

**Table S1** Feature summary of the lung specimens

| No | Patient id | Samples | Sex    | Age (years) | Tissue origins | Histology                          | Grade (differentiated) | pTNM:T | pTNM:N | pTNM:M | KRAS | Stages |
|----|------------|---------|--------|-------------|----------------|------------------------------------|------------------------|--------|--------|--------|------|--------|
| 1  | A100       | P1      | Male   | 63          | Primary        | Lung<br>adenosquamous<br>carcinoma | Low                    | T2a    | N0     | M0     | G12C | IB     |
| 2  | A101       | P2      | Female | 54          | Primary        | Lung<br>adenocarcinoma             | Low                    | T1b    | N0     | M0     | G12C | IA2    |
| 3  | A108       | P3      | Male   | 62          | Primary        | Lung<br>adenocarcinoma             | Low                    | T2a    | N1     | M0     | G12C | IIB    |

**Table S2** List of canonical markers to assign the cell types

| Class                   | Figures   | Cell types                       | Genes                                                   |
|-------------------------|-----------|----------------------------------|---------------------------------------------------------|
| 8 cell lineages         | Figure 1B | Epithelial cells                 | <i>EPCAM, KRT19, CDH1, KRT18</i>                        |
|                         | Figure 1B | T lymphocytes                    | <i>CD3D, CD3E, CD3G, TRAC</i>                           |
|                         | Figure 1B | B lymphocytes                    | <i>CD79A, IGHM, IGHG3, IGHA2</i>                        |
|                         | Figure 1B | Myeloid cells                    | <i>CD68, MARCO, FCGR3A (CD16), LYZ</i>                  |
|                         | Figure 1B | NK cells                         | <i>NCAM1 (CD56), NKG7, GNLY, KLRD1</i>                  |
|                         | Figure 1B | MAST cells                       | <i>KIT, MS4A2, GATA2</i>                                |
|                         | Figure 1B | Fibroblasts                      | <i>DCN, COL1A1, COL1A2, THY1</i>                        |
|                         | Figure 1B | Endothelial cells                | <i>PECAM1, CLDN5, FLT1, RAMP2</i>                       |
| A subset of fibroblasts | Figure 1F | antigen-presenting CAFs (apCAFs) | <i>SLPI, HLA-DQA1, HLA-DQB1, SLC9A3R1, CD74, MSLN</i>   |
|                         | Figure 1F | inflammatory CAFs (iCAFs)        | <i>IL6, GSN, CFD, SOD2</i>                              |
|                         | Figure 1F | myofibroblastic CAFs (myCAFs)    | <i>ACTA2, MYH11, TAGLN, ACTG2, MYLK, COL12A1, MMP11</i> |

**Table S3** Gene list of function modules

| Module/pathway                                           | Gene symbol                                                                                                                                                                                                                                      |
|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Signature genes of iCAFs (in literature) used for Ucell  | <i>CLEC3B, GSN, PTX3, EFEMP1, FIGF, TNFAIP6, DPT, ADM, PLPP3, TNXB, CXCL12, GSTM1, C4B, OGN, C3, PCOLCE2, CXCL1, COL14A1, SVEP1, ADAMTS5, HP, HAS1, SCARA3, DPEP1, SFRP4, PRSS23, ACKR3, HTRA3, APOE, CCL7, IL6, SFRP2, PLA1A, SCARA5, SNED1</i> |
| Signature genes of apCAFs (in literature) used for Ucell | <i>SLPI, CD74, SERPINB2, MSLN, LGALS7, UPK3B, KRT19, NKAIN4, CALCA, SLC9A3R1, CLU, ENPP2, KRT8, HSPB1, UPK1B, PTGIS, HSPB1, UPK1B, PTGIS, CXADR, KRT18, EZR, DMKN, ANGPTL7, KRT7, ARHGDIB, CAV1, FTH1, CXCL5, GPM6A, SDC4, SPINT2</i>            |
| Signature genes of myCAFs (in literature) used for Ucell | <i>SPP1, SERPINE2, CXCL14, CRLF1, IGFBP3, ACTA2, TAGLN, THY1, COL8A1, CTHRC1, SFRP1, TNC, SPARCL1, COL15A1, COL12A1, TGFB1, COL1A1, SDC1, CILP, H19, THBS2</i>                                                                                   |
| Immunotherapy nonresponsive signature used for ssGSEA    | <i>CTHRC1, CALD1, COL1A1, TPM2, SERPINH1, CTSK, ITGB1, COL3A1, THY1, S100A16, COL6A3, MXRA5, NNMT, PCOLCE, PRKCBP, MFGE8, MYL9, IGFBP5, COL5A2, THBS2, ISLR</i>                                                                                  |
| Immunotherapy responsive signature used for ssGSEA       | <i>HLA-DRA, TYROBP, HLA-DPA1, AIF1, HLA-DPB1, FCER1G, LST1, HLA-DQB1, CXCL8, MS4A6A, HLA-DQA1, C1QA, LYZ, CCL3, C1QC, C1QB, CCL3L3</i>                                                                                                           |

**Table S4** Top20 Differentially expressed genes of CAF-14 subsets

| Gene            | P      | avg_log2FC | pct.1 | pct.2 | P_adjust | Cluster |
|-----------------|--------|------------|-------|-------|----------|---------|
| <i>MS4A6A</i>   | <0.001 | 1.46360533 | 0.783 | 0.035 | <0.001   | 14      |
| <i>LST1</i>     | <0.001 | 1.53184098 | 0.87  | 0.074 | <0.001   | 14      |
| <i>AIF1</i>     | <0.001 | 1.59614732 | 0.87  | 0.078 | <0.001   | 14      |
| <i>C1QC</i>     | <0.001 | 1.40551855 | 0.696 | 0.056 | <0.001   | 14      |
| <i>HLA-DQB1</i> | <0.001 | 1.71740177 | 0.957 | 0.147 | <0.001   | 14      |
| <i>CXCL8</i>    | <0.001 | 1.7831755  | 1     | 0.168 | <0.001   | 14      |
| <i>TYROBP</i>   | <0.001 | 1.93530243 | 1     | 0.18  | <0.001   | 14      |
| <i>FCER1G</i>   | <0.001 | 1.53619032 | 0.87  | 0.133 | <0.001   | 14      |
| <i>HLA-DMA</i>  | <0.001 | 1.36282133 | 0.87  | 0.13  | <0.001   | 14      |
| <i>LAPTM5</i>   | <0.001 | 1.36221409 | 0.87  | 0.134 | <0.001   | 14      |
| <i>HLA-DQA1</i> | <0.001 | 1.7200798  | 0.913 | 0.169 | <0.001   | 14      |
| <i>LYZ</i>      | <0.001 | 1.75720817 | 0.913 | 0.172 | <0.001   | 14      |
| <i>CCL3L3</i>   | <0.001 | 1.46993603 | 0.696 | 0.094 | <0.001   | 14      |
| <i>C1QB</i>     | <0.001 | 1.51222365 | 0.783 | 0.136 | <0.001   | 14      |
| <i>CCL3</i>     | <0.001 | 1.60857324 | 0.783 | 0.147 | <0.001   | 14      |
| <i>HLA-DPA1</i> | <0.001 | 1.67449239 | 0.957 | 0.337 | <0.001   | 14      |
| <i>C1QA</i>     | <0.001 | 1.54714085 | 0.783 | 0.177 | <0.001   | 14      |
| <i>HLA-DRA</i>  | <0.001 | 1.62288795 | 1     | 0.59  | <0.001   | 14      |
| <i>HLA-DPB1</i> | <0.001 | 1.71475388 | 0.957 | 0.429 | <0.001   | 14      |
| <i>HLA-DRB1</i> | <0.001 | 1.43551789 | 0.957 | 0.443 | <0.001   | 14      |

A two-sided Wilcoxon signed-rank test was used to assess statistical significance.

Table S5 Differentially expressed genes of CAF-C3 and CAF-C14

| Gene         | P      | avg_log2FC | pct.1 | pct.2 | P_adjust |
|--------------|--------|------------|-------|-------|----------|
| CD74         | <0.001 | −1.6785465 | 0.624 | 1     | <0.001   |
| HLA-DRA      | <0.001 | −1.9073352 | 0.45  | 1     | <0.001   |
| HLA-DRB1     | <0.001 | −1.775648  | 0.296 | 0.957 | <0.001   |
| TYROBP       | <0.001 | −1.9288299 | 0.19  | 1     | <0.001   |
| HLA-DPB1     | <0.001 | −2.0987025 | 0.222 | 0.957 | <0.001   |
| HLA-DPA1     | <0.001 | −1.9163487 | 0.201 | 0.957 | <0.001   |
| CXCL8        | <0.001 | −1.8072689 | 0.185 | 1     | <0.001   |
| HLA-DQB1     | <0.001 | −1.7854704 | 0.116 | 0.957 | <0.001   |
| HLA-DQA1     | <0.001 | −1.790173  | 0.143 | 0.913 | <0.001   |
| FTL          | <0.001 | −0.3684668 | 0.995 | 1     | <0.001   |
| CLEC7A       | <0.001 | −1.0555075 | 0.011 | 0.826 | <0.001   |
| LST1         | <0.001 | −1.5745293 | 0.042 | 0.87  | <0.001   |
| MS4A7        | <0.001 | −1.1235549 | 0.005 | 0.783 | <0.001   |
| FCER1G       | <0.001 | −1.4936967 | 0.159 | 0.87  | <0.001   |
| C1orf162     | <0.001 | −1.2883391 | 0.032 | 0.87  | <0.001   |
| AIF1         | <0.001 | −1.6203994 | 0.053 | 0.87  | <0.001   |
| MS4A6A       | <0.001 | −1.4971724 | 0.016 | 0.783 | <0.001   |
| LAPTM5       | <0.001 | −1.4113128 | 0.116 | 0.87  | <0.001   |
| CCL3         | <0.001 | −1.5163293 | 0.228 | 0.783 | <0.001   |
| FYB          | <0.001 | −1.0826767 | 0.005 | 0.739 | <0.001   |
| RGS1         | <0.001 | −1.4967788 | 0.111 | 0.87  | <0.001   |
| SPI1         | <0.001 | −1.1307583 | 0.016 | 0.739 | <0.001   |
| EVI2B        | <0.001 | −0.9019838 | 0.011 | 0.739 | <0.001   |
| ADH1B        | <0.001 | −1.2118097 | 0.011 | 0.739 | <0.001   |
| LYZ          | <0.001 | −1.7433548 | 0.196 | 0.913 | <0.001   |
| HLA-DMA      | <0.001 | −1.4301178 | 0.074 | 0.87  | <0.001   |
| SRGN         | <0.001 | −1.5003345 | 0.243 | 0.957 | <0.001   |
| ADAP2        | <0.001 | −0.6614503 | 0     | 0.609 | <0.001   |
| CD37         | <0.001 | −1.0482397 | 0.063 | 0.87  | <0.001   |
| C1QA         | <0.001 | −1.54359   | 0.185 | 0.783 | <0.001   |
| CTSS         | <0.001 | −1.2863146 | 0.127 | 0.913 | <0.001   |
| GPR183       | <0.001 | −1.3277594 | 0.053 | 0.783 | <0.001   |
| IL10RA       | <0.001 | −0.5229928 | 0     | 0.565 | <0.001   |
| PHACTR1      | <0.001 | −0.9866262 | 0.048 | 0.783 | <0.001   |
| HLA-DMB      | <0.001 | −1.1732898 | 0.063 | 0.826 | <0.001   |
| FCGR2A       | <0.001 | −1.0464073 | 0.042 | 0.783 | <0.001   |
| C1QC         | <0.001 | −1.4161859 | 0.058 | 0.696 | <0.001   |
| VAMP8        | <0.001 | −1.2284049 | 0.19  | 0.913 | <0.001   |
| IGSF6        | <0.001 | −1.0009101 | 0.011 | 0.652 | <0.001   |
| PECAM1       | <0.001 | −0.7281258 | 0.011 | 0.652 | <0.001   |
| PTGER4       | <0.001 | −0.9664241 | 0.021 | 0.696 | <0.001   |
| ARRB2        | <0.001 | −0.80658   | 0.048 | 0.783 | <0.001   |
| CD83         | <0.001 | −1.2655034 | 0.058 | 0.783 | <0.001   |
| CTHRC1       | <0.001 | 1.32694069 | 0.963 | 0.348 | <0.001   |
| CD84         | <0.001 | −0.618786  | 0     | 0.522 | <0.001   |
| CD93         | <0.001 | −0.6219787 | 0     | 0.522 | <0.001   |
| MPEG1        | <0.001 | −0.6370215 | 0     | 0.522 | <0.001   |
| CD86         | <0.001 | −0.8361797 | 0.016 | 0.652 | <0.001   |
| BCL2A1       | <0.001 | −1.0102184 | 0.026 | 0.696 | <0.001   |
| C7           | <0.001 | −1.5163842 | 0.074 | 0.739 | <0.001   |
| C1QB         | <0.001 | −1.4417172 | 0.19  | 0.783 | <0.001   |
| LGALS1       | <0.001 | 0.35969677 | 1     | 1     | <0.001   |
| NFKBIA       | <0.001 | −1.0680205 | 0.566 | 1     | <0.001   |
| PLEK         | <0.001 | −1.0546228 | 0.021 | 0.652 | <0.001   |
| CYBB         | <0.001 | −0.92923   | 0.032 | 0.696 | <0.001   |
| ITGB2        | <0.001 | −1.1450396 | 0.116 | 0.87  | <0.001   |
| CALD1        | <0.001 | 0.64924606 | 0.989 | 0.913 | <0.001   |
| ALOX5AP      | <0.001 | −1.2329461 | 0.079 | 0.739 | <0.001   |
| PDE4B        | <0.001 | −0.8570959 | 0.021 | 0.652 | <0.001   |
| RNASE6       | <0.001 | −0.7660658 | 0.021 | 0.652 | <0.001   |
| IFI30        | <0.001 | −0.8511418 | 0.005 | 0.565 | <0.001   |
| ALOX5        | <0.001 | −0.695704  | 0.005 | 0.565 | <0.001   |
| HLA-DRB5     | <0.001 | −1.3528827 | 0.037 | 0.652 | <0.001   |
| HAVCR2       | <0.001 | −0.5232089 | 0     | 0.478 | <0.001   |
| COL1A1       | <0.001 | 0.76249974 | 0.968 | 0.957 | <0.001   |
| CFD          | <0.001 | −1.363435  | 0.19  | 0.913 | <0.001   |
| FGL2         | <0.001 | −0.8270676 | 0.026 | 0.652 | <0.001   |
| LCP2         | <0.001 | −0.7696747 | 0.042 | 0.696 | <0.001   |
| OLR1         | <0.001 | −0.842899  | 0.011 | 0.565 | <0.001   |
| GPSM3        | <0.001 | −0.8933363 | 0.122 | 0.87  | <0.001   |
| CD53         | <0.001 | −0.7821264 | 0.032 | 0.652 | <0.001   |
| CXCR4        | <0.001 | −1.0876239 | 0.101 | 0.783 | <0.001   |
| TNFAIP3      | <0.001 | −1.1057946 | 0.132 | 0.87  | <0.001   |
| ARHGAP30     | <0.001 | −0.5376436 | 0.011 | 0.565 | <0.001   |
| TNFRSF1B     | <0.001 | −0.8061677 | 0.032 | 0.652 | <0.001   |
| COTL1        | <0.001 | −1.0245431 | 0.323 | 0.826 | <0.001   |
| LCP1         | <0.001 | −0.9556484 | 0.048 | 0.696 | <0.001   |
| SORL1        | <0.001 | −0.6224151 | 0.005 | 0.522 | <0.001   |
| LILRB4       | <0.001 | −0.6467018 | 0.005 | 0.522 | <0.001   |
| FMNL1        | <0.001 | −0.643198  | 0.053 | 0.696 | <0.001   |
| TPM2         | <0.001 | 0.91903871 | 0.968 | 0.783 | <0.001   |
| SERPINH1     | <0.001 | 0.70656142 | 0.894 | 0.87  | <0.001   |
| LAIR1        | <0.001 | −0.6121928 | 0.021 | 0.565 | <0.001   |
| NCKAP1L      | <0.001 | −0.5204246 | 0     | 0.435 | <0.001   |
| RBM47        | <0.001 | −0.6774482 | 0     | 0.435 | <0.001   |
| SIGLEC1      | <0.001 | −0.4331499 | 0     | 0.435 | <0.001   |
| APOC1        | <0.001 | −1.2725652 | 0.286 | 0.913 | <0.001   |
| CD69         | <0.001 | −0.46408   | 0.032 | 0.609 | <0.001   |
| MYO1F        | <0.001 | −0.6036899 | 0.032 | 0.609 | <0.001   |
| G0S2         | <0.001 | −1.3386721 | 0.122 | 0.696 | <0.001   |
| LITAF        | <0.001 | −0.9148009 | 0.508 | 0.957 | <0.001   |
| CPVL         | <0.001 | −0.7443194 | 0.016 | 0.565 | <0.001   |
| SLCO2B1      | <0.001 | −0.7920679 | 0.021 | 0.565 | <0.001   |
| TNFSF13B     | <0.001 | −0.8835022 | 0.122 | 0.826 | <0.001   |
| ITGAX        | <0.001 | −0.5402783 | 0.011 | 0.522 | <0.001   |
| CCL3L3       | <0.001 | −1.3849657 | 0.143 | 0.696 | <0.001   |
| CD63         | <0.001 | 0.40469525 | 0.995 | 0.957 | <0.001   |
| DUSP2        | <0.001 | −0.9827057 | 0.079 | 0.739 | <0.001   |
| FCGR3A       | <0.001 | −1.0650928 | 0.048 | 0.652 | <0.001   |
| DOK2         | <0.001 | −0.6247144 | 0.011 | 0.522 | <0.001   |
| PTPRC        | <0.001 | −0.7019685 | 0.032 | 0.609 | <0.001   |
| GMFG         | <0.001 | −0.8829192 | 0.127 | 0.826 | <0.001   |
| C5AR1        | <0.001 | −0.5868237 | 0.005 | 0.478 | <0.001   |
| SERPINA1     | <0.001 | −0.9287838 | 0.085 | 0.739 | <0.001   |
| CSF2RA       | <0.001 | −0.64638   | 0.005 | 0.478 | <0.001   |
| RP5-117110.5 | <0.001 | −0.5543028 | 0.005 | 0.478 | <0.001   |
| CCL4         | <0.001 | −1.2457577 | 0.18  | 0.783 | <0.001   |
| IL1B         | <0.001 | −1.1465286 | 0.048 | 0.565 | <0.001   |
| SPARC        | <0.001 | 0.59054702 | 0.952 | 0.957 | <0.001   |
| COL1A2       | <0.001 | 0.51982403 | 0.974 | 1     | <0.001   |
| FAM49B       | <0.001 | −0.703425  | 0.111 | 0.783 | <0.001   |

Table S5 (continued)

Table S5 (continued)

| Gene          | P      | avg_log2FC | pct.1 | pct.2 | P_adjust |
|---------------|--------|------------|-------|-------|----------|
| KYNU          | <0.001 | −0.4851818 | 0     | 0.391 | <0.001   |
| B3GNT5        | <0.001 | −0.5281609 | 0     | 0.391 | <0.001   |
| DOCK2         | <0.001 | −0.4726272 | 0     | 0.391 | <0.001   |
| APOE          | <0.001 | −1.1262233 | 0.487 | 0.87  | <0.001   |
| HCST          | <0.001 | −0.8366767 | 0.058 | 0.652 | <0.001   |
| SAMHD1        | <0.001 | −0.8358198 | 0.116 | 0.783 | <0.001   |
| ZFP36         | <0.001 | −1.0148255 | 0.556 | 0.957 | <0.001   |
| MRC1          | <0.001 | −0.7588007 | 0.016 | 0.522 | <0.001   |
| ARHGD1B       | <0.001 | −1.021664  | 0.228 | 0.87  | <0.001   |
| IFITM3        | <0.001 | 0.44445485 | 0.995 | 0.957 | <0.001   |
| CTSK          | <0.001 | 0.80713165 | 0.836 | 0.696 | <0.001   |
| ITGB1         | <0.001 | 0.64291579 | 0.905 | 0.87  | <0.001   |
| UCP2          | <0.001 | −0.8242956 | 0.063 | 0.652 | <0.001   |
| FRMD4B        | <0.001 | −0.5474996 | 0.053 | 0.609 | <0.001   |
| NR4A2         | <0.001 | −0.999581  | 0.138 | 0.783 | <0.001   |
| LAT2          | <0.001 | −0.5891168 | 0.011 | 0.478 | <0.001   |
| RP11-1143G9.4 | <0.001 | −0.8147894 | 0.011 | 0.478 | <0.001   |
| 1-Mar         | <0.001 | −0.458825  | 0.011 | 0.478 | <0.001   |
| JAML          | <0.001 | −0.5287382 | 0.011 | 0.478 | <0.001   |
| MNDA          | <0.001 | −0.6628031 | 0.011 | 0.478 | <0.001   |
| RASSF4        | <0.001 | −0.5364675 | 0.021 | 0.522 | <0.001   |
| CREM          | <0.001 | −0.875946  | 0.233 | 0.913 | <0.001   |
| CCL4L2        | <0.001 | −1.2553063 | 0.148 | 0.696 | <0.001   |
| STX11         | <0.001 | −0.4679069 | 0.005 | 0.435 | <0.001   |
| OGFRL1        | <0.001 | −0.7503556 | 0.048 | 0.609 | <0.001   |
| REL           | <0.001 | −0.9483701 | 0.18  | 0.826 | <0.001   |
| NCF2          | <0.001 | −0.6948963 | 0.005 | 0.435 | <0.001   |
| HLA-DOA       | <0.001 | −0.6251776 | 0.005 | 0.435 | <0.001   |
| COL3A1        | <0.001 | 0.64068328 | 0.984 | 0.913 | <0.001   |
| APBB1IP       | <0.001 | −0.4330148 | 0.016 | 0.478 | <0.001   |
| KDM6B         | <0.001 | −0.8277327 | 0.18  | 0.826 | <0.001   |
| CEBPA         | <0.001 | −0.3407963 | 0     | 0.348 | <0.001   |
| GPRIN3        | <0.001 | −0.2815944 | 0     | 0.348 | <0.001   |
| APOBR         | <0.001 | −0.3085437 | 0     | 0.348 | <0.001   |
| GPR34         | <0.001 | −0.4834463 | 0     | 0.348 | <0.001   |
| ZNF331        | <0.001 | −0.8273067 | 0.095 | 0.696 | <0.001   |
| NPC2          | <0.001 | −0.5296217 | 0.878 | 1     | <0.001   |
| PTAFR         | <0.001 | −0.4600313 | 0.011 | 0.435 | <0.001   |
| CSF1R         | <0.001 | −0.5914613 | 0.026 | 0.522 | <0.001   |
| FCGR2B        | <0.001 | −0.4507547 | 0.005 | 0.391 | <0.001   |
| NAMPT         | <0.001 | −0.9388193 | 0.217 | 0.783 | <0.001   |
| SELM          | <0.001 | 0.41345458 | 0.963 | 0.957 | <0.001   |
| CECR1         | <0.001 | −0.7103278 | 0.042 | 0.565 | <0.001   |
| RAB20         | <0.001 | −0.5658555 | 0.058 | 0.609 | <0.001   |
| COL6A2        | <0.001 | 0.58217022 | 0.937 | 0.87  | <0.001   |
| SH2B3         | <0.001 | −0.5812362 | 0.063 | 0.609 | <0.001   |
| THY1          | <0.001 | 0.9089523  | 0.873 | 0.609 | <0.001   |
| TREM2         | <0.001 | −0.6882023 | 0.032 | 0.522 | <0.001   |
| GPX3          | <0.001 | −0.934123  | 0.079 | 0.652 | <0.001   |
| GPCPD1        | <0.001 | −0.5758094 | 0.09  | 0.652 | <0.001   |
| PSAP          | <0.001 | −0.444325  | 0.899 | 0.957 | <0.001   |
| IL18          | <0.001 | −0.6732389 | 0.032 | 0.522 | <0.001   |
| IL2RG         | <0.001 | −0.4249331 | 0.026 | 0.478 | <0.001   |
| DOCK8         | <0.001 | −0.4353457 | 0.005 | 0.391 | <0.001   |
| SYNGR2        | <0.001 | −0.6717163 | 0.159 | 0.783 | <0.001   |
| S100A16       | <0.001 | 0.8316776  | 0.847 | 0.565 | <0.001   |
| IKZF1         | <0.001 | −0.3989857 | 0.005 | 0.391 | <0.001   |
| INPP5D        | <0.001 | −0.4722174 | 0.021 | 0.478 | <0.001   |
| PTPN6         | <0.001 | −0.4491554 | 0.016 | 0.435 | <0.001   |
| BTG1          | <0.001 | −0.6801508 | 0.714 | 0.913 | <0.001   |
| COL6A3        | <0.001 | 0.65920565 | 0.947 | 0.783 | <0.001   |
| CD68          | <0.001 | −0.8930477 | 0.296 | 0.783 | <0.001   |
| C10orf128     | <0.001 | −0.4095009 | 0.005 | 0.391 | <0.001   |
| RASGRP3       | <0.001 | −0.5374217 | 0.005 | 0.391 | <0.001   |
| LINC01272     | <0.001 | −0.5578854 | 0.005 | 0.391 | <0.001   |
| CST3          | <0.001 | −0.4581038 | 0.937 | 1     | <0.001   |
| CD48          | <0.001 | −0.7771997 | 0.026 | 0.478 | <0.001   |
| CXCL2         | <0.001 | −1.0103201 | 0.212 | 0.783 | <0.001   |
| MXRA5         | <0.001 | 0.94543996 | 0.788 | 0.435 | <0.001   |
| RARRES2       | <0.001 | 0.57747935 | 0.958 | 0.913 | <0.001   |
| SLC11A1       | <0.001 | −0.647883  | 0.026 | 0.478 | <0.001   |
| TAGAP         | <0.001 | −0.4854688 | 0.016 | 0.435 | <0.001   |
| LGALS2        | <0.001 | −0.6618732 | 0     | 0.304 | <0.001   |
| LILRB1        | <0.001 | −0.2853358 | 0     | 0.304 | <0.001   |
| CYTH4         | <0.001 | −0.3040554 | 0     | 0.304 | <0.001   |
| CD163         | <0.001 | −0.4472846 | 0     | 0.304 | <0.001   |
| CD33          | <0.001 | −0.3163575 | 0     | 0.304 | <0.001   |
| TLR7          | <0.001 | −0.2954939 | 0     | 0.304 | <0.001   |
| FCGR1A        | <0.001 | −0.4366119 | 0     | 0.304 | <0.001   |
| SAT1          | <0.001 | −0.5775579 | 0.878 | 1     | <0.001   |
| MS4A4A        | <0.001 | −0.6087443 | 0.016 | 0.435 | <0.001   |
| NBL1          | <0.001 | 0.58154581 | 0.963 | 0.87  | <0.001   |
| NR4A3         | <0.001 | −0.7978865 | 0.042 | 0.522 | <0.001   |
| NNMT          | <0.001 | 0.67171962 | 0.937 | 0.783 | <0.001   |
| CORO1A        | <0.001 | −0.7601266 | 0.063 | 0.565 | <0.001   |
| IER3          | <0.001 | −0.9367563 | 0.524 | 0.957 | <0.001   |
| IRF8          | <0.001 | −0.7382193 | 0.032 | 0.478 | <0.001   |
| SP110         | <0.001 | −0.476979  | 0.069 | 0.565 | <0.001   |
| EEF2K         | <0.001 | −0.3865956 | 0.026 | 0.435 | <0.001   |
| UNC93B1       | <0.001 | −0.3896056 | 0.09  | 0.565 | <0.001   |
| CTSH          | <0.001 | −0.7296497 | 0.254 | 0.87  | <0.001   |
| IER5          | <0.001 | −0.7413245 | 0.18  | 0.783 | <0.001   |
| CYBA          | <0.001 | −0.5694421 | 0.804 | 1     | <0.001   |
| BIN1          | <0.001 | −0.4711406 | 0.153 | 0.696 | 0.001    |
| CXCL3         | <0.001 | −0.9340121 | 0.063 | 0.522 | 0.001    |
| PCOLCE        | <0.001 | 0.69067586 | 0.926 | 0.783 | 0.001    |
| FN1           | <0.001 | 0.51008964 | 0.989 | 0.957 | 0.001    |
| GIMAP4        | <0.001 | −0.3484191 | 0.005 | 0.348 | 0.001    |
| YTHDF1        | <0.001 | −0.3740248 | 0.138 | 0.652 | 0.001    |
| LY86          | <0.001 | −0.4716541 | 0.032 | 0.478 | 0.001    |
| FAM129A       | <0.001 | −0.383201  | 0.037 | 0.435 | 0.001    |
| SAMSN1        | <0.001 | −0.5686119 | 0.048 | 0.522 | 0.001    |
| PRKCDBP       | <0.001 | 0.7585782  | 0.841 | 0.565 | 0.002    |
| TIMP2         | <0.001 | 0.50671559 | 0.857 | 0.826 | 0.002    |
| SERPINB9      | <0.001 | −0.7806155 | 0.053 | 0.522 | 0.002    |
| MICAL1        | <0.001 | −0.4124034 | 0.042 | 0.478 | 0.002    |
| LPXN          | <0.001 | −0.4641503 | 0.021 | 0.435 | 0.002    |
| TBXAS1        | <0.001 | −0.5467578 | 0.021 | 0.435 | 0.002    |
| C15orf48      | <0.001 | −0.9526488 | 0.148 | 0.652 | 0.002    |
| ARHGAP15      | <0.001 | −0.309401  | 0.005 | 0.348 | 0.002    |

Table S5 (continued)

Table S5 (continued)

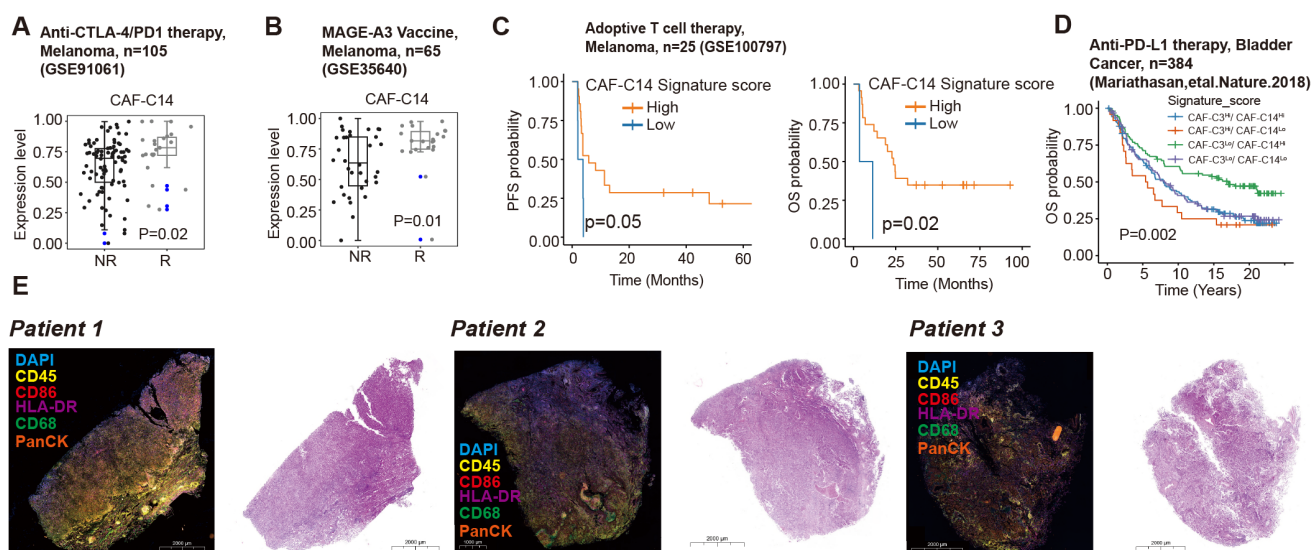
| Gene     | P      | avg_log2FC | pct.1 | pct.2 | P_adjust |
|----------|--------|------------|-------|-------|----------|
| MFGE8    | <0.001 | 0.70669457 | 0.762 | 0.652 | 0.002    |
| SEMA4A   | <0.001 | −0.4202652 | 0.09  | 0.565 | 0.002    |
| SLC8A1   | <0.001 | −0.3342778 | 0.032 | 0.435 | 0.002    |
| MYL9     | <0.001 | 0.79725655 | 0.921 | 0.696 | 0.002    |
| MYL6     | <0.001 | 0.36972359 | 0.989 | 0.957 | 0.002    |
| ST3GAL6  | <0.001 | −0.3565619 | 0.042 | 0.435 | 0.002    |
| NFKBIZ   | <0.001 | −0.8548    | 0.354 | 0.913 | 0.002    |
| RNASET2  | <0.001 | −0.7851706 | 0.259 | 0.783 | 0.002    |
| CSRNP1   | <0.001 | −0.619136  | 0.164 | 0.739 | 0.002    |
| CSF3R    | <0.001 | −0.3454256 | 0.005 | 0.348 | 0.003    |
| CYTIP    | <0.001 | −0.4619141 | 0.005 | 0.348 | 0.003    |
| SPN      | <0.001 | −0.4888809 | 0.005 | 0.348 | 0.003    |
| CPM      | <0.001 | −0.4236435 | 0.005 | 0.348 | 0.003    |
| CIITA    | <0.001 | −0.3094946 | 0.005 | 0.348 | 0.003    |
| SOD2     | <0.001 | −0.8152808 | 0.487 | 0.957 | 0.003    |
| SGK1     | <0.001 | −0.8494392 | 0.143 | 0.696 | 0.003    |
| OTUD1    | <0.001 | −0.6502228 | 0.09  | 0.609 | 0.003    |
| ARHGAP18 | <0.001 | −0.6756354 | 0.138 | 0.696 | 0.004    |
| MRPL51   | <0.001 | 0.55652919 | 0.878 | 0.783 | 0.004    |
| RARA     | <0.001 | −0.2815652 | 0.19  | 0.652 | 0.004    |
| TSPAN33  | <0.001 | −0.3601845 | 0.016 | 0.391 | 0.004    |
| CD14     | <0.001 | −0.8329006 | 0.053 | 0.478 | 0.005    |
| CD52     | <0.001 | −0.8785172 | 0.185 | 0.696 | 0.005    |
| IGFBP5   | <0.001 | 0.77145596 | 0.593 | 0.609 | 0.005    |
| METRNL   | <0.001 | −0.4480166 | 0.106 | 0.609 | 0.005    |
| COL5A2   | <0.001 | 0.77504175 | 0.862 | 0.565 | 0.005    |
| COL6A1   | <0.001 | 0.54325472 | 0.852 | 0.87  | 0.005    |
| HSPB1    | <0.001 | 0.41143296 | 0.974 | 0.957 | 0.006    |
| MBP      | <0.001 | −0.3757685 | 0.016 | 0.391 | 0.006    |
| GPR132   | <0.001 | −0.2795199 | 0     | 0.261 | 0.006    |
| ITGAL    | <0.001 | −0.2599442 | 0     | 0.261 | 0.006    |
| LMO2     | <0.001 | −0.2525292 | 0     | 0.261 | 0.006    |
| FFAR4    | <0.001 | −0.2969811 | 0     | 0.261 | 0.006    |
| NLRP3    | <0.001 | −0.2739388 | 0     | 0.261 | 0.006    |
| PILRA    | <0.001 | −0.3316035 | 0     | 0.261 | 0.006    |
| CD99     | <0.001 | 0.46035291 | 0.937 | 0.913 | 0.006    |
| MSR1     | <0.001 | −0.7523214 | 0.048 | 0.478 | 0.007    |
| S100B    | <0.001 | −0.4340871 | 0.011 | 0.348 | 0.007    |
| CXCL16   | <0.001 | −0.7075739 | 0.127 | 0.652 | 0.007    |
| FAM26F   | <0.001 | −0.5552619 | 0.058 | 0.522 | 0.007    |
| MYDGF    | <0.001 | 0.56676507 | 0.878 | 0.739 | 0.007    |
| F13A1    | <0.001 | −0.6878418 | 0.058 | 0.522 | 0.008    |
| ALCAM    | <0.001 | −0.6201488 | 0.058 | 0.522 | 0.008    |
| NFKBID   | <0.001 | −0.5751966 | 0.042 | 0.478 | 0.008    |
| LRRFIP1  | <0.001 | −0.7138857 | 0.291 | 0.87  | 0.008    |
| SPARCL1  | <0.001 | −0.664946  | 0.481 | 1     | 0.008    |
| THBS2    | <0.001 | 0.89634536 | 0.841 | 0.522 | 0.009    |
| PKM      | <0.001 | 0.38297378 | 0.931 | 0.957 | 0.009    |
| ABI3     | <0.001 | −0.3042385 | 0.011 | 0.348 | 0.009    |
| ISLR     | <0.001 | 0.8263504  | 0.804 | 0.609 | 0.01     |
| TTF2     | <0.001 | −0.3879553 | 0.021 | 0.391 | 0.01     |
| THEMIS2  | <0.001 | −0.4466812 | 0.095 | 0.565 | 0.01     |
| IGHA1    | <0.001 | −0.8351826 | 0.275 | 0.783 | 0.01     |
| RGS19    | <0.001 | −0.5705279 | 0.101 | 0.609 | 0.01     |
| OSM      | <0.001 | −0.6201054 | 0.021 | 0.391 | 0.01     |
| IGLC2    | <0.001 | −0.8476108 | 0.222 | 0.783 | 0.01     |
| ATF5     | <0.001 | −0.3179394 | 0.106 | 0.522 | 0.01     |
| SYK      | <0.001 | −0.3319935 | 0.011 | 0.348 | 0.01     |
| MGP      | <0.001 | −0.7627414 | 0.767 | 1     | 0.01     |
| ZNF385A  | <0.001 | −0.5061641 | 0.063 | 0.522 | 0.01     |
| C3       | <0.001 | −0.9330522 | 0.259 | 0.826 | 0.01     |
| PARVG    | <0.001 | −0.2705621 | 0.005 | 0.304 | 0.01     |
| TPM1     | <0.001 | 0.7496336  | 0.942 | 0.696 | 0.02     |
| HMOX1    | <0.001 | −0.4460902 | 0.074 | 0.522 | 0.02     |
| PER1     | <0.001 | −0.469066  | 0.09  | 0.565 | 0.02     |
| RGS10    | <0.001 | −0.8121136 | 0.339 | 0.826 | 0.02     |
| VMA21    | <0.001 | −0.3254403 | 0.159 | 0.609 | 0.02     |
| CALU     | <0.001 | 0.68070261 | 0.847 | 0.609 | 0.02     |
| TPM4     | <0.001 | 0.5107026  | 0.937 | 0.87  | 0.02     |
| EDF1     | <0.001 | 0.33825728 | 0.958 | 0.913 | 0.02     |
| TRIB1    | <0.001 | −0.4634503 | 0.074 | 0.522 | 0.02     |
| SLC15A3  | <0.001 | −0.4375581 | 0.058 | 0.478 | 0.02     |
| MMP11    | <0.001 | 1.39363942 | 0.762 | 0.261 | 0.02     |
| EPB41L3  | <0.001 | −0.4704191 | 0.021 | 0.391 | 0.02     |
| ATF3     | <0.001 | −0.558753  | 0.286 | 0.826 | 0.02     |
| GRB2     | <0.001 | −0.6426088 | 0.265 | 0.826 | 0.02     |
| PTMS     | <0.001 | 0.46652522 | 0.952 | 0.913 | 0.02     |
| RPS6KA1  | <0.001 | −0.3123187 | 0.005 | 0.304 | 0.03     |
| AEBP1    | <0.001 | 0.57406762 | 0.931 | 0.87  | 0.03     |
| CELF2    | <0.001 | −0.591152  | 0.196 | 0.739 | 0.03     |
| PDLIM2   | <0.001 | 0.55952277 | 0.804 | 0.696 | 0.03     |
| ALDH2    | <0.001 | −0.7545341 | 0.259 | 0.783 | 0.03     |
| RHOC     | <0.001 | 0.45269708 | 0.889 | 0.826 | 0.03     |
| ANTXR1   | <0.001 | 0.6480021  | 0.81  | 0.696 | 0.03     |
| CLEC4A   | <0.001 | −0.3331582 | 0.005 | 0.304 | 0.03     |
| LRRC25   | <0.001 | −0.3103054 | 0.005 | 0.304 | 0.03     |
| GNA13    | <0.001 | −0.5327832 | 0.09  | 0.565 | 0.03     |
| PABPC1   | <0.001 | −0.4479563 | 0.862 | 1     | 0.03     |
| NCF4     | <0.001 | −0.3779034 | 0.005 | 0.304 | 0.03     |
| MXRA8    | <0.001 | 0.62336216 | 0.915 | 0.739 | 0.03     |
| STAT5A   | <0.001 | −0.3704574 | 0.042 | 0.435 | 0.03     |
| NFIA     | <0.001 | −0.4879473 | 0.127 | 0.609 | 0.03     |
| PHB      | <0.001 | 0.51318462 | 0.661 | 0.522 | 0.04     |
| PDLIM7   | <0.001 | 0.58760115 | 0.725 | 0.652 | 0.04     |
| GRN      | <0.001 | −0.5963301 | 0.661 | 0.957 | 0.04     |
| POLR2F   | <0.001 | 0.40837623 | 0.698 | 0.696 | 0.04     |
| FOS      | <0.001 | −0.4761443 | 0.91  | 1     | 0.04     |
| RHBDF2   | <0.001 | −0.3793494 | 0.074 | 0.478 | 0.04     |
| PREX1    | <0.001 | −0.4205646 | 0.026 | 0.391 | 0.04     |
| KLF4     | <0.001 | −0.824155  | 0.36  | 0.826 | 0.04     |
| SLAMF8   | <0.001 | −0.368082  | 0.026 | 0.391 | 0.04     |
| LGALS8   | <0.001 | −0.2666346 | 0.19  | 0.609 | 0.04     |
| MAGED2   | <0.001 | 0.54645023 | 0.672 | 0.565 | 0.04     |
| CSTB     | <0.001 | −0.5278875 | 0.778 | 0.957 | 0.045    |
| RENBP    | <0.001 | −0.3325554 | 0.016 | 0.348 | 0.046    |
| AP1M1    | <0.001 | −0.3108087 | 0.169 | 0.609 | 0.047    |
| ADRBK2   | <0.001 | −0.4130001 | 0.026 | 0.391 | 0.049    |

**Table S6** Results of the univariate Cox regression in the TCGA-LUAD cohort

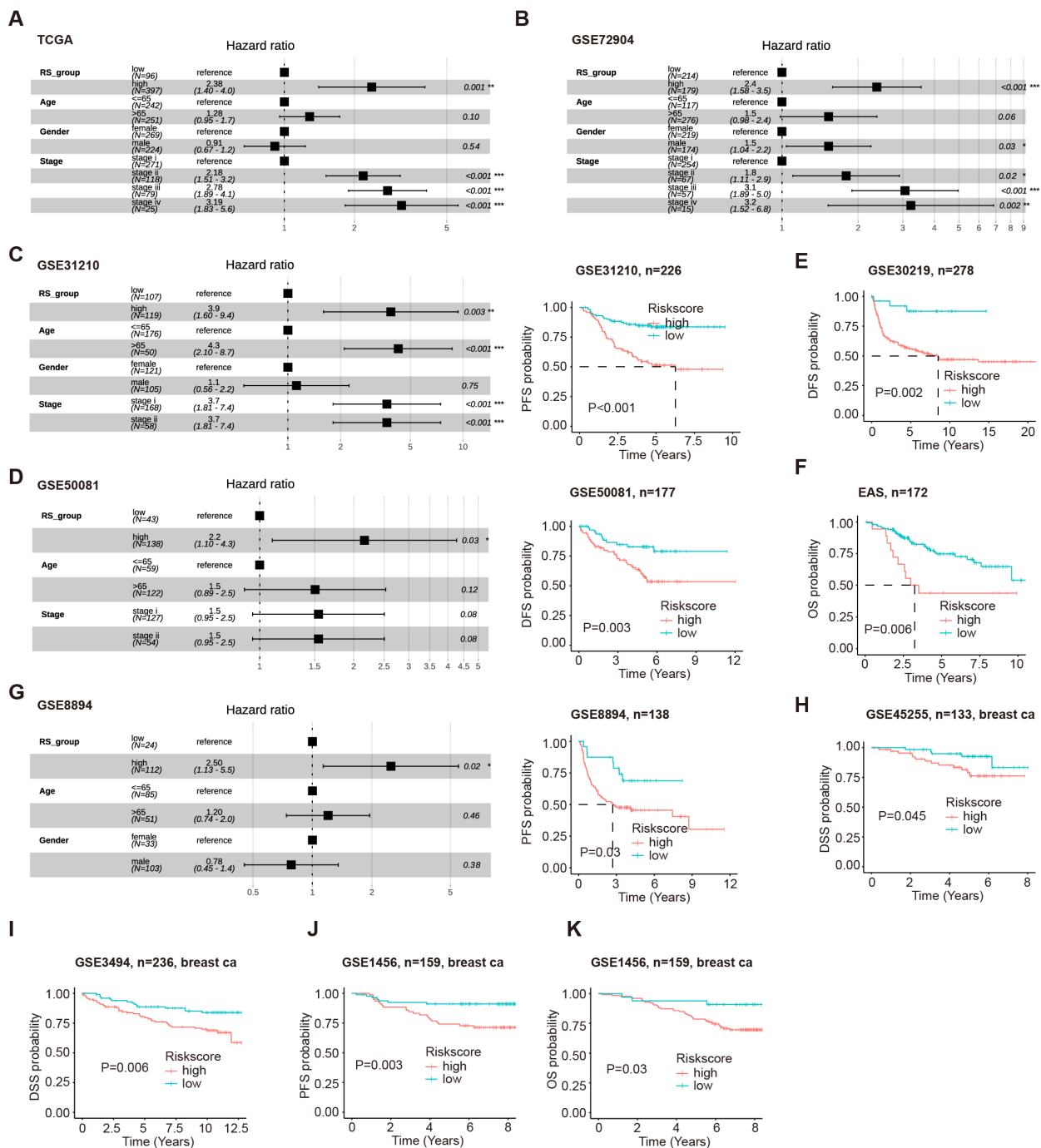
| Gene            | HR    | lower_95 | upper_95 | P     |
|-----------------|-------|----------|----------|-------|
| <i>HLA-DMA</i>  | 0.829 | 0.736    | 0.935    | 0.002 |
| <i>HLA-DMB</i>  | 0.849 | 0.758    | 0.952    | 0.005 |
| <i>HLA-DQA1</i> | 0.877 | 0.797    | 0.964    | 0.007 |
| <i>ADH1B</i>    | 0.906 | 0.842    | 0.974    | 0.008 |
| <i>HLA-DPB1</i> | 0.874 | 0.788    | 0.97     | 0.01  |
| <i>C7</i>       | 0.909 | 0.844    | 0.979    | 0.01  |
| <i>HLA-DRA</i>  | 0.88  | 0.795    | 0.974    | 0.01  |
| <i>CLEC7A</i>   | 0.864 | 0.769    | 0.972    | 0.01  |
| <i>HLA-DQB1</i> | 0.899 | 0.822    | 0.983    | 0.02  |
| <i>IGSF6</i>    | 0.866 | 0.763    | 0.982    | 0.02  |
| <i>HLA-DRB1</i> | 0.895 | 0.812    | 0.987    | 0.03  |
| <i>HLA-DPA1</i> | 0.894 | 0.81     | 0.988    | 0.03  |
| <i>CD74</i>     | 0.893 | 0.805    | 0.99     | 0.03  |
| <i>CXCR4</i>    | 0.856 | 0.742    | 0.988    | 0.03  |
| <i>CD37</i>     | 0.871 | 0.764    | 0.993    | 0.04  |
| <i>LST1</i>     | 0.882 | 0.778    | 1        | 0.049 |

**Table S7** The C-index scores of each model in the 6 validation cohorts

| Model                            | TCGA       | GSE68465   | GSE72904   | GSE13210   | GSE30219-OS | GSE50081-OS |
|----------------------------------|------------|------------|------------|------------|-------------|-------------|
| StepCox[both] + survival-SVM     | 0.5842332  | 0.55613964 | 0.50620789 | 0.50754172 | 0.54500368  | 0.50263678  |
| StepCox[backward] + survival-SVM | 0.58555103 | 0.55074697 | 0.50733659 | 0.50754172 | 0.5425948   | 0.50439464  |
| survival-SVM                     | 0.59808029 | 0.5628918  | 0.52416459 | 0.54284339 | 0.54897126  | 0.52175346  |
| RSF + survival-SVM               | 0.59808029 | 0.5628918  | 0.52416459 | 0.54284339 | 0.54897126  | 0.52175346  |
| StepCox[backward] + RSF          | 0.90216558 | 0.52030936 | 0.48720799 | 0.51412067 | 0.51907272  | 0.4993408   |
| CoxBoost + Enet[a=0]             | 0.60144372 | 0.55873778 | 0.61333242 | 0.57349166 | 0.45879386  | 0.53054274  |
| CoxBoost + Ridge                 | 0.60144372 | 0.55873778 | 0.61333242 | 0.57349166 | 0.45879386  | 0.53054274  |
| CoxBoost + StepCox[forward]      | 0.59912276 | 0.56052023 | 0.61446113 | 0.59531451 | 0.54738423  | 0.53790376  |
| Lasso + StepCox[forward]         | 0.59912276 | 0.56052023 | 0.61446113 | 0.59531451 | 0.54738423  | 0.53790376  |
| StepCox[both] + RSF              | 0.90724022 | 0.52832284 | 0.48920888 | 0.48483633 | 0.51978122  | 0.4945067   |
| Enet[a=0]                        | 0.60335163 | 0.55940243 | 0.55614461 | 0.54845956 | 0.54248144  | 0.52450011  |
| Ridge                            | 0.60335163 | 0.55940243 | 0.55614461 | 0.54845956 | 0.54248144  | 0.52450011  |
| RSF + Enet[a=0]                  | 0.6033713  | 0.55943264 | 0.55617882 | 0.5482991  | 0.5424531   | 0.52460998  |
| RSF + Ridge                      | 0.6033713  | 0.55943264 | 0.55617882 | 0.5482991  | 0.5424531   | 0.52460998  |
| RSF + SuperPC                    | 0.59945713 | 0.56385855 | 0.53209974 | 0.56033376 | 0.54514538  | 0.52911448  |
| SuperPC                          | 0.59945713 | 0.56385855 | 0.53209974 | 0.56033376 | 0.54514538  | 0.52911448  |
| CoxBoost + GBM                   | 0.71003718 | 0.5054833  | 0.59361426 | 0.51379974 | 0.56309868  | 0.56998462  |
| Lasso + GBM                      | 0.71003718 | 0.5054833  | 0.59361426 | 0.51379974 | 0.56309868  | 0.56998462  |
| CoxBoost                         | 0.59906375 | 0.56011239 | 0.61743681 | 0.59772144 | 0.55373236  | 0.53922215  |
| Lasso + CoxBoost                 | 0.59906375 | 0.56011239 | 0.61743681 | 0.59772144 | 0.55373236  | 0.53922215  |
| RSF + CoxBoost                   | 0.59906375 | 0.56011239 | 0.61743681 | 0.59772144 | 0.55373236  | 0.53922215  |
| Enet[a=0.6]                      | 0.59985051 | 0.56002175 | 0.61678695 | 0.59627728 | 0.55177691  | 0.53911228  |
| RSF + Enet[a=0.6]                | 0.59990952 | 0.56000665 | 0.61685536 | 0.59627728 | 0.55172023  | 0.53933202  |
| CoxBoost + Enet[a=0.4]           | 0.59965382 | 0.56020302 | 0.61647912 | 0.59338896 | 0.55052996  | 0.53878269  |
| Enet[a=0.5]                      | 0.60004721 | 0.5598707  | 0.61661593 | 0.59435173 | 0.55143683  | 0.53867282  |
| CoxBoost + Enet[a=0.5]           | 0.59949647 | 0.56008217 | 0.61641071 | 0.59483312 | 0.55052996  | 0.53977148  |
| RSF + Enet[a=0.5]                | 0.60014555 | 0.55993112 | 0.61654753 | 0.59435173 | 0.55138015  | 0.53856295  |
| CoxBoost + Enet[a=0.6]           | 0.59933912 | 0.56029365 | 0.6163081  | 0.59531451 | 0.55007652  | 0.53988135  |
| Enet[a=1]                        | 0.59959482 | 0.55985559 | 0.61702637 | 0.5978819  | 0.55282548  | 0.53944188  |
| Lasso                            | 0.59959482 | 0.55985559 | 0.61702637 | 0.5978819  | 0.55282548  | 0.53944188  |
| RSF + Enet[a=1]                  | 0.59961448 | 0.55984049 | 0.61706057 | 0.59804236 | 0.55279714  | 0.53944188  |
| RSF + Lasso                      | 0.59961448 | 0.55984049 | 0.61706057 | 0.59804236 | 0.55279714  | 0.53944188  |
| Enet[a=0.8]                      | 0.59967349 | 0.56026344 | 0.61688956 | 0.59691913 | 0.55191861  | 0.53889255  |
| RSF + Enet[a=0.8]                | 0.59969316 | 0.56021812 | 0.61688956 | 0.59691913 | 0.55189027  | 0.53889255  |
| RSF + Enet[a=0.9]                | 0.59979151 | 0.56026344 | 0.61692376 | 0.59707959 | 0.55208865  | 0.53933202  |
| Enet[a=0.9]                      | 0.59979151 | 0.56024834 | 0.61699217 | 0.59707959 | 0.55206031  | 0.53922215  |
| Enet[a=0.7]                      | 0.59979151 | 0.56023323 | 0.61678695 | 0.59643774 | 0.55194695  | 0.53911228  |
| RSF + Enet[a=0.7]                | 0.59977184 | 0.56023323 | 0.61675275 | 0.59627728 | 0.55191861  | 0.53911228  |
| Enet[a=0.3]                      | 0.60006688 | 0.55956859 | 0.61545302 | 0.59499358 | 0.55010486  | 0.53779389  |
| RSF + Enet[a=0.3]                | 0.60000787 | 0.55950817 | 0.61558984 | 0.59483312 | 0.55007652  | 0.53779389  |
| CoxBoost + Enet[a=0.8]           | 0.59916209 | 0.56020302 | 0.61617129 | 0.59643774 | 0.55004818  | 0.53988135  |
| CoxBoost + Enet[a=0.7]           | 0.59900474 | 0.56026344 | 0.61617129 | 0.59579589 | 0.55004818  | 0.53988135  |
| CoxBoost + Enet[a=0.9]           | 0.59908342 | 0.56018791 | 0.61620549 | 0.59595635 | 0.54979312  | 0.54021094  |
| CoxBoost + Enet[a=1]             | 0.59908342 | 0.56018791 | 0.61620549 | 0.59611682 | 0.54976478  | 0.54032081  |
| CoxBoost + Lasso                 | 0.59908342 | 0.56018791 | 0.61620549 | 0.59611682 | 0.54976478  | 0.54032081  |
| CoxBoost + Enet[a=0.3]           | 0.59961448 | 0.56021812 | 0.61671854 | 0.59242619 | 0.55016154  | 0.53867282  |
| CoxBoost + Enet[a=0.2]           | 0.5997325  | 0.56005196 | 0.6162397  | 0.59114249 | 0.5495664   | 0.53768403  |
| CoxBoost + Enet[a=0.1]           | 0.60026357 | 0.55964411 | 0.61620549 | 0.5885751  | 0.54778099  | 0.53526697  |
| CoxBoost + survival-SVM          | 0.59322201 | 0.56434193 | 0.61808667 | 0.63350449 | 0.55313722  | 0.55669084  |
| Lasso + survival-SVM             | 0.59322201 | 0.56434193 | 0.61808667 | 0.63350449 | 0.55313722  | 0.55669084  |
| RSF + Enet[a=0.1]                | 0.60223048 | 0.5596139  | 0.60396074 | 0.59050064 | 0.54789435  | 0.53493738  |
| Enet[a=0.1]                      | 0.60228949 | 0.5595988  | 0.60385813 | 0.59050064 | 0.54783767  | 0.53482751  |
| Enet[a=0.4]                      | 0.59988985 | 0.55953838 | 0.61596607 | 0.59467266 | 0.55078501  | 0.53834322  |
| RSF + Enet[a=0.4]                | 0.59987018 | 0.55953838 | 0.61600027 | 0.59483312 | 0.55084169  | 0.53856295  |
| Enet[a=0.2]                      | 0.60014555 | 0.55922116 | 0.61370866 | 0.59338896 | 0.54882956  | 0.53845309  |
| RSF + Enet[a=0.2]                | 0.60020456 | 0.55916074 | 0.61370866 | 0.59338896 | 0.54882956  | 0.53845309  |
| CoxBoost + SuperPC               | 0.58417419 | 0.56506699 | 0.61473475 | 0.6567715  | 0.55512101  | 0.56515052  |
| Lasso + SuperPC                  | 0.58417419 | 0.56506699 | 0.61473475 | 0.6567715  | 0.55512101  | 0.56515052  |
| CoxBoost + StepCox[backward]     | 0.59304498 | 0.5694778  | 0.62530355 | 0.63270218 | 0.56620189  | 0.56185454  |
| CoxBoost + StepCox[both]         | 0.59304498 | 0.5694778  | 0.62530355 | 0.63270218 | 0.56620189  | 0.56185454  |
| Lasso + StepCox[backward]        | 0.59304498 | 0.5694778  | 0.62530355 | 0.63270218 | 0.56620189  | 0.56185454  |
| Lasso + StepCox[both]            | 0.59304498 | 0.5694778  | 0.62530355 | 0.63270218 | 0.56620189  | 0.56185454  |
| CoxBoost + plsRcox               | 0.60435475 | 0.52991647 | 0.54906454 | 0.51572529 | 0.45995579  | 0.52395078  |
| Lasso + plsRcox                  | 0.60435475 | 0.52991647 | 0.54906454 | 0.51572529 | 0.45995579  | 0.52395078  |
| RSF + plsRcox                    | 0.60435475 | 0.52991647 | 0.54906454 | 0.51572529 | 0.45995579  | 0.52395078  |
| plsRcox                          | 0.60435475 | 0.52991647 | 0.54906454 | 0.51572529 | 0.45995579  | 0.52395078  |
| RSF + StepCox[forward]           | 0.60431542 | 0.52996178 | 0.54926976 | 0.51588575 | 0.45944567  | 0.52406065  |
| StepCox[forward]                 | 0.60431542 | 0.52996178 | 0.54926976 | 0.51588575 | 0.45944567  | 0.52406065  |
| StepCox[both] + Enet[a=0.1]      | 0.60179776 | 0.53458407 | 0.54236071 | 0.52743902 | 0.5541858   | 0.52911448  |
| StepCox[both] + Enet[a=0]        | 0.60193545 | 0.53595867 | 0.54116359 | 0.52759949 | 0.55429916  | 0.52779609  |
| StepCox[both] + Ridge            | 0.60193545 | 0.53595867 | 0.54116359 | 0.52759949 | 0.55429916  | 0.52779609  |
| StepCox[both] + Enet[a=0.2]      | 0.60134537 | 0.53381369 | 0.54260013 | 0.52792041 | 0.5544692   | 0.52944408  |
| StepCox[both] + Enet[a=0.6]      | 0.59988985 | 0.53334542 | 0.54352362 | 0.52920411 | 0.55415746  | 0.52900461  |
| StepCox[both] + Enet[a=0.5]      | 0.60008654 | 0.53331521 | 0.54311318 | 0.52824134 | 0.55427082  | 0.52911448  |
| StepCox[both] + Enet[a=0.9]      | 0.60012588 | 0.53304331 | 0.54366043 | 0.52743902 | 0.55401576  | 0.52900461  |
| StepCox[both] + Enet[a=0.8]      | 0.60016522 | 0.5330282  | 0.54366043 | 0.52743902 | 0.55401576  | 0.52900461  |
| StepCox[both] + Enet[a=1]        | 0.60012588 | 0.53305841 | 0.54359202 | 0.52743902 | 0.55401576  | 0.52911448  |
| StepCox[both] + Lasso            | 0.60012588 | 0.53305841 | 0.54359202 | 0.52743902 | 0.55401576  | 0.52911448  |
| StepCox[both] + CoxBoost         | 0.60053894 | 0.53361732 | 0.54318159 | 0.52856226 | 0.55469591  | 0.52922435  |
| StepCox[both] + Enet[a=0.7]      | 0.60020456 | 0.53305841 | 0.54366043 | 0.52727856 | 0.55398742  | 0.52900461  |
| StepCox[both] + Enet[a=0.3]      | 0.60065695 | 0.53358711 | 0.54321579 | 0.5284018  | 0.55441252  | 0.52911448  |
| StepCox[both] + Enet[a=0.4]      | 0.60038158 | 0.53349647 | 0.54311318 | 0.52775995 | 0.55424248  | 0.52933421  |
| StepCox[both] + plsRcox          | 0.59981118 | 0.53257504 | 0.54369463 | 0.52695764 | 0.55350564  | 0.52889475  |
| CoxBoost + RSF                   | 0.91839264 | 0.47689612 | 0.61028833 | 0.53786906 | 0.54416766  | 0.57388486  |
| Lasso + RSF                      | 0.91839264 | 0.47689612 | 0.61028833 | 0.53786906 | 0.54416766  | 0.57388486  |
| StepCox[backward] + Enet[a=0]    | 0.59613304 | 0.54482561 | 0.54410507 | 0.52230424 | 0.55548943  | 0.51889695  |
| StepCox[backward] + Ridge        | 0.59613304 | 0.54482561 | 0.54410507 | 0.52230424 | 0.55548943  | 0.51889695  |
| StepCox[both] + GBM              | 0.70113688 | 0.53063398 | 0.50126552 | 0.52029846 | 0.53790455  | 0.49049659  |
| StepCox[backward] + Enet[a=0.1]  | 0.59485455 | 0.54363227 | 0.5433526  | 0.52294609 | 0.55602789  | 0.52021534  |
| StepCox[backward] + Enet[a=0.2]  | 0.59493322 | 0.54355674 | 0.54301057 | 0.52310655 | 0.55602789  | 0.52043507  |
| StepCox[backward] + Enet[a=0.7]  | 0.5929073  | 0.54313379 | 0.54266854 | 0.5237484  | 0.55580117  | 0.52076467  |
| StepCox[backward] + Enet[a=0.4]  | 0.59408745 | 0.54342079 | 0.54280535 | 0.52342747 | 0.55605623  | 0.52043507  |
| StepCox[backward] + GBM          | 0.69041718 | 0.5241235  | 0.50126552 | 0.50810334 | 0.53790455  | 0.49049659  |
| StepCox[backward] + Enet[a=0.5]  | 0.59363506 | 0.54340569 | 0.54290796 | 0.52358793 | 0.55597121  | 0.52076467  |
| StepCox[backward] + Enet[a=0.6]  | 0.59369407 | 0.54340569 | 0.54283955 | 0.52358793 | 0.55594287  | 0.5206548   |
| StepCox[backward] + CoxBoost     | 0.59306465 | 0.54320932 | 0.54277115 | 0.5237484  | 0.55571615  | 0.52054494  |
| StepCox[backward] + Enet[a=0.3]  | 0.59481521 | 0.54346611 | 0.54290796 | 0.52342747 | 0.55599955  | 0.5206548   |
| StepCox[backward] + Enet[a=0.9]  | 0.59276962 | 0.54319421 | 0.54246332 | 0.5237484  | 0.55577283  | 0.52054494  |
| StepCox[backward] + Enet[a=0.8]  | 0.5926516  | 0.54317911 | 0.54246332 | 0.5237484  | 0.55571615  | 0.52076467  |
| StepCox[backward] + Enet[a=1]    | 0.59267127 | 0.54304316 | 0.54246332 | 0.52406932 | 0.55577283  | 0.52109427  |
| StepCox[backward] + Lasso        | 0.59267127 | 0.54304316 | 0.54246332 | 0.52406932 | 0.55577283  | 0.52109427  |
| StepCox[backward] + plsRcox      | 0.59223855 | 0.54225767 | 0.54215549 | 0.52390886 | 0.55520603  | 0.5216436   |
| RSF + StepCox[backward]          | 0.59223855 | 0.54225767 | 0.54215549 | 0.52390886 | 0.55520603  | 0.5216436   |
| StepCox[backward]                | 0.59223855 | 0.54225767 | 0.54215549 | 0.52390886 | 0.55520603  | 0.5216436   |
| RSF + StepCox[both]              | 0.59981118 | 0.53257504 | 0.54369463 | 0.52695764 | 0.55350564  | 0.52889475  |
| StepCox[both]                    | 0.59981118 | 0.53257504 | 0.54369463 | 0.52695764 | 0.55350564  | 0.52889475  |
| RSF                              | 0.93932063 | 0.50070241 | 0.60337928 | 0.52695764 | 0.55925863  | 0.51527137  |
| GBM                              | 0.73818375 | 0.54059606 | 0.60380682 | 0.4963896  | 0.56376467  | 0.49560536  |
| RSF + GBM                        | 0.73838044 | 0.54067159 | 0.60380682 | 0.4963896  | 0.56376467  | 0.49560536  |
| StepCox[backward] + SuperPC      | 0.58519699 | 0.55020317 | 0.50914937 | 0.50754172 | 0.54046931  | 0.50406504  |
| StepCox[both] + SuperPC          | 0.58519699 | 0.55020317 | 0.50914937 | 0.50754172 | 0.54046931  | 0.50406504  |



**Figure S1** CAF-C14 correlated with good response to immunotherapy. (A,B) Boxplot comparing the expression levels of immunotherapy responsive signatures between two treatment response groups. (C) Kaplan-Meier survival analysis of LUAD patients stratified by indicated groups according to immunotherapy responsive signatures in GSE100797 (n=25) cohort. (D) Kaplan-Meier survival analysis of bladder cancer patients receiving anti-PD-L1 therapy, stratified by specified groups. (E) The whole slide scan of H&E and IF staining of human LUAD tissues (Patient 1, Patient 2, and Patient 3). Scale bars, 2,000  $\mu\text{m}$ . Unpaired two-sided Student's *t*-test was used in A and B. CTLA-4, cytotoxic T lymphocyte-associated antigen 4; H&E, hematoxylin and Eosin; IF, immunofluorescence; LUAD, lung adenocarcinoma; MAGE-A3, melanoma-associated antigen 3; NR, nonresponse; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R, response.



**Figure S2** Machine learning-derived immune-related scores predicted patient survival and treatment response. (A-G) Multivariate Cox analysis of clinicopathologic and machine-learning-based riskscore characteristics in TCGA-LUAD (A), GSE72904 (B), GSE31210 (C), GSE50081 (D) and GSE8894 (G) cohorts. P values, hazard ratios, and 95% confidence intervals represented. Kaplan-Meier curves in GSE31210 (log-rank test:  $P < 0.001$ ) (C), GSE50081 (log-rank test:  $P = 0.003$ ) (D), GSE30219 (log-rank test:  $P = 0.002$ ) (E), EAS (log-rank test:  $P = 0.006$ ) (F), GSE8894 (log-rank test:  $P = 0.03$ ) (G). (H-K) Kaplan-Meier curves in three chemotherapy datasets, including GSE45255 (logrank test:  $P = 0.045$ ) (H), GSE3494 (logrank test:  $P = 0.006$ ) (I) and GSE1456 (logrank test:  $P = 0.003$  of PFS,  $P = 0.03$  of OS) (J,K). \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ . DFS, disease-free survival; DSS, disease-specific survival; LUAD, lung adenocarcinoma; OS, overall survival; PFS, progression-free survival; RS, riskscore; TCGA, The Cancer Genome Atlas.