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Supplemental Information

$CD103^+CD8^+$ T_{RM} Cells Accumulate in Tumors of Anti-PD-1-Responder Lung Cancer Patients and Are Tumor-Reactive Lymphocytes Enriched with Tc17

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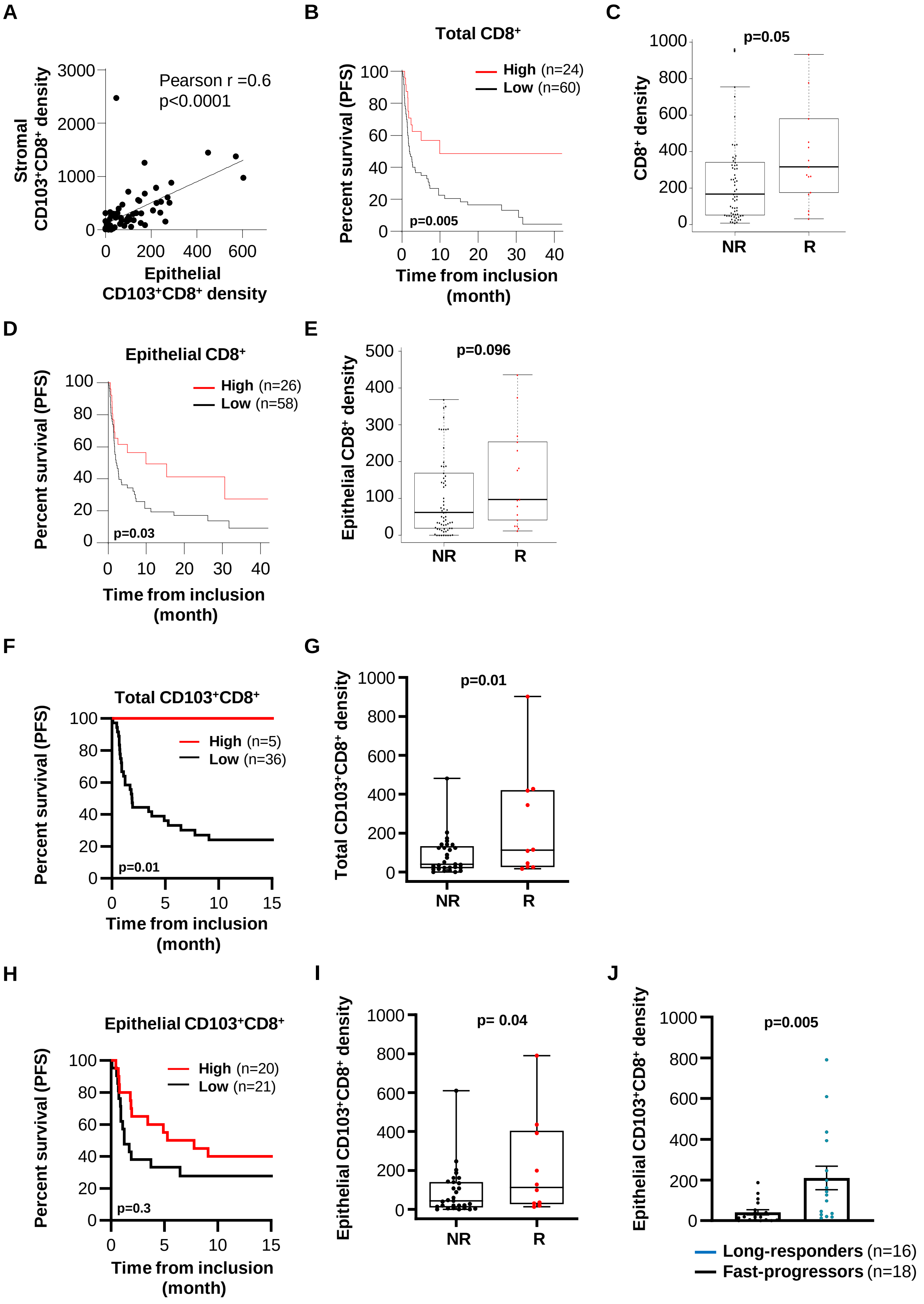
A
Pearson r =0.6
p<0.0001
Stromal CD103⁺CD8⁺ density
3000
2000
1000
0
0
200
400
600
Epithelial CD103⁺CD8⁺ density
B
Total CD8⁺
High (n=24)
Low (n=60)
Percent survival (PFS)
100
80
60
40
20
0
p=0.005
0
10
20
30
40
Time from inclusion (month)
C
p=0.05
CD8⁺ density
1000
800
600
400
200
0
NR
R
D
Epithelial CD8⁺
High (n=26)
Low (n=58)
Percent survival (PFS)
100
80
60
40
20
0
p=0.03
0
10
20
30
40
Time from inclusion (month)
E
p=0.096
Epithelial CD8⁺ density
500
400
300
200
100
0
NR
R
F
Total CD103⁺CD8⁺
High (n=5)
Low (n=36)
Percent survival (PFS)
100
80
60
40
20
0
p=0.01
0
5
10
15
Time from inclusion (month)
G
p=0.01
Total CD103⁺CD8⁺ density
1000
800
600
400
200
0
NR
R
H
Epithelial CD103⁺CD8⁺
High (n=20)
Low (n=21)
Percent survival (PFS)
100
80
60
40
20
0
p=0.3
0
5
10
15
Time from inclusion (month)
I
p= 0.04
Epithelial CD103⁺CD8⁺ density
1000
800
600
400
200
0
NR
R
J
p=0.005
Epithelial CD103⁺CD8⁺ density
1000
800
600
400
200
0
Long-responders (n=16)
Fast-progressors (n=18)

Figure S1. Density of CD8$^+$ T cells in anti-PD-(L)1-treated patients. (Related to Figure 1)
(**A**) Correlation between the density of CD103$^+$CD8$^+$ cells in the stroma and in epithelial tumor regions.
r-value indicates Pearson correlation coefficient. (**B**) Kaplan-Meier curve shows iPFS of PD-1 blockade-treated patients with tumors harboring a high density (CD8^{high}>350/mm^2) or a low density (CD8^{low}<350/mm^2) of CD8$^+$ cells (n=86). **(C)** Density of CD8$^+$ cells in tumors depending on iORR of non-responder (NR; n=65) and responder (R; n=17) patients to PD-1 blockade. (**D**) Kaplan-Meier curve shows iPFS of anti-PD-1-treated patients with epithelial tumor regions harboring a high (>169/mm^2) or low (<169/mm^2) density of CD8$^+$ cells (n=86). **(E)**. Density of CD8$^+$ cells in epithelial tumor regions depending on iORR of NR (n=65) and R (n=17) patients to PD-1 blockade. (**A-E**) Discovery cohort. (**F**) Kaplan-Meier curve shows iPFS of PD-1 blockade-treated patients from a validation cohort with tumors harboring high (>252/mm^2) or low (<252/mm^2) densities of CD103$^+$CD8$^+$ cells (n=41). **(G)** Density of total CD103$^+$CD8$^+$ cells in tumors depending on iORR of NR (n=29) and R (n=10) patients to PD-1 blockade. (**H**) Kaplan-Meier curve shows iPFS of anti-PD-1-treated patients with tumor epithelial regions harboring a high (>48/mm^2) or low (<48/mm^2) density of CD103$^+$CD8$^+$ cells. (**I**) Density of CD103$^+$CD8$^+$ cells in epithelial tumor regions depending on iORR of NR (n=29) and R (n=10) patients to anti-PD-1. (**J**) Density of CD103$^+$CD8$^+$ cells in epithelial tumor regions of anti-PD-1-treated patients undergoing a long-response (PFS>6 months and OS>12 months; n=16) or a fast-progression (defined by an “early death” occurring during the first 12 weeks since the beginning of ICB; n=18).
(F-J) validation cohort. p-value was determined by log-rank (**B**, **D, F** and **H**) or Chi2 test (**C** and **E**) or unpaired t-test (**G, I** and **J**). PFS: progression-free survival.

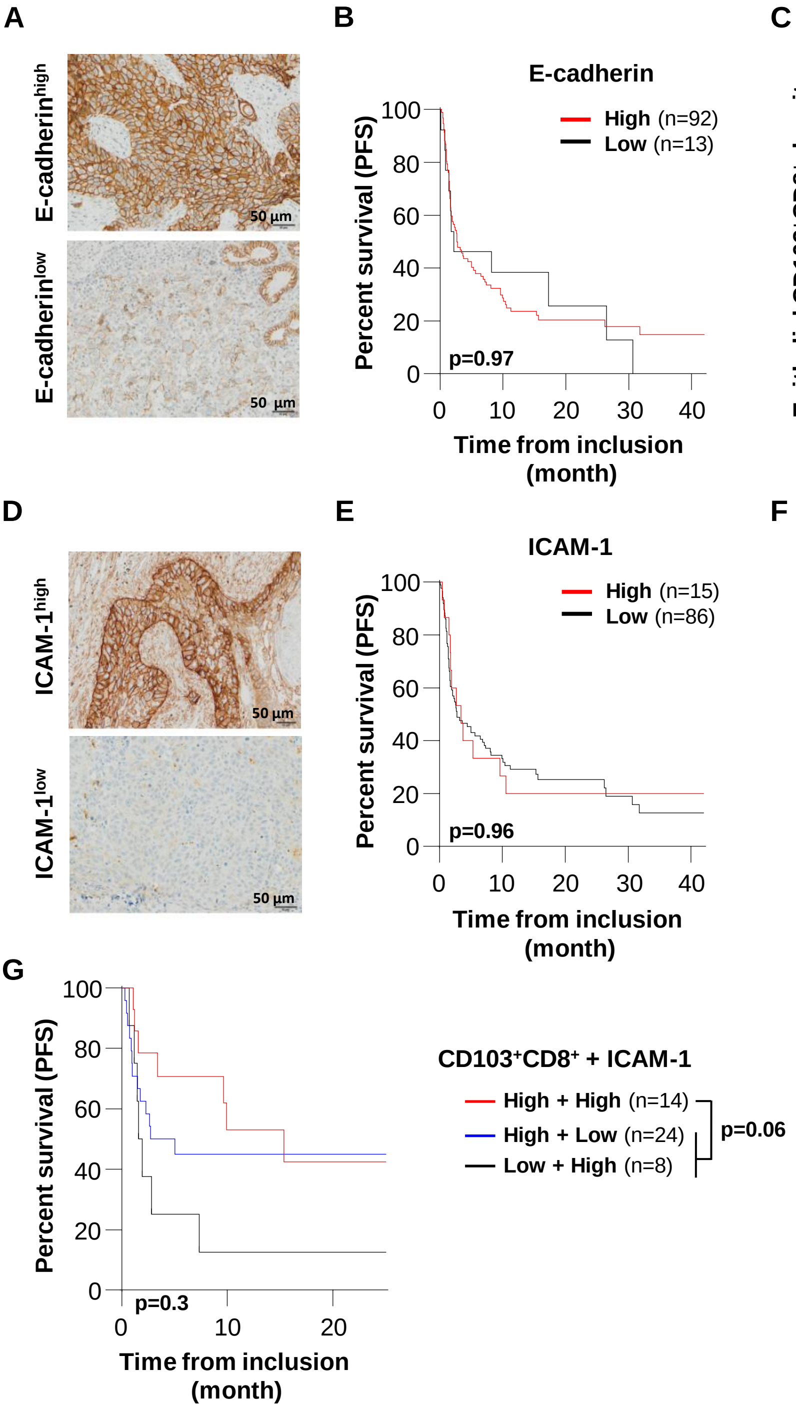

Figure S2. E-cadherin and ICAM-1 expression on tumor cells and patient survival. (Related to Figure 1) **(A)** Representative images of positive and negative expression of E-cadherin by tumor cells. Scale bar 50µm **(B)** Kaplan-Meier curve shows iPFS of PD-1 blockade-treated patients with tumors harboring high and low expression of E-cadherin (n=105). **(C)** Density of CD103$^+$CD8$^+$ cells in epithelial tumor regions depending on E-cadherin expression on tumor cells (low, n=13; high, n=92). **(D)** Representative images of high and low expression of ICAM-1 on tumor cells. Scale bar 50µm **(E)** Kaplan-Meier curve shows iPFS of anti-PD-1-treated patients with tumors harboring high or low expression of ICAM-1 (n=101). **(F)** Density of CD103$^+$CD8$^+$ cells in epithelial tumor regions depending on ICAM-1 expression on tumor cells (low, n=86; high, n=15). **(G)** Kaplan-Meier curve shows iPFS of anti-PD-1-treated patients with epithelial tumor regions harboring high CD103$^+$CD8$^+$ infiltration and high ICAM-1 expression (red) or high CD103$^+$CD8$^+$ infiltration and weak expression of ICAM-1 (blue) or low CD103$^+$CD8$^+$ infiltration and high ICAM-1 expression (n=84). p-value was determined by log-rank test (**B, E** and **G**) or Chi2 test (**C** and **F**). The number of analyzed samples for each patient group is shown in parentheses.

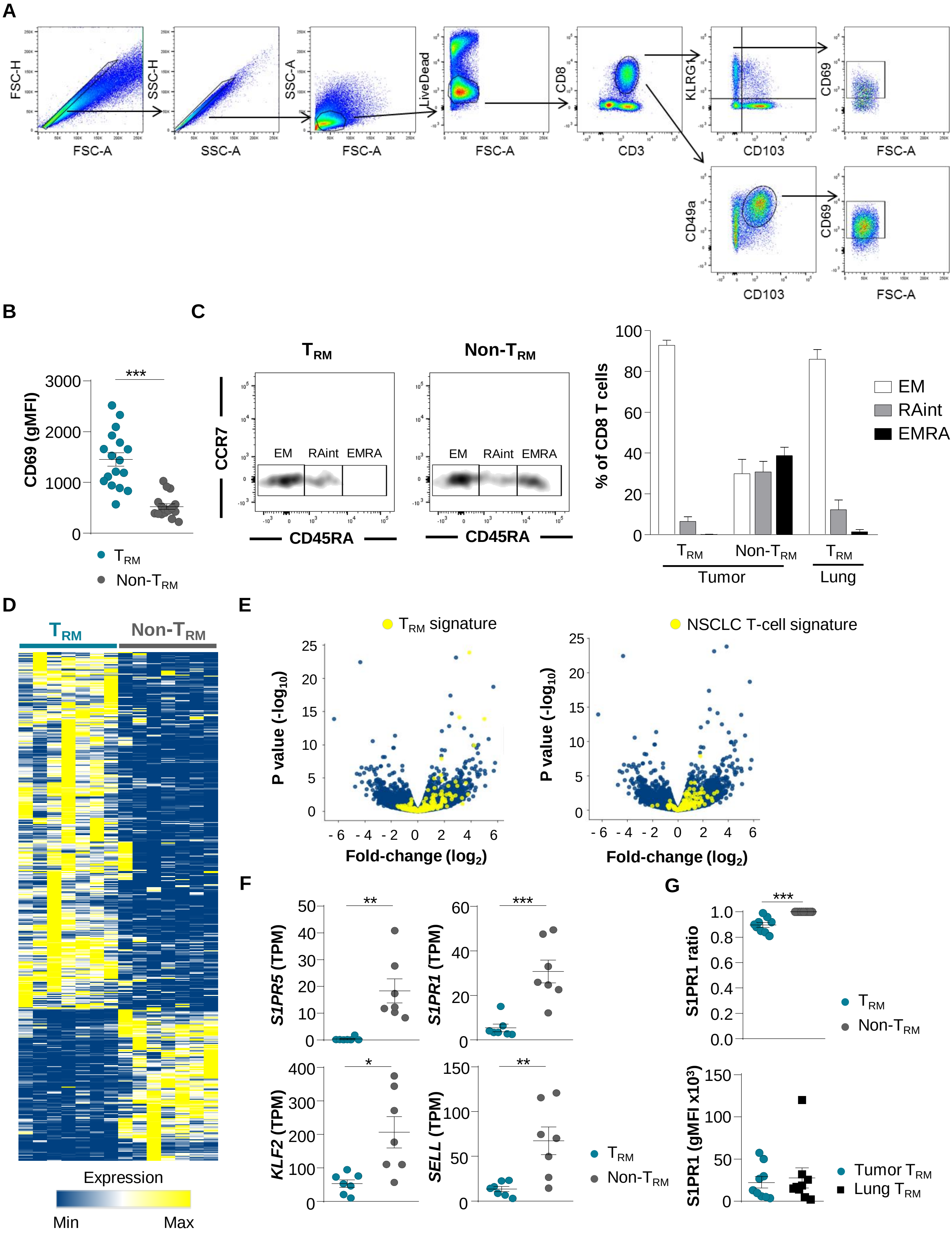
A
FSC-H
FSC-A
SSC-H
SSC-A
SSC-A
FSC-A
LiveDead
FSC-A
CD8
CD3
KLRG1
CD103
CD69
FSC-A
CD49a
CD103
CD69
FSC-A
B
CD69 (gMFI)
3000
2000
1000
0
***
T_{RM}
Non-T_{RM}
C
T_{RM}
Non-T_{RM}
CCR7
EM
RAint
EMRA
CD45RA
CD45RA
% of CD8 T cells
100
80
60
40
20
0
EM
RAint
EMRA
T_{RM}
Non-T_{RM}
T_{RM}
Tumor
Lung
D
T_{RM}
Non-T_{RM}
Expression
Min
Max
E
T_{RM} signature
NSCLC T-cell signature
P value ($-\log_{10}$)
25
20
15
10
5
0
-6 -4 -2 0 2 4 6
Fold-change ($\log_2$)
F
S1PR5 (TPM)
50
40
30
20
10
0
**
S1PR1 (TPM)
60
40
20
0
***
KLF2 (TPM)
400
300
200
100
0
*
SELL (TPM)
150
100
50
0
**
T_{RM}
Non-T_{RM}
G
S1PR1 ratio
1.0
0.8
0.6
0.4
0.2
0.0
***
T_{RM}
Non-T_{RM}
S1PR1 (gMFI x10^3)
150
100
50
0
Tumor T_{RM}
Lung T_{RM}

Figure S3. Expression of T_{RM} markers on $CD8^+$ TIL and transcriptional profiles of $CD103^+$ (T_{RM}) and $KLRG1^+$ (non-T_{RM}) $CD8^+$ T cells. (Related to Figures 2 and 3)

(**A)** Gating strategy for analysis of KLRG1, CD103, CD49a and CD69 by $CD3^+CD8^+$ TIL. (**B)** Expression of CD69 on tumor T_{RM} and non-T_{RM} (gMFI). (**C)** Dot plot showing expression of CCR7 and CD45RA on T_{RM} and non-T_{RM} from one representative NSCLC patient. Right, percentages of effector memory (EM), effector memory CD45RA intermediate (RAint) and effector memory $CD45RA^+$ (EMRA) cells among T_{RM} and non-T_{RM} from tumor and paired T_{RM} from healthy lung (n=6). (**D)** Heat map of transcripts differentially expressed in paired $CD103^+$ and $KLRG1^+$ $CD8^+$ TIL (n=7). Genes of interest (n=500) were selected using fold-change (FC) ≥2 and p-value ≤0.05. Data were bi-clustered by transcript using Pearson's coefficient as the distance metric. The magnitude of relative expression of a particular transcript is shown in color. Each column represents an individual patient. (**E)** Differential gene expression profiles in $CD103^+$ and paired $KLRG1^+$ CD8 T cells. T_{RM} up-gene signature: all transcripts (blue), upregulated gene sets related to T_{RM} (yellow)[13]. Right, differential expression of NSCLC T-cell signature genes in tumor T_{RM} and paired non-T_{RM} (n=7). All transcripts (blue) and upregulated genes related to NSCLC T-cell signature[18] (yellow) are included. (**F)** Expression of *S1PR5, S1PR1*, *KLF2* and *SELL* genes in $CD103^+$ and paired $KLRG1^+$ CD8 T cells (n=7). Transcripts per million (TPM) are shown. (**G)** Ratio (T_{RM}/non-T_{RM}) of geometric mean fluorescence intensity (gMFI) of S1pr1 in paired samples of tumor T_{RM} and non-T_{RM} (n=9). Down, expression of S1pr1 (gMFI) in T_{RM} cells from tumors or paired healthy lung tissues. Histograms represent mean ± SEM. * $P<0.05$, ** $P<0.01$, *** $P<0.001$ (paired t-test).

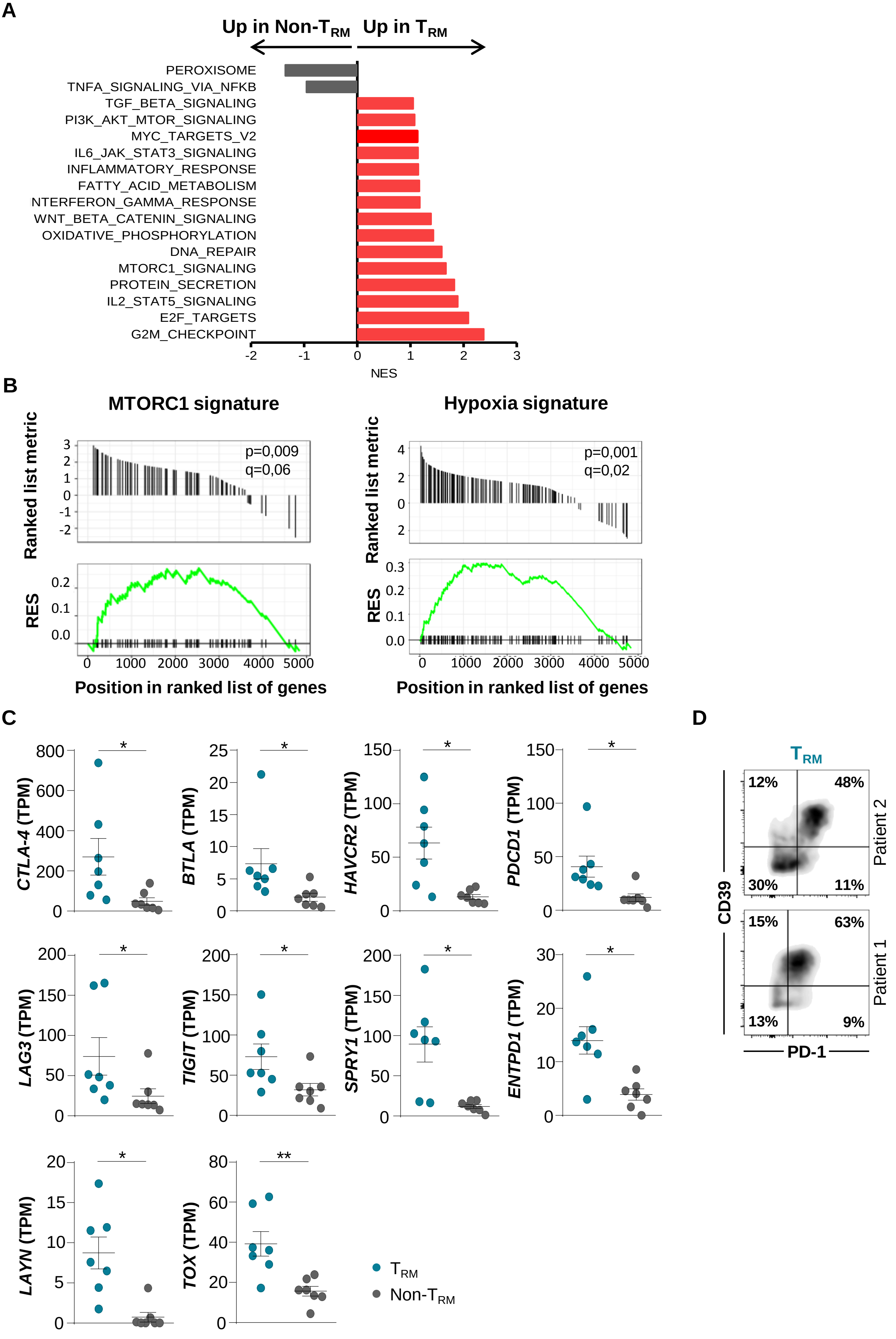
A
Up in Non-T_{RM}
Up in T_{RM}
PEROXISOME
TNFA_SIGNALING_VIA_NFKB
TGF_BETA_SIGNALING
PI3K_AKT_MTOR_SIGNALING
MYC_TARGETS_V2
IL6_JAK_STAT3_SIGNALING
INFLAMMATORY_RESPONSE
FATTY_ACID_METABOLISM
NTERFERON_GAMMA_RESPONSE
WNT_BETA_CATENIN_SIGNALING
OXIDATIVE_PHOSPHORYLATION
DNA_REPAIR
MTORC1_SIGNALING
PROTEIN_SECRETION
IL2_STAT5_SIGNALING
E2F_TARGETS
G2M_CHECKPOINT
-2
-1
0
1
2
3
NES
B
MTORC1 signature
Ranked list metric
3
2
1
0
-1
-2
p=0,009
q=0,06
RES
0.2
0.1
0.0
0
1000
2000
3000
4000
5000
Position in ranked list of genes
Hypoxia signature
Ranked list metric
4
2
0
2
p=0,001
q=0,02
RES
0.3
0.2
0.1
0.0
0
1000
2000
3000
4000
5000
Position in ranked list of genes
C
CTLA-4 (TPM)
800
600
400
200
0
*
BTLA (TPM)
25
20
15
10
5
0
*
HAVCR2 (TPM)
150
100
50
0
*
PDCD1 (TPM)
150
100
50
0
*
LAG3 (TPM)
200
150
100
50
0
*
TIGIT (TPM)
200
150
100
50
0
*
SPRY1 (TPM)
200
150
100
50
0
*
ENTPD1 (TPM)
30
20
10
0
*
LAYN (TPM)
20
15
10
5
0
*
TOX (TPM)
80
60
40
20
0
**
● T_{RM}
● Non-T_{RM}
D
T_{RM}
CD39
12%
48%
30%
11%
Patient 2
15%
63%
13%
9%
Patient 1
PD-1

Figure S4. Transcriptional and phenotypic profiles of CD8$^+$ T$_{RM}$ and non-T$_{RM}$. (Related to Figure 3)
(**A)** Gene set enrichment analysis (GSEA) of paired tumor T$_{RM}$ and non-T$_{RM}$ cells showing hallmark gene sets enriched in T$_{RM}$ subset. Normalized enrichment scores (*NES*) are shown. (**B)** GSEA of mTORC1 (left) signature genes (Gene set M5924) and GSEA of hypoxia (right) signature genes (Gene set M48562) upregulated in the transcriptome of tumor T$_{RM}$ relative to non-T$_{RM}$. Running enrichment score (RES) for gene set, as analysis 'walks down' ranked list of genes; position of the gene set members (black vertical lines) in ranked list of genes and value of ranking metric are shown.
(**C**) Expression of *CTLA4, BTLA, HAVCR2*, *PDCD1, LAG3, TIGIT*, *SPRY1*, *ENTPD1*, *LAYN* and *TOX* genes in CD103$^+$ and KLRG1$^+$ CD8$^+$ TIL. Values are TPM. (**D)** Representative dot plots of co-expression of CD39 and PD-1 on T$_{RM}$ from two NSCLC patients (patients 1 and 2). Horizontal lines are mean ± SEM. * $P<0.05$, ** $P<0.01$ (paired t-test).

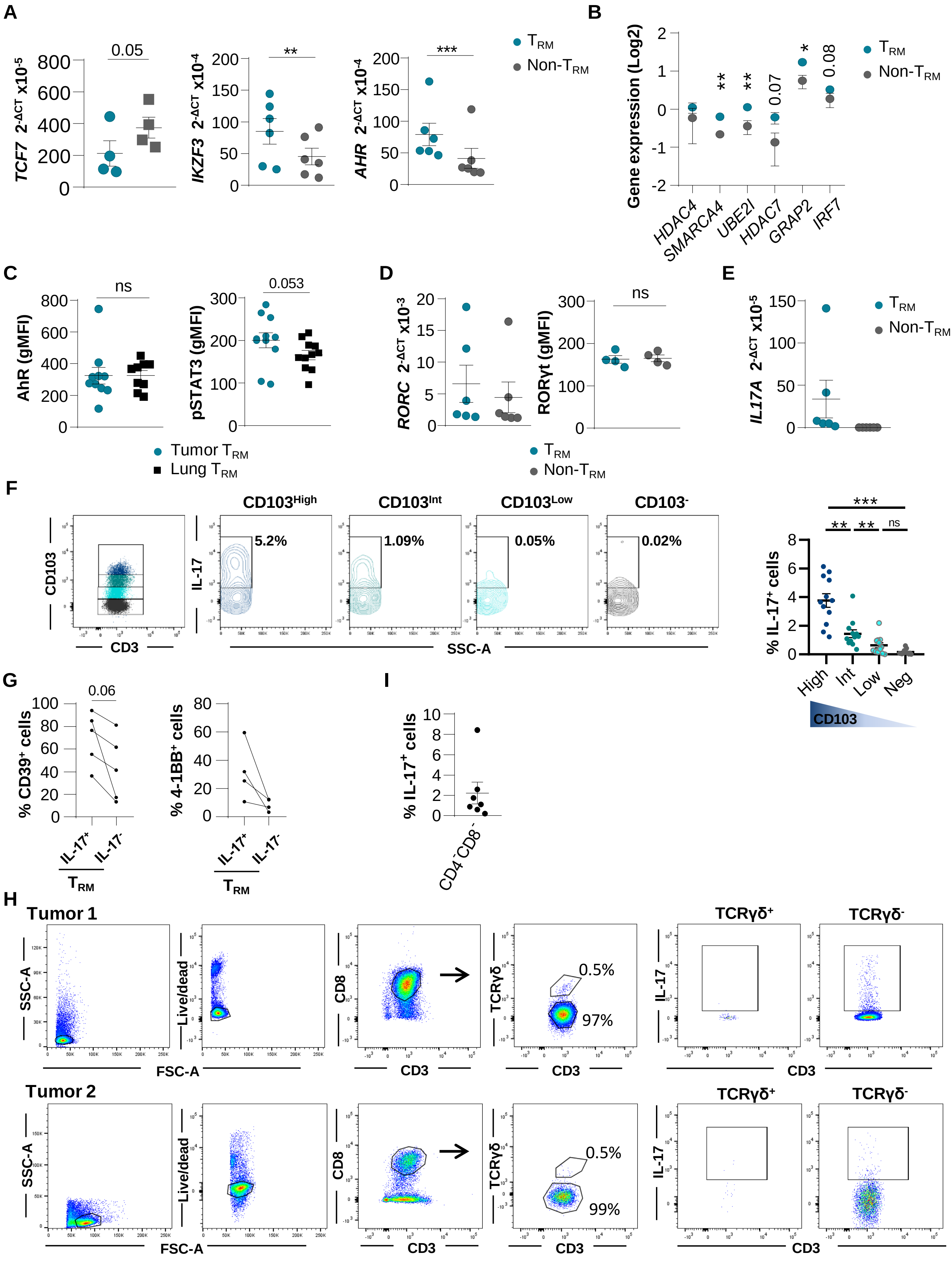
A
TCF7 2-ΔCT x10-5
0.05
IKZF3 2-ΔCT x10-4
**
AHR 2-ΔCT x10-4
***
TRM
Non-TRM
B
Gene expression (Log2)
**
**
0.07
*
0.08
HDAC4
SMARCA4
UBE2I
HDAC7
GRAP2
IRF7
TRM
Non-TRM
C
AhR (gMFI)
ns
pSTAT3 (gMFI)
0.053
Tumor TRM
Lung TRM
D
RORC 2-ΔCT x10-3
RORγt (gMFI)
ns
TRM
Non-TRM
E
IL17A 2-ΔCT x10-5
TRM
Non-TRM
F
CD103High
CD103Int
CD103Low
CD103-
CD103
CD3
IL-17
5.2%
1.09%
0.05%
0.02%
SSC-A
***
**
**
ns
% IL-17+ cells
High
Int
Low
Neg
CD103
G
% CD39+ cells
0.06
% 4-1BB+ cells
IL-17+
IL-17-
TRM
I
% IL-17+ cells
CD4-CD8-
H
Tumor 1
Tumor 2
SSC-A
FSC-A
Live/dead
CD8
CD3
TCRγδ
0.5%
97%
99%
TCRγδ+
TCRγδ-
IL-17

Figure S5. Lung tumor CD103$^+$CD8$^+$ T$_{RM}$ display a Tc17-polarized pattern. (Related to Figures 4 and 5)
(**A)** *TCF7* (left), *IKZF3* (middle) and *AHR* (right) gene expression in T$_{RM}$ and paired non-T$_{RM}$ cells determined by RT-qPCR (n=4-6). Delta-CT values are shown. (**B)** Expression of genes involved in the Aiolos pathway in tumor T$_{RM}$ and paired non-T$_{RM}$ (n=7). Mean ± SEM of gene expression (Log2) are shown. (**C)** Expression (gMFI) of AhR (left) or pSTAT3 (right) in T$_{RM}$ cells from tumor and paired healthy lung tissues (n=10). (**D)** Left, *RORC* gene expression (Delta-CT values) determined by RT-qPCR (n=6) and right, expression (gMFI) of RORγt in tumor T$_{RM}$ and paired non-T$_{RM}$ (n=4). (**E)** *IL17A* gene expression in tumor T$_{RM}$ and paired non-T$_{RM}$ determined by RT-qPCR (n=6). Delta-CT values are shown. **(F)** Dot plots of IL-17 expression in CD103$^+$CD8$^+$ TIL displaying CD103^{high}, CD103^{int} and CD103^{low} phenotype, and CD103$^-$CD8$^+$ TIL from one representative tumor. Right, percentages of IL-17-producing cells among CD103^{high}, CD103^{int}, CD103^{low} and CD103$^-$ TIL (n=12). **(G)** Percentages of CD39$^+$ (n=5) and 4-1BB$^+$ (n=4) cells among IL17-producing (IL-17$^+$) and IL17-non-producing (IL-17$^-$) CD103$^+$CD8$^+$ T cells from NSCLC tumors. (**H)** Dot plots of TCRγδ expression on CD3$^+$CD8$^+$ TIL from two representative tumors. Right, IL-17 production by TCRγδ$^+$ and TCRγδ$^-$ CD8$^+$ T cells stimulated 3h with PMA plus ionomycin. Two representative tumor samples are shown. (**I**). Percentages of IL-17$^+$ cells among CD8$^-$CD4$^-$ T cells from NSCLC tumors after 4h stimulation with PMA/ionomycin (n=7). Each symbol represents one individual patient, horizontal lines are the mean ± SEM. * $P<0.05$ ** $P<0.01$, *** $P<0.001$ (paired t-test,**A, B, C,** and **G or** ANOVA with Bonferroni post-hoc test, **F**).

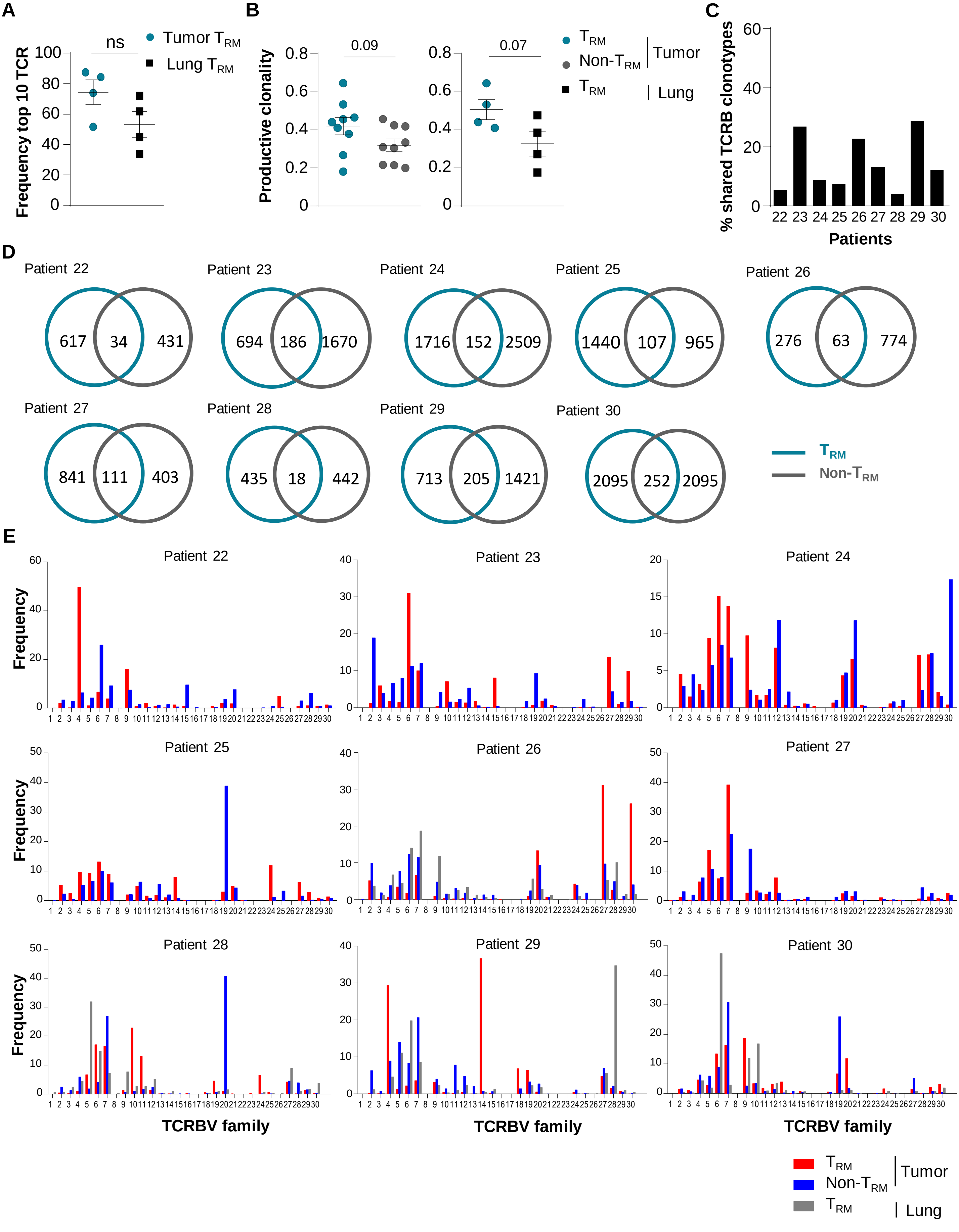
A
ns
Tumor T_{RM}
Lung T_{RM}
Frequency top 10 TCR
0
20
40
60
80
100
B
Productive clonality
0.09
0.07
0
0.2
0.4
0.6
0.8
T_{RM}
Non-T_{RM}
Tumor
T_{RM}
Lung
C
% shared TCRB clonotypes
0
20
40
60
22 23 24 25 26 27 28 29 30
Patients
D
Patient 22
617
34
431
Patient 23
694
186
1670
Patient 24
1716
152
2509
Patient 25
1440
107
965
Patient 26
276
63
774
Patient 27
841
111
403
Patient 28
435
18
442
Patient 29
713
205
1421
Patient 30
2095
252
2095
T_{RM}
Non-T_{RM}
E
Patient 22
Patient 23
Patient 24
Patient 25
Patient 26
Patient 27
Patient 28
Patient 29
Patient 30
Frequency
TCRBV family
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
T_{RM}
Non-T_{RM}
Tumor
T_{RM}
Lung

Figure S6. Tumor CD103$^+$CD8$^+$ T$_{RM}$ displays a more oligoclonal TCR repertoire than non-T$_{RM}$ counterparts. (Related to Figure 7)

(**A)** Frequency of the top ten TCR sequences in T$_{RM}$ from tumors and healthy lung counterparts (n=4). (**B**) Productive clonality of tumor T$_{RM}$ and paired non-T$_{RM}$ (n=9). Right, productive clonality of T$_{RM}$ from tumors and healthy lung tissues (n=4). Each symbol represents one individual patient; horizontal lines are the mean ± SEM. p-values are calculated with paired t-test. **(C)** Percentages of shared TCRβ clonotypes between tumor T$_{RM}$ and non-T$_{RM}$ in each patient (n=9). **(D)** Number of individual and overlap sequence diversities of TCRβ CDR3 repertoires from tumor T$_{RM}$ and paired non-T$_{RM}$ (n=9). (**E)** Histograms represent productive frequencies of the 30 TCRBV gene segments for tumor T$_{RM}$ and paired non-T$_{RM}$ (n=9), and paired healthy lung T$_{RM}$ (n=4).

Table S1: Population description and IHC data of the discovery cohort (Related to Figure 1)

Population description		**Overall population (n=86)**	**Density CD103^{+}CD8^{+} low (n=67)**	**Density CD103^{+}CD8^{+} high (n=19)**	**p-value**
Age	Median, range	63 (30-84)	63 (30-84)	63 (43-73)	0.98
Gender	Female Male	27 (32%) 57 (68%)	20 (31%) 45 (69%)	7 (37%) 12 (63%)	0.62
Smoking status	Current Former Non-smoker	28 (33%) 47 (56%) 9 (11%)	22 (34%) 35 (54%) 8 (12%)	6 (32%) 12 (63%) 1 (5%)	0.75
Histology	Adenocarcinoma NSCLC, other Squamous	51 (61%) 6 (7%) 27 (32%)	41 (63%) 5(8%) 19 (29%)	10 (53%) 1 (5%) 8 (42%)	0.65
Stage at diagnosis	I-IIIA IIIB IVA- IVB NA	29 (35%) 14 (17%) 40 (48%) 0	21 (32%) 11 (17%) 33 (51%) 0	8 (44%) 3 (17%) 7 (39%) 0	0.34
Molecular status	*EGFR* mutation *ALK* fusion *KRAS mutation* *BRAF* mutation	5 (6%) 1 (1%) 19 (23%) 2 (2%)	4 (6%) 1 (2%) 14 (22%) 2 (3%)	1 (5%) 0 5 (26%) 0	0.81 0.42 0.58 0.87
Previous therapies	Platinum-based chemo Second-line chemo Other therapies No prior therapy Chemo-radiation	33 (41%) 14 (17%) 17 (21%) 6 (7%) 11 (14%)	25 (40%) 14 (11%) 17 (27%) 5 (8%) 6 (10%)	8 (44%) 4 (22%) 4 (22%) 1 (6%) 5 (28%)	0.037
Line of immunotherapy	≤ 2 > 2	45 (54%) 39 (46%)	32 (49%) 33 (51%)	13 (68%) 6 (32%)	0.14
Number of metastatic sites	≤ 2 > 2 NA	46 (55%) 38 (45%) 2	35 (54%) 30 (46%) 2	11 (58%) 8 (42%) 0	0.75
Type of immunotherapy	PD-1 inhibitor PD-L1 inhibitor	69 (82%) 15 (18%)	54 (83%) 11 (17%)	15 (79%) 4 (21%)	0.74
Performance status	0-1 ≥2 NA	68 (82%) 15 (18%) 3	50 (78%) 14 (22%) 3	18 (95%) 1 (5%) 0	0.17
Response rate	Complete response Partial response Stable disease Progressive disease NA	2 (3%) 15 (18%) 28 (34%) 37 (45%) 4	1 (2%) 8 (13%) 22 (34%) 33 (51%) 3	1 (6%) 7 (39%) 6 (33%) 4 (22%) 1	**0.024**
Objective response rate	CR + PR NA	17 (21%) 4	9 (14%) 3	8 (44%) 1	**0.005**
ICAM-1 expression	Median, range NA	80 (0-300) 3	70 (0-300) 3	140 (0-300) 0	0.23
ICAM-1 expression by category	Low High NA	61 (73%) 22 (27%) 0	49 (77%) 15 (23%) 0	12 (63%) 7 (37%) 0	0.25
E-Cadherin expression by category	0-1 2-3 NA	10 (12%) 74 (88%) 2	7 (11%) 58 (89%) 2	3 (16%) 16 (84%) 0	0.73
PD-L1 expression	Median, range NA	28 (0-100) 46	10 (0-95) 36	80 (10-100) 10	0.023
Epithelial CD8^{+} density	Low High	59 (69%) 27 (31%)	57 (85%) 10 (15%)	2 (11%) 17 (89%)	<0.001
Density stromal CD8^{+}	Low High NA	60 (71%) 24 (29%) 2	60 (90%) 7 (10%) 0	0 17 (100%) 2	<0.001
Total CD8^{+} density	Low High	62 (72%) 24 (28%)	61 (91%) 6 (9%)	1 (5%) 18 (95%)	<0.001
Epithelial CD103^{+}CD8^{+} density	Low High	45 (52%) 41 (48%)	44 (66%) 23 (34%)	1 (5%) 18 (95%)	<0.001
Stromal CD103^{+}CD8^{+} density	Low High	61 (71%) 25 (29%)	60 (90%) 7 (10%)	1 (5%) 18 (95%)	<0.001
Total CD103^{+}CD8^{+} density	Low High	67 (78%) 19 (22%)	67 (100%) 0	0 19 (100%)	<0.001
Epithelial CD103^{-}CD8^{+} density	Low High	41 (48%) 45 (52%)	36 (54%) 31 (46%)	5 (26%) 14 (74%)	0.01
Stromal CD103^{-}CD8^{+} density	Low High	50 (58%) 36 (42%)	48 (72%) 19 (28%)	2 (11%) 17 (89%)	0.001
Total CD103^{-}CD8^{+} density	Low High	70 (81%) 16 (19%)	62 (93%) 5 (7%)	8 (42%) 11 (58%)	0.001
Total CD103^{+}CD8^{+} density (number)		102.59 (0;1320.75)	65.96 (0;246.8)	466.21 (252.42;1320.75)	<0.001
Epithelial CD103^{+}CD8^{+} density (number)		44.56 (0;603.82)	21.56 (0;262.13)	240.23 (48.14;603.82)	<0.001
Stromal CD103^{+}CD8^{+} density (number)		152.75 (0;2477.96)	93.81 (0;478.15)	678.6 (283.59;2477.96)	<0.001
Percentage of CD103+ among CD8+ in epithelial regions		76.19 (0;100)	67.48 (0;100)	83.33 (29.87;100)	0.001
Percentage of CD103+ among CD8+ in stromal regions		47.62 (0;94.44)	42.6 (0;94.44)	58.61 (26.47;87.69)	0.046

NA: not available; CR: complete response; PR: partial response.

Table S2: Immunotherapy progression-free survival (iPFS) median (Discovery cohort) (Related to Figure 1)

Variables			Total patient number	Percentage (%)	Events number	Median (95%CI) (month)	Log-rank p-value
			84	**100**	**62**	**2.69 (1.74-7.13)**	
CD8$^+$ cells	**Total**	Low	60	71.4	51	2.05 (1.51-5.03)	0.005
		High	24	28.6	11	9.92 (2.73-NR)	
	Stromal	Low	58	69	50	2.05 (1.51-5.03)	0.001
		High	24	28.6	11	30.62 (3.42-NR)	
	Epithelial	Low	58	69	48	2.22 (1.64-4.99)	0.03
		High	26	31	14	9.92 (1.74-NR)	
CD103$^+$CD8$^+$ cells	**Total**	Low	65	77.4	54	2.3 (1.68-5.03)	0.008
		High	19	22.6	8	30.6 (2.73-NR)	
	Stromal	Low	59	70.2	50	2.14 (1.51 -5.03)	0.006
		High	25	29.8	12	30.62 (2.30-NR)	
	Epithelial	Low	44	52.4	37	1.76 (1.48-4.99)	0.01
		High	40	47.6	25	9.63 (2.56-NR)	
CD103$^-$CD8$^+$ cells	**Total**	Low	68	81	55	2.5 (1.68-6.54)	0.02
		High	16	19	7	NR (1.58-NR)	
	Stromal	Low	49	58.3	43	2.14 (1.64-5.03)	0.001
		High	35	41.7	19	9.92 (1.81-NR)	
	Epithelial	Low	41	48.8	27	6.90 (2.76-26.22)	0.03
		High	43	51.2	35	1.68 (1.31-3.42)	
CD103/CD8 score	**Good**		12	14.3	5	26.22 (15.34-NR)	<0.0001
	Intermediate		57	67.9	42	2.76 (1.70-7.33)	
	Poor		15	17.9	15	1.38 (0.72-1.97)	
ICAM-1	**Low**		86	85.1	66	2.79 (1.97-7.33)	0.96
	High		15	14.9	12	3.42 (1.81-NR)	
E-cadherin	**Low**		13	12.4	11	2.23 (1.41-NR)	0.97
	High		92	87.6	73	2.74 (1.94-5.68)	
Epithelial CD103$^+$CD8$^+$ cells and ICAM-1	**High/High**		14	16.6	8	15.34	0.3
	High/Low		24	28.5	15	3.87	
	Low/High		8	9.5	7	1.75	

NR: not reached, CI: confidence interval

Table S3: Multivariate analysis for progression-free survival (Discovery cohort) (Related to Figure 1)

Variables	**HR (95% CI)**	**p-value**
Age ≥65	1.79 (0.73-4.37)	0.20
Histology squamous	1.5 (0.83-2.73)	0.18
Smoker	0.35 (0.14-0.84)	0.02
Performance status ≥2	1.12 (0.57-2.21)	0.73
Number of metastatic sites	1.83 (1.02-3.29)	0.04
High $CD103^+CD8^+$ density	**0.39 (0.18-0.85)**	0.02

HR: hazard ratio; CI: confidence interval.

Table S4: Population description and immunohistochemistry data of the validation cohort (Related to Figure 1)

Population description		**Overall population (n=41)**
Age	Median, range	64 (42-85)
Gender	Female	20 (49%)
	Male	21 (51%)
Smoking status	Current	18 (44%)
	Former	19 (46%)
	Non-smoker	4 (10%)
Histology	Adenocarcinoma	34 (83%)
	NSCLC, others	1 (2.5%)
	Squamous	6 (14.5%)
Stage at diagnosis	IIA	2 (5%)
	IIB	1 (2.5%)
	IIIA	3 (7%)
	IIIB	2 (5%)
	IVA	7 (17%)
	IVB	26 (63.5%)
Molecular status	*EGFR* mutation	2 (5%)
	ALK fusion	2 (5%)
	KRAS mutation	16 (42%)
	BRAF mutation	2 (5%)
Line of immunotherapy	≤ 2	33 (80%)
	> 2	8 (20%)
Number of metastatic sites	≤ 2	12 (29%)
	> 2	29 (71%)
Type of immunotherapy	PD-1 inhibitor	41 (100%)
Performance status	0-1	26 (63%)
	≥ 2	15 (37%)
Response rate	Complete response	2 (5%)
	Partial response	8 (20%)
	Stable disease	10 (26%)
	Progressive disease	19 (49%)
	NA	2
Objective response rate	CR + PR	10 (26%)
	NA	2
PD-L1 expression	Median, range	10 (0-100)
Epithelial $CD8^+$ density	Low	21 (51%)
	High	20 (49%)
Stromal $CD8^+$ density	Low	26 (63%)
	High	15 (37%)
Total $CD8^+$ density	Low	24 (59%)
	High	17 (41%)
Epithelial $CD103^+CD8^+$ density	Low	21 (51%)
	High	20 (49%)
Stromal $CD103^+CD8^+$ density	Low	34 (83%)
	High	7 (17%)
Total $CD103^+CD8^+$ density	Low	36 (88%)
	High	5 (12%)
Epithelial $CD103^-CD8^+$ density	Low	7 (17%)
	High	34 (83%)
Stromal $CD103^-CD8^+$ density	Low	20 (49%)
	High	21 (51%)
Total $CD103^-CD8^+$ density	Low	23 (56%)
	High	18 (44%)
Total $CD103^+CD8^+$ density (number)	Median (range)	120.4 (0;902.4)
Epithelial $CD103^+CD8^+$ density (number)	Median (range)	118 (0;789.85)
Stromal $CD103^+CD8^+$ density (number)	Median (range)	150.95 (0;1147.28)

CR: complete response; PR: partial response; NA: not available

Table S5: Patient characteristics and density of cells pre- and post-treatment (Related to Figure 1)

Group of patients	Patient N°	Number of ICB cycles	RECIST/ Radiologic response (tumor volume reduction)	Responder/ Non-responder	Stage diagnosis	OS (months)	Site of pre-biopsy	Site of post-biopsy	Days from last ICB to post-biopsy	Density of intra-epithelial CD103$^+$CD8$^+$ cells		Density of total CD103$^+$CD8$^+$ cells		Density of total CD8$^+$ cells	
										Pre-ICB	Post-ICB	Pre-ICB	Post-ICB	Pre-ICB	Post-ICB
1	**1**	7	SD	R	IIIA	11.5	Lung	Lung	24	**161**	**682**	**204**	**931**	**417**	**1779**
	2	NA	SD	R	IVB	13.9	Lung	Lung	135	**358**	**511**	**129**	**518**	**493**	**1081**
	3	NA	SD	R	IVB	14.3	Kidney meta	Kidney meta	174	162	134	173	159	729	666
	4	1	PD	NR	IVA	2	Lung	Lung	14	19	0	25	0	58	30
	5	NA	PD	NR	IIIA	18.4	Lung	Lung	34	18	6	44	21	221	600
2	**6**	1	-17%	R	NA	25.3	Lung	Lung	28	**172**	**555**	**159**	**534**	**322**	**895**
	7	1	-17%	R	IIIA	31.5	Lung	Lung	27	**25**	**155**	**33**	**155**	**135**	**342**
	8	1	-5%	NR	IB	37.1	Lung	Lung	21	230	133	258	322	1691	1775
	9	1	0%	NR	IIA	31.2	Lung	Lung	25	267	95	208	225	781	538

ICB: immune checkpoint blockade, OS : overall survival ; SD: stable disease; PD: progressive disease; R: responder; NR: non-responder; Meta: metastasis; NA: not available

Table S6: Population description of ICAM and E-cadherin cohort (Discovery cohort) (Related to Figure 1)

Population description		**Overall population (N=111)**
Age	Median, range	63 (30-92)
Gender	Female	35 (32%)
	Male	76 (68%)
Smoking status	Current	36 (32%)
	Former	64 (58%)
	Non-smoker	11 (10%)
Histology	Adenocarcinoma	66 (60%)
	NSCLC, other	16 (14%)
	Squamous	29 (26%)
Stage at diagnosis	I-IIIA	4 (4%)
	IIIB	11 (10%)
	IVA- IVB	95 (86%)
	Missing	1
Molecular status	*EGFR* mutation	5 (6%)
	ALK fusion	2 (2%)
	KRAS mutation	24 (30%)
	BRAF mutation	3 (4%)
Previous therapies	Platinum-based chemo	55 (50%)
	Second-line chemo	14 (13%)
	Other therapies	22 (20%)
	No prior therapy	6 (5%)
	Chemo-radiation	13 (12%)
Line of immunotherapy	≤ 2	64 (58%)
	> 2	47 (42%)
Number of metastatic sites	≤ 2	54 (49%)
	> 2	57 (51%)
	Missing	0
Type of immunotherapy	PD-1 inhibitor	96 (86%)
	PD-L1 inhibitor	15 (14%)
Performance status	0-1	90 (82%)
	≥2	20 (18%)
	Missing	1
Response rate	Complete response	2 (2%)
	Partial response	23 (22%)
	Stable disease	38 (36%)
	Progressive disease	44 (40%)
	Missing	4
Objective response rate	CR + PR	63 (58%)
	Missing	3
ICAM-1 expression	Median range	80 (0-300)
	Missing	10
ICAM-1 expression by category	Low	86 (85%)
	High	15 (15%)
	Missing	10
E-Cadherin expression by category	0-1	13 (12%)
	2-3	92 (88%)
	Missing	6

CR: complete response; PR: partial response.

Table S7: Frequencies of T_{RM} and non-T_{RM} cells in lung tumors and autologous adjacent normal lung tissues (Related to Figure 2)

	Lung tumor				**Adjacent normal lung**			
Patient	**CD103$^+$CD49a$^+$CD49a$^+$**		**KLRG1$^+$**		**CD103$^+$CD49a$^+$CD49a$^+$**		**KLRG1$^+$**	
	%	**Number/mg**	**%**	**Number/mg**	**%**	**Number/mg**	**%**	**Number/mg**
1	55	320	28	164	56	44	28	22
2	52	2340	31	1271	31	44	38	47
3	44	614	37	515	8	76	85	845
4	27	354	53	706	25	369	44	656
5	36	57	41	67	7	48	57	394
6	37	374	40	401	28	12	46	20
7	62	781	20	254	13	315	77	1881
8	30	3013	37	3767	27	64	61	144
9	25	143	50	287	5	6	79	111
10	81	540	10	70	41	49	30	36
11	35	314	32	310	43	126	31	90
12	87	3823	5	204	52	44	24	22
13	51	547	23	249	2	17	82	623
14	80	1727	4	93	59	640	6	60
15	48	368	31	238	16	28	51	89
16	59	797	15	204	28	85	21	63
17	40	133	38	126	2	1	91	37
18	67	499	18	135	49	81	13	22

The total number of T_{RM} per milligram of tissue was included

Table S8: Differential gene expression profiles of CD103$^+$CD8$^+$ TIL and autologous KLRG1$^+$CD8$^+$ TIL (Related to Figures 3, 4 and 5)

Gene	Fold change	p-value
Activation/Th17		
IL17A	23.62	$1.08\ 10^{-10}$
TNFSF4	20.32	$1.69\ 10^{-7}$
TMIGD2	9.32	$8.97\ 10^{-4}$
IL12RB2	7.87	$5.28\ 10^{-4}$
CKLF	7.74	$3.74\ 10^{-3}$
CD2	7.32	$3.67\ 10^{-3}$
CD82	7.26	$6.52\ 10^{-3}$
CPNE1	7.25	$5.64\ 10^{-3}$
ICOS	6.72	$4.59\ 10^{-3}$
CD6	6.61	$4.29\ 10^{-2}$
CD226	6.12	$1.33\ 10^{-3}$
IL26	5.69	$1.41\ 10^{-4}$
CD63	5.53	$8.10\ 10^{-3}$
CD109	5.21	$2.61\ 10^{-2}$
IL32	5.11	$2.81\ 10^{-2}$
CSF2	4.36	$3.76\ 10^{-3}$
IRF5	4.31	$1.02\ 10^{-2}$
CD101	4.08	$9.70\ 10^{-6}$
CD70	3.21	$1.14\ 10^{-2}$
CD7	2.99	$3.76\ 10^{-2}$
RAB27A	2.99	$3.80\ 10^{-2}$
HAVCR1	2.90	$1.26\ 10^{-2}$
IL17RA	2.75	$2.88\ 10^{-2}$
GZMB	2.54	$5.54\ 10^{-4}$
IL18RAP	2.20	$7.86\ 10^{-3}$
IFNG	1.99	$4.44\ 10^{-2}$
GZMA	1.68	$2.89\ 10^{-2}$
CD244	1.52	$1.18\ 10^{-2}$
IL2RG	1.45	$4.89\ 10^{-2}$
TNFRSF25	1.39	$2.34\ 10^{-2}$
TGFBR3	-1.64	$1.81\ 10^{-2}$
IL15	-1.96	$3.90\ 10^{-2}$
CD28	-2.13	$3.97\ 10^{-3}$
GZMK	-3.44	$7.07\ 10^{-3}$
IL12A	-3.47	$7.91\ 10^{-3}$
Inhibition/exhaustion		
ENTPD1	56.05	$5.21\ 10^{-6}$
LAYN	21.84	$1.22\ 10^{-6}$
SPRY1	9.09	$2.28\ 10^{-4}$
CD200	7.74	$2.71\ 10^{-3}$
CTLA4	5.14	$1.48\ 10^{-2}$
BTLA	4.70	$1.98\ 10^{-3}$
HAVCR2	2.78	$3.66\ 10^{-3}$
PDCD1	2.63	$1.79\ 10^{-2}$
LAG3	2.20	$8.93\ 10^{-3}$
TIGIT	1.86	$5.22\ 10^{-3}$
CBLB	1.43	$4.85\ 10^{-2}$
TOX	1.96	$3.15\ 10^{-4}$
TOX2	12.96	$3.71\ 10^{-4}$
SPRY2	-2.91	$3.97\ 10^{-2}$
Transcription factors		
ILF3	17.93	$6.01\ 10^{-3}$
ATP8B4	17.50	$1.53\ 10^{-8}$
GFI1	9.24	$5.20\ 10^{-4}$
IRF3	7.75	$9.65\ 10^{-4}$
ZEB1	7.38	$8.53\ 10^{-4}$
ZNF683	6.55	$4.10\ 10^{-4}$
ZNF384	5.28	$3.91\ 10^{-2}$
FOXJ3	5.22	$1.72\ 10^{-2}$
IKZF4	5.05	$1.10\ 10^{-2}$
FOXP3	4.80	$9.39\ 10^{-4}$
BACH1	4.43	$1.62\ 10^{-2}$
E2F7	4.00	$5.09\ 10^{-2}$
ATF2	3.90	$2.29\ 10^{-2}$
ZBED2	3.89	$5.34\ 10^{-7}$
PRDM1	3.87	$7.71\ 10^{-3}$
TSC2	3.77	$2.20\ 10^{-2}$
PRDM5	3.53	$1.08\ 10^{-2}$
IKBKB	3.40	$2.84\ 10^{-2}$
BATF3	3.03	$2.86\ 10^{-2}$
PRDM2	2.72	$4.35\ 10^{-2}$
RUNX2	2.50	$3.70\ 10^{-2}$
RUNX3	2.24	$1.95\ 10^{-3}$
E2F2	2.13	$2.45\ 10^{-2}$
IKZF3	2.01	$1.54\ 10^{-3}$
BATF	1.52	$4.20\ 10^{-2}$
E2F3	-1.60	$2.35\ 10^{-2}$
IKZF2	-1.63	$2.06\ 10^{-2}$
BCL6	-1.93	$2.13\ 10^{-2}$
EOMES	-2.38	$1.34\ 10^{-3}$
KLF2	-2.58	$8.57\ 10^{-4}$
KLF3	-3.60	$1.26\ 10^{-3}$
TCF7	-4.03	$1.39\ 10^{-2}$
Adhesion/migration		
ITGAE	31.99	$1.37\ 10^{-14}$
CXCL13	18.40	$1.28\ 10^{-10}$
ITGA7	8.16	$2.30\ 10^{-3}$
KLRC1	8.10	$1.81\ 10^{-4}$
CCR5	6.41	$1.90\ 10^{-2}$
ITGA1	5.96	$6.27\ 10^{-3}$
VCAM1	5.27	$1.59\ 10^{-2}$
CD9	5.25	$1.32\ 10^{-2}$
ILK	4.63	$5.04\ 10^{-2}$
ITGB7	4.17	$3.69\ 10^{-2}$
CCR6	3.86	$4.03\ 10^{-2}$
CXCR6	3.54	$3.28\ 10^{-3}$
ITGAD	3.47	$1.69\ 10^{-3}$
CD248	2.64	$1.61\ 10^{-2}$
KLRC2	2.54	$4.00\ 10^{-2}$
CD44	-1.61	$2.73\ 10^{-2}$
CXCR5	-1.89	$1.31\ 10^{-2}$
CCR4	-2.29	$1.93\ 10^{-2}$
CCR7	-2.68	$1.34\ 10^{-3}$
ITGA5	-3.62	$1.36\ 10^{-2}$
ITGAM	-3.67	$4.45\ 10^{-2}$
SELL	-4.88	$1.12\ 10^{-2}$
S1PR1	-5.12	$3.80\ 10^{-2}$
KLRF1	-5.23	$1.58\ 10^{-3}$
CXCR2	-8.84	$2.02\ 10^{-3}$
CXCR1	-8.99	$3.23\ 10^{-6}$
CX3CR1	-10.57	$2.67\ 10^{-11}$
KLRG1	-14.79	$3.38\ 10^{-7}$
ICAM2	-19.03	$2.51\ 10^{-7}$
S1PR5	-20.95	$3.07\ 10^{-6}$
T$_{RM}$ signature		
GSG2	8.75	$4.73\ 10^{-20}$
GPR34	7.45	$8.42\ 10^{-3}$
ITGAE	5.90	$1.51\ 10^{-38}$
CXCR6	3.29	$3.89\ 10^{-8}$
ACP5	2.64	$5.14\ 10^{-3}$
LDLRAD4	2.33	$1.28\ 10^{-3}$
AMICA1	2.21	$9.58\ 10^{-3}$
ATP10D	2.15	$2.28\ 10^{-3}$
IFNG	2.00	$3.24\ 10^{-3}$
ABTB2	1.83	$1.24\ 10^{-2}$
QPCT	1.80	$6.25\ 10^{-2}$
XCL1	1.67	$2.53\ 10^{-2}$
CD244	1.59	$4.16\ 10^{-3}$
KCNN4	1.57	$2.78\ 10^{-2}$
RACGAP1	1.53	$8.43\ 10^{-2}$
MAPKAPK3	1.52	$6.95\ 10^{-4}$
P2RY10	1.45	$6.20\ 10^{-2}$
CCL5	1.42	$5.59\ 10^{-2}$
PCED1B	1.41	$1.04\ 10^{-2}$
VOPP1	1.31	$2.05\ 10^{-2}$
ABI3	1.30	$3.85\ 10^{-2}$
DOCK2	1.27	$5.22\ 10^{-2}$
CDC25B	-1.22	$6.84\ 10^{-2}$
LITAF	-1.25	$3.67\ 10^{-2}$
NEDD4	-1.36	$4.25\ 10^{-2}$
BCL9L	-1.38	$2.85\ 10^{-2}$
STK38	-1.41	$1.52\ 10^{-3}$
FAM65B	-1.48	$6.78\ 10^{-2}$
SAMHD1	-1.50	$1.78\ 10^{-3}$
FRMD4B	-1.84	$2.72\ 10^{-2}$
LEF1	-1.87	$8.56\ 10^{-3}$
PDE2A	-1.90	$9.30\ 10^{-2}$
ICAM2	-1.94	$2.59\ 10^{-4}$
RASA3	-2.34	$1.88\ 10^{-7}$
EOMES	-2.35	$2.18\ 10^{-3}$
KLF2	-2.46	$1.58\ 10^{-4}$
TCF7	-2.47	$7.30\ 10^{-4}$
FAM49A	-2.95	$9.02\ 10^{-3}$
KLF3	-3.57	$3.29\ 10^{-6}$
S1PR1	-3.62	$5.05\ 10^{-10}$
S1PR5	-19.54	$3.11\ 10^{-10}$
Lung cancer T-cell signature		
CTLA4	3.45	$3.63\ 10^{-4}$
CXCR6	3.29	$3.89\ 10^{-8}$
PDCD1	2.43	$5.61\ 10^{-6}$
SIRPG	2.43	$8.78\ 10^{-4}$
PTPN22	1.98	$2.52\ 10^{-9}$
CD2	1.85	$7.75\ 10^{-4}$
SIT1	1.70	$2.32\ 10^{-3}$
TIGIT	1.71	$1.41\ 10^{-2}$
UBASH3A	1.60	$4.88\ 10^{-3}$
GPR174	1.59	$6.17\ 10^{-3}$
CD96	1.56	$1.82\ 10^{-2}$
SLAMF1	1.51	$6.32\ 10^{-2}$
SLA2	1.49	$8.64\ 10^{-3}$
CCR5	1.45	$5.51\ 10^{-2}$
P2RY10	1.45	$6.20\ 10^{-2}$
CCL5	1.42	$5.59\ 10^{-2}$
LCK	1.41	$2.99\ 10^{-2}$
SASH3	1.37	$7.11\ 10^{-2}$
TBC1D10C	1.37	$9.11\ 10^{-2}$
IL2RG	1.33	$2.67\ 10^{-2}$
IL12RB1	1.25	$7.00\ 10^{-2}$
CST7	-1.54	$2.73\ 10^{-2}$

Table S9: Hallmark gene sets enriched in T_{RM} cells (Related to Figure 4)

Hallmark gene set	**NES**	**p-value**	**Core enrichment**
TNFA_SIGNALING_VIA_NFKB	-0,95	0,54	ZBTB10,SQSTM1,CLCF1,DENND5A,KLF2,CFLAR,IFNGR2,ICAM1,ACKR3,PLEK,NINJ1,SOD2,SLC2A6
PEROXISOME	-1,35	0,11	LONP2,SOD2,IDE,TSPO,SLC23A2
TGF_BETA_SIGNALING	1,05	0,42	NCOR2,SMURF2,CTNNB1
PI3K_AKT_MTOR_SIGNALING	1,08	0,39	CAMK4,PIK3R3,TSC2,MKNK1,RPS6KA1,CDK1,MYD88,AP2M1,MAPKAP1,CDK1,ACTR2,FASLG,ARPC3,MKNK1,RAF1,RPS6KA3,PIN1,CAB39,RPTOR
MYC_TARGETS_V2	1,13	0,32	LAS1L,UNG,PES1,MCM5,TBRG4,SLC19A1,PLK4,MCM4,MCM5,IMP4
IL6_JAK_STAT3_SIGNALING	1,14	0,29	CXCL13,CD9,IL4R,CSF2,MYD88,CSF1,IRF9,CSF1,IL17RA,ITGA4,EBI3,FAS,IL6ST,
INFLAMMATORY_RESPONSE	1,15	0,27	ABI1,CD82,SRI,P2RX4,SRI,P2RX7,NLRP3,IRF7,ATP2C1,IL4R,LTA,SEMA4D
FATTY_ACID_METABOLISM	1,17	0,28	DLST,GCDH,ECI2,PPARA,ACOX1,AUH,ECI2,SDHC,CRYZ,HPGD,D2HGDH,GSTZ1,HIBCH,ECI2
INTERFERON_GAMMA_RESPONSE	1,18	0,25	PTPN6,DDX58,SRI,TRIM25,VCAM1,IRF7,IL4R,NCOA3,GPR18,RNF31,IRF5,TRAFD1,RNF31,ITGB7,MYD88,ST3GAL5,RSAD2,IFI35,IFNAR2,XAF1,IRF9
WNT_BETA_CATENIN_SIGNALING	1,39	0,11	NCOR2,RBPJ,PPARD,CTNNB1,NCSTN,JAG2,NCSTN,NUMB
OXIDATIVE_PHOSPHORYLATION	1,43	0,07	SLC25A12,ATP6V1H,DLST,COX4I1,NDUFV1,BAX,IMMT,MGST3,VDAC3,NNT,MAOB,ATP5A1,PHYH,SLC25A11,ATP6V0B,RHOT1,SDHC,ATP5G1,ATP5G2, HTRA2,MGST3,ATP5J,ATP5L
DNA_REPAIR	1,59	0,02	RNMT,NME3,LIG1,TAF6,NT5C,ERCC2,POLA2,ZWINT,TSG101,RAD51,ERCC2,ZWINT,POLD1,ITPA,PRIM1,POLD3,POLR1C,CANT1,POLR2D,GTF2H3
MTORC_SIGNALING	1,67	0,01	BUB1,QDPR,AURKA,SYTL2,SYTL2,CDC25A,PIK3R3,ELOVL6,SHMT2,GSR,CD9,VLDLR,IMMT,DHFR,UNG,RRM2,SYTL2,ASNS,AURKA,UCHL5,EPRS,CCT6A,TFRC,AK4,SYTL2,PFKL,ATP5G1,PSMA4,SYTL2,TFRC,EBP,TM7SF2,NFYC,ACTR2,P4HA1,NAMPT,MTHFD2,FDXR,MCM4,G6PD,GBE1,SYTL2,MCM4,STIP1,NAMPT,HMBS,SYTL2
PROTEIN_SECRETION	1,83	0,01	STX16,ATP6V1H,SEC31A,CD63,TSG101,PAM,ARFIP1,VPS45,RAB2A,PAM,AP2M1,GOLGA4,COPB1,ICA1,SGMS1,CLTA,GOSR2,SGMS1,SNAP23,TPD52
IL2_STAT5_SIGNALING	1,89	0,001	ITGAE,CAPG,NCS1,BCL2L1,HOPX,ICOS,TNFRSF8,MYO1E,P2RX4,SNX14,CTLA4,IKZF4,RABGAP1L,IL4R,NCOA3,FLT3LG,FAH,PHTF2,MYO1E,CSF2,TNFRSF8, ST3GAL4,PLAGL1,PLEC,MYO1C
E2F_TARGETS	2,09	0,001	ILF3,BUB1B,MELK,LIG1,BIRC5,DLGAP5,AURKA,CDC25A,CIT,POLA2,ESPL1,MELK,WDR90,AURKB,MCM3,RAD51C,BRCA1,HMMR,SMC4,POLD1,UNG,POLD2,RRM2,CDK1,POLD3,STAG1,MKI67,RAD51AP1,PSMC3IP,AURKA,CDKN2A,SMC4,BRCA2,CDKN3,WEE1,CENPE,AURKB,GINS3,TFRC,EIF2S1,NUP107,MYBL2,AURKB,TMPO,RACGAP1,MCM5,TBRG4,CENPM,KIF2C,TFRC,CDC20,LIG1,ORC6,CDK1,ATAD2,CCNE1,CDCA3,EZH2,RFC2,DEPDC1,SMC4,SPAG5,CIT,CDCA3,HELLS,SMC4,STAG1,MTHFD2,RAD51AP1,POLE,TCF19,CKS1B,PRKDC,PLK4,MCM4,DNMT1,SMC6,CDKN2A,TRIP13,POLD3,DEK,EXOSC8,PLK4,KPNA2,RAD51C,BARD1
G2M_CHECKPOINT	2,38	0,001	ILF3,MTF2,SMC2,BUB1,PRC1,BIRC5,TPX2,AURKA,CDC25A,NUSAP1,KIF15,EXO1,TROAP,POLA2,ESPL1,NUSAP1,AURKB,MCM3,KIF23,HMMR,PRC1,SMC4,SMC2,CBX1,TLE3,STIL,TNPO2,CDK1,STAG1,CHMP1A,MKI67,KIF23,AURKA,NUSAP1,TRAIP,BRCA2,EXO1,TTK,SS18,SS18,CDKN3,ODF2,CENPE,CDC7,AURKB,DKC1,CASP8AP2,PBK,CDC27,TROAP,MYBL2,AURKB,EWSR1,TRAIP,KIF23,TMPO,RACGAP1,MCM5,SMC2,TRAIP,KIF2C,SRSF10,CDC20, ORC6,PAFAH1B1,CDK1,RBM14,EZH2

NES: Normalized enrichment score

Table S10: Primer pair sequences for RT-PCR (Related to STAR methods)

IKZF3 Forward	AGATTTGAATGTGCCCTGGT
IKZF3 Reverse	TGTCTTGCCTCCGCACTT
RORC Forward	CTTGCCGTAGGGATGTCTCG
RORC Reverse	GAAGTTCCGTCAGCCCGTT
AHR Forward	TAACCCAGACCAGATTCCTCCAGA
AHR Reverse	CCCTTGGAAATTCATTGCCAGA
IL17A Forward	AACGATGACTCCTGGGAAGA
IL17A Reverse	GGATTTCGTGGGATTGTGAT
TCF7 Forward	CGGGACAGGACCATTACAACTAGATCAAGGAC
TCF7 Reverse	CCACCTGCCTCGGCCTGCCAAAGT
S1PR1 Forward	CAGACAAGCAAAACAAAGTG
S1PR1 Reverse	CATCAACAAAAGTGCCAAAG
18S Forward	CGGACAGGATTGACAGATTG
18S Reverse	CAATCGCTCCACCAACTAA