



Figure S1 Flowchart of patient enrollment. BMs, brain metastases; NSCLC, non-small cell lung cancer; PD-(L)1, programmed death receptor (ligand) 1; uCRT, upfront cranial radiotherapy.

Table S1 Brain metastases and treatment characteristics of 110 patients with BMs at baseline

Characteristics	N=110
No. of BMs, n (%)	
1–4	83 (75.5)
>4	27 (24.5)
Diameter of largest BM, n (%)	
<10 mm	32 (29.1)
≥10 mm	78 (70.9)
Symptomatic BMs at PD-(L)1 inhibitor treatment initiation, n (%)	
Yes	22 (20.0)
No	88 (80.0)
Extracranial metastases, n (%)	
Yes	90 (81.8)
No	20 (18.2)
History of brain surgery, n (%)	
Yes	10 (9.1)
No	100 (90.9)
History of brain RT, n (%)	
Yes	
WBRT	26 (23.6)
SRT	14 (12.7)
SRS	6 (5.5)
No	64 (58.2)
uCRT*, n (%)	
Yes	
WBRT	6 (5.5)
SRT	12 (10.9)
SRS	8 (7.3)
No	84 (76.4)

*, uCRT was defined as the receipt of cranial irradiation at any point between the initiation of anti-PD-1/PD-L1 therapy and the first subsequent progression event. BMs, brain metastases; PD-(L)1, programmed death receptor (ligand) 1; RT, radiotherapy; uCRT, upfront cranial radiotherapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; WBRT, whole-brain radiation therapy.

Table S2 Cox proportional-hazards analyses for PFS in the whole study population

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≤ 60 vs. > 60 years)	0.93	0.76-1.14	0.466			
Sex (male vs. female)	1.38	1.08-1.77	0.011	1.12	0.87-1.45	0.371
Smoking status (never vs. current or former)	1.10	0.98-1.23	0.111			
Histology (adenocarcinoma vs. non-adenocarcinoma)	1.04	0.84-1.29	0.733			
ECOG PS (≥ 2 vs. 0-1)	1.92	1.52-2.42	< 0.001	1.49	1.16-1.91	0.002
No. of organs harboring metastases (> 2 vs. ≤ 2)	2.60	2.06-3.29	< 0.001	1.94	1.48-2.53	< 0.001
Lines of PD-(L)1 inhibitor treatment (≥ 2 vs. 1)	1.71	1.39-2.11	< 0.001	1.53	1.22-1.91	< 0.001
Treatment regimen (monotherapy vs. combination therapy)	1.07	0.87-1.32	0.514			
BMs (yes vs. no)	1.52	1.20-1.91	< 0.001	1.13	0.88-1.44	0.353
PD-L1 status						
Positive	0.53	0.34-0.83	0.005	0.66	0.44-0.99	0.046
Unknown	0.65	0.44-0.97	0.033	0.67	0.42-1.06	0.085
Negative	Ref	–	–	Ref	–	–

BMs, brain metastases; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PD-(L)1, programmed death receptor (ligand) 1; PFS, progression-free survival.

Table S3 Cox proportional-hazards analyses for OS in the whole study population

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≤ 60 vs. > 60 years)	0.93	0.70-1.24	0.623			
Sex (male vs. female)	1.17	0.99-1.39	0.063	1.19	0.84-1.68	0.340
Smoking status (never vs. current or former)	1.13	0.97-1.33	0.114			
Histology (adenocarcinoma vs. non-adenocarcinoma)	1.02	0.75-1.38	0.902			
ECOG PS (≥ 2 vs. 0-1)	1.87	1.37-2.54	< 0.001	1.36	0.96-1.94	0.089
No. of organs harboring metastases (> 2 vs. ≤ 2)	2.47	1.81-3.36	< 0.001	2.07	1.45-2.97	< 0.001
Line of PD-(L)1 inhibitor treatment (≥ 2 vs. 1)	1.31	0.98-1.74	0.071	1.14	0.84-1.55	0.393
Treatment regimen (monotherapy vs. combination therapy)	1.05	0.79-1.40	0.722			
BMs (yes vs. no)	1.24	0.90-1.70	0.182			
PD-L1 status						
Positive	0.69	0.39-1.24	0.214	0.97	0.53-1.77	0.918
Unknown	0.64	0.38-1.08	0.095	0.74	0.44-1.26	0.271
Negative	Ref	–	–	Ref	–	–

BM, brain metastases; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-(L)1, programmed death receptor (ligand) 1.

Table S4 Predictors of the development of BMs for patients without baseline BMs who were treated with anti-PD-(L)1 therapy

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≤ 60 vs. > 60 years)	1.27	0.83-1.96	0.272			
Sex (female vs. male)	0.75	0.36-1.55	0.430			
Smoking status (never vs. current or former)	0.73	0.40-1.34	0.308			
Histology (adenocarcinoma vs. non-adenocarcinoma)	2.03	0.74-5.54	0.167			
ECOG PS (≥ 2 vs. 0-1)	1.59	0.53-4.76	0.405			
No. of organs harboring metastases (> 2 vs. ≤ 2)	5.60	1.88-16.67	0.002	5.07	1.70-15.10	0.004
Primary tumor size (> 2 vs. ≤ 2 cm)	6.39	1.88-21.71	0.003	5.79	1.70-19.69	0.005
Line of PD-(L)1 inhibitor treatment (≥ 2 vs. 1)	2.03	0.84-4.94	0.117			
Treatment regimen (monotherapy vs. combination therapy)	0.54	0.21-1.39	0.200			
N stage (N1-3 vs. N0)	1.63	0.55-4.84	0.381			
PD-L1 status						
Positive	0.59	0.18-1.96	0.388			
Unknown	0.42	0.14-1.23	0.112			
Negative	Ref	-	-			

BMs, brain metastases; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PD-(L)1, programmed death receptor (ligand) 1.

Table S5 Univariate and multivariate Cox proportional-hazards model for OS in patients with BMs

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≤ 60 vs. > 60 years)	0.85	0.50-1.46	0.563			
Sex (female vs. male)	1.38	1.03-1.85	0.030	1.66	0.91-3.04	0.030
Smoking status (never vs. current or former)	1.00	0.74-1.36	0.995			
Histology (adenocarcinoma vs. non-adenocarcinoma)	0.93	0.66-1.31	0.674			
ECOG PS (≥ 2 vs. 0-1)	1.36	0.74-2.49	0.325			
Extracranial metastases (yes vs. no)	2.01	0.93-4.32	0.075	1.68	0.76-3.71	0.098
Lines of PD-(L)1 inhibitor treatment (≥ 2 vs. 1)	1.77	0.97-3.23	0.065	1.30	0.69-2.47	0.153
Treatment regimen (monotherapy vs. combination therapy)	1.21	0.71-2.08	0.478			
Symptomatic BMs (yes vs. no)	0.72	0.34-1.53	0.390			
Diameter of largest BM (≥ 10 vs. < 10 mm)	0.98	0.55-1.78	0.956			
Receipt of uCRT (yes vs. no)	0.50	0.25-0.99	0.045	0.55	0.28-1.10	0.055
PD-L1 status						
Positive	0.65	0.21-2.06	0.467			
Unknown	0.67	0.24-1.89	0.448			
Negative	Ref	-	-			

BMs, brain metastases; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-(L)1, programmed death receptor (ligand) 1; uCRT, upfront cranial radiotherapy.

Table S6 Baseline characteristics of patients with 1-4 BMs, stratified according to the receipt of uCRT

Characteristics	Total (N=83)	uCRT group (N=18)	Non-uCRT group (N=65)	P value [†]
Median age at initiation of PD-(L)1 inhibitor treatment, years (range)	60 (34-74)	60 (41-74)	61 (34-72)	0.891
Sex, n (%)				
Male	65 (78.3)	15 (83.3)	50 (76.9)	0.794
Female	18 (21.7)	3 (16.7)	15 (23.1)	
Smoking status at PD-(L)1 inhibitor treatment initiation, n (%)				
Current	26 (31.3)	7 (38.9)	19 (29.2)	0.491
Former	40 (48.2)	9 (50.0)	31 (47.7)	
Never	17 (20.5)	2 (11.1)	15 (23.1)	
ECOG PS, n (%)				
0-1	61 (73.5)	13 (72.2)	48 (73.8)	1.00
≥2	22 (26.5)	5 (27.8)	17 (26.2)	
Histology, n (%)				
Adenocarcinoma	71 (85.5)	15 (83.3)	56 (86.2)	0.473
Squamous cell	9 (10.8)	3 (16.7)	6 (9.2)	
NSCLC, other	3 (3.6)	0 (0.0)	3 (4.6)	
PD-L1 status, n (%)				
Positive	22 (26.5)	4 (22.2)	18 (27.7)	0.608
Negative	5 (6.0)	0 (0.0)	5 (7.7)	
Unknown	56 (67.5)	14 (77.8)	42 (64.6)	
Extracranial metastases, n (%)				
Yes	64 (77.1)	12 (66.7)	52 (80.0)	0.382
No	19 (22.9)	6 (33.3)	13 (20.0)	
PD-(L)1 inhibitor therapy line, range 1-7				
1	31 (37.3)	9 (50.0)	22 (33.8)	0.392
2	22 (26.5)	3 (16.7)	19 (29.2)	
≥3	30 (36.1)	6 (33.3)	24 (36.9)	
Type of inhibitor				
PD-1	77 (92.8)	15 (83.3)	62 (95.4)	0.113
PD-L1	6 (7.2)	3 (16.7)	3 (4.6)	
Monotherapy or combination				
Anti-PD-1/PD-L1 monotherapy				
1 st line	9 (10.8)	1 (5.6)	8 (12.3)	0.235
≥2 nd line	35 (42.2)	5 (27.8)	30 (46.2)	
Combination*				
1 st line	22 (26.5)	8 (44.4)	14 (21.5)	
≥2 nd line	17 (20.5)	4 (22.2)	13 (20.0)	
Diameter of largest BM, n (%)				
<10 mm	27 (32.5)	3 (16.7)	24 (36.9)	0.105
≥10 mm	56 (67.5)	15 (83.3)	41 (63.1)	
Symptomatic BMs at PD-(L)1 inhibitor treatment initiation, n (%)				
Yes	13 (15.7)	6 (33.3)	7 (10.8)	0.049
No	70 (84.3)	12 (66.7)	58 (89.2)	

[†], patients treated with and without upfront cranial radiotherapy are compared; *, combination of anti-PD-1/PD-L1 therapy and chemotherapy or anti-PD-1/PD-L1 therapy and EGFR-TKIs. BMs, brain metastases; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; PD-(L)1, programmed death receptor (ligand) 1; uCRT, upfront cranial radiotherapy.