Table S1 The characteristics of the included clinical trials

Clinical trial	Study name	Study period	Line of therapy	Treatment comparison	N	Patients with baseline BMs, N	Patients receiving previous cranial radiotherapy, N
Randomized controlled trial							
Fehrenbacher *et al.* (24)	POPLAR	2013–2018	2 or 3	Atezo *vs.* Doc	144 *vs.* 143	10 *vs.* 18	10 *vs.* 15
Rittmeyer *et al.* (4)	OAK	2014–2019	2 or 3	Atezo *vs.* Doc	613 *vs.* 612	84 *vs.* 87	75 *vs.* 71
Socinski *et al.* (23)	IMpower150	2015–2020	1	Atezo + Bev + CP *vs.* Atezo + CP *vs.* Bev + CP	400 *vs.* 402 *vs.* 400	51 *vs.* 53 *vs.* 45	51 *vs.* 53 *vs.* 45
Jotte *et al.* (22)	IMpower131	2015–2021	1	Atezo + CnP *vs.* CnP *vs.* Atezo + CP	343 *vs.* 340 *vs.* 338	19 *vs.* 16 *vs.* 18	19 *vs.* 16 *vs.* 18
West *et al.* (21)	IMpower130	2015–2021	1	Atezo + CnP *vs.* CnP	483 *vs.* 240	102 *vs.* 49	95 *vs.* 45
Single-arm phase II trial							
Spigel *et al.* (20)	FIR	2013–2017	≥1	Atezo	138	10	0
Peters *et al.* (19)	BIRCH	2014–2019	≥1	Atezo	667	3	1

Atezo, atezolizumab; Doc, docetaxel; Bev, bevacizumab; CP, carboplatin plus paclitaxel; CnP, carboplatin plus nab-paclitaxel; BMs, brain metastases.
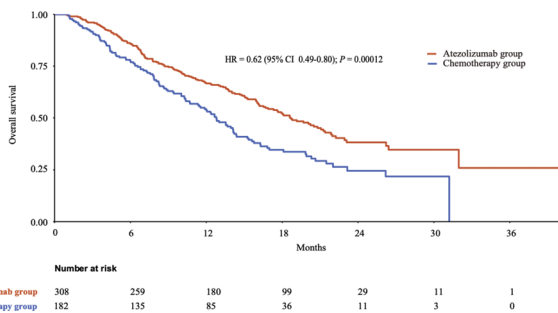

Figure S1 Kaplan-Meier curves of overall survival for patients with BM in the atezolizumab group and the chemotherapy group.
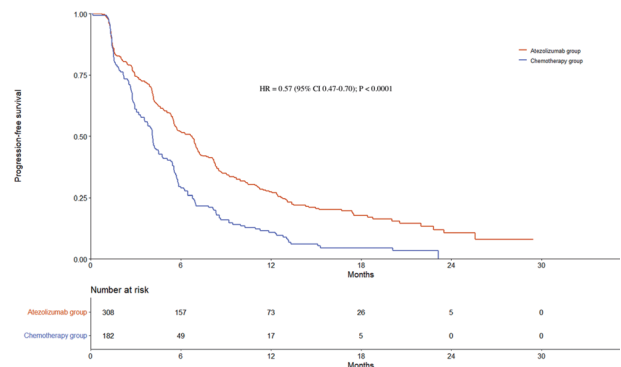

Figure S2 Kaplan-Meier curves of progression-free survival for patients with BM in the atezolizumab group and the chemotherapy group.

Table S2 Baseline characteristics of patients with baseline BM treated with atezolizumab according to their history of cranial radiotherapy

Baseline characteristics	Total (n=308)	No previous cranial radiotherapy (n=28)	Previous cranial radiotherapy (n=280)	P value*
Age (years)				0.713
≥65	122 (40%)	12 (43%)	110 (39%)	
<65	186 (60%)	16 (57%)	170 (61%)	
Sex				0.942
Male	174 (56%)	16 (57%)	158 (56%)	
Female	134 (44%)	12 (43%)	122 (44%)	
ECOG PS				0.129
0	118 (38%)	7 (25%)	111 (40%)	
≥1	190 (62%)	21 (75%)	169 (60%)	
Histology				0.395
Squamous	44 (14%)	2 (7%)	42 (15%)	
Non-squamous	264 (86%)	26 (93%)	238 (85%)	
Tobacco use history				>0.999
Never	47 (15%)	4 (14%)	43 (15%)	
Current or previous	261 (85%)	24 (86%)	237 (85%)	
Number of prior lines of systemic therapies				<0.001
0	217 (70%)	7 (25%)	210 (75%)	
≥1	91 (30%)	21 (75%)	70 (25%)	
Treatment regimen				<0.001
Monotherapy	91 (30%)	21 (75%)	70 (25%)	
Combination therapy	217 (70%)	7 (25%)	210 (75%)	
Previous extracranial radiotherapy				<0.001
Yes	81 (26%)	18 (64%)	63 (23%)	
No	227 (74%)	10 (36%)	217 (78%)	
PD-L1 expression				0.043
TC2/3 or IC2/3	111 (36%)	15 (54%)	96 (34%)	
TC0/1 or IC0/1	197 (64%)	13 (46%)	184 (66%)	

*, patients with and without previous cranial radiotherapy are compared. ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1. TC, tumor cell (TC2/3: ≥5% and <50%/≥50% PD-L1 staining; TC0/1: <1%/≥1% and <5% PD-L1 staining); IC, tumor-infiltrating immune cell (IC2/3: ≥5% and <10%/≥10% PD-L1 staining; IC0/1: <1%/≥1% and <5% PD-L1 staining).

Table S3 Baseline characteristics of patients without baseline BMs and those with previously irradiated BMs before and after propensity score matching in the atezolizumab group

Baseline characteristics	Before PSM				After PSM			
	Patients without baseline BMs (n=2,849)	Patients with previously irradiated BMs (n=280)	P value[†]	SMD	Patients without baseline BMs (n=560)	Patients with previously irradiated BMs (n=280)	P value[†]	SMD
Age (years)			0.004	0.184			0.568	0.048
≥65	1378 (48%)	110 (39%)			233 (42%)	110 (39%)		
<65	1471 (52%)	170 (61%)			327 (58%)	170 (61%)		
Sex			0.005	0.173			0.902	0.014
Male	1848 (65%)	158 (56%)			312 (56%)	158 (56%)		
Female	1001 (35%)	122 (44%)			248 (44%)	122 (44%)		
Race			0.399	0.054			0.758	0.029
White	2344 (82%)	236 (84%)			478 (85%)	236 (84%)		
Others	505 (18%)	44 (16%)			82 (15%)	44 (16%)		
ECOG PS			0.878	0.010			0.783	0.027
0	1116 (39%)	111 (40%)			215 (38%)	111 (40%)		
≥1	1733 (61%)	169 (60%)			345 (62%)	169 (60%)		
Tobacco use history			0.789	0.017			0.973	0.010
Never	455 (16%)	43 (15%)			84 (15%)	43 (15%)		
Current or previous	2394 (84%)	237 (85%)			476 (85%)	237 (85%)		
Histology			<0.001	0.435			>0.999	<0.001
Squamous	945 (33%)	42 (15%)			84 (15%)	42 (15%)		
Non-squamous	1904 (67%)	238 (85%)			476 (85%)	238 (85%)		
Treatment regimen			<0.001	0.436			0.978	0.082
Monotherapy	1292 (45%)	70 (25%)			138 (25%)	70 (25%)		
Combination therapy	1557 (55%)	210 (75%)			422 (75%)	210 (75%)		
Previous extracranial radiotherapy			0.002	0.203			0.613	0.043
Yes	896 (31%)	63 (23%)			116 (21%)	63 (23%)		
No	1953 (69%)	217 (78%)			444 (79%)	217 (78%)		
PD-L1 expression			<0.001	0.262			0.779	0.026
TC2/3 or IC2/3	1341 (47%)	96 (34%)			199 (36%)	96 (34%)		
TC0/1 or IC0/1	1508 (53%)	184 (66%)			361 (64%)	184 (66%)		

[†], patients without brain metastases and patients with previously irradiated brain metastases are compared. PSM, propensity score matching; BMs, brain metastases; SMD, standardized mean difference; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; TC, tumor cell (TC2/3: ≥5% and <50%/≥50% PD-L1 staining; TC0/1: <1%/≥1% and <5% PD-L1 staining); IC, tumor-infiltrating immune cell (IC2/3: ≥5% and <10%/≥10% PD-L1 staining; IC0/1: <1%/≥1% and <5% PD-L1 staining).

Table S4 Baseline characteristics of patients without baseline BMs and those with previously irradiated BMs before and after propensity score matching in the chemotherapy group

Baseline characteristics	Before PSM				After PSM			
	Patients without baseline BMs (n=1,344)	Patients with previously irradiated BMs (n=165)	P value[†]	SMD	Patients without baseline BMs (n=330)	Patients with previously irradiated BMs (n=165)	P value[†]	SMD
Age (years)			0.059	0.157			>0.999	<0.001
≥65	634 (47%)	65 (39%)			130 (39%)	65 (39%)		
<65	710 (53%)	100 (61%)			200 (61%)	100 (61%)		
Sex			<0.001	0.291			>0.999	0.006
Male	891 (66%)	86 (52%)			173 (52%)	86 (52%)		
Female	453 (34%)	79 (48%)			157 (48%)	79 (48%)		
Race			0.279	0.087			>0.999	0.007
White	1090 (81%)	128 (78%)			257 (78%)	128 (78%)		
Others	254 (19%)	37 (22%)			73 (22%)	37 (22%)		
ECOG PS			0.519	0.053			0.766	0.038
0	540 (40%)	62 (38%)			118 (36%)	62 (38%)		
≥1	804 (60%)	103 (62%)			212 (64%)	103 (62%)		
Tobacco use history			0.846	0.016			0.740	0.044
Never	180 (13%)	23 (14%)			41 (12%)	23 (14%)		
Current or former	1164 (87%)	142 (86%)			289 (88%)	142 (86%)		
Histology			<0.001	0.484			>0.999	0.009
Squamous	457 (34%)	23 (14%)			47 (14%)	23 (14%)		
Non-squamous	887 (66%)	142 (86%)			283 (86%)	142 (86%)		
Previous extracranial radiotherapy			0.856	0.015			0.972	0.013
Yes	392 (29%)	47 (28%)			92 (28%)	47 (28%)		
No	952 (71%)	118 (72%)			238 (72%)	118 (72%)		
PD-L1 expression			0.064	0.150			0.870	0.025
TC2/3 or IC2/3	425 (32%)	64 (39%)			124 (38%)	64 (39%)		
TC0/1 or IC0/1	919 (68%)	101 (61%)			206 (62%)	101 (61%)		

[†], patients without brain metastases and patients with previously irradiated brain metastases are compared. PSM, propensity score matching; BMs, brain metastases; SMD, standardized mean difference; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; TC, tumor cell (TC2/3: ≥5% and <50%/≥50% PD-L1 staining; TC0/1: <1%/≥1% and <5% PD-L1 staining); IC, tumor-infiltrating immune cell (IC2/3: ≥5% and <10%/≥10% PD-L1 staining; IC0/1: <1%/≥1% and <5% PD-L1 staining).

Table S5 Baseline characteristics of patients without baseline BMs and those with non-irradiated BMs before and after propensity score matching in the atezolizumab group

Baseline characteristics	Before PSM				After PSM			
	Patients without baseline BMs (n=2,849)	Patients with non-irradiated BMs (n=28)	P value[†]	SMD	Patients without baseline BMs (n=56)	Patients with non-irradiated BMs (n=28)	P value[†]	SMD
Age (years)			0.562	0.111			>0.999	<0.001
≥65	1378 (48%)	12 (43%)			24 (43%)	12 (43%)		
<65	1471 (52%)	16 (57%)			32 (57%)	16 (57%)		
Sex			0.395	0.159			>0.999	<0.001
Male	1848 (65%)	16 (57%)			32 (57%)	16 (57%)		
Female	1001 (35%)	12 (43%)			24 (43%)	12 (43%)		
Race			0.050	0.471			0.333	0.193
White	2344 (82%)	27 (96%)			56 (100%)	27 (96%)		
Others	505 (18%)	1 (4%)			0 (0%)	1 (4%)		
ECOG PS			0.126	0.307			>0.999	<0.001
0	1116 (39%)	7 (25%)			14 (25%)	7 (25%)		
≥1	1733 (61%)	21 (75%)			42 (75%)	21 (75%)		
Tobacco use history			0.809	0.047			>0.999	<0.001
Never	455 (16%)	4 (14%)			8 (14%)	4 (14%)		
Current or previous	2394 (84%)	24 (86%)			48 (86%)	24 (86%)		
Histology			0.004	0.686			0.713	0.139
Squamous	945 (33%)	2 (7%)			6 (11%)	2 (7%)		
Non-squamous	1904 (67%)	26 (93%)			50 (89%)	26 (93%)		
Treatment regimen			0.002	0.636			>0.999	<0.001
Monotherapy	1292 (45%)	21 (75%)			42 (75%)	21 (75%)		
Combination therapy	1557 (55%)	7 (25%)			14 (25%)	7 (25%)		
Previous extracranial radiotherapy			<0.001	0.696			>0.999	<0.001
Yes	896 (31%)	18 (64%)			36 (64%)	18 (64%)		
No	1953 (69%)	10 (36%)			20 (36%)	10 (36%)		
PD-L1 expression			0.493	0.130			>0.999	<0.001
TC2/3 or IC2/3	1341 (47%)	15 (54%)			30 (54%)	15 (54%)		
TC0/1 or IC0/1	1508 (53%)	13 (46%)			26 (46%)	13 (46%)		

[†], patients without brain metastases and patients with previously irradiated brain metastases are compared. PSM, propensity score matching; BMs, brain metastases; SMD, standardized mean difference; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; TC, tumor cell (TC2/3: ≥5% and <50%/≥50% PD-L1 staining; TC0/1: <1%/≥1% and <5% PD-L1 staining); IC, tumor-infiltrating immune cell (IC2/3: ≥5% and <10%/≥10% PD-L1 staining; IC0/1: <1%/≥1% and <5% PD-L1 staining).

Table S6 Baseline characteristics of patients without baseline BMs and those with non-irradiated BMs before and after propensity score matching in the chemotherapy group

Baseline characteristics	Before PSM				After PSM			
	Patients without baseline BMs (n=1,344)	Patients with non-irradiated BMs (n=17)	P value†	SMD	Patients without baseline BMs (n=34)	Patients with non-irradiated BMs (n=17)	P value†	SMD
Age (years)			0.330	0.243			>0.999	<0.001
≥65	634 (47%)	6 (35%)			12 (35%)	6 (35%)		
<65	710 (53%)	11 (65%)			22 (65%)	11 (65%)		
Sex			0.248	0.275			>0.999	<0.001
Male	891 (66%)	9 (53%)			18 (53%)	9 (53%)		
Female	453 (34%)	8 (47%)			16 (47%)	8 (47%)		
Race			0.088	0.375			0.266	0.332
White	1090 (81%)	11 (65%)			27 (79%)	11 (65%)		
Others	254 (19%)	6 (35%)			7 (21%)	6 (35%)		
ECOG PS			0.368	0.227			>0.999	<0.001
0	540 (40%)	5 (29%)			10 (29%)	5 (29%)		
≥1	804 (60%)	12 (71%)			24 (71%)	12 (71%)		
Tobacco use history			0.610	0.118			0.789	0.077
Never	180 (13%)	3 (18%)			5 (15%)	3 (18%)		
Current or previous	1164 (87%)	14 (82%)			29 (85%)	14 (82%)		
Histology			0.691	0.099			0.827	0.065
Squamous	457 (34%)	5 (29%)			9 (26%)	5 (29%)		
Non-squamous	887 (66%)	12 (71%)			25 (74%)	12 (71%)		
Previous extracranial radiotherapy			0.008	0.626			>0.999	<0.001
Yes	392 (29%)	10 (59%)			20 (59%)	10 (59%)		
No	952 (71%)	7 (41%)			14 (41%)	7 (41%)		
PD-L1 expression			0.846	0.048			>0.999	<0.001
TC2/3 or IC2/3	425 (32%)	5 (29%)			10 (29%)	5 (29%)		
TC0/1 or IC0/1	919 (68%)	12 (71%)			24 (71%)	12 (71%)		

†, patients without brain metastases and patients with previously irradiated brain metastases are compared. PSM, propensity score matching; BMs, brain metastases; SMD, standardized mean difference; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; TC, tumor cell (TC2/3: ≥5% and <50%/≥50% PD-L1 staining; TC0/1: <1%/≥1% and <5% PD-L1 staining); IC, tumor-infiltrating immune cell (IC2/3: ≥5% and <10%/≥10% PD-L1 staining; IC0/1: <1%/≥1% and <5% PD-L1 staining).

Table S7 Atezolizumab-related neurologic adverse events

Atezolizumab-related neurologic adverse event	Patients without baseline BM (n=2868)	Patients with non-irradiated BM (n=28)	Patients with previously irradiated BM (n=280)
Dizziness	58 (2%)	1 (4%)	9 (3%)
Dysgeusia	56 (2%)	0	7 (3%)
Headache	83 (3%)	1 (4%)	14 (5%)
Neurotoxicity	9 (0.3%)	0	2 (1%)
Neuropathy peripheral	50 (2%)	2 (7%)	7 (3%)
Paraesthesia	39 (1%)	1 (4%)	1 (0.4%)
Peripheral neuropathy*	42 (1%)	0	3 (1%)

*, includes peripheral sensory neuropathy and peripheral motor neuropathy. BM, brain metastasis.