

SUPPLEMENTARY MATERIAL

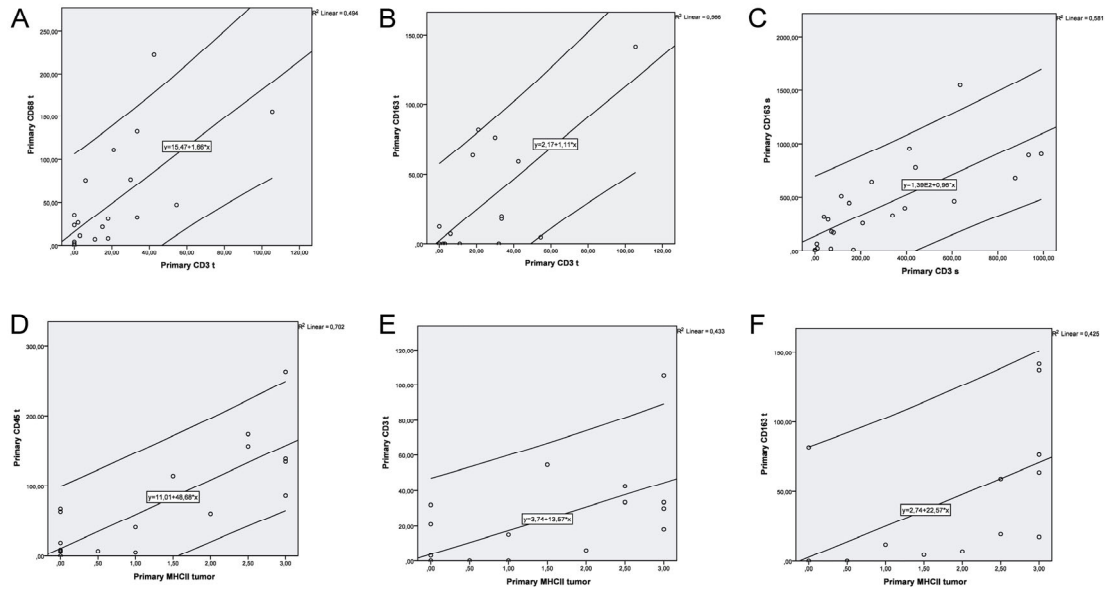


Figure S1. Regression analysis of macrophage (CD68, CD163, CD33), MHCII, immune cell (CD45), and lymphocyte (CD3) marker tissue expression in SCLC tumor samples.

The expression of CD68 and CD163 showed a very strong and strong positive correlation with CD3 expression in tumor nests ($r=0.807$, $p<0.001$; A and $r=0.707$, $p<0.001$; B), respectively. The cellular density of CD163+ cells showed very strong positive correlation with CD3+ T-lymphocyte density in the stroma compartment ($r=0.864$, $p<0.001$; C).

The cellular density of CD45+ immune cells and CD3+ T-lymphocytes in tumor nests showed a strong positive correlation with MHCII expression on tumor cells ($r=0.753$, $p<0.001$, D and $r=0.705$, $p=0.001$, E). Cellular density of CD163+ macrophages in tumor nests showed very strong positive correlation with MHCII expression on tumor cells ($r=0.801$, $p<0.001$, F).

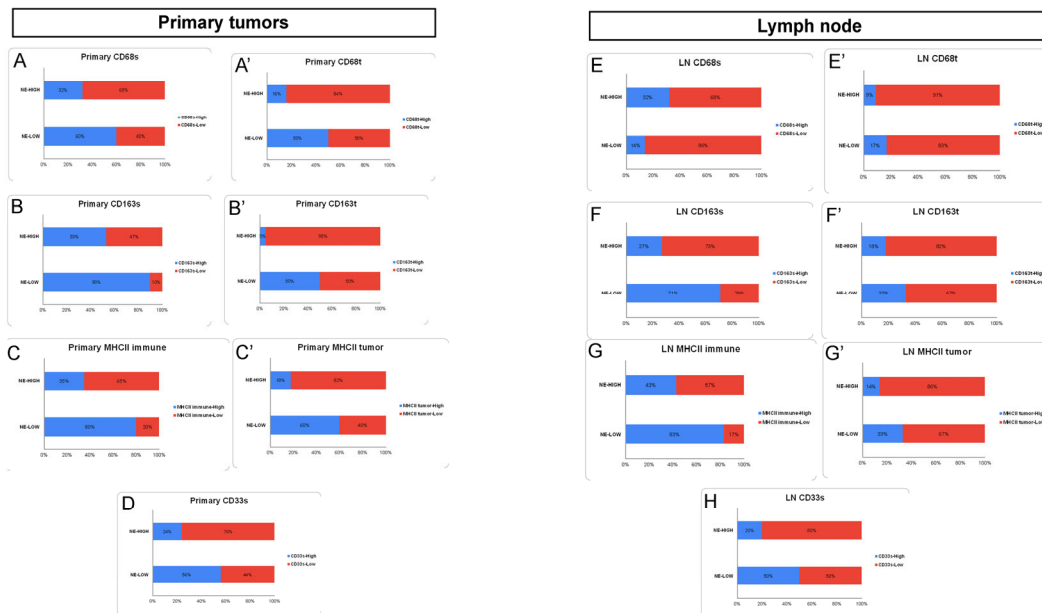


Figure S2. Distribution of CD68-, CD163-, CD33-, and MHCII HIGH- and LOW primary tumors and LN metastases according to NE phenotype.

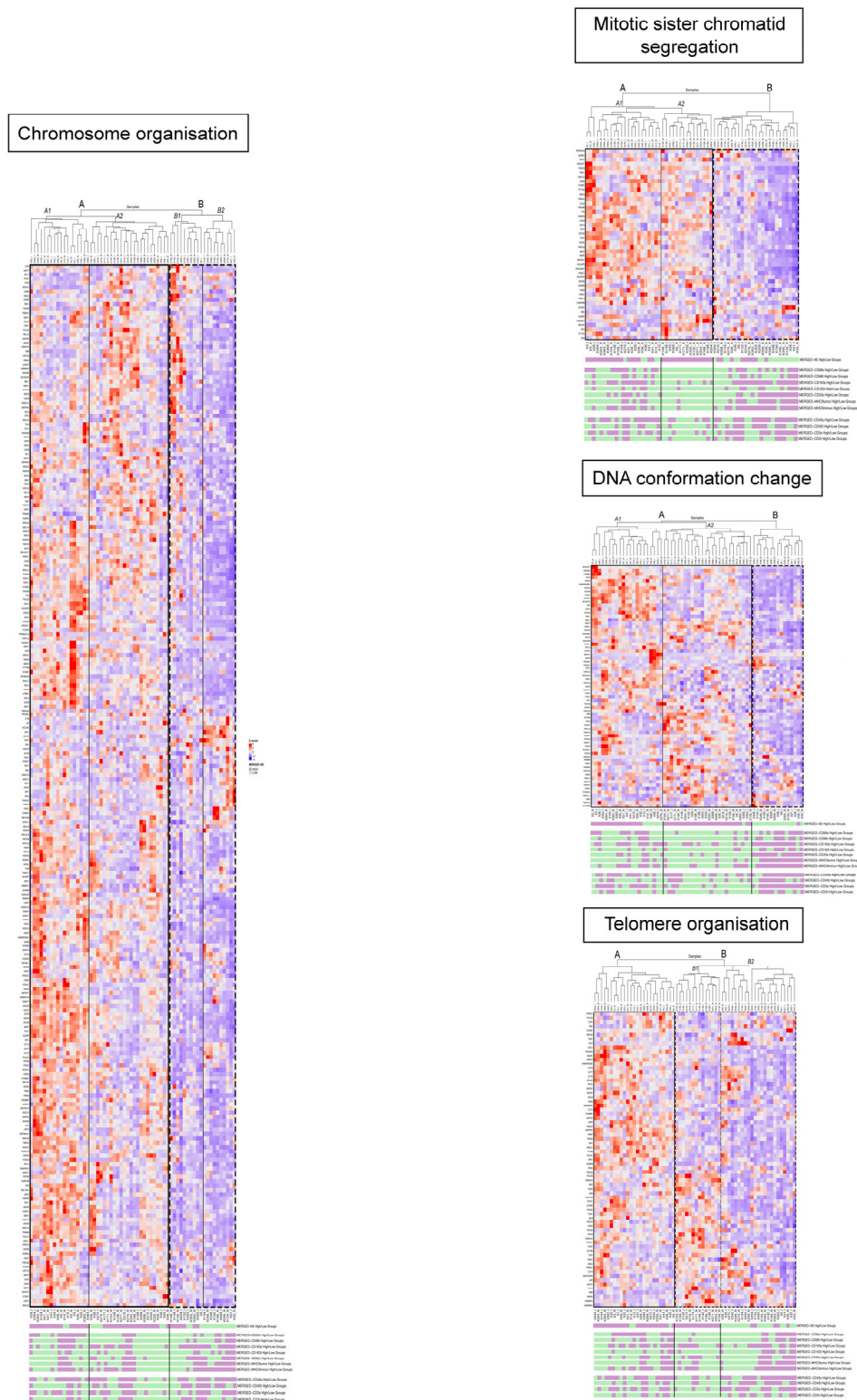


Figure S4. Gene expression data of additional oncogenic pathways

Heatmaps show gene expression profile of GO pathways, *chromosome organization*, *mitotic sister chromatid segregation*, *DNA conformation change*, and *telomere organization* at the level of individual tumor samples (primary and LN merged). The first two clusters (A1 and A2, A and B1 in *telomere organization*) represent mainly NE-high tumors with low or variable levels of macrophage- and T-cell infiltration. These tumors show strong overall expression in most genes of

their corresponding pathway. The third cluster (B, B2 in telomere organization) comprises NE-low phenotype tumors in all of the oncogenic pathways, where it is associated with macrophage-high and lymphocyte-high tumors.

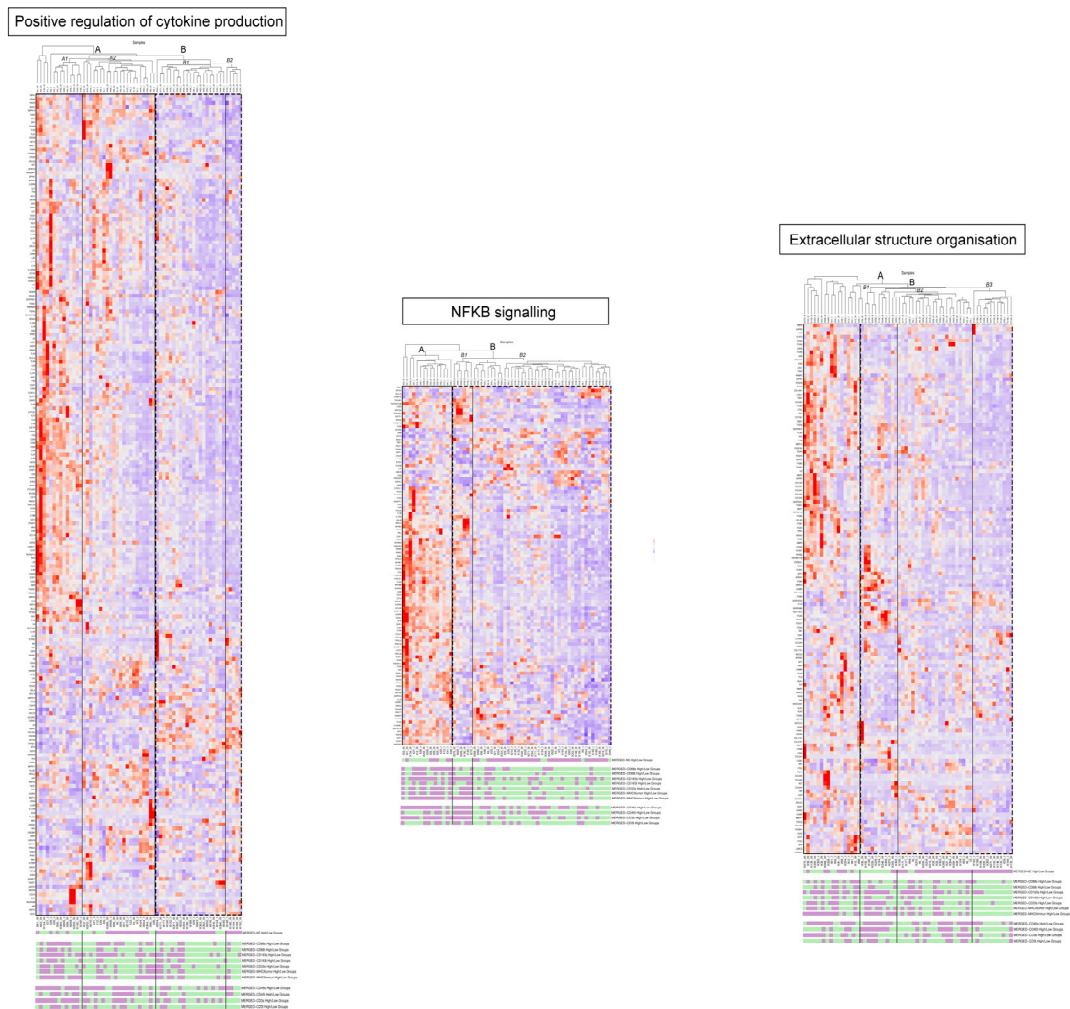


Figure S5. Gene expression data of pathways on cytokine production, signaling, and extracellular structure organization

Heatmaps show gene expression profile of GO pathways, *positive regulation of cytokine production*, *NFKB signaling* and *extracellular structure organization* at the level of individual tumor samples (primary and LN merged). The first two clusters (A1 and A2, A and B1 in *extracellular structure organization*) represent in majority NE-low tumors variable or high levels of macrophage- and T-cell infiltration. These tumors show strong overall expression in most genes of their corresponding pathway. The last clusters (B1 and B2 in *positive regulation of cytokine production*, B in *NFKB signaling*, and B2 and B3 in *extracellular structure organization*) comprises tumors of mainly NE-high phenotype, where they are associated with variable or low macrophage- and lymphocyte-densities.

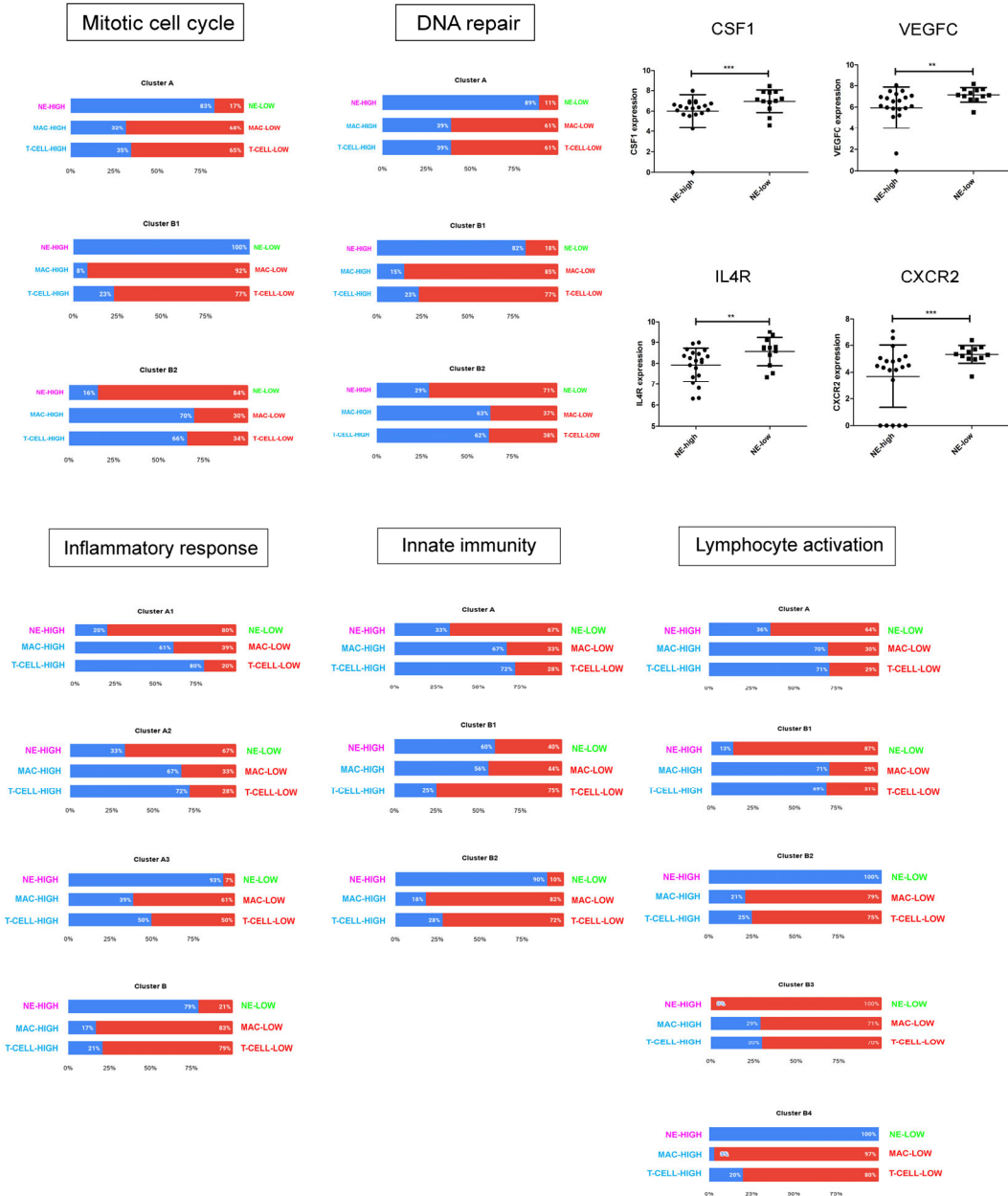


Figure S6. Composition of patient tumor clusters according to NE-phenotype, macrophage- and T-cell infiltration. Stacked bar charts show tumor-phenotype composition of different clusters according to oncogenic (*mitotic cell cycle*, *DNA-repair*), and immunogenic (*inflammatory response*, *innate immunity*, *lymphocyte activation*) GO pathways. Scatter plots show the differential expression of CSF1, VEGFC, IL4R and CXCR2 in NE-low compared to NE-high tumors.

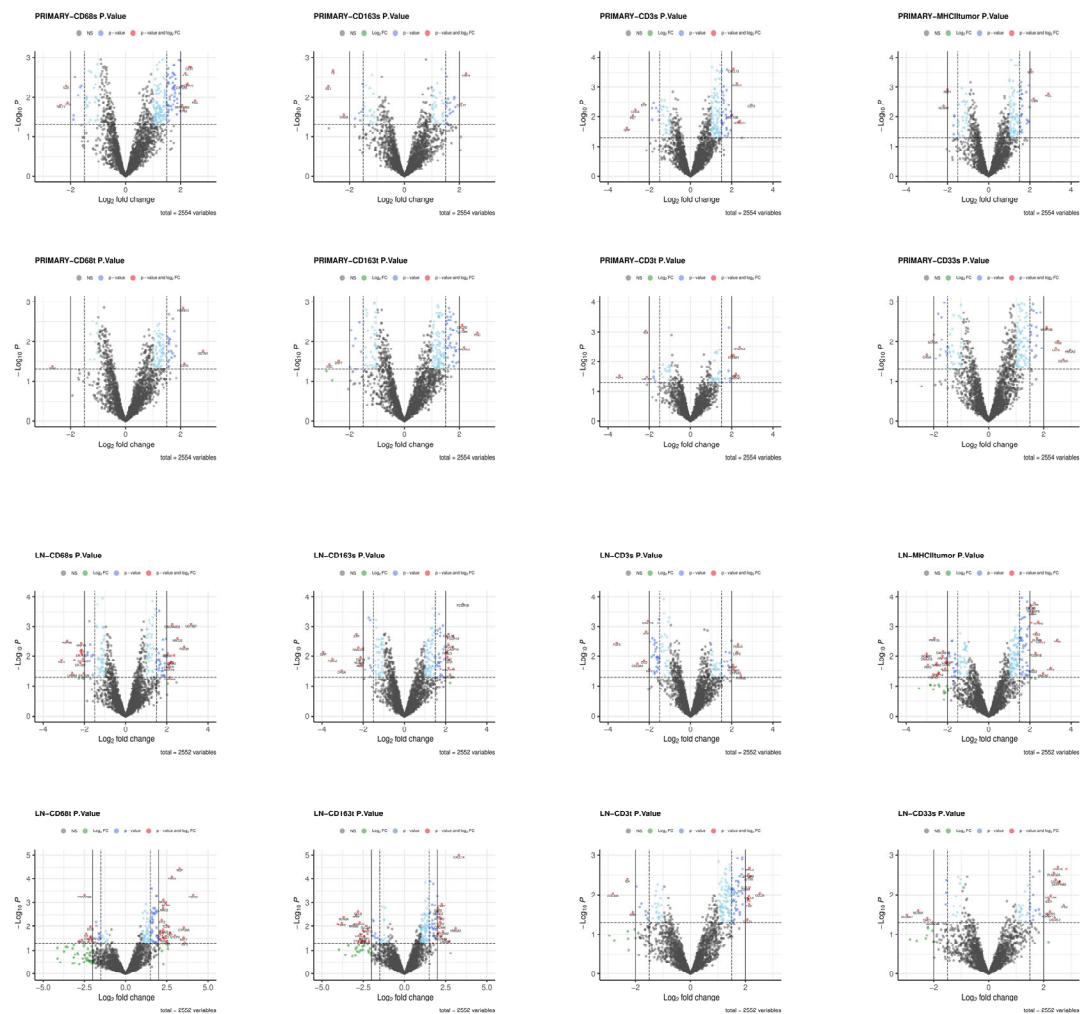


Figure S7. Volcano plots for parameters of selected IHC biomarkers in different tumor compartments

Immun oasis tumors	
NE-low	6-I
NE-low	21-I
NE-low	39-I
NE-low	270-I
NE-low	209-I
NE-low	190-I
NE-low	134-I
NE-low	12-III
NE-low	270-III
NE-low	209-III
NE-low	190-III
NE-low	33-III
NE-low	36-III
NE-low	134-III
NE-high	28-I
NE-high	33-I
NE-high	352-I
NE-high	3-I
NE-high	41-I
NE-high	171-III
NE-high	26-III
NE-high	28-III
NE-high	6-III
NE-high	29-III
NE-high	39-III
NE-low	NE-high
14	11

Immun desert tumors	
NE-low	12-I
NE-low	346-I
NE-low	36-I
NE-low	346-III
NE-high	104-I
NE-high	126-I
NE-high	132-I
NE-high	148-I
NE-high	171-I
NE-high	188-I
NE-high	204-I
NE-high	210-I
NE-high	216-I
NE-high	268-I
NE-high	271-I
NE-high	29-I
NE-high	354-I
NE-high	363-I
NE-high	104-III
NE-high	126-III
NE-high	132-III
NE-high	148-III
NE-high	188-III
NE-high	204-III
NE-high	210-III
NE-high	216-III
NE-high	268-III
NE-high	21-III
NE-high	271-III
NE-high	352-III
NE-high	354-III
NE-high	363-III
NE-low	NE-high
4	28

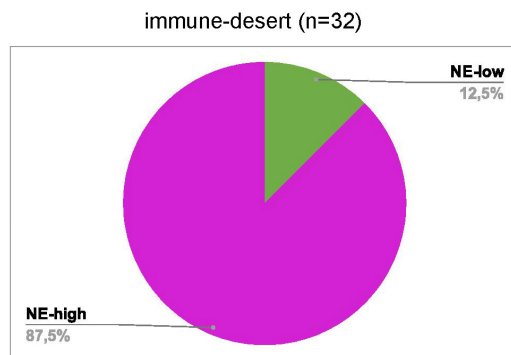
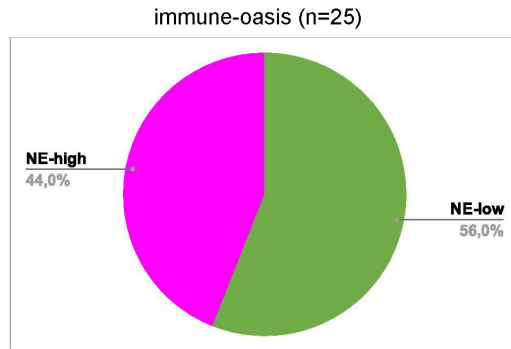


Figure S9. Immune-oasis and immune-desert tumors and their NE-phenotype

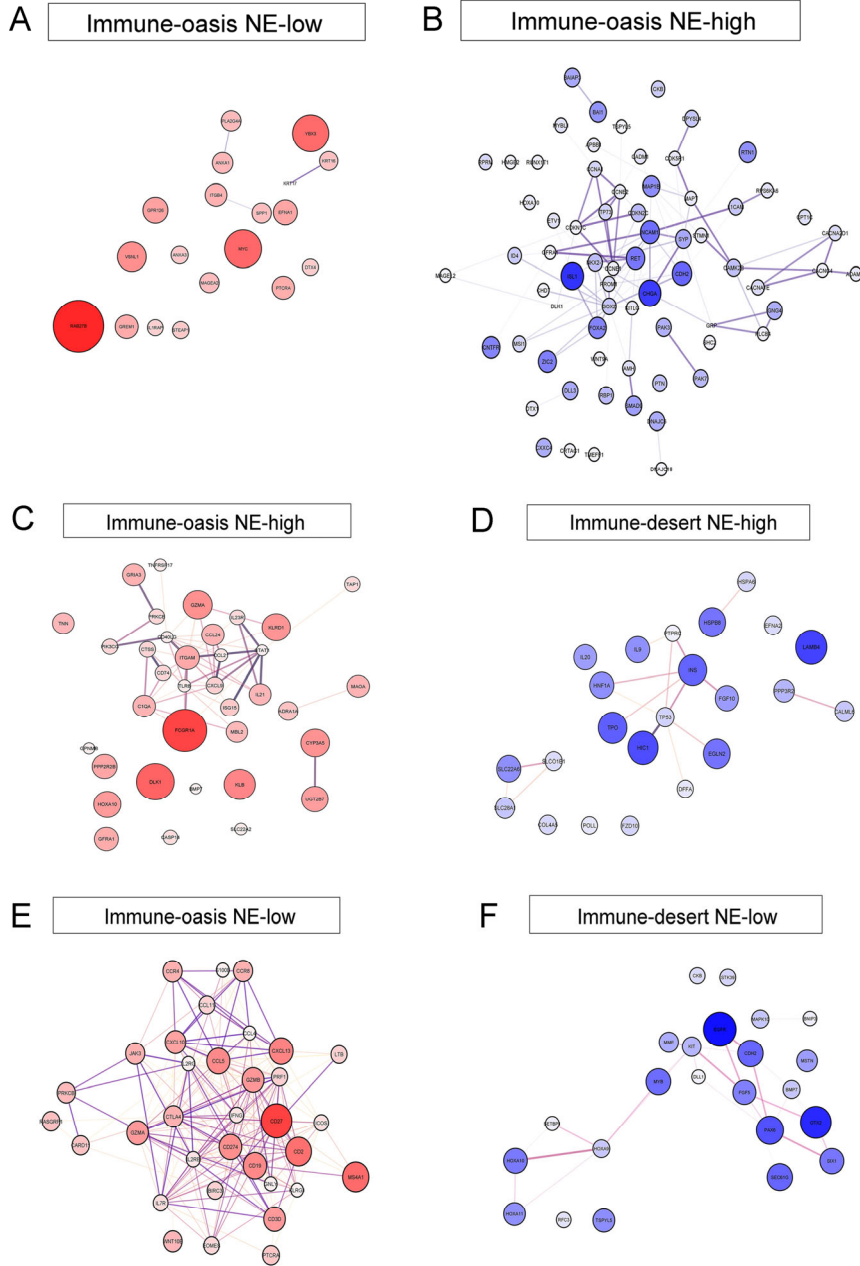


Figure S10. Additional string maps for the comparison of SCLC tumor phenotypes

In immune oasis NE-low tumors (vs immune oasis NE-high), the low number of differentially expressed genes show minimal interconnectedness, whereas central genes of immune oasis NE-high (vs immune oasis NE-low) tumors are interconnected moderately (A-B). Immune oasis NE-high tumors (vs immune desert NE-high) show a moderate level of interconnectedness, with an average of 1.54 edges/node and a total 36.72 connection score. Immune desert NE-high tumors (vs immune oasis NE-high) however represent weak interconnectedness with average 0.69 edges/node and 9.52 total connection score (C-D). Immune oasis NE-low (vs immune desert NE-low) tumors display strong interconnectedness among their differentially expressed genes with average 6 edges/node and 145.03 total connection score. In contrast, top genes of immune desert NE-low (vs immune oasis NE-low) tumors are interconnected weakly with average 1.42 edges/node and 19.51 total connection score (E-F).

Table S1. Correlation between the tissue expression of different macrophage markers (CD68, CD163, and CD33), MHCII expression on tumor cells, CD45 immune cell marker and CD3 T-lymphocyte marker in stroma and tumor nests.

MACROPHAGE MARKERS									
PRIMARY	CD68s								
CD68t	r=0.945 p<0.001	CD68t							
CD163s	r=0.455 p=0.02	r=0.653 p=0.001	CD163s						
CD163t	r=0.628 p=0.01	r=0.764 p=0.001	r=0.594 p=0.003	CD163t					
CD33s	r=0.405 p=0.034	r=0.500 p=0.018	r=0.651 p=0.001	r=0.605 p=0.003	CD33s				
MHCII tumor	r=0.570 p=0.006	r=0.703 p=0.001	r=0.511 p=0.018	r=0.801 p<0.001	r=0.505 p=0.019				

LN	CD68s								
CD68t	r=0.694 p<0.001	CD68t							
CD163s	r=0.651 p<0.001	r=0.478 p=0.016	CD163s						
CD163t	r=0.488 p=0.013	r=0.410 p=0.042	r=0.792 p<0.001	CD163t					
CD33s	r=0.302 p=0.181	r=0.270 p=0.224	r=0.368 p=0.084	r=0.382 p=0.097	CD33s				
MHCII tumor	r=0.529 p=0.011	r=0.314 p=0.155	r=0.757 p<0.001	r=0.720 p<0.001	r=0.499 p=0.021				

MACROPHAGE- CD45 - CD3									
PRIMARY	CD45s	CD45t	CD3s	CD3t					
CD68s	r=0.575 p=0.002	r=0.581 p=0.004	r=0.515 p=0.007	r=0.502 p=0.011					
CD68t	r=0.735 p<0.001	r=0.807 p<0.001	r=0.735 p<0.001	r=0.812 p<0.001					
CD163s	r=0.811 p<0.001	r=0.791 p<0.001	r=0.864 p<0.001	r=0.783 p<0.001					
CD163t	r=0.749 p<0.001	r=0.759 p<0.001	r=0.743 p<0.001	r=0.707 p<0.001					
CD33s	r=0.601 p=0.002	r=0.602 p=0.002	r=0.629 p=0.001	r=0.631 p=0.001					
MHCII tumor	r=0.661 p<0.001	r=0.753 p<0.001	r=0.626 p=0.001	r=0.705 p=0.001					

LN	CD45s	CD45t	CD3s	CD3t					
CD68s	r=0.410 p=0.047	r=0.584 p=0.008	r=0.448 p=0.028	r=0.633 p=0.002					
CD68t	r=0.374 p=0.079	r=0.452 p=0.035	r=0.350 p=0.102	r=0.478 p=0.025					
CD163s	r=0.447 p=0.028	r=0.729 p<0.001	r=0.349 p=0.095	r=0.676 p=0.001					
CD163t	r=0.359 p=0.092	r=0.738 p<0.001	r=0.210 p=0.335	r=0.573 p=0.005					
CD33s	r=0.705 p<0.001	r=0.638 p=0.002	r=0.680 p=0.001	r=0.627 p=0.003					
MHCII tumor	r=0.422 p=0.050	r=0.654 p<0.001	r=0.416 p=0.054	r=0.605 p=0.004					

very strong, significant correlation r > 0.8 p < 0.001	moderate, significant correlation 0.4 < r > 0.6 p < 0.05
strong, significant correlation r > 0.6 p < 0.01	weak, insignificant correlation r < 0.4 p > 0.05

Table S2. Cut-off values for macrophage related IHC biomarkers (HIGH- and LOW tumor categories)
Percentages represent the ratios of HIGH- and LOW tumors from the whole patient cohort.

	CD68s	CD68t	CD163s	CD163t	MHCII immune	MHCII tumor	CD33s	NE
PRIMARY								
HIGH	13/29 (45%)	10/29 (34%)	20/29 (69%)	8/29 (28%)	15/29 (52%)	10/29 (34%)	12/29 (41%)	19/29 (66%)
LOW	16/29 (55%)	19/29 (66%)	9/29 (31%)	21/29 (72%)	14/29 (48%)	19/29 (66%)	17/29 (59%)	10/29 (34%)
cut-off (cell/mm ² score (0-3))	291.23	39.68	413.33	63.65	0-1 --> LOW --> 2-3 --> HIGH	0-1 --> LOW --> 2-3 --> HIGH	0-1 --> LOW --> 2-3 --> HIGH	
LN								
HIGH	10/29 (34%)	5/29 (17%)	13/29 (45%)	7/29 (24%)	16/29 (55%)	10/29 (34%)	10/29 (34%)	22/29 (76%)
LOW	19/29 (66%)	24/29 (83%)	16/29 (55%)	22/29 (76%)	13/29 (45%)	19/29 (66%)	19/29 (66%)	7/29 (24%)
cut-off (cell/mm ² score (0-3))	631.25	115.48	246.94	27.82	0-1 --> LOW --> 2-3 --> HIGH	0-1 --> LOW --> 2-3 --> HIGH	0-1 --> LOW --> 2-3 --> HIGH	

Table S3. Cut-off values for IHC biomarkers CD45 and CD3 (HIGH- and LOW tumor categories)

Percentages represent the ratios of HIGH- and LOW tumors from the whole patient cohort.

	CD45s	CD45t	CD3s	CD3t
PRIMARY				
HIGH	15/28 (54%)	13/28 (46%)	11/28 (39%)	11/28 (39%)
LOW	13/28 (46%)	15/28 (54%)	17/28 (61%)	17/28 (61%)
cut-off (cell/mm ²) score (0-3)	568.93	45.51	201.55	15.96
LN				
HIGH	20/28 (69%)	8/29 (28%)	18/29 (62%)	5/29 (17%)
LOW	9/29 (31%)	21/29 (72%)	11/29 (38%)	24/29 (83%)
cut-off (cell/mm ²) score (0-3)	848.98	86.08	298.48	43.24

Table S4. HIGH and LOW annotation for NE-high and NE-low tumors according to protein marker expression

	CD68		CD163		MHCII			CD45		CD3	
PRIMARY	CD68s	CD68t	CD163s	CD163t	MHCII immune	MHCII tumor	CD33s	CD45s	CD45t	CD3s	CD3t
12-I	HIGH	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	LOW	LOW
6-I	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	HIGH	HIGH	HIGH	HIGH
21-I	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	HIGH	LOW
26-I	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	NA	NA	NA
36-I	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
39-I	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	NA	HIGH	HIGH	HIGH	HIGH
355-I	LOW	LOW	HIGH	LOW	HIGH	LOW	LOW	LOW	LOW	LOW	LOW
346-I	LOW	LOW	HIGH	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	LOW
270-I	LOW	LOW	HIGH	HIGH	HIGH	HIGH	LOW	HIGH	HIGH	HIGH	HIGH
209-I	HIGH	LOW	HIGH	LOW	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH
190-I	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH
134-I	LOW	HIGH	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	HIGH	HIGH
104-I	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
126-I	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
132-I	LOW	LOW	HIGH	LOW	LOW	LOW	LOW	HIGH	HIGH	LOW	HIGH
148-I	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
171-I	LOW	LOW	HIGH	LOW	NA	NA	HIGH	HIGH	HIGH	HIGH	LOW
188-I	LOW	LOW	HIGH	LOW	LOW	LOW	NA	LOW	LOW	LOW	LOW
204-I	LOW	LOW	HIGH	LOW	NA	NA	NA	HIGH	HIGH	LOW	HIGH
210-I	LOW	LOW	HIGH	LOW	NA	NA	NA	HIGH	HIGH	LOW	HIGH
216-I	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
268-I	LOW	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	LOW	LOW	LOW
271-I	LOW	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	LOW	LOW	LOW
28-I	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	LOW	HIGH	HIGH	HIGH	HIGH
29-I	HIGH	LOW	LOW	LOW	NA	NA	LOW	LOW	LOW	LOW	LOW
332-I	LOW	LOW	HIGH	HIGH	HIGH	HIGH	LOW	HIGH	LOW	LOW	LOW
33-I	HIGH	HIGH	HIGH	LOW	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH
352-I	HIGH	HIGH	LOW	LOW	HIGH	HIGH	LOW	HIGH	HIGH	LOW	LOW
354-I	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
363-I	LOW	LOW	HIGH	LOW	HIGH	LOW	HIGH	HIGH	LOW	HIGH	LOW
3-I	HIGH	LOW	HIGH	LOW	NA	NA	LOW	LOW	LOW	LOW	LOW
43-I	LOW	LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	LOW	LOW	LOW
LN											
12-III	HIGH	HIGH	HIGH	LOW	HIGH	LOW	LOW	HIGH	LOW	HIGH	LOW
33-III	LOW	LOW	LOW	LOW	NA	NA	NA	HIGH	HIGH	HIGH	HIGH
36-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	HIGH	LOW
355-III	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH
346-III	LOW	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	LOW	LOW	LOW
270-III	LOW	LOW	HIGH	HIGH	HIGH	LOW	LOW	LOW	LOW	HIGH	LOW
209-III	LOW	LOW	HIGH	LOW	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	LOW
190-III	LOW	LOW	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH
134-III	LOW	LOW	HIGH	LOW	NA	NA	HIGH	HIGH	LOW	HIGH	LOW
104-III	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	HIGH	LOW	HIGH	LOW
126-III	LOW	LOW	LOW	LOW	NA	NA	NA	LOW	LOW	LOW	LOW
132-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	HIGH	LOW
148-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
171-III	LOW	LOW	HIGH	HIGH	HIGH	HIGH	LOW	HIGH	HIGH	LOW	LOW
188-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	HIGH	LOW
204-III	LOW	LOW	LOW	LOW	NA	NA	LOW	LOW	LOW	LOW	LOW
210-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
216-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
21-III	HIGH	LOW	HIGH	LOW	HIGH	LOW	LOW	LOW	LOW	HIGH	LOW
268-III	LOW	LOW	LOW	LOW	HIGH	LOW	NA	LOW	LOW	LOW	LOW
26-III	HIGH	LOW	HIGH	LOW	HIGH	HIGH	NA	HIGH	HIGH	HIGH	HIGH
271-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
28-III	HIGH	HIGH	HIGH	HIGH	HIGH	NA	NA	HIGH	HIGH	HIGH	HIGH
29-III	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH	HIGH	HIGH	HIGH	HIGH
332-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW
352-III	LOW	LOW	LOW	HIGH	HIGH	LOW	LOW	HIGH	HIGH	LOW	LOW
354-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	HIGH	LOW
363-III	LOW	LOW	LOW	LOW	LOW	LOW	NA	HIGH	LOW	LOW	LOW
39-III	HIGH	LOW	LOW	LOW	HIGH	NA	HIGH	HIGH	LOW	HIGH	LOW
3-III	HIGH	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	HIGH	LOW
43-III	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH	LOW	HIGH	LOW
6-III	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	HIGH	LOW	LOW	LOW

Table S5. Node and edge data for string maps

NE-low Nodes Edges edges/node total edge score (SUM)	VS	NE-high Nodes Edges edges/node total edge score (SUM)
68 148 2.18 94.147		65 77 1.18 51.35
Immune-oasis Nodes Edges edges/node total edge score (SUM)	VS	Immune-desert Nodes Edges edges/node total edge score (SUM)
27 53 1.963 36.98		20 21 1.05 13.51
Immune-oasis NE-high Nodes Edges edges/node total edge score (SUM)	VS	Immune-oasis NE-low Nodes Edges edges/node total edge score (SUM)
32 17 0.531 11.39		90 133 1.48 90.58
Immune-oasis NE-low Nodes Edges edges/node total edge score (SUM)	VS	Immune-desert NE-high Nodes Edges edges/node total edge score (SUM)
37 57 1.54 36.72		23 16 0.69 9.52
Immune-oasis NE-low Nodes Edges edges/node total edge score (SUM)	VS	Immune-desert NE-low Nodes Edges edges/node total edge score (SUM)
36 216 6 145.032		24 34 1.42 19.51

Supplemental Table 6. Possible therapeutic interventions on eligible molecular targets.

List of NE-low and NE-high molecular targets against which drugs are already available or under development. *N.A.*:

no available drug

PDF with links as attachment