

Table S1. Clinical features of 12 LUAD patients involved in the scRNA-seq of this study.

| Patient ID | Histological Type ^a | Morphologic pattern | Tumor location ^b | Tumor size (cm) | Gender | Age | Smoking | pTNM | Stage | Driver mutation ^c | PD-L1 (TPS ^d) | CD8 staining | TME classification ^e |
|------------|--------------------------------|--|-----------------------------|-----------------|--------|-----|---------|---------|-------|------------------------------|---------------------------|--------------|---------------------------------|
| P1 | MIA | lepidic | LLL | 1.0 | Female | 62 | No | T1aN0M0 | IA1 | <i>EGFR</i> L858R | <1% | + | III, tolerance |
| P2 | IA | acinar, papillary, micropapillary | RML | 1.5 | Male | 58 | Yes | T1bN0M0 | IA2 | <i>BRAF</i> V600X | <1% | + | III, tolerance |
| P3 | IA | papillary, acinar, lepidic | LUL | 3.8 | Female | 60 | No | T2aN0M0 | IB | <i>EGFR</i> G719A | <1% | + | III, tolerance |
| P4 | IA | solid, acinar, papillary, micropapillary | LUL | 1.1 | Male | 63 | No | T1bN2M0 | IIIA | <i>CD74-ROSI</i> (C6:R34) | <1% | + | III, tolerance |
| P5 | AIS | lepidic | LLL | 1.0 | Female | 66 | No | TisN0M0 | 0 | <i>EGFR</i> L858R | <1% | + | III, tolerance |
| P6 | MIA | lepidic | LUL | 1.1 | Male | 59 | No | T1aN0M0 | IA1 | NA | <1% | + | III, tolerance |
| P7 | MIA | lepidic | RUL | 1.3 | Female | 50 | No | T1aN0M0 | IA1 | <i>EGFR</i> 19del | <1% | + | III, tolerance |
| P8 | IA | lepidic, papillary, acinar | LUL | 3.1 | Female | 64 | No | T2aN0M0 | IB | <i>EGFR</i> 19del | <1% | + | III, tolerance |
| P9 | AIS | lepidic | LUL | 1.0 | Female | 38 | No | TisN0M0 | 0 | NA | <1% | + | III, tolerance |
| P10 | MIA | lepidic | RLL | 1.0 | Female | 63 | No | T1aN0M0 | IA1 | <i>EGFR</i> 20ins | <1% | + | III, tolerance |
| P11 | MIA | lepidic | LUL | 1.8 | Female | 75 | No | T1aN0M0 | IA1 | <i>EGFR</i> L858R | <1% | + | III, tolerance |
| P12 | IA | acinar, lepidic | LUL | 2.5 | Female | 54 | No | T1cN0M0 | IA3 | <i>EGFR</i> L858R | <1% | + | III, tolerance |

a: AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma;

b: LLL, left lower lobe; LUL, left upper lobe; RML, right middle lobe; RUL, right upper lobe; RLL, right lower lobe;

c: NA denotes detection for gene mutations not performed.

d: TPS, tumor proportion score.

e: Referring to Kim, T.K., et al., 2022. (PMID: 35701637)

Table S2. Summary of 10x genomics scRNA-seq data.

| Sample ID | Patient ID | Estimated Number of Cells | Mean Reads per Cell | Median Genes per Cell | Number of Reads | Valid Barcodes | Sequencing Saturation | Q30 Bases in Barcode | Q30 Bases in RNA Read | Q30 Bases in UMI | Reads Mapped to Genome |
|------------------|-------------------|----------------------------------|----------------------------|------------------------------|------------------------|-----------------------|------------------------------|-----------------------------|------------------------------|-------------------------|-------------------------------|
| NC_1 | P1 | 7,525 | 74,243 | 1,828 | 558,682,362 | 96.90% | 68.30% | 94.10% | 90.00% | 93.50% | 94.70% |
| MIA_1 | P1 | 7,846 | 63,896 | 1,695 | 501,333,637 | 97.20% | 66.10% | 94.30% | 90.20% | 93.70% | 94.50% |
| NC_2 | P2 | 14,206 | 36,149 | 1,707 | 513,535,824 | 97.40% | 45.50% | 94.30% | 90.50% | 93.70% | 94.40% |
| IA_2 | P2 | 7,567 | 72,809 | 1,653 | 550,946,592 | 97.70% | 63.70% | 94.30% | 90.10% | 93.70% | 94.70% |
| IA_3 | P3 | 9,623 | 53,333 | 1,448 | 513,226,577 | 97.70% | 43.70% | 96.20% | 92.00% | 95.40% | 94.60% |
| IA_4 | P4 | 7,378 | 70,932 | 1,483 | 523,342,506 | 97.40% | 47.00% | 96.20% | 92.00% | 95.50% | 95.60% |
| AIS_5 | P5 | 9,172 | 55,451 | 1,754 | 508,603,001 | 98.40% | 56.70% | 96.20% | 90.00% | 96.00% | 94.10% |
| NC_6 | P6 | 10,026 | 54,559 | 1,439 | 547,017,116 | 98.40% | 64.20% | 96.30% | 91.20% | 96.10% | 95.00% |
| MIA_6 | P6 | 12,792 | 41,668 | 1,943 | 533,022,264 | 98.40% | 52.50% | 96.30% | 91.00% | 96.10% | 95.40% |
| MIA_7 | P7 | 9,783 | 54,519 | 1,671 | 533,367,842 | 98.20% | 60.20% | 97.00% | 93.10% | 96.90% | 95.60% |
| IA_8 | P8 | 8,459 | 66,558 | 1,898 | 563,017,785 | 98.20% | 62.80% | 96.90% | 93.20% | 96.80% | 96.10% |
| AIS_9 | P9 | 14,470 | 37,399 | 1,321 | 541,174,263 | 98.10% | 65.00% | 95.40% | 91.30% | 94.20% | 96.10% |
| MIA_10 | P10 | 9,053 | 56,940 | 1,509 | 515,484,301 | 98.10% | 73.90% | 97.00% | 92.90% | 96.70% | 96.20% |
| MIA_11 | P11 | 7,070 | 71,358 | 2,466 | 504,507,123 | 98.20% | 62.10% | 97.00% | 93.20% | 96.80% | 96.20% |
| IA_12 | P12 | 9,806 | 53,092 | 1,323 | 520,628,946 | 98.20% | 66.70% | 97.00% | 93.10% | 96.80% | 96.30% |

Table S2 continued

| Sample ID | Patient ID | Reads Mapped Confidently to Genome | Reads Mapped Confidently to Intergenic Regions | Reads Mapped Confidently to Intronic Regions | Reads Mapped Confidently to Exonic Regions | Reads Mapped Confidently to Transcriptome | Reads Mapped Antisense to Gene | Fraction Reads in Cells | Total Genes Detected | Median UMI Counts per Cell |
|-----------|------------|------------------------------------|--|--|--|---|--------------------------------|-------------------------|----------------------|----------------------------|
| NC_1 | P1 | 91.20% | 6.80% | 37.80% | 46.60% | 42.40% | 1.90% | 84.80% | 24,354 | 4,691 |
| MIA_1 | P1 | 92.20% | 7.30% | 39.70% | 45.20% | 41.20% | 1.70% | 83.70% | 24,644 | 4,458 |
| NC_2 | P2 | 91.20% | 8.30% | 30.70% | 52.10% | 47.80% | 1.90% | 90.90% | 24,884 | 3,859 |
| IA_2 | P2 | 92.30% | 7.70% | 27.90% | 56.70% | 53.10% | 1.30% | 94.00% | 24,688 | 5,089 |
| IA_3 | P3 | 91.80% | 11.60% | 25.90% | 54.30% | 50.80% | 1.20% | 87.70% | 25,267 | 4,233 |
| IA_4 | P4 | 93.10% | 9.90% | 28.80% | 54.30% | 50.50% | 1.50% | 92.70% | 25,410 | 4,346 |
| AIS_5 | P5 | 91.30% | 8.70% | 24.40% | 58.20% | 54.40% | 1.20% | 83.10% | 24,787 | 5,593 |
| NC_6 | P6 | 92.50% | 7.60% | 21.10% | 63.80% | 59.90% | 1.30% | 91.90% | 24,169 | 4,042 |
| MIA_6 | P6 | 93.00% | 8.40% | 25.30% | 59.30% | 55.60% | 1.30% | 92.70% | 24,655 | 5,874 |
| MIA_7 | P7 | 92.00% | 9.00% | 24.60% | 58.30% | 55.00% | 1.00% | 90.10% | 24,490 | 5,242 |
| IA_8 | P8 | 92.60% | 6.20% | 20.20% | 66.30% | 62.70% | 1.00% | 94.70% | 24,036 | 6,543 |
| AIS_9 | P9 | 92.40% | 9.10% | 21.50% | 61.90% | 58.10% | 1.30% | 90.70% | 24,371 | 3,679 |
| MIA_10 | P10 | 93.10% | 6.00% | 18.80% | 68.30% | 64.10% | 1.40% | 81.60% | 24,177 | 4,365 |
| MIA_11 | P11 | 93.40% | 8.70% | 21.50% | 63.20% | 59.50% | 1.30% | 92.40% | 24,250 | 7,781 |
| IA_12 | P12 | 93.50% | 7.50% | 17.50% | 68.50% | 64.50% | 1.20% | 90.00% | 24,270 | 4,577 |

Table S3. Canonical markers used to annotate each cell type.

| Celltype | Sub celltype | Canonical markers | | |
|-------------|-------------------------------|-------------------|----------|-------|
| | | | | |
| Epithelial | - | EPCAM | KRT8 | |
| Epithelial | AT1 | AGER | CLIC5 | |
| Epithelial | AT2 | SFTPB | MUC1 | |
| Epithelial | Ciliated | TPPP3 | C20orf85 | |
| Epithelial | Club | SCGB1A1 | | |
| T cells | - | CD3D | CD3E | |
| T cells | CD4 ⁺ T cells | CD4 | | |
| T cells | CD4 ⁺ CCR7 | CCR7 | | |
| T cells | CD4 ⁺ CXCR6 | CXCR6 | | |
| T cells | CD4 ⁺ FOXP3 (Treg) | FOXP3 | | |
| T cells | CD4 ⁺ NR4A3 | NR4A3 | | |
| T cells | CD8 ⁺ T cells | CD8A | CD8B | |
| T cells | CD8 ⁺ GZMK (Teff) | GZMK | | |
| T cells | CD8 ⁺ CXCL13 | CXCL13 | | |
| T cells | CD8 ⁺ ZNF683 | ZNF683 | | |
| T cells | CD8 ⁺ KLRD1 | KLRD1 | | |
| T cells | CD8 ⁺ KLRD1-CCL4L2 | KLRD1 | CCL4L2 | |
| B cells | - | MS4A1 | | |
| B cells | Plasma | JCHAIN | | |
| NK cells | - | NKG7 | KLRF1 | |
| Myeloids | - | CD68 | MSR1 | |
| Myeloids | Macrophages | MRC1 | C1QA | APOE |
| Myeloids | ARM | FABP4 | MCEMP1 | MARCO |
| Myeloids | TAM-FOLR2 | FOLR2 | | |
| Myeloids | TAM-MIK67 | MKI67 | | |
| Myeloids | CD14 ⁺ monocytes | CD14 | VCAN | |
| Myeloids | CD16 ⁺ monocytes | FCGR3A | | |
| Myeloids | Neutrophil | FCGR3B | | |
| Myeloids | Mast | TPSAB1 | | |
| Myeloids | DC | CD1C | | |
| Stromal | - | COL1A1 | ACTA2 | |
| Endothelial | - | CDH5 | VWF | |

Table S4. Top 10 significantly differential expressed genes for epithelial cell clusters.

| cluster | gene | avg_log2FC | pct.1 | pct.2 | p_val | p_val_adj |
|----------|-----------------|-------------|-------|-------|-----------|-------------|
| AT2 | NAPSA | 3.027576059 | 0.947 | 0.44 | 0 | 0 |
| AT2 | NPC2 | 3.027231195 | 0.938 | 0.337 | 0 | 0 |
| AT2 | SFTPA1 | 2.854441507 | 0.668 | 0.242 | 0 | 0 |
| AT2 | C4BPA | 2.845622961 | 0.725 | 0.108 | 0 | 0 |
| AT2 | SFTPB | 2.7250115 | 0.955 | 0.44 | 0 | 0 |
| AT2 | SERPINA1 | 2.45894219 | 0.688 | 0.182 | 0 | 0 |
| AT2 | SFTPA2 | 2.904788639 | 0.686 | 0.298 | 1.01E-296 | 2.56E-292 |
| AT2 | SPINK1 | 2.152811441 | 0.201 | 0.03 | 7.78E-108 | 1.97E-103 |
| AT2 | SFTPC | 3.52408706 | 0.605 | 0.6 | 1.63E-09 | 4.13E-05 |
| AT2 | MUC1 | 1.801458833 | 0.887 | 0.416 | 0 | 0 |
| Ciliated | C9orf24 | 4.722751442 | 0.944 | 0.022 | 0 | 0 |
| Ciliated | C20orf85 | 4.628528094 | 0.933 | 0.013 | 0 | 0 |
| Ciliated | C11orf88 | 4.031508792 | 0.908 | 0.006 | 0 | 0 |
| Ciliated | RSPH1 | 4.01873317 | 0.949 | 0.041 | 0 | 0 |
| Ciliated | C1orf194 | 4.015958232 | 0.928 | 0.01 | 0 | 0 |
| Ciliated | SNTN | 3.730391019 | 0.877 | 0.011 | 0 | 0 |
| Ciliated | C5orf49 | 3.711643971 | 0.918 | 0.041 | 0 | 0 |
| Ciliated | CAPS | 5.643283534 | 0.99 | 0.157 | 1.51E-274 | 3.83E-270 |
| Ciliated | GSTA1 | 3.691812941 | 0.795 | 0.115 | 1.93E-207 | 4.90E-203 |
| Ciliated | TPPP3 | 3.970365781 | 0.964 | 0.243 | 1.01E-187 | 2.55E-183 |
| AT1 | AGER | 3.797691756 | 0.906 | 0.38 | 0 | 0 |
| AT1 | RTKN2 | 3.371489417 | 0.781 | 0.125 | 0 | 0 |
| AT1 | CAV1 | 3.222083855 | 0.92 | 0.56 | 0 | 0 |
| AT1 | EMP2 | 3.060426223 | 0.923 | 0.777 | 0 | 0 |
| AT1 | S100A4 | 2.802138312 | 0.807 | 0.581 | 0 | 0 |
| AT1 | MT1G | 3.906373606 | 0.246 | 0.039 | 6.54E-184 | 1.66E-179 |
| AT1 | MT2A | 3.400665946 | 0.567 | 0.61 | 1.31E-41 | 3.32E-37 |
| AT1 | MT1E | 3.272162441 | 0.595 | 0.675 | 5.85E-34 | 1.48E-29 |
| AT1 | MT1X | 3.696305468 | 0.377 | 0.419 | 5.34E-13 | 1.35E-08 |
| AT1 | CLIC5 | 2.124860594 | 0.759 | 0.353 | 0 | 0 |
| Club | BPIFB1 | 5.916865654 | 0.637 | 0.022 | 0 | 0 |
| Club | MSMB | 4.607143101 | 0.399 | 0.006 | 0 | 0 |
| Club | CXCL1 | 3.245080238 | 0.544 | 0.063 | 2.70E-206 | 6.83E-202 |
| Club | SCGB1A1 | 8.346279916 | 0.954 | 0.338 | 1.16E-202 | 2.94E-198 |
| Club | SLPI | 3.536651811 | 0.979 | 0.637 | 6.50E-136 | 1.65E-131 |
| Club | SCGB3A1 | 3.710658636 | 0.975 | 0.507 | 1.53E-135 | 3.87E-131 |
| Club | LCN2 | 3.318209539 | 0.754 | 0.227 | 1.57E-135 | 3.96E-131 |
| Club | TFF3 | 3.096110148 | 0.616 | 0.134 | 4.09E-121 | 1.04E-116 |
| Club | MGP | 3.069883528 | 0.68 | 0.236 | 7.14E-83 | 1.81E-78 |
| Club | SCGB3A2 | 3.155398816 | 0.516 | 0.448 | 3.09E-08 | 0.000781934 |

Table S5. Top 10 significantly differential expressed genes for myeloid clusters.

| cluster | gene | avg_log2FC | pct.1 | pct.2 | p_val | p_val_adj |
|-----------|----------|-------------|-------|-------|-------|-----------|
| ARM-RETN | RETN | 3.006328226 | 0.959 | 0.335 | 0 | 0 |
| ARM-RETN | CCL20 | 2.193048328 | 0.648 | 0.213 | 0 | 0 |
| ARM-RETN | IFI27 | 2.178853976 | 0.521 | 0.184 | 0 | 0 |
| ARM-RETN | FABP4 | 2.171497789 | 0.788 | 0.241 | 0 | 0 |
| ARM-RETN | LYZ | 2.099935247 | 0.999 | 0.807 | 0 | 0 |
| ARM-RETN | MARCO | 2.093261741 | 0.978 | 0.332 | 0 | 0 |
| ARM-RETN | INHBA | 1.784264933 | 0.835 | 0.224 | 0 | 0 |
| ARM-RETN | FBP1 | 1.68836059 | 0.993 | 0.527 | 0 | 0 |
| ARM-RETN | LPL | 1.654510572 | 0.909 | 0.27 | 0 | 0 |
| ARM-RETN | MCEMP1 | 1.342202038 | 0.966 | 0.263 | 0 | 0 |
| DC | CCL17 | 3.614418936 | 0.295 | 0.02 | 0 | 0 |
| DC | S100B | 2.75663214 | 0.46 | 0.064 | 0 | 0 |
| DC | GPR183 | 2.288456636 | 0.919 | 0.294 | 0 | 0 |
| DC | CD1C | 2.114086958 | 0.597 | 0.036 | 0 | 0 |
| DC | FCER1A | 2.097069232 | 0.514 | 0.064 | 0 | 0 |
| DC | LTB | 1.914413462 | 0.62 | 0.253 | 0 | 0 |
| DC | HLA-DQB2 | 1.902749759 | 0.347 | 0.094 | 0 | 0 |
| DC | CLEC10A | 1.856974602 | 0.645 | 0.121 | 0 | 0 |
| DC | CD1E | 1.828553224 | 0.533 | 0.023 | 0 | 0 |
| DC | HLA-DPB1 | 1.76662412 | 0.998 | 0.813 | 0 | 0 |
| Mast | TPSB2 | 7.117379717 | 0.981 | 0.033 | 0 | 0 |
| Mast | TPSAB1 | 6.561950138 | 0.981 | 0.013 | 0 | 0 |
| Mast | CPA3 | 5.434207547 | 0.988 | 0.011 | 0 | 0 |
| Mast | MS4A2 | 4.403679726 | 0.976 | 0.007 | 0 | 0 |
| Mast | CD69 | 4.276853431 | 0.963 | 0.402 | 0 | 0 |
| Mast | HPGD | 3.487610427 | 0.904 | 0.318 | 0 | 0 |
| Mast | HPGDS | 3.442615499 | 0.965 | 0.318 | 0 | 0 |
| Mast | C1orf186 | 3.330334154 | 0.916 | 0.013 | 0 | 0 |
| Mast | KIT | 3.314534091 | 0.917 | 0.008 | 0 | 0 |
| Mast | GATA2 | 3.087340741 | 0.841 | 0.007 | 0 | 0 |
| Mono-CD14 | EREG | 3.611849312 | 0.817 | 0.205 | 0 | 0 |
| Mono-CD14 | VCAN | 3.433317955 | 0.875 | 0.27 | 0 | 0 |
| Mono-CD14 | FCN1 | 2.76937259 | 0.986 | 0.195 | 0 | 0 |
| Mono-CD14 | THBS1 | 2.409535221 | 0.67 | 0.365 | 0 | 0 |
| Mono-CD14 | IL1B | 2.361463035 | 0.856 | 0.585 | 0 | 0 |
| Mono-CD14 | TIMP1 | 2.055915423 | 0.933 | 0.678 | 0 | 0 |
| Mono-CD14 | S100A9 | 1.897816845 | 0.984 | 0.739 | 0 | 0 |
| Mono-CD14 | NLRP3 | 1.886006202 | 0.857 | 0.318 | 0 | 0 |
| Mono-CD14 | CD300E | 1.77685775 | 0.743 | 0.097 | 0 | 0 |

| | | | | | | |
|------------|----------|-------------|-------|-------|-------------|-------------|
| Mono-CD14 | CXCL2 | 1.762294672 | 0.712 | 0.431 | 2.43E-252 | 6.16E-248 |
| Mono-CD16 | CDKN1C | 2.628527207 | 0.791 | 0.097 | 0 | 0 |
| Mono-CD16 | LYPD2 | 2.569816612 | 0.393 | 0.005 | 0 | 0 |
| Mono-CD16 | LILRB2 | 2.101027351 | 0.961 | 0.311 | 0 | 0 |
| Mono-CD16 | TIMP1 | 2.094071271 | 0.978 | 0.685 | 0 | 0 |
| Mono-CD16 | FCGR3A | 2.085756881 | 0.973 | 0.64 | 0 | 0 |
| Mono-CD16 | MTSS1 | 1.955370981 | 0.916 | 0.147 | 0 | 0 |
| Mono-CD16 | CD48 | 1.93658843 | 0.986 | 0.452 | 0 | 0 |
| Mono-CD16 | HES4 | 1.923887654 | 0.821 | 0.129 | 0 | 0 |
| Mono-CD16 | LST1 | 1.897203492 | 1 | 0.856 | 0 | 0 |
| Mono-CD16 | POU2F2 | 1.874959504 | 0.898 | 0.22 | 0 | 0 |
| Neutrophil | FCGR3B | 5.216160191 | 0.854 | 0.016 | 0 | 0 |
| Neutrophil | G0S2 | 4.648403089 | 0.916 | 0.289 | 0 | 0 |
| Neutrophil | IFITM2 | 4.460400317 | 0.959 | 0.613 | 0 | 0 |
| Neutrophil | S100A8 | 4.098121809 | 0.924 | 0.552 | 0 | 0 |
| Neutrophil | CMTM2 | 3.894735696 | 0.556 | 0.029 | 0 | 0 |
| Neutrophil | NAMPT | 3.763289605 | 0.969 | 0.885 | 0 | 0 |
| Neutrophil | PTGS2 | 3.754686017 | 0.772 | 0.408 | 0 | 0 |
| Neutrophil | CXCR2 | 3.717177043 | 0.543 | 0.077 | 0 | 0 |
| Neutrophil | SLC25A37 | 3.618983517 | 0.647 | 0.351 | 0 | 0 |
| Neutrophil | SMCHD1 | 3.320401893 | 0.685 | 0.602 | 0 | 0 |
| TAM-c12 | AIF1 | 1.242434352 | 0.855 | 0.846 | 7.97E-75 | 2.02E-70 |
| TAM-c12 | TUBA1B | 1.283237297 | 0.774 | 0.839 | 8.59E-50 | 2.18E-45 |
| TAM-c12 | LGALS1 | 1.17242625 | 0.811 | 0.856 | 1.15E-48 | 2.90E-44 |
| TAM-c12 | FTL | 1.217937994 | 0.995 | 0.999 | 6.57E-36 | 1.66E-31 |
| TAM-c12 | SPP1 | 1.479182342 | 0.215 | 0.115 | 6.56E-16 | 1.66E-11 |
| TAM-c12 | S100B | 2.217111069 | 0.187 | 0.114 | 3.09E-10 | 7.82E-06 |
| TAM-c12 | IGHA1 | 2.053395246 | 0.093 | 0.154 | 0.000605418 | 1 |
| TAM-c12 | IGKC | 3.016172256 | 0.255 | 0.287 | 0.352866172 | 1 |
| TAM-c12 | IGLC2 | 3.54548639 | 0.124 | 0.142 | 0.659106186 | 1 |
| TAM-c12 | SCGB3A1 | 1.127496813 | 0.301 | 0.387 | 0.85072054 | 1 |
| TAM-c18 | CAV1 | 2.775892708 | 0.779 | 0.058 | 0 | 0 |
| TAM-c18 | EMP2 | 2.434911514 | 0.805 | 0.124 | 8.02E-162 | 2.03E-157 |
| TAM-c18 | NAPSA | 2.736901588 | 0.55 | 0.186 | 2.06E-41 | 5.22E-37 |
| TAM-c18 | SLPI | 2.702781077 | 0.45 | 0.121 | 5.93E-40 | 1.50E-35 |
| TAM-c18 | SFTPB | 3.198054973 | 0.685 | 0.39 | 9.79E-27 | 2.48E-22 |
| TAM-c18 | SFTPA2 | 2.774559596 | 0.477 | 0.187 | 3.23E-23 | 8.18E-19 |
| TAM-c18 | SCGB3A1 | 4.258639762 | 0.537 | 0.384 | 8.48E-08 | 0.002147751 |
| TAM-c18 | SCGB3A2 | 3.265786611 | 0.295 | 0.162 | 1.50E-07 | 0.003809572 |
| TAM-c18 | SFTPC | 4.131168285 | 0.644 | 0.512 | 0.00028427 | 1 |
| TAM-c18 | SCGB1A1 | 3.697705214 | 0.416 | 0.369 | 0.45664016 | 1 |
| TAM-FOLR2 | SEPP1 | 3.544691252 | 0.793 | 0.079 | 0 | 0 |
| TAM-FOLR2 | SPP1 | 3.152646559 | 0.415 | 0.073 | 0 | 0 |
| TAM-FOLR2 | LGMN | 2.926280999 | 0.923 | 0.257 | 0 | 0 |
| TAM-FOLR2 | RNASE1 | 2.861752955 | 0.784 | 0.158 | 0 | 0 |

| | | | | | | |
|-----------|----------|-------------|-------|-------|-----------|-----------|
| TAM-FOLR2 | APOE | 2.554146003 | 0.921 | 0.574 | 0 | 0 |
| TAM-FOLR2 | FOLR2 | 2.518206142 | 0.876 | 0.165 | 0 | 0 |
| TAM-FOLR2 | A2M | 2.469549338 | 0.966 | 0.212 | 0 | 0 |
| TAM-FOLR2 | SLC40A1 | 2.382171432 | 0.81 | 0.106 | 0 | 0 |
| TAM-FOLR2 | CCL13 | 2.255573099 | 0.442 | 0.03 | 0 | 0 |
| TAM-FOLR2 | CCL18 | 2.289413222 | 0.524 | 0.28 | 2.67E-217 | 6.75E-213 |
| TAM-MKI67 | STMN1 | 2.997634899 | 0.986 | 0.506 | 0 | 0 |
| TAM-MKI67 | HIST1H4C | 2.927138902 | 0.781 | 0.278 | 0 | 0 |
| TAM-MKI67 | HMGB2 | 2.734587559 | 0.97 | 0.612 | 0 | 0 |
| TAM-MKI67 | KIAA0101 | 2.400344279 | 0.865 | 0.021 | 0 | 0 |
| TAM-MKI67 | TYMS | 2.287835888 | 0.79 | 0.018 | 0 | 0 |
| TAM-MKI67 | TUBB | 2.233377409 | 0.949 | 0.694 | 0 | 0 |
| TAM-MKI67 | CCL5 | 2.331661343 | 0.455 | 0.17 | 1.82E-139 | 4.60E-135 |
| TAM-MKI67 | NKG7 | 2.509363316 | 0.37 | 0.127 | 4.39E-121 | 1.11E-116 |
| TAM-MKI67 | GPLY | 2.434969564 | 0.188 | 0.077 | 5.21E-40 | 1.32E-35 |
| TAM-MKI67 | MKI67 | 2.087943551 | 0.704 | 0.008 | 0 | 0 |

Table S6. Top 10 significantly differential expressed genes for T lymphocyte clusters.

| cluster | gene | avg_log2FC | pct.1 | pct.2 | p_val | p_val_adj |
|-----------|----------|-------------|-------|-------|-----------|-----------|
| CD4-CCR7 | KLF2 | 1.318569604 | 0.805 | 0.507 | 0 | 0 |
| CD4-CCR7 | LTB | 1.219432252 | 0.922 | 0.532 | 0 | 0 |
| CD4-CCR7 | CCR7 | 1.098495163 | 0.449 | 0.122 | 0 | 0 |
| CD4-CCR7 | GPR183 | 0.901727024 | 0.783 | 0.448 | 0 | 0 |
| CD4-CCR7 | JUNB | 0.812783967 | 0.967 | 0.85 | 0 | 0 |
| CD4-CCR7 | LDHB | 0.778527789 | 0.873 | 0.598 | 0 | 0 |
| CD4-CCR7 | RPS6 | 0.743755168 | 1 | 0.991 | 0 | 0 |
| CD4-CCR7 | RPL32 | 0.731657182 | 1 | 0.996 | 0 | 0 |
| CD4-CCR7 | EEF1B2 | 0.712710083 | 0.995 | 0.927 | 0 | 0 |
| CD4-CCR7 | NFKBIA | 0.72402555 | 0.878 | 0.718 | 3.22E-213 | 8.15E-209 |
| CD4-CXCR6 | CD40LG | 1.102078035 | 0.564 | 0.205 | 0 | 0 |
| CD4-CXCR6 | ALOX5AP | 1.084450058 | 0.839 | 0.521 | 0 | 0 |
| CD4-CXCR6 | RBPJ | 1.074518242 | 0.634 | 0.282 | 0 | 0 |
| CD4-CXCR6 | BATF | 1.019363661 | 0.536 | 0.276 | 0 | 0 |
| CD4-CXCR6 | CXCR6 | 0.935340591 | 0.415 | 0.145 | 0 | 0 |
| CD4-CXCR6 | CD52 | 0.900850697 | 0.984 | 0.906 | 0 | 0 |
| CD4-CXCR6 | S100A4 | 0.869610741 | 0.991 | 0.914 | 0 | 0 |
| CD4-CXCR6 | SH3BGRL3 | 0.809776939 | 0.989 | 0.942 | 0 | 0 |
| CD4-CXCR6 | CAPG | 0.795597101 | 0.486 | 0.218 | 0 | 0 |
| CD4-CXCR6 | PLIN2 | 1.020182879 | 0.53 | 0.299 | 6.65E-262 | 1.68E-257 |
| CD4-FOXP3 | TNFRSF4 | 2.77156298 | 0.651 | 0.118 | 0 | 0 |
| CD4-FOXP3 | TNFRSF18 | 2.236753097 | 0.611 | 0.104 | 0 | 0 |
| CD4-FOXP3 | PMAIP1 | 1.918484491 | 0.65 | 0.2 | 0 | 0 |
| CD4-FOXP3 | TIGIT | 1.909787644 | 0.731 | 0.173 | 0 | 0 |
| CD4-FOXP3 | LAIR2 | 1.833105652 | 0.511 | 0.06 | 0 | 0 |
| CD4-FOXP3 | CTLA4 | 1.761446025 | 0.685 | 0.158 | 0 | 0 |
| CD4-FOXP3 | PMCH | 1.565253623 | 0.108 | 0.001 | 0 | 0 |
| CD4-FOXP3 | ICA1 | 1.533563162 | 0.412 | 0.024 | 0 | 0 |
| CD4-FOXP3 | CARD16 | 1.451557765 | 0.664 | 0.288 | 0 | 0 |
| CD4-FOXP3 | FOXP3 | 1.286707722 | 0.345 | 0.012 | 0 | 0 |
| CD4-NR4A3 | PABPC1 | 1.487155355 | 0.95 | 0.747 | 0 | 0 |
| CD4-NR4A3 | YPEL5 | 1.445988882 | 0.872 | 0.55 | 0 | 0 |
| CD4-NR4A3 | ATP1B3 | 1.405269257 | 0.683 | 0.399 | 0 | 0 |
| CD4-NR4A3 | CREM | 1.369125716 | 0.893 | 0.577 | 0 | 0 |
| CD4-NR4A3 | REL | 1.367751457 | 0.742 | 0.435 | 0 | 0 |
| CD4-NR4A3 | KDM6B | 1.348970729 | 0.576 | 0.222 | 0 | 0 |
| CD4-NR4A3 | LMNA | 1.342897089 | 0.734 | 0.387 | 0 | 0 |
| CD4-NR4A3 | HP | 1.32372204 | 0.349 | 0.017 | 0 | 0 |
| CD4-NR4A3 | IRS2 | 1.293879553 | 0.44 | 0.112 | 0 | 0 |
| CD4-NR4A3 | NR4A3 | 1.236197009 | 0.443 | 0.129 | 0 | 0 |
| CD4-c9 | FKBP5 | 1.073768729 | 0.876 | 0.457 | 0 | 0 |
| CD4-c9 | XIST | 1.15235493 | 0.757 | 0.351 | 1.66E-302 | 4.21E-298 |

| | | | | | | |
|------------|---------------|-------------|-------|-------|-------------|-------------|
| CD4-c9 | AIM1 | 1.054457161 | 0.821 | 0.42 | 6.47E-269 | 1.64E-264 |
| CD4-c9 | IL7R | 1.013126686 | 0.95 | 0.729 | 1.28E-260 | 3.25E-256 |
| CD4-c9 | SC5D | 0.93719792 | 0.559 | 0.215 | 7.85E-232 | 1.99E-227 |
| CD4-c9 | CELF2 | 0.849786084 | 0.871 | 0.514 | 2.57E-226 | 6.51E-222 |
| CD4-c9 | RP11-138A9.1 | 0.861611009 | 0.64 | 0.272 | 7.95E-222 | 2.01E-217 |
| CD4-c9 | AHNAK | 1.031549725 | 0.911 | 0.67 | 3.42E-197 | 8.65E-193 |
| CD4-c9 | ANKRD28 | 0.85602349 | 0.643 | 0.328 | 3.90E-149 | 9.87E-145 |
| CD4-c9 | KLRB1 | 0.918293849 | 0.666 | 0.376 | 1.50E-136 | 3.80E-132 |
| CD4-c10 | GIMAP7 | 0.754990702 | 0.533 | 0.435 | 1.29E-42 | 3.27E-38 |
| CD4-c10 | LTB | 0.646361203 | 0.663 | 0.597 | 2.12E-36 | 5.37E-32 |
| CD4-c10 | GIMAP4 | 0.693093746 | 0.457 | 0.356 | 6.30E-35 | 1.59E-30 |
| CD4-c10 | N4BP2L2 | 0.636737408 | 0.678 | 0.678 | 1.39E-31 | 3.52E-27 |
| CD4-c10 | NKTR | 0.779349543 | 0.437 | 0.4 | 3.90E-18 | 9.86E-14 |
| CD4-c10 | SFTPC | 1.353558669 | 0.272 | 0.41 | 2.05E-13 | 5.20E-09 |
| CD4-c10 | DDX17 | 0.645032798 | 0.525 | 0.55 | 2.20E-11 | 5.56E-07 |
| CD4-c10 | ANKRD36C | 0.668849225 | 0.167 | 0.129 | 3.51E-08 | 0.000888087 |
| CD4-c10 | IGKC | 2.173717453 | 0.209 | 0.29 | 3.66E-06 | 0.092655164 |
| CD4-c10 | IGHA1 | 2.221410193 | 0.084 | 0.124 | 0.000113648 | 1 |
| CD8-CXCL13 | CXCL13 | 3.285524942 | 0.436 | 0.012 | 0 | 0 |
| CD8-CXCL13 | KRT86 | 2.593839354 | 0.685 | 0.008 | 0 | 0 |
| CD8-CXCL13 | KRT81 | 1.935788281 | 0.473 | 0.003 | 0 | 0 |
| CD8-CXCL13 | FAM3C | 2.073549684 | 0.679 | 0.092 | 5.17E-160 | 1.31E-155 |
| CD8-CXCL13 | CTLA4 | 2.079241011 | 0.83 | 0.194 | 2.63E-112 | 6.66E-108 |
| CD8-CXCL13 | CTSW | 2.04162721 | 0.879 | 0.253 | 1.05E-100 | 2.65E-96 |
| CD8-CXCL13 | AC092580.4 | 1.908459657 | 0.788 | 0.207 | 7.07E-94 | 1.79E-89 |
| CD8-CXCL13 | CD7 | 2.249250367 | 0.939 | 0.443 | 1.52E-84 | 3.85E-80 |
| CD8-CXCL13 | RGS1 | 1.910314125 | 0.976 | 0.667 | 1.86E-70 | 4.70E-66 |
| CD8-CXCL13 | GZMB | 1.870274525 | 0.77 | 0.247 | 1.05E-56 | 2.65E-52 |
| CD8-GZMK | GZMK | 3.42387827 | 0.954 | 0.161 | 0 | 0 |
| CD8-GZMK | CCL4L2 | 3.032351851 | 0.612 | 0.147 | 0 | 0 |
| CD8-GZMK | CCL3 | 2.292251407 | 0.327 | 0.089 | 0 | 0 |
| CD8-GZMK | CCL4 | 2.069719195 | 0.943 | 0.453 | 0 | 0 |
| CD8-GZMK | CCL3L3 | 1.971815865 | 0.406 | 0.057 | 0 | 0 |
| CD8-GZMK | GZMA | 1.667125534 | 0.946 | 0.479 | 0 | 0 |
| CD8-GZMK | CST7 | 1.592735482 | 0.941 | 0.469 | 0 | 0 |
| CD8-GZMK | DUSP2 | 1.57388347 | 0.923 | 0.682 | 0 | 0 |
| CD8-GZMK | CMC1 | 1.566853821 | 0.608 | 0.244 | 0 | 0 |
| CD8-GZMK | CRTAM | 1.558377987 | 0.439 | 0.082 | 0 | 0 |
| CD8-KLRD1 | GNLY | 3.055892031 | 0.838 | 0.107 | 0 | 0 |
| CD8-KLRD1 | KLRD1 | 2.249034268 | 0.875 | 0.187 | 0 | 0 |
| CD8-KLRD1 | FGFBP2 | 2.123363443 | 0.761 | 0.084 | 0 | 0 |
| CD8-KLRD1 | ZEB2 | 1.739782969 | 0.851 | 0.239 | 0 | 0 |
| CD8-KLRD1 | GZMB | 1.658839314 | 0.866 | 0.213 | 0 | 0 |
| CD8-KLRD1 | TRGC2 | 1.655383879 | 0.689 | 0.215 | 0 | 0 |
| CD8-KLRD1 | NKG7 | 1.632873494 | 0.996 | 0.396 | 0 | 0 |

| | | | | | | |
|------------------|---------------|-------------|-------|-------|-----------|-----------|
| CD8-KLRD1 | PRF1 | 1.599722794 | 0.836 | 0.251 | 0 | 0 |
| CD8-KLRD1 | GZMH | 1.528296372 | 0.914 | 0.272 | 0 | 0 |
| CD8-KLRD1 | FCGR3A | 1.426458294 | 0.487 | 0.074 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | FGFBP2 | 2.93486646 | 0.804 | 0.058 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | NKG7 | 2.778023667 | 0.998 | 0.376 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | GNLY | 2.737641966 | 0.6 | 0.106 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | GZMH | 2.436962983 | 0.932 | 0.249 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | GZMB | 2.01032333 | 0.791 | 0.198 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | KLRD1 | 1.800063181 | 0.741 | 0.178 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | PRF1 | 1.735444758 | 0.821 | 0.233 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | FCGR3A | 1.618248243 | 0.486 | 0.06 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | CST7 | 1.534361936 | 0.969 | 0.485 | 0 | 0 |
| CD8-KLRD1-CCL4L2 | CCL4L2 | 1.103032243 | 0.481 | 0.178 | 2.20E-284 | 5.56E-280 |
| CD8-ZNF683 | KLRC1 | 1.952568408 | 0.334 | 0.025 | 0 | 0 |
| CD8-ZNF683 | TOB1 | 1.351531081 | 0.673 | 0.397 | 0 | 0 |
| CD8-ZNF683 | ITGA1 | 1.34828884 | 0.413 | 0.07 | 0 | 0 |
| CD8-ZNF683 | XCL1 | 1.340269272 | 0.377 | 0.089 | 0 | 0 |
| CD8-ZNF683 | CD8A | 1.182580432 | 0.634 | 0.232 | 0 | 0 |
| CD8-ZNF683 | YBX3 | 1.024693013 | 0.361 | 0.119 | 0 | 0 |
| CD8-ZNF683 | HSP90AA1 | 1.022213599 | 0.961 | 0.941 | 0 | 0 |
| CD8-ZNF683 | HSPA1A | 1.214270443 | 0.646 | 0.426 | 1.22E-269 | 3.08E-265 |
| CD8-ZNF683 | HSPH1 | 1.038286568 | 0.531 | 0.345 | 3.55E-210 | 9.00E-206 |
| CD8-ZNF683 | ZNF683 | 0.905504074 | 0.271 | 0.05 | 0 | 0 |

Table S7. IHC validation in an independent cohort (n=15).

| IHC validation sample ID | Clinical features of IHC validation samples | | | | | IHC evaluation for NR4A3 | | | | | |
|--------------------------|---|---|-----------------|--------|-----|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------|
| | Histological Type ^a | Morphologic pattern | Tumor size (cm) | Gender | Age | NR4A3-area1/mm ² | NR4A3-area2/mm ² | NR4A3-area3/mm ² | NR4A3-area4/mm ² | NR4A3-area5/mm ² | NR4A3-mean No./mm ² |
| V1 | AIS | lepidic | 1.2 | Female | 36 | 8 | 9 | 1 | 3 | 8 | 5.8 |
| V2 | AIS | lepidic | 1.5 | Female | 75 | 7 | 2 | 3 | 2 | 3 | 3.4 |
| V3 | AIS | lepidic | 1.3 | Female | 71 | 2 | 0 | 4 | 1 | 3 | 2 |
| V4 | AIS | lepidic | 1.3 | Female | 45 | 11 | 4 | 12 | 3 | 0 | 6 |
| V5 | AIS | lepidic | 1.1 | Female | 68 | 8 | 2 | 3 | 4 | 7 | 4.8 |
| V6 | MIA | lepidic | 0.7 | Female | 49 | 9 | 21 | 4 | 10 | 6 | 10 |
| V7 | MIA | lepidic | 1.1 | Female | 51 | 22 | 20 | 29 | 10 | 8 | 17.8 |
| V8 | MIA | lepidic | 1.3 | Female | 48 | 8 | 13 | 16 | 70 | 10 | 23.4 |
| V9 | MIA | lepidic | 1.4 | Female | 54 | 5 | 14 | 5 | 2 | 7 | 6.6 |
| V10 | MIA | lepidic | 1.2 | Female | 60 | 2 | 31 | 4 | 22 | 13 | 14.4 |
| V11 | IA | acinar, complex glandular, micropapillary | 2.3 | Female | 59 | 201 | 13 | 44 | 69 | 39 | 73.2 |
| V12 | IA | acinar, lepidic, complex glandular | 1.8 | Female | 62 | 75 | 62 | 43 | 70 | 61 | 62.2 |
| V13 | IA | cribriform, acinar, micropapillary, complex glandular | 1.5 | Male | 62 | 34 | 39 | 26 | 30 | 35 | 32.8 |
| V14 | IA | complex glandular, acinar, solid | 2.2 | Female | 74 | 9 | 15 | 16 | 5 | 29 | 14.8 |
| V15 | IA | acinar,papillary, lepidic | 2.4 | Male | 66 | 38 | 34 | 19 | 45 | 34 | 34 |

Table S7 continued

| IHC validation sample ID | IHC evaluation for FOXP3 | | | | | | IHC evaluation for FOLR2 | | | | | |
|--------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------|
| | FOXP3-area1/mm ² | FOXP3-area2/mm ² | FOXP3-area3/mm ² | FOXP3-area4/mm ² | FOXP3-area5/mm ² | FOXP3-mean No./mm ² | FOLR2-area1/mm ² | FOLR2-area2/mm ² | FOLR2-area3/mm ² | FOLR2-area4/mm ² | FOLR2-area5/mm ² | FOLR2-mean No./mm ² |
| V1 | 31 | 62 | 73 | 33 | 44 | 48.6 | 743 | 514 | 587 | 477 | 587 | 581.6 |
| V2 | 130 | 59 | 101 | 65 | 63 | 83.6 | 514 | 624 | 1101 | 917 | 404 | 712 |
| V3 | 18 | 46 | 11 | 28 | 45 | 29.6 | 514 | 881 | 587 | 551 | 734 | 653.4 |
| V4 | 38 | 29 | 41 | 41 | 30 | 35.8 | 110 | 294 | 917 | 550 | 440 | 462.2 |
| V5 | 46 | 47 | 20 | 27 | 29 | 33.8 | 771 | 330 | 697 | 1431 | 734 | 792.6 |
| V6 | 64 | 91 | 67 | 113 | 52 | 77.4 | 1468 | 1064 | 1027 | 917 | 1027 | 1100.6 |
| V7 | 45 | 22 | 31 | 85 | 67 | 50 | 844 | 587 | 807 | 587 | 954 | 755.8 |
| V8 | 209 | 162 | 118 | 82 | 80 | 130.2 | 991 | 1248 | 440 | 477 | 1349 | 901 |
| V9 | 73 | 81 | 82 | 136 | 64 | 87.2 | 734 | 1101 | 917 | 514 | 514 | 756 |
| V10 | 81 | 103 | 108 | 123 | 120 | 107 | 954 | 330 | 634 | 1615 | 1248 | 956.2 |
| V11 | 68 | 162 | 421 | 137 | 309 | 219.4 | 2202 | 2092 | 1908 | 1394 | 1615 | 1842.2 |
| V12 | 235 | 348 | 346 | 241 | 346 | 303.2 | 2055 | 1909 | 1615 | 1431 | 2312 | 1864.4 |
| V13 | 201 | 157 | 227 | 237 | 215 | 207.4 | 1505 | 1358 | 2129 | 2276 | 1468 | 1747.2 |
| V14 | 207 | 238 | 122 | 217 | 183 | 193.4 | 1175 | 1725 | 2092 | 1909 | 2533 | 1886.8 |
| V15 | 176 | 141 | 132 | 256 | 282 | 197.4 | 1358 | 1394 | 991 | 1872 | 1578 | 1438.6 |

a: AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma.