

Table S1. Correlation of brain metastasis immunohistochemical profile with clinical and pathologic features

	PD-L1 (n=229)			CD8 peritumoral (n=223)			CD8 intratumoral (n=219)		
	No	Yes	<i>p</i> / <i>Cramer's V</i>	Low	High	<i>p</i> / <i>Cramer's V</i>	Low	High	<i>p</i> / <i>Cramer's V</i>
Primary tumor histological type (n=233)									
Adenocarcinoma	79	26	0.8	38	65	0.07	62	38	0.007/0.3
Undifferentiated carcinoma	27	10		11	25		23	13	
Melanoma	20	7		3	23		7	20	
Squamous cell carcinoma	18	6		7	17		14	7	
Clear cell carcinoma	16	3		3	15		6	12	
High grade serous carcinoma	9	2		5	6		6	5	
Urothelial carcinoma	2	0		3	1		3	1	
Large cell neuroendocrine carcinoma	4	0		0	1		2	0	
Primary tumor origin (n=233)									
Lung	51	29	0.04/0.3	18	60	0.0002/0.4	45	33	0.008/0.3
Breast	27	4		12	18		19	11	
Gastrointestinal tract	25	1		15	11		19	5	
Melanoma	20	7		3	23		7	20	
Kidney	15	3		2	15		6	12	
Ovary	9	3		5	7		5	6	
Head and neck	8	0		5	3		5	1	
Endometrium	4	2		1	5		5	1	
Thyroid gland	4	2		5	1		4	2	
Bladder	4	2		0	5		3	3	
Prostate	5	0		2	3		4	1	
Unknown	3	1		2	2		1	1	
Metastasis localization (n=219)									
Frontal	51	13	0.4	20	42	0.7	33	28	0.8
Cerebellar	49	13		16	44		36	24	
Temporal	20	9		9	19		15	13	
Parietal	21	5		8	18		14	11	
Occipital	16	10		9	17		16	9	
Thalamic	2	0		0	2		0	1	
Multiple brain metastases (n=216)									
Yes	42	11	0.5	15	34	0.9	27	20	0.9
No	120	40		49	109		88	68	
Brain metastasis size (n=113)									
≤ 30 mm	43	16	0.4	17	40	0.4	33	22	0.5
> 30 mm	42	11		19	33		29	24	
Age									
≤ 60 years	86	22	0.3	30	74	0.4	58	65	0.8
> 60 years	89	31		40	78		46	49	
Sex									
M	103	27	0.2	39	86	0.9	68	55	0.7
F	72	27		31	67		55	41	
Performance status (n=206)									
0-1	104	36	0.1	42	95	0.4	74	60	0.1

2-4	53	10		22	39		39	20	
Metastases revealing the primary tumor (n=228)									
yes	59	18	0.9	21	54	0.4	38	33	0.5
no	112	35		47	96		82	61	
Symptomatic metastasis with corticosteroid treatment (n=205)									
Yes	141	42	0.1	60	117	0.2	104	70	0.2
No	12	7		4	16		8	10	
T stage of the primary tumor (n=86)									
T1-T2	29	14	0.3	12	29	0.5	7	4	0.5
T3-T4	32	10		15	28		10	11	
N stage of the primary tumor (n=98)									
Negative	33	9	0.3	13	28	0.3	26	15	0.5
Positive	37	18		19	36		30	24	
M stage of the primary tumor (n=103)									
Negative	44	30	0.6	22	40	0.3	38	22	0.3
Positive	30	10		10	28		21	18	
Type of brain metastasis material									
Resection	145	49	0.1	52	138	0.004	104	87	0.1
Biopsy	22	3		13	10		13	5	

n denotes the number of cases which for the information was available.
 PD-L1: Programmed death ligand 1

Table S2. Correlation of primary tumor's immunohistochemical profile with clinical and pathologic features

	PD-L1 (n=107)			CD8 peritumoral (n=106)			CD8 intratumoral (n=96)		
	No	Yes	<i>p</i>	Low	High	<i>p</i> / <i>Cramer's V</i>	Low	High	<i>p</i>
Primary tumor histological type (n=233)									
Adenocarcinoma	30	16	0.5	9	47	0.3	20	28	0.8
Undifferentiated carcinoma	10	3		1	12		3	8	
Melanoma	9	3		2	10		6	6	
Squamous cell carcinoma	14	4		1	15		6	10	
Clear cell carcinoma	1	2		0	3		1	2	
High grade serous carcinoma	1	1		0	2		0	2	
Urothelial carcinoma	0	1		0	1		0	1	
Large cell neuroendocrine carcinoma	1	1		0	3		1	2	
Primary tumor origin (n=233)									
Lung	39	19	0.3	4	54	0.3	16	34	0.3
Breast	10	1		3	8		7	3	
Gastrointestinal tract	8	3		2	9		5	6	
Melanoma	9	3		2	10		6	6	
Kidney	1	2		0	3		1	2	
Ovary	1	1		0	2		0	2	
Head and neck	3	0		1	2		1	1	
Endometrium	0	0		0	0		0	0	
Thyroid gland	0	0		0	0		0	0	
Prostate	0	0		0	0		0	0	
Unknown	0	0		0	0		0	0	
Metastasis location (n=219)									
Frontal	15	7	0.9	2	20	0.02/ 0.5	5	13	0.7
Cerebellar	20	9		2	26		20	16	
Temporal	12	6		1	16		6	9	
Parietal	6	2		0	8		2	6	
Occipital	9	6		2	13		6	8	
Thalamic	1	0		1	0		1	0	
Multiple brain metastases (n=216)									
Yes	18	4	0.1	4	18	0.2	10	7	0.04
No	4	26		7	66		22	46	
Brain metastasis size (n=113)									
≤30 mm	21	8	0.6	3	26	0.4	9	18	0.5
>30	16	8		4	20		9	13	
Type of primary tumor material (n=105)									
Resection	44	24	0.07	10	58	0.3	21	45	0.04
Biopsy	30	7		3	34		15	13	
T stage									
1	22	11	0.9	1	9	0.9	4	5	0.2
2	19	9		2	22		4	18	
3	18	10		2	17		8	11	
4	30	12		1	8		3	3	
N stage									
	18	10	0.5	2	26	0.4	6	21	0.05

negative	30	12		6	36		16	21	
positive									
Sex	29	8	0.2	7	31	0.1	17	16	0.05
Female	47	23		6	62		20	43	
Male									
Metastasis revealing the primary tumor									
Yes	27	10	0.6	4	34	0.6	17	14	0.02
No	17	21		9	57		19	44	
M stage									
negative	28	15	0.4	5	38	0.9	8	31	0.005
positive	19	7		3	23		13	11	

n denotes the number of cases which for the information was available.

PD-L1: Programmed death ligand 1

Table S3. Analysis of brain metastasis free survival (from primary tumor diagnosis to brain metastasis diagnosis)

	Brain-metastasis free survival (months)	<i>p</i>
PD-L1 brain-metastasis expression		
Yes	29	0.2
No	35	
PD-L1 primary tumor expression		
Yes	22	0.6
No	20	
Correlated brain metastasis and primary tumor PD-L1 expression		
Yes	22	0.4
No	25	
CD8 peritumoral brain metastasis expression		
Low	35	0.3
High	29	
CD8 peritumoral primary tumor expression		
Low	14	0.6
High	20	
Correlated brain metastasis and primary tumor peritumoral CD8 expression		
Yes	20	0.05
No	27	
CD8 intratumoral brain metastasis expression		
Low	33	0.9
High	33	
CD8 intratumoral primary tumor expression		
Low	17	0.3
High	20	
Correlated brain metastasis and primary tumor intratumoral CD8 expression		
Yes	20	0.9
No	20	
Primary tumor origin		
Lung	15	<0.0001
Breast	55	
Melanoma	45	
GI	17	
Renal	21	
Ovary	41	
Head and Neck	41	
Age at brain-metastasis diagnosis		
> 60 years	34	0.6
≤ 60 years	32	
Sex		
Female	39	0.004
Male	27	

Histologic type		
Adenocarcinoma	32	0.01
Squamous cell carcinoma	20	
Clear cell carcinoma	41	
Melanoma	45	
Undifferentiated	41	
Large cell neuroendocrine carcinoma	12	
T stage of the primary tumor		
1-2	27	0.8
3-4	27	
N stage of the primary tumor		
N-	33	0.1
N+	27	
M stage of the primary tumor		
M0	27	0.8
M1	29	

PD-L1: Programmed death ligand 1, GI: gastrointestinal,

Supplementary figure legends

Figure S1. A. Overall survival (OS) after brain metastasis diagnosis. B. OS according to sex C. OS according to age. D. Time to brain metastasis development after the diagnosis of the primary tumor represented as progression-free survival (PFS) E. PFS according to sex. F. Tumors with concordant CD8 expression between the primary tumor and the metastasis have shorter time to brain metastasis development.

Figure S2. Simple regression analysis comparing PD-L1 expression (in %) between brain metastasis and paired primary tumors

Figure S3. Comparison of PD-L1 and CD8 expression between brain metastasis and corresponding primary tumor.

BM=brain metastasis, PT=primary tumor

Figure S4. A. Overall survival after brain metastasis diagnosis according to performance status. B. Overall survival after brain metastasis diagnosis

according to the administration of adjuvant treatment.