

**Table S1.** Exclusion criteria for PD-1<sup>T</sup> TILs assessment

<b>List of Exclusion criteria:</b>
- Samples containing <10,000 cells
- Samples obtained >2 years before start of ICB
- Samples from the bronchus site
- Samples containing normal lymphoid tissue

**Table S2.** Overview of all analyzed biomarkers per patient.

Sample ID	1 = DCR 6 months, 0= PD	1 = DCR 12 months, 0= PD	T= Training, V= validation	PD1 <sup>T</sup> TILs per mm <sup>2</sup> tumor area	PD-L1 TPS	TLS per mm <sup>2</sup>	TLS+LA per mm <sup>2</sup>	CD20-positive area per mm <sup>2</sup>
NKI-AvL 001	1	1	T	265	1	0.00	0.14	0.22
NKI-AvL 002	0	0	T	25	40	0.00	0.35	0.57
NKI-AvL 003	0	0	T	80	0	0.19	0.50	2.62
NKI-AvL 004	0	0	T	67	90	0.00	0.00	0.10
NKI-AvL 005	1	1	T	298	0	0.00	0.55	0.34
NKI-AvL 006	0	0	T	6	0	0.00	0.00	0.36
NKI-AvL 007	0	0	T	204	0	0.00	0.24	0.38
NKI-AvL 008	1	1	T	367	80	0.28	0.44	1.08
NKI-AvL 009	0	0	T	43	0	0.01	0.04	0.17
NKI-AvL 010	0	0	T	21	0	0.00	0.00	0.01
NKI-AvL 011	0	0	T	31	30	0.00	0.01	0.08
NKI-AvL 012	0	0	T	150	1	0.00	0.22	0.34
NKI-AvL 013	0	0	T	18	0	0.00	0.02	0.21
NKI-AvL 014	0	0	T	230	100	0.08	0.24	1.45
NKI-AvL 015	0	0	T	55	0	0.00	0.02	0.15
NKI-AvL 016	1	1	T	181	1	0.05	0.16	0.51
NKI-AvL 017	0	0	T	126	0	0.00	0.00	0.03
NKI-AvL 018	1	1	T	226	30	0.16	0.47	1.80
NKI-AvL 019	0	0	T	244	10	0.00	0.00	0.02
NKI-AvL 020	1	1	T	319	100	0.07	0.31	1.31
NKI-AvL 021	1	1	T	352	1	0.66	1.33	5.93
NKI-AvL 022	0	0	T	51	40	0.01	0.07	0.20
NKI-AvL 023	0	0	T	80	30	0.02	0.06	0.20
NKI-AvL 024	0	0	T	31	0	NA	NA	NA
NKI-AvL 025	1	1	T	104	0	NA	NA	NA
NKI-AvL 026	1	1	T	1	5	0	0	0.05
NKI-AvL 027	0	0	T	27	0	0	0	0.04
NKI-AvL 028	0	0	T	44	20	NA	NA	NA
NKI-AvL 029	1	0	T	31	0	0	0.13	0.21
NKI-AvL 030	0	0	T	29	30	0	0	0.08
NKI-AvL 031	0	0	V	152	40	0.12	0.12	0.19
NKI-AvL 032	0	0	V	67	0	0.00	0.48	2.73
NKI-AvL 033	1	1	V	537	0	0.00	0.00	0.63
NKI-AvL 034	1	0	V	24	90	0.00	0.00	0.00
NKI-AvL 035	0	0	V	70	0	0.00	0.00	0.10
NKI-AvL 036	1	0	V	828	0	0.21	0.43	1.87
NKI-AvL 037	0	0	V	434	0	0.45	0.63	3.41
NKI-AvL 038	0	0	V	83	0	0.00	0.00	0.03
NKI-AvL 039	1	1	V	115	0	0.14	0.28	0.45
NKI-AvL 040	0	0	V	34	0	0.22	0.77	1.89
NKI-AvL 041	1	1	V	130	100	0.00	0.00	0.29
NKI-AvL 042	0	0	V	98	0	0.00	0.00	0.01
NKI-AvL 043	0	0	V	44	40	0.00	0.00	0.05
NKI-AvL 044	0	0	V	68	0	0.00	0.00	0.01
NKI-AvL 045	1	1	V	210	5	0.00	0.00	0.25
NKI-AvL 046	0	0	V	1875	0	0.89	2.98	11.07
NKI-AvL 047	0	0	V	25	1	0.00	0.65	0.79
NKI-AvL 048	0	0	V	351	40	0.00	0.00	0.07
NKI-AvL 049	1	1	V	110	40	0.00	0.11	0.33
NKI-AvL 050	0	0	V	43	1	0.00	0.03	0.17
NKI-AvL 051	0	0	V	6	0	0.00	0.00	0.02
NKI-AvL 052	0	0	V	457	0	0.00	0.00	0.51
NKI-AvL 053	0	0	V	321	1	0.00	0.00	0.06
NKI-AvL 054	1	1	V	280	95	0.03	0.33	1.40
NKI-AvL 055	0	0	V	201	10	0.00	0.21	0.78
NKI-AvL 056	1	1	V	213	0	0.03	0.30	1.08
NKI-AvL 057	1	1	V	409	0	0.48	1.28	2.03
NKI-AvL 058	0	0	V	41	0	0.11	0.49	0.97
NKI-AvL 059	0	0	V	21	0	0.05	0.17	0.66
NKI-AvL 060	0	0	V	9	10	0.00	0.00	0.05
NKI-AvL 061	1	0	V	17	0	0.00	0.00	0.76
NKI-AvL 062	0	0	V	3	1	0.00	0.00	0.01

NKI-AvL 063	0	0	V	26	0	0.08	0.58	1.43
NKI-AvL 064	0	0	V	17	60	0.00	0.00	0.19
NKI-AvL 065	0	0	V	13	0	0.00	0.00	0.00
NKI-AvL 066	0	0	V	128	0	0.00	0.00	0.02
NKI-AvL 067	1	1	V	211	0	0.00	0.55	1.58
NKI-AvL 068	0	0	V	85	0	0.00	0.00	0.06
NKI-AvL 069	0	0	V	152	0	0.03	0.20	0.63
NKI-AvL 070	0	0	V	13	0	0.00	0.00	0.04
NKI-AvL 071	0	0	V	7	0	0.00	0.00	0.00
NKI-AvL 072	0	0	V	236	0	0.14	0.60	2.00
NKI-AvL 073	0	0	V	56	0	0.00	0.00	0.09
NKI-AvL 074	0	0	V	15	0	0.00	0.00	0.04
NKI-AvL 075	0	0	V	152	1	0.00	0.00	0.41
NKI-AvL 076	0	0	V	206	80	0.00	0.00	0.03
NKI-AvL 077	0	0	V	2	0	0.00	0.00	0.00
NKI-AvL 078	0	0	V	6	0	0.00	0.00	0.03
NKI-AvL 079	0	0	V	35	0	0.01	0.05	0.38
NKI-AvL 080	0	0	V	22	10	0.00	0.00	0.08
NKI-AvL 081	1	0	V	214	0	0.29	0.58	1.86
NKI-AvL 082	0	0	V	49	0	0.01	0.09	0.31
NKI-AvL 083	1	0	V	160	0	0.05	0.22	0.21
NKI-AvL 084	1	0	V	67	0	0.00	0.06	0.18
NKI-AvL 085	0	0	V	66	60	0.00	0.00	0.05
NKI-AvL 086	0	0	V	49	0	0.00	0.00	0.03
NKI-AvL 087	1	1	V	193	95	0.00	0.00	0.01
NKI-AvL 088	0	0	V	24	40	0.00	0.00	0.00
NKI-AvL 089	0	0	V	11	0	0.00	0.00	0.10
NKI-AvL 090	1	1	V	60	100	0.00	0.00	0.02
NKI-AvL 091	0	0	V	380	1	0.13	0.33	1.33
NKI-AvL 092	0	0	V	2	0	0.00	0.00	0.07
NKI-AvL 093	1	1	V	139	0	0.02	0.14	0.28
NKI-AvL 094	0	0	V	0	0	0.00	0.00	0.02
NKI-AvL 095	1	1	T	459	60	NA	NA	NA
NKI-AvL 096	1	1	T	245	80	NA	NA	NA
NKI-AvL 097	1	1	T	595	0	NA	NA	NA
NKI-AvL 098	1	0	T	13	0	NA	NA	NA
NKI-AvL 099	0	0	T	39	0	NA	NA	NA
NKI-AvL 100	0	0	T	4	0	NA	NA	NA
NKI-AvL 101	0	0	T	85	30	NA	NA	NA
NKI-AvL 102	0	0	T	28	0	NA	NA	NA
NKI-AvL 103	0	0	T	84	0	NA	NA	NA
NKI-AvL 104	0	0	T	83	0	NA	NA	NA
NKI-AvL 105	0	0	T	65	80	NA	NA	NA
NKI-AvL 106	0	0	T	2	0	NA	NA	NA
NKI-AvL 107	0	0	T	57	0	NA	NA	NA
NKI-AvL 108	0	0	V	161	0	NA	NA	NA
NKI-AvL 109	0	0	V	194	0	NA	NA	NA
NKI-AvL 110	0	0	V	42	0	NA	NA	NA
NKI-AvL 111	0	0	V	552	0	NA	NA	NA
NKI-AvL 112	0	0	V	193	3	NA	NA	NA
NKI-AvL 113	0	0	V	7	0	NA	NA	NA
NKI-AvL 114	1	0	V	139	0	NA	NA	NA
NKI-AvL 115	0	0	V	25	0	NA	NA	NA
NKI-AvL 116	1	0	V	12	0	NA	NA	NA
NKI-AvL 117	1	1	V	868	2	NA	NA	NA
NKI-AvL 118	1	1	V	96	40	NA	NA	NA
NKI-AvL 119	0	0	V	66	0	NA	NA	NA
NKI-AvL 120	0	0	V	0	1	NA	NA	NA

**Table S3.** Patient characteristics and treatment outcomes for training and validation set.

		Training cohort (n=43)	Validation cohort (n=77)
Sex	<i>p</i> =0.13		
Male, no.(%)		18 (42%)	44 (57%)
Female, no.(%)		25 (58%)	33 (43%)
Age (years), mean (s.d.)	<i>p</i> =0.21	64 (8)	62 (9)
Smoking (never/ex/current)	<i>p</i> =0.84	3/35/5	8/58/11
Pack years, median (IQR)	<i>p</i> =0.62	30 (21)	28 (28)
PS, no.(%)	<i>p</i> =0.53		
0		12 (28%)	24 (31%)
1		22 (51%)	43 (56%)
≥2		9 (21%)	10 (13%)
Pathology, no.(%)	<i>p</i> =0.90		
Adeno		26 (60%)	50 (65%)
Squamous		9 (21%)	12 (16%)
LCNEC, NSCLC-type		1 (2%)	2 (2%)
NSCLC, NOS		7 (16%)	13 (17%)
Mutations, no. (%)	<i>p</i> =0.18		
KRAS positive		22 (51%)	29 (38%)
PD-L1 TPS, no. (%)			
Negative <1%	<i>p</i> =0.17	22 (51%)	50 (65%)
Positive ≥1%		21 (49%)	27 (35%)
Negative <50%	<i>p</i> =0.39	36 (84%)	69 (90%)
Positive ≥50%		7 (16%)	8 (10%)
Brain metastases, no. (%)	<i>p</i> =1.00	7 (16%)	14 (18%)
Treatment, no. (%)	<i>p</i> =0.11		
Nivolumab		30 (70%)	64 (83%)
Pembrolizumab		13 (30%)	13 (17%)
Line of treatment, no (%)	<i>p</i> =0.19		
1		0 (0%)	1 (1%)
2		35 (81%)	52 (68%)
>2		8 (19%)	24 (31%)
Best Overall Response	<i>p</i> =0.47		
CR/PR		12 (28%)	12 (16%)
SD (PFS ≥6 months)		2 (5%)	11 (14%)
SD (PFS <6 months)		2 (5%)	4 (5%)
PD		27 (63%)	50 (65%)
DC			
6 months	<i>p</i> =0.68	33% (14/43)	29% (22/77)
12 months	<i>p</i> =0.25	28% (12/43)	18% (14/77)

*s.d.*, standard deviation; *IQR*, interquartile range; *PS*, Performance Score, based on the European Cooperative Oncology group (ECOG) performance status score. This is a score ranging from 0 to 5, where 0 indicates no symptoms, 1 indicates mild symptoms and above 1 indicates greater disability; *LCNEC NSCLC type*, large cell neuroendocrine carcinoma non-small cell lung cancer type; *NOS*, not otherwise specified; *KRAS*, Kirsten Rat Sarcoma viral oncogene; *PD-L1*, programmed death ligand 1; *TPS*, tumor proportion score; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease; *DC*, disease control.

**Table S4.** Tissue sample properties of the training and validation set.

		Training cohort (n=43)	Validation cohort (n=77)
Sample type	<i>p</i> =0.33		
Biopsy		30 (70%)	58 (75%)
Resection		13 (30%)	19 (25%)
Sample site	<i>p</i> =0.46		
Primary		19 (44%)	32 (41%)
Metastasis		16 (37%)	36 (47%)
<i>Lung</i>		1	5
<i>Adrenal gland</i>		3	7
<i>Bone</i>		0	7
<i>Pleurae</i>		0	1
<i>Brain</i>		0	2
<i>Muscle / Subcutaneous</i>		3	8
<i>Liver</i>		6	3
<i>Mamma</i>		2	1
<i>Gastrointestinal</i>		1	2
Lymph node metastasis		8 (19%)	9 (12%)

**Table S5.** The relationship between PD-1<sup>T</sup> and clinicopathological variables as categories.

		PD1 <sup>T</sup> <90 per mm <sup>2</sup>	PD1 ≥90 per mm <sup>2</sup>
		n=69	n=51
Sex	<i>p</i> =0.58		
Male, no.(%)		34 (49%)	28 (55%)
Female, no.(%)		35 (51%)	23 (45%)
Age (years), median (IQR)	<i>p</i> = 0.96	63 (57 - 70)	64 (58 - 68)
Smoking (never/ex/current)	<i>p</i> = 0.47	8/52/9	3/41/7
Pack years, median (IQR)	<i>p</i> = 0.18	25 (13 - 40)	30 (20 - 40)
PS, no. (%)	<i>p</i> =0.11		
0		18 (26%)	18 (35%)
1		37 (54%)	28 (55%)
≥2		14 (20%)	5 (10%)
Pathology, no.(%)	<i>p</i> =0.20		
Adeno		48 (69%)	28 (55%)
Squamous		8 (12%)	13 (25%)
LCNEC, NSCLC-type		2 (3%)	1 (2%)
NSCLC, NOS		11 (16%)	9 (18%)
Mutations, no. (%)	<i>p</i> =1		
KRAS positive		31 (45%)	20 (39%)
KRAS negative		26 (38%)	17 (33%)
Kras unknown		12 (17%)	14 (28%)
Brain metastases, no. (%)	<i>p</i> =0.22	15 (22%)	6 (12%)
Treatment, no. (%)	<i>p</i> =0.66		
Nivolumab		53 (77%)	41 (80%)
Pembrolizumab		16 (23%)	10 (20%)
Line of treatment, no (%)	<i>p</i> =0.21		
1		1 (1%)	0 (0%)
2		53 (77%)	34 (67%)
>2		15 (22%)	17 (%)

**Table S6.** The relationship between PD-1<sup>T</sup> and clinicopathological variables as continuous variable.

		PD1 <sup>T</sup> TILs per mm <sup>2</sup> (quantiles)				
		0%	25%	50%	75%	100%
Sex	<i>p</i> =0.67					
Male (n=62)		0	25	67	201	1875
Female (n=58)		1	26	69	199	868
Smoking	<i>p</i> = 0.86					
Never (n=11)		6	30	67	145	459
Ex (n=93)		0	24	66	194	1875
Current (n=16)		7	40	82	207	457
PS	<i>p</i> =0.19					
0 (n=36)		2	25	85	238	868
1 (n=65)		0	27	80	181	1875
≥2 (n=19)		0	26	66	118	457
Pathology	<i>p</i> = 0.60					
Adeno (n=76)		0	25	63	184	1875
Squamous (n=21)		2	31	139	213	595
LCNEC, NSCLC-type (n=3)		0	21	82	264	552
NSCLC, NOS (n=20)		7	37	67	97	126
Mutations	<i>p</i> = 0.42					
KRAS positive (n=51)		0	30	80	200	1875
KRAS negative (n=43)		2	20	66	212	595
Kras unknown (n=26)		0	26	101	185	298
Brain metastases	<i>p</i> = 0.38					
Yes (n=21)		0	29	60	152	828
No (n=99)		0	25	80	207	1875
Treatment	<i>p</i> = 0.81					
Nivolumab (n=94)		0	25	68	206	1875
Pembrolizumab (n=26)		0	26	75	185	868
Line of treatment	<i>p</i> = 0.13					
1 (n=1)						
2 (n=87)		0	25	66	187	868
>2 (n=32)		0	26	104	258	1875

**Table S7.** Predictive accuracy of PD-L1 TPS at 1%, 5%, 10% and 50% cut-off in the validation set (n=77).

Clinical outcome	Biomarker	AUC	Cut-off	Sensitivity	Specificity	NPV	PPV
DC 6m	% PD-L1 TPS	0.58 <i>95% CI: 0.43-0.74</i>	<1% vs ≥1%	41%	67%	74%	33%
			<5% vs ≥5%	36%	82%	76%	44%
			<10% vs ≥10%	32%	82%	75%	41%
			<50% vs ≥50%	23%	95%	75%	63%
DC 12m	% PD-L1 TPS	0.68 <i>95% CI: 0.51-0.86</i>	<1% vs ≥1%	57%	70%	88%	30%
			<5% vs ≥5%	50%	83%	88%	39%
			<10% vs ≥10%	43%	83%	87%	35%
			<50% vs ≥50%	29%	94%	86%	50%

**Table S8.** Predictive accuracy of composite biomarkers PD-L1 TPS+PD-L1 IC in all nivolumab treated patients (n=94).

Clinical outcome	Biomarker	Cut-off	Sensitivity	Specificity	NPV	PPV
DC 6 months	% PD-L1 TPS + PD-L1 IC	<50%+<2 VS ≥50%+<2 and <50%+≥2 and ≥50%+≥2	82	44	85	38
DC 6 months	% PD-L1 TPS + PD-L1 IC	<1%+<2 VS ≥1%+<2 and <1%+≥2 and ≥1%+≥2	82	53	88	43
DC 12 months	% PD-L1 TPS + PD-L1 IC	<50%+<2 VS ≥50%+<2 and <50%+≥2 and ≥50%+≥2	90	44	94	32
DC 12 months	% PD-L1 TPS + PD-L1 IC	<1%+<2 VS ≥1%+<2 and <1%+≥2 and ≥1%+≥2	90	52	95	35

**Table S9.** Predictive accuracy of composite biomarkers PD-1<sup>T</sup> TILs+PD-L1.

Clinical outcome	Biomarker	Cut-off	Sensitivity	Specificity	NPV	PPV
DC 6 months	PD-1 <sup>T</sup> TILs per mm <sup>2</sup> + % PD-L1 TPS	<90+<50% VS ≥90+<50% and <90+≥50% and ≥90+≥50%	86%	64%	92%	49%
DC 6 months	PD-1 <sup>T</sup> TILs per mm <sup>2</sup> + % PD-L1 TPS	<90+<1% VS ≥90+<1% and <90+≥1% and ≥90+≥1%	86%	49%	90%	40%
DC 12 months	PD-1 <sup>T</sup> TILs per mm <sup>2</sup> + % PD-L1 TPS	<90+<50% VS ≥90+<50% and <90+≥50% and ≥90+≥50%	100%	60%	100%	36%
DC 12 months	PD-1 <sup>T</sup> TILs per mm <sup>2</sup> + % PD-L1 TPS	<90+<1% VS ≥90+<1% and <90+≥1% and ≥90+≥1%	100%	48%	100%	30%