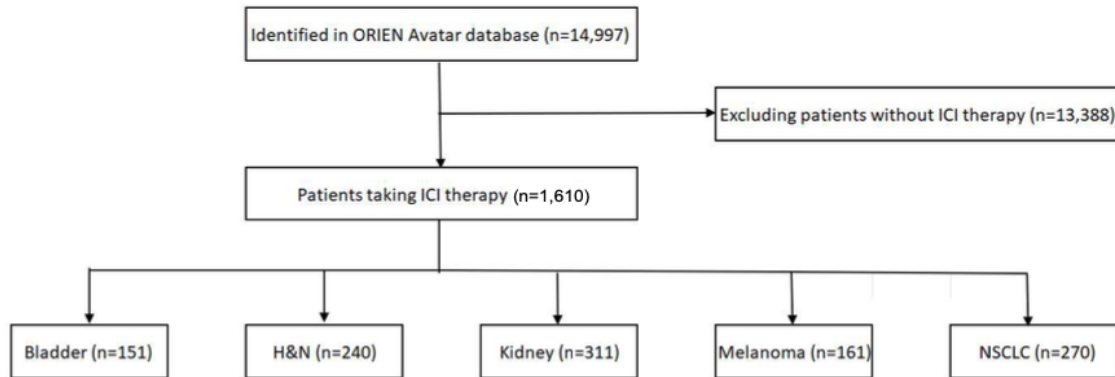
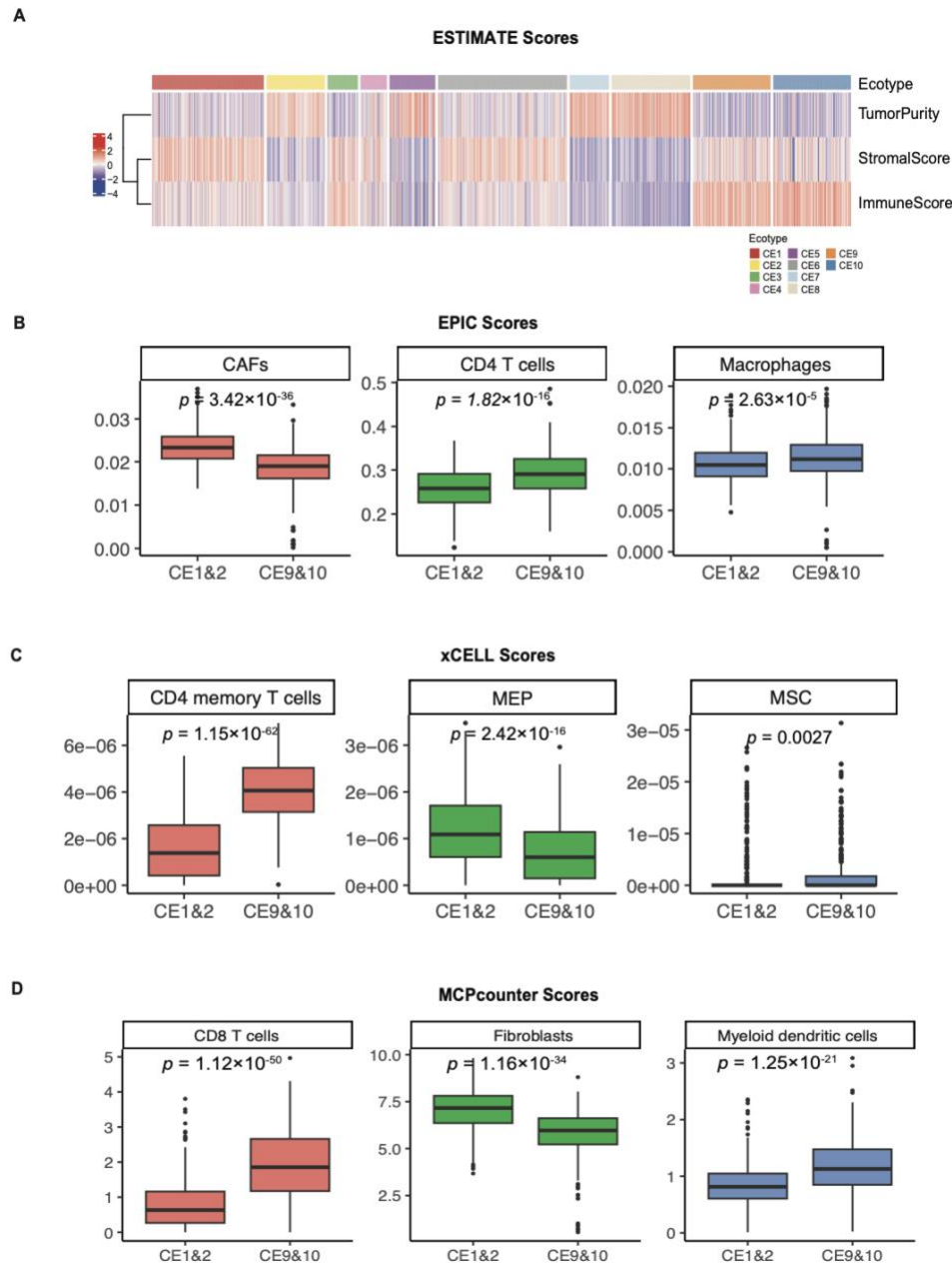


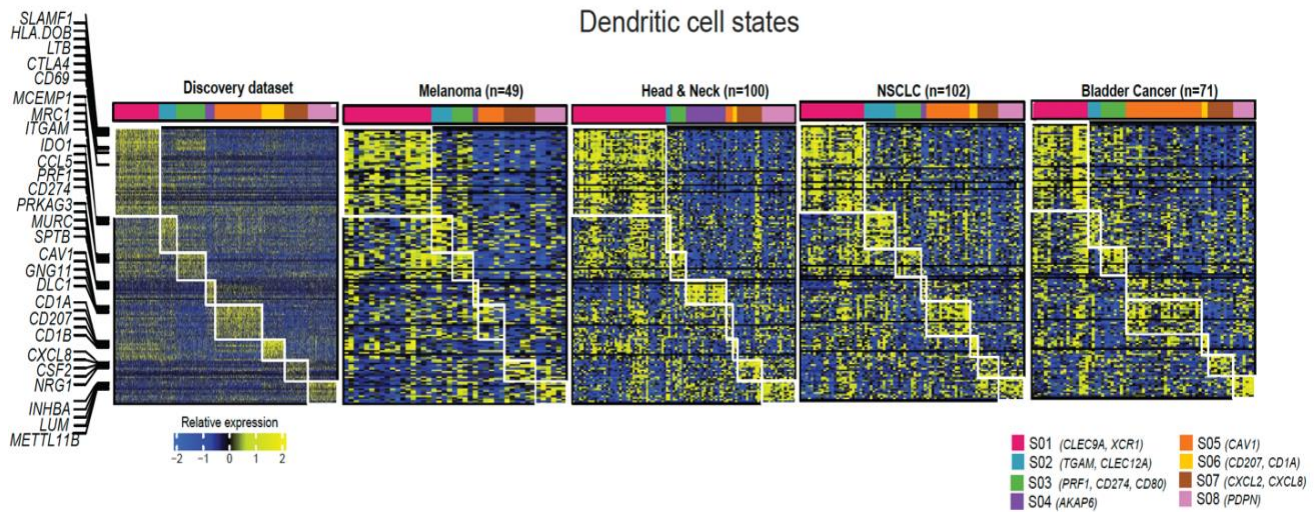
Supplementary Figures



Supplementary Figure 1. Patient selection workflow for the ORIEN-ICI cohort. H&N; head and neck, IO; immuno-oncology, NSCLC; non-small cell lung cancer, ORIEN; Oncology Research Information Exchange Network.

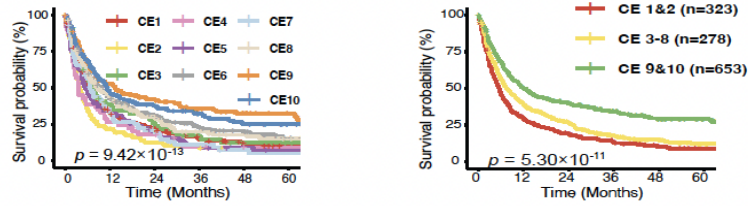


Supplementary Figure 2. Association of carcinoma ecotypes (CE) and immune deconvolution scores. (A) Heatmap showing ESTIMATE scores (ImmuneScore, StromalScore, and TumorPurity) across $n=1,340$ RNAseq samples. (B-D) Boxplots comparing selected tumor-immune cell-type scores between CE1&2 ($n=338$) and CE9&10 ($n=308$) using three deconvolution methods. Boxplots show center line = median; box limits = IQR; whiskers = $1.5 \times \text{IQR}$; points = outliers. All reported p-values are from two-sided Wilcoxon rank-sum tests. Source data are provided in the Source Data file.

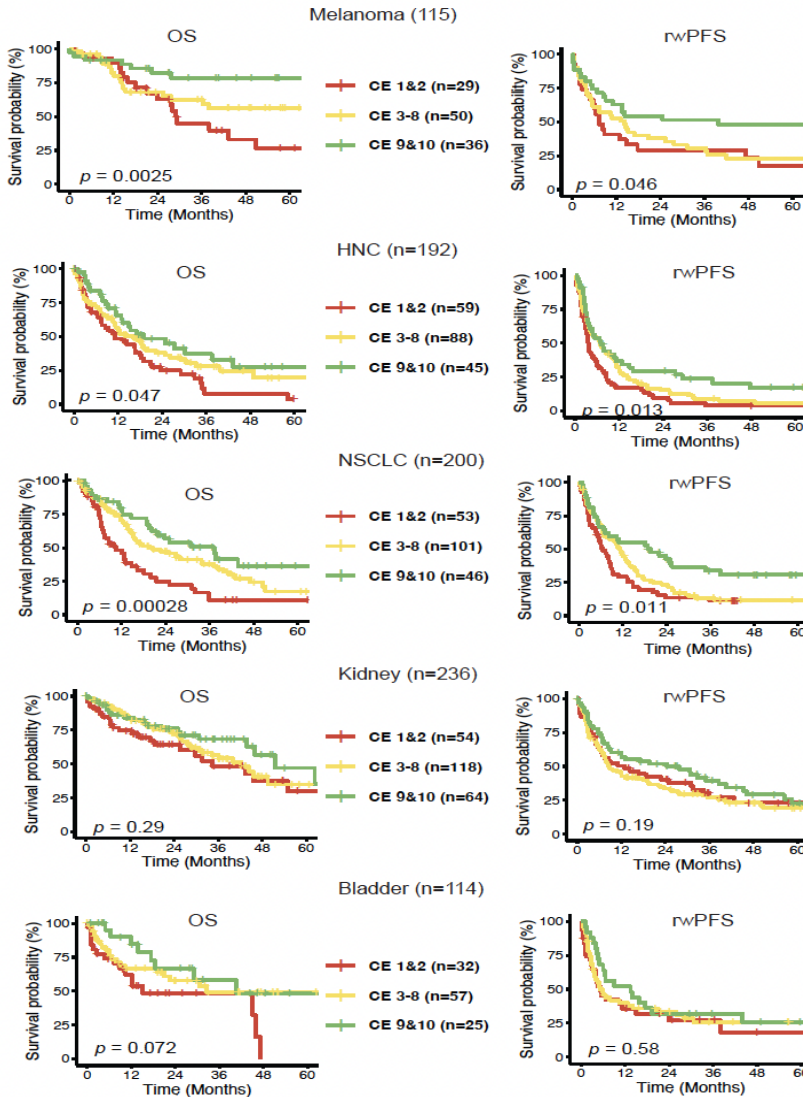


Supplementary Figure 3. Dendritic cell states across four major cancer types in the ORIEN-ICI dataset. The figure presents heatmaps displaying expression profiles of dendritic cell states identified from the discovery dataset and projected onto melanoma ($n=49$), head and neck ($n=100$), NSCLC ($n=102$), and bladder cancer ($n=71$) cohorts in the ORIEN-ICI dataset. Each row represents a marker gene, and each column corresponds to a tumor sample. Source data are provided in Source Data file.

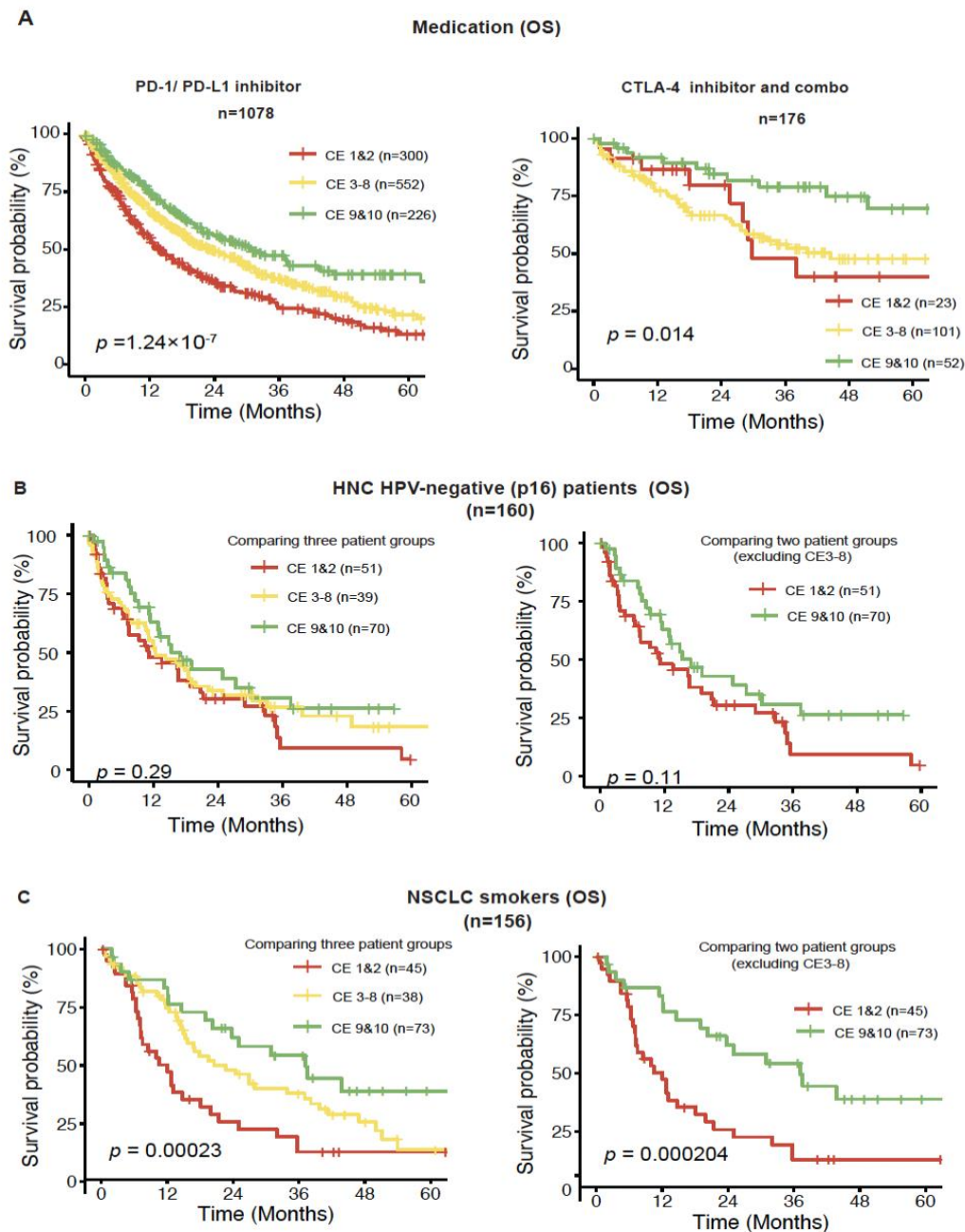
A Pan-Cancer Ecotype (rwPFS)



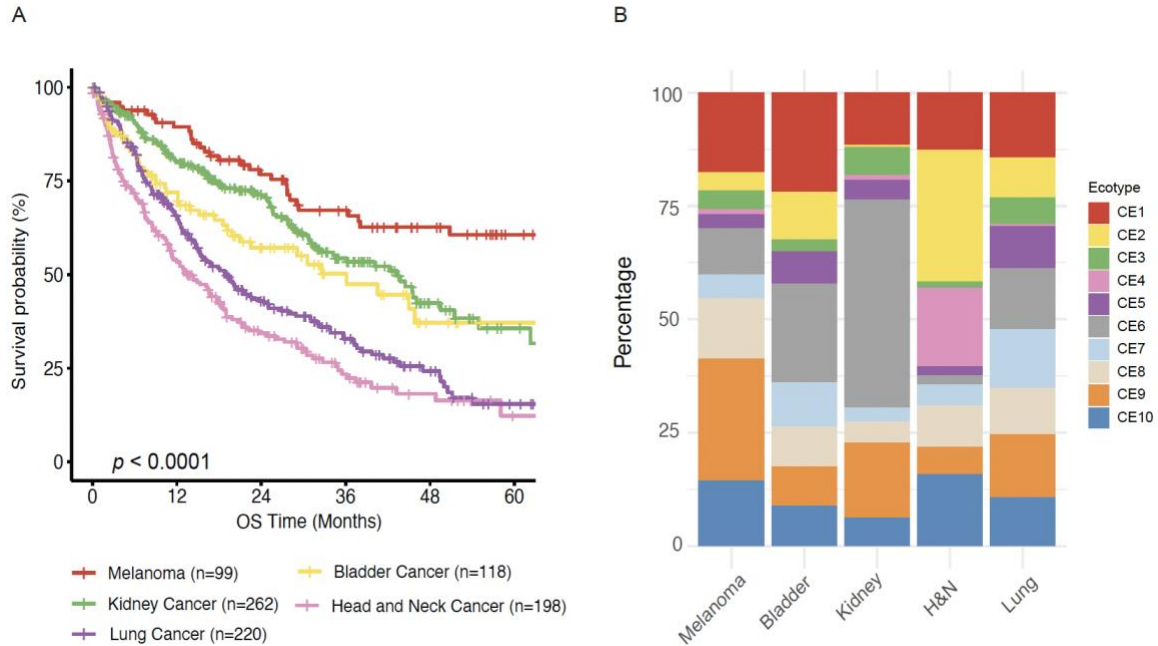
B Major cancer types



Supplementary Figure 4. Prognostic value of carcinoma ecotypes in real-world progression-free survival (rwPFS). (A) Kaplan-Meier curves showing pan-cancer association between ecotype classification and rwPFS in the ORIEN-ICI cohort ($n=1,254$ patients). (B) Kaplan-Meier plots evaluating ecotype-group-based survival stratification in five major cancer types, with both OS (left) and rwPFS (right) outcomes. Exact log-rank p-values are shown in the plot. Source data are provided in Source Data file.



Supplementary Figure 5. Stratified survival analysis by ecotype groups in selected patient subgroups. (A) OS in patients treated with PD-1/PD-L1 inhibitors ($n=1078$ patients) and CTLA-4 inhibitors or combination therapy ($n=176$ patients). (B) HPV-negative HNC patients ($n=160$ patients). (C) NSCLC smokers ($n=156$ patients). P values shown in the Kaplan-Meier plots are based on the log-rank test. Kaplan-Meier curves were compared using log-rank tests. Exact P values are shown in the plots. Source data are provided in Source Data file.



Supplementary Figure 6. Cancer-type-specific overall survival (A) and ecotype distribution (B). *P* value shown in the Kaplan-Meier plot (A) are based on the log-rank test. Source data are provided in Source Data file. (The *n* for each cancer types are as follows: Melanoma *n*=99, Bladder *n*=118, Kidney *n*=262, H&N *n*=198, Lung *n*=220.)

A Melanoma Multivariable Cox model (EcoRIS)

OS

Variable	N	Hazard ratio	p
Sex			
Female	62		Reference
Male	98	1.03 (0.64, 1.67)	0.90
Age	160	1.02 (1.00, 1.04)	0.05
EcoRIS	160	2.78 (1.83, 4.24)	<0.001
Tumor type			Reference
Primary	57		
Metastatic	103	1.37 (0.82, 2.28)	0.23

rwPFS

Variable	N	Hazard ratio	p
Sex			
Female	59		Reference
Male	97	1.01 (0.68, 1.48)	0.975
Age	156	1.02 (1.01, 1.04)	0.004
EcoRIS	156	1.47 (1.14, 1.88)	0.003
Tumor type			Reference
Primary	54		
Metastatic	102	1.04 (0.70, 1.56)	0.829

B Melanoma Univariable Cox model (Ecotypes)

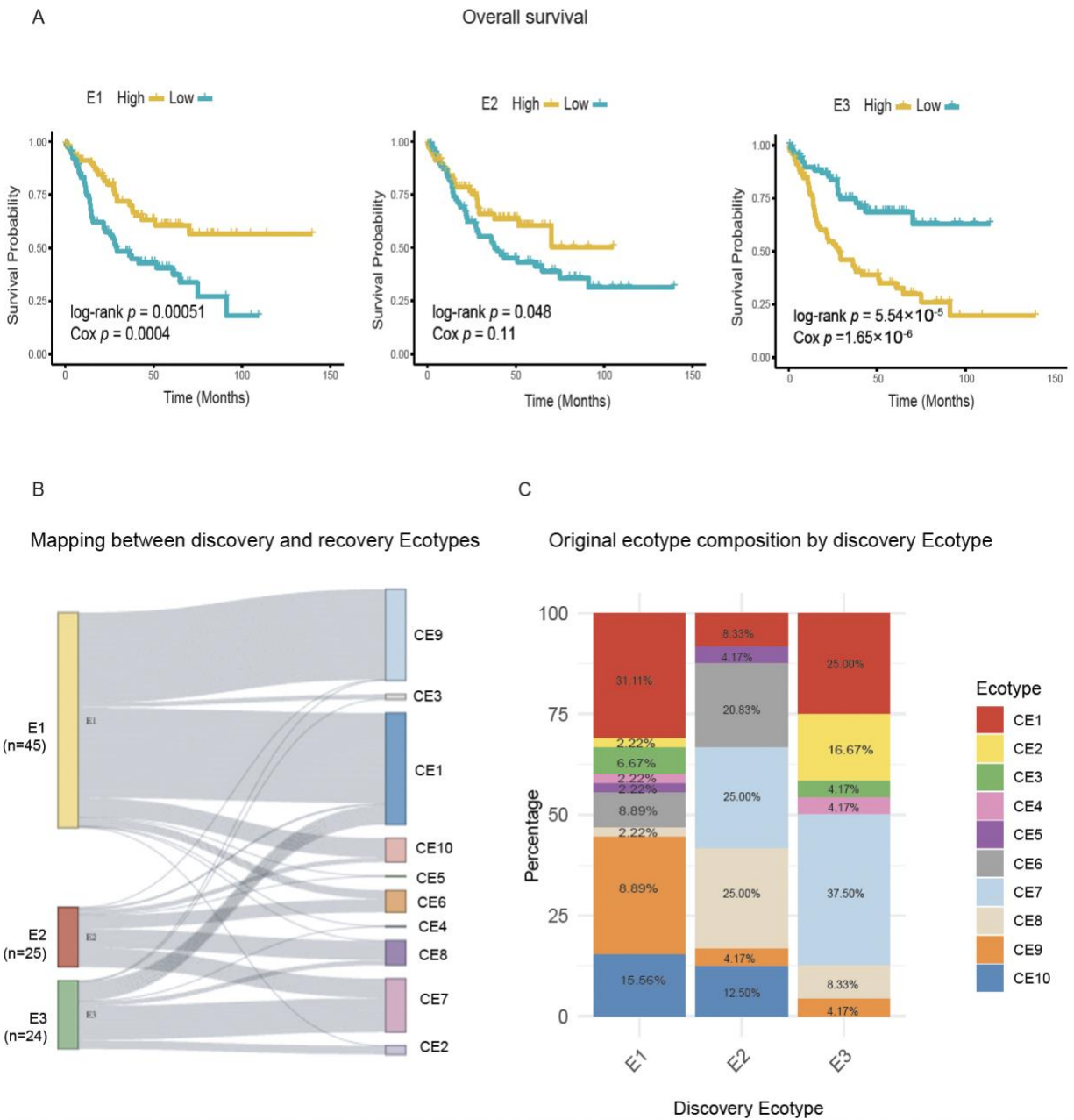
OS

Ecotype	HR	p-val
CE1	9.3923	0.049
CE5	0.3322	0.017
CE7	0.3580	0.001
CE9	0.0010	0.000
CE10	0.0002	0.000

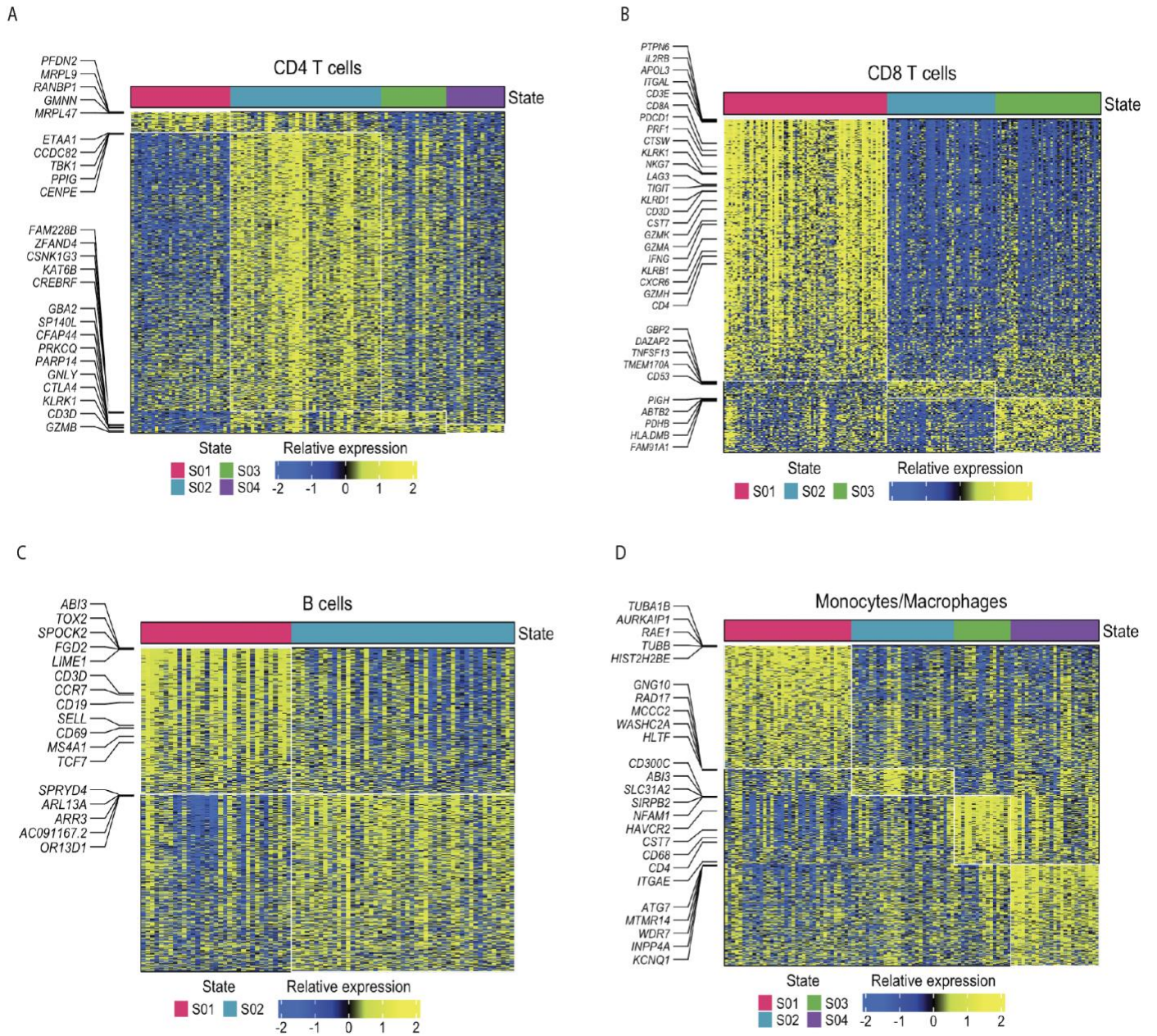
rwPFS

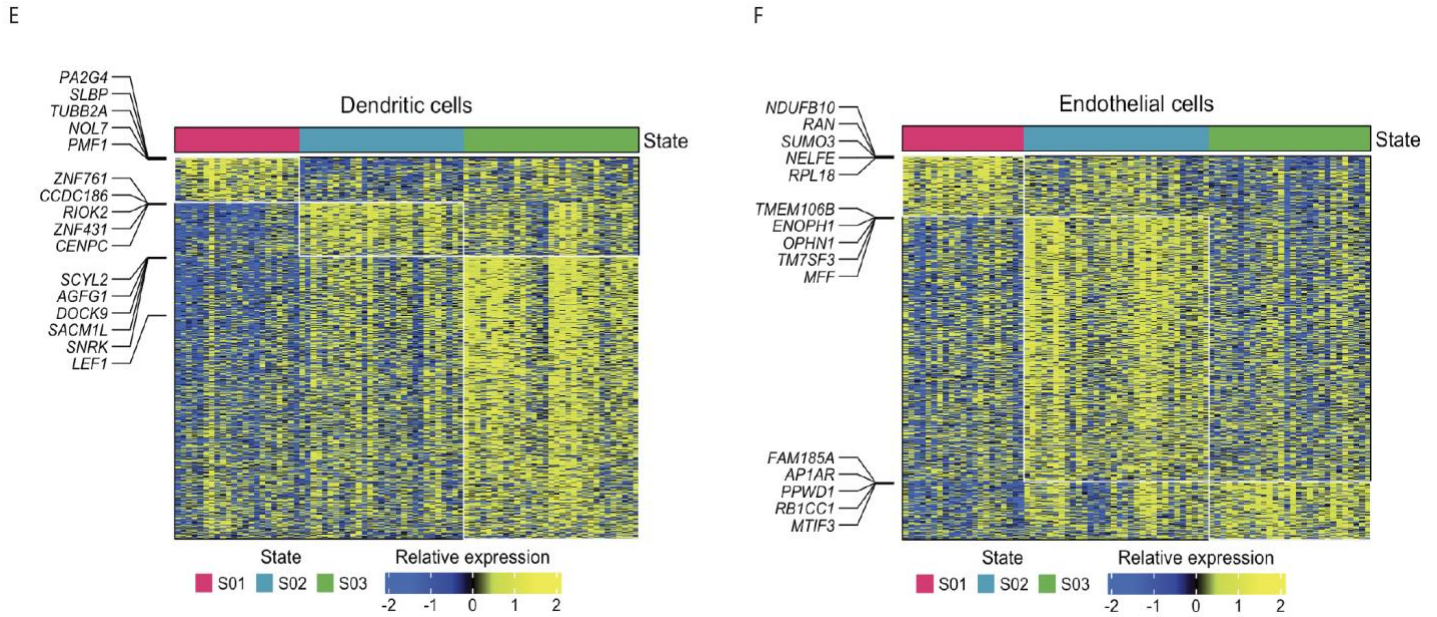
Ecotype	HR	p-val
CE1	5.8681	0.107
CE5	4.5748	0.255
CE7	8.7681	0.021
CE9	0.1469	0.012
CE10	0.0970	0.024

Supplementary Figure 7. Cox regression analysis of carcinoma ecotypes in melanoma. (A) Multivariable Cox models evaluating the association of EcoRIS classification with OS (left) and rwPFS (right), adjusting for sex, age, and tumor type (primary vs metastatic) based on $n=160$ melanoma patients. Two-sided Wald Cox p-values reported. (B) Univariable Cox models assessing the prognostic value of individual ecotypes. Two-sided Wald Cox p-values reported ($n=160$).



Supplementary Figure 8. Characterization of melanoma-specific ecotypes. (A) Kaplan-Meier plots showing OS differences between high- and low-ecotyper groups (E1, E2, and E3) of $n=160$ patients. Log-rank test and two-sided Wald Cox based p-values reported. (B) Sankey diagram showing the mapping between new ecotypes (E1 $n=45$; E2 $n=25$; E3 $n=24$) and the original ten ecotypes. (C) Bar plots showing the composition of original ecotypes within each discovery ecotype.





Supplementary Figure 9. Heatmaps of cell states in discovery ecotypes for melanoma.

Gene expression heatmaps of cell states for six major immune and stromal cell types: (A) CD4 T cells ($n=110$ samples), (B) CD8 T cells ($n=164$), (C) B cells ($n=82$), (D)

Monocytes/Macrophages ($n=106$), (E) Dendritic cells ($n=82$), and (F) Endothelial cells ($n=81$).

Each heatmap column corresponds to one tumor sample. Source data are provided as a Source Data file.