

Supplementary Table 1. mIF first panel

Primary antibody	Clone	Vendor	Cell population
CD68	KP1	Agilent	Pan-macrophages
CD8	C8/144B	Agilent	Cytotoxic T cells
FoxP3	D2W8E	Cell Signalling	T regulatory cells (CD4+FoxP3+)
CD4	4B12	Thermo Fisher Scientifics	T helper lymphocytes
CD20	L26	Agilent	B lymphocytes
CD163	10D6	Leica Biosystems	M2-like macrophages (CD68+CD163+)
HLA-I	EMR8-5	Abcam	Human leukocyte antigen-class I
Synaptophysin Chromogranin-A NCAM	27G12 5H7 123C3	Leica Biosystems Leica Biosystems Agilent	Tumor cells

Supplementary Table 2. mIF second panel

Primary antibody	Clone	Vendor	Cell population
PD-1	EPR4877-2	Abcam	Exhausted T cells (CD8+PD-1+)
PD-L1	E1L3N	Cell Signalling	Immunosuppressive cells
CD68	KP1	Agilent	Pan-macrophages
CD8	C8/144B	Agilent	Cytotoxic T cells
ASCL1	24B72D11.1	Becton Dickinson	SCLC-A subtype
NEUROD1	EPR20766	Abcam	SCLC-N subtype
POU2F3	Polyclonal	BioTechne	SCLC-P subtype
Synaptophysin Chromogranin-A NCAM	27G12 5H7 123C3	Leica Biosystems Leica Biosystems Agilent	Tumor cells

Supplementary table 3. Univariate and multivariate analysis for TTF (Log-rank and cox proportional hazard)

Variable	N (%)	Univariate analysis		Multivariate analysis	
		P	Coefficient	P	HR (95% CI)
Number of cases	42 (100.0)				
Gender		0.032			
Male	25 (59.5)				
Female	17 (40.5)		-1.040	0.090	0.353 (0.106 - 1.177)
Age					
< 68	20 (47.6)	0.226	0.741	0.383	0.512 (0.122-2.149)
>= 68	22 (52.4)				
Smoking status					
Never smokers	3 (7.2)	0.170	-2.101	0.075	0.122 (0.012-1.232)
Smokers	39 (92.8)				
Stage at diagnosis					
IIIC/IVA	5 (11.9)	0.390	0.741	0.390	2.098 (0.396 - 11.110)
IVB	37 (88.1)				
ECOG PS					
0-1	34 (81.0)	0.260	-0.598	0.492	0.550 (0.100 - 3.023)
≥2	8 (9.0)				
Charlson Comorbidity Index					
6-7	12 (28.6)	0.074	1.280	0.091	3.598 (0.816 - 15.863)
>7	30 (71.4)				
Number of metastatic sites at diagnosis					
<3	27 (64.3)	0.001			
≥3	15 (35.7)		1.491	0.044	4.440 (1.043 - 18.910)
Brain metastasis at diagnosis					
Present	12 (28.6)	0.467	0.157	0.764	1.170 (0.421 - 3.252)
Absent	30 (71.4)				
Liver metastasis at diagnosis					
Present	18 (42.9)	0.189			
Absent	24 (57.1)		-0.325	0.597	0.723 (0.217 - 2.409)
Steroid therapy at treatment start					
No	23 (54.7)	0.007	-1.588	0.019	0.204 (0.0543 - 0.769)
Yes	19 (45.2)				
Antibiotic therapy at treatment start					
No	37 (88.1)	0.314			
Yes	5 (10.2)		0.0632	0.946	1.065 (0.172 - 6.586)

Abbreviations: N, number; HR, hazard ratio; CI, confidence interval; PD, performance status; TTF, time-to-treatment failure..

Supplementary Table 4. Univariate and multivariate analysis for PFS (Log-rank and cox proportional hazard)

Variable	N (%)	Univariate analysis		Multivariate analysis PFS	
		P	Coefficient	P	HR (95% CI)
Number of cases	42 (100.0)				
Gender					
Male	25 (59.5)	0.014	-1.381		
Female	17 (40.5)			0.026	0.251 (0.0744 - 0.850)
Age					
< 68	20 (47.6)	0.121	0.280	0.564	1.323 (0.322 - 5.432)
>= 68	22 (52.4)				
Smoking status					
Never smokers	3 (7.2)	0.101	-1.978	0.090	0.138 (0.0141 - 1.358)
Smokers	39 (92.8)				
Stage at diagnosis					
IIIC/IVA	5 (11.9)	0.333	0.669	0.436	1.953 (0.362 - 10.525)
IVB	37 (88.1)				
ECOG PS					
0-1	34 (81.0)	0.422	-1.094	0.201	0.335 (0.0628 - 1.788)
≥2	8 (9.0)				
Charlson Comorbidity Index					
6-7	12 (28.6)	0.187	0.406	0.564	1.501 (0.377 - 5.973)
>7	30 (71.4)				
Number of metastatic sites at diagnosis					
<3	27 (64.3)	0.001	0.379		
≥3	15 (35.7)			0.591	1.461 (0.367 - 5.819)
Brain metastasis at diagnosis					
Present	12 (28.6)	0.365	0.186	0.710	1.205 (0.451 - 3.221)
Absent	30 (71.4)				
Liver metastasis at diagnosis					
Present	18 (42.9)	0.491	-0.155		
Absent	24 (57.1)			0.770	0.856 (0.302 - 2.430)
Steroid therapy at treatment start					
No	23 (54.7)	0.061	-1.440	0.022	0.237 (0.0691 - 0.813)
Yes	19 (45.2)				
Antibiotic therapy at treatment start					
No	37 (88.1)	0.201	-0.763		
Yes	5 (10.2)			0.419	0.466 (0.073 - 2.962)

Abbreviations: N, number; HR, hazard ratio; CI, confidence interval; PD, performance status, PFS, progression-free survival.

Supplementary table 5. Univariate and multivariate analysis for OS (Log-rank and cox proportional hazard)

Variable	N (%)	Univariate analysis		Multivariate analysis OS	
		P	Coefficient	P	HR (95% CI)
Number of cases	42 (100.0)				
Gender					
Male	25 (59.5)	0.071	-0.904		
Female	17 (40.5)			0.151	0.405 (0.118 - 1.390)
Age					
< 68	20 (47.6)	0.704	-0.738	0.319	0.478 (0.112 - 2.042)
>= 68	22 (52.4)				
Smoking status					
Never smokers	3 (7.2)	0.160	-2.995	0.016	0.0500 (0.004 - 0.573)
Smokers	39 (92.8)				
Stage at diagnosis					
IIIC/IVA	5 (11.9)	0.247	-1.577	0.112	0.207 (0.023 - 1.447)
IVB	37 (88.1)				
ECOG PS					
0-1	34 (81.0)	0.009	-1.891	0.053	0.151 (0.022 - 1.027)
≥2	8 (9.0)				
Charlson Comorbidity Index					
6-7	12 (28.6)	0.800	-0.152	0.837	0.859 (0.200 - 3.682)
>7	30 (71.4)				
Number of metastatic sites at diagnosis					
<3	27 (64.3)	<0.001			
≥3	15 (35.7)		1.943	0.007	6.981 (1.685 - 28.920)
Brain metastasis at diagnosis					
Present	12 (28.6)	0.347	0.650	0.258	1.916 (0.621 - 5.909)
Absent	30 (71.4)				
Liver metastasis at diagnosis					
Present	18 (42.9)	0.517	-1.243		
Absent	24 (57.1)			0.088	0.289 (0.069 - 1.202)
Steroid therapy at treatment start					
No	23 (54.7)	0.011	-0.908	0.142	0.403 (0.120 - 1.354)
Yes	19 (45.2)				
Antibiotic therapy at treatment start					
No	37 (88.1)	0.290	-1.187		
Yes	5 (10.2)			0.353	0.305 (0.025 - 3.737)
Response to treatment					
Responders	26 (61.9)	0.072	1.572		
Non-responders/ Not evaluated	16 (38.0)			0.023	4.816 (1.237 - 18.748)

Abbreviations: N, number; HR, hazard ratio; CI, confidence interval; PD, performance status; OS, overall survival.

Supplementary table 6. Multivariate analysis for TTF (a), PFS (b) and OS (c) including clinical features and biomarkers.

Variables	Coefficient	p
a. Multivariate for TTF		
Exhausted CD8-related pathway	-2.16431	0.00011
CD20+ cells	-1.12347	0.03678
ASCL1+ tumor cells	-2.55669	3.51e-05
Tumor cells within 20 µm from CD163+ macrophages (%)	0.90877	0.08766
No steroid therapy at treatment start	-0.98979	0.06652
b. Multivariate for PFS		
Exhausted CD8-related pathway	-1.9959	0.000213
ASCL1+ tumor cells	-1.8617	0.000720
No steroid therapy at treatment start	-1.3267	0.007095
Male gender	1.0353	0.041718
b. Multivariate for OS		
CD20+ cells	-1.0495	0.065873
ASCL1+ tumor cells	-2.1548	0.000305
POU2F3+ cells	1.7535	0.003566
CD8 T cells within 20 µm from CD4 T cells	-1.5487	0.005276
Less than 3 metastatic sites	-1.0442	0.047800

Abbreviations: PFS, progression-free survival; TTF, time to treatment failure; OS, overall survival; CD cluster of differentiation;