nature medicine

Article

https://doi.org/10.1038/s41591-023-02392-7

Pembrolizumab in brain metastases of diverse histologies: phase 2 trial results

Received: 8 March 2023

Accepted: 9 May 2023

Published online: 02 June 2023

Check for updates

Priscilla K. Brastianos[1,6] ✉, Albert E. Kim[1,2,6], Anita Giobbie-Hurder[3], Eudocia Q. Lee[3], Nancy U. Lin[3], Beth Overmoyer[3], Patrick Y. Wen[3], Lakshmi Nayak[3], Justine V. Cohen[4], Jorg Dietrich[1], April Eichler[1], Rebecca S. Heist[1], Ian Krop[5], Donald Lawrence[1], Jennifer Ligibel[3], Sara Tolaney[3], Erica Mayer[3], Eric Winer[5], Brittany Bent[1], Magali A. de Sauvage[1], Nazanin Ijad[1], Juliana M. Larson[1], Braxton Marion[1], Sally Nason[3], Naina Murthy[1], Sherry Ratcliff[1], Elizabeth J. Summers[1], Maura Mahar[1], Helen A. Shih[1], Kevin Oh[1], Daniel P. Cahill[1], Elizabeth R. Gerstner[1,2,7] & Ryan J. Sullivan[1,7]

Brain metastases (BMs) are an emerging challenge in oncology due to increasing incidence and limited treatments. Here, we present results of a single-arm, open-label, phase 2 trial evaluating intracranial efficacy of pembrolizumab, a programmed cell death protein 1 inhibitor, in 9 patients with untreated BMs (cohort A) and 48 patients with recurrent and progressive BMs (cohort B) across different histologies. The primary endpoint was the proportion of patients achieving intracranial benefit, defined by complete response, partial response or stable disease. The primary endpoint was met with an intracranial benefit rate of 42.1% (90% confidence interval (CI): 31–54%). The median overall survival, a secondary endpoint, was 8.0 months (90% CI: 5.5–8.7 months) across both cohorts, 6.5 months (90% CI: 4.5–18.7 months) for cohort A and 8.1 months (90% CI: 5.3–9.6 months) for cohort B. Seven patients (12.3%), encompassing breast, melanoma and sarcoma histologies, had overall survival greater than 2 years. Thirty patients (52%; 90% CI: 41–64%) had one or more grade-3 or higher adverse events that were at least possibly treatment related. Two patients had grade-4 adverse events (cerebral edema) that were deemed at least possibly treatment related. These results suggest that programmed cell death protein 1 blockade may benefit a select group of patients with BMs, and support further studies to identify biomarkers and mechanisms of resistance. ClinicalTrials.gov identifier: NCT02886585

BMs have emerged as a growing problem in modern oncology due to their rising incidence and neuro-cognitive morbidity. Due to recent guidelines that recommend expanded screening for BMs[1], an increasing number of cancer patients present with intracranial lesions that are relatively small and minimally symptomatic. Other patients possess BMs in an inoperable location. These cases represent opportunities for central nervous system (CNS)-penetrant systemic therapy. However, many systemic therapies have demonstrated limited intracranial efficacy, and the development of more effective treatments is an unmet need.

A full list of affiliations appears at the end of the paper. ✉e-mail: pbrastianos@mgh.harvard.edu

https://doi.org/10.1038/s41591-023-02392-7

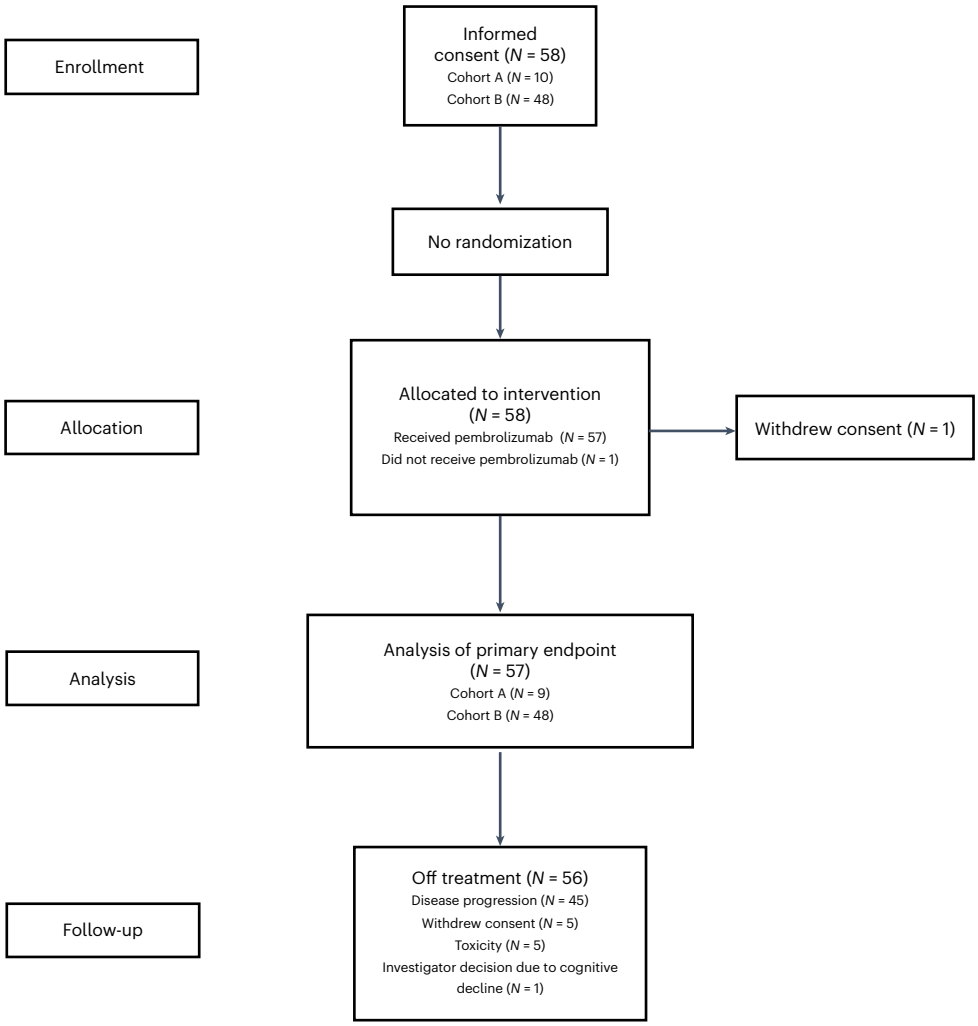


Fig. 1 | Trial schema. A total of 58 patients with BMs were consented and enrolled to the study between October 2016 and October 2018. Cohort A enrolled 10 patients with at least one untreated BM, and cohort B enrolled 48 patients with progressive BMs.

The difficulty in treating BMs is due, in part, to distinct mutational and transcriptional differences between BMs and extracranial metastases (ECMs)[2–4]. Recent work suggests that the BM tumor microenvironment (TME) is more immunosuppressive compared to that of primary tumors or ECMs. Several studies comparing patient-matched primary tumors and BMs found reduced T cell infiltration and expansion, as well as inhibition of dendritic cell maturation and helper T cell signaling pathways, in BMs[4,5]. Single-cell profiling of patient-matched primary lung cancer, ECMs and BMs illustrated a profound shift toward immunosuppressive T cell phenotypes in BMs[5]. Therefore, a logical therapeutic strategy for BMs is to evaluate immune-based strategies that augment T cell cytotoxicity within BMs.

Recent studies have demonstrated considerable promise for immune checkpoint inhibitors (ICIs) in BMs[6–8]. The randomized phase 2 CheckMate204 study (NCT02320058), which evaluated ipilimumab and nivolumab patients with asymptomatic BMs from melanoma, reported an intracranial benefit rate of 57% and a complete response (CR) rate of 26% (ref. 6). At the 3-year follow-up, the study population had an overall survival (OS) rate of 71.9% (refs. 8,9), suggesting that combination ICI therapy should be considered as a frontline option for melanoma patients with BMs. A subsequent open-label phase 2 study (NCT02085070) reported a 29.7% intracranial response rate (RR) with pembrolizumab in non-small-cell lung cancer (NSCLC) patients with programmed death-ligand 1 (PD-L1) expression ≥ 1%, and 0% RR in patients with PD-L1 expression < 1% (ref. 7), suggesting that PD-L1 expression may be a biomarker for ICI response. On the basis of these studies, ICIs are often used as first-line treatment for patients with BMs from melanoma and NSCLC.

However, investigations of ICI therapy for BMs of non-melanoma or lung histologies in prospective clinical trials have been limited. This clinical scenario is of increasing importance, given the rising incidence of BMs for histologies that do not classically have a high CNS tropism (for example, gastrointestinal cancers)[10]. Furthermore, effective ICI therapy could have paradigm-shifting ramifications for patients with BMs. With improved intracranial antitumor activity, these treatments would reduce the need for surgical resection and intracranial radiation. Deferring, or at least decreasing the dose of, radiation would improve quality of life and functional outcomes through minimizing radiation-induced neurotoxicity (for example, radiation necrosis and neurocognitive impairment). These survivorship considerations are timely issues, particularly as patients are living longer with both intracranial and extracranial disease control. However, while ICI-based paradigms have shown durable efficacy for many solid tumors, the majority of trials historically excluded patients with BMs. Therefore, based on translational work suggesting that the immunosuppressive TME of BMs drives treatment resistance, we hypothesized that pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, would result in antitumor activity within the CNS. Given intracranial activity of pembrolizumab, coupled with studies showing

https://doi.org/10.1038/s41591-023-02392-7

Table 1 | Patient demographics and disease characteristics at enrollment

	All		Cohort			
			A		B	
	N	%	*N*	%	*N*	%
Sex						
Female	46	80.7	6	66.7	40	83.3
Male	11	19.3	3	33.3	8	16.7
ECOG performance status						
0	25	43.9	5	55.6	20	41.7
1	28	49.1	4	44.4	24	50.0
2	4	7.0	0	0	4	8.3
Median age, years (range)	53 (28–80)		53 (34–75)		52 (28–80)	
Initial primary tumor diagnosis						
Breast	35	61.4	4	44.4	31	64.6
HR+HER2$^+$	9	–	–	–	9	–
HR+HER2$^-$	7	–	–	–	7	–
HR+HER2 unknown	1	–	–	–	1	–
HR−HER2$^+$	7	–	–	–	7	–
Triple-negative	11	–	4	–	7	–
Melanoma	2	3.5	–	–	2	4.2
BRAF mutation	1	–	–	–	1	–
NSCLC-not otherwise specified	7	12.3	1	11.1	6	12.5
EGFR mutation	2	–	–	–	2	–
ALK rearrangement	1	–	–	–	1	–
Ovarian	1	1.8	1	11.1	–	–
Renal cell carcinoma	1	1.8	–	–	1	2.1
Extraosseous osteosarcoma	1	1.8	–	–	1	2.1
Esophageal	1	1.8	–	–	1	2.1
Neuroendocrine carcinoma	1	1.8	1	11.1	–	–
Pituitary	2	3.5	–	–	2	4.2
Carcinoma	1	1.8	–	–	1	1.8
Neuroendocrine tumor	1	1.8	–	–	1	1.8
Prostate	1	1.8	–	–	1	2.1
Small-cell lung cancer	2	3.5	1	11.1	1	2.1
Unknown primary	1	1.8	1	11.1	–	–
Advanced sinonasal ACC	1	1.8	–	–	1	2.1
Alveolar soft-part sarcoma	1	1.8	–	–	1	2.1
Extracranial metastatic disease?	40	70.2	8	88.9	32	66.7
Lung	28	–	4	–	24	–
Lymph node	22	–	8	–	14	–
Bone	14	–	0	–	14	–
Liver	9	–	3	–	6	–
Visceral	7	–	2	–	5	–
Adrenal	3	–	0	–	3	–
More than 1 BM?						
No	11	19.3	4	44.4	7	14.6
Yes	46	80.7	5	55.6	41	83.4
Months since diagnosis of primary tumor, median (range)	36 (1–295)		23 (3–69)		38 (1–295)	
Prior systemic therapies	50	87.7	8	88.9	42	87.5
Median number of systemic therapies (range)	3 (1–16)		4 (1–6)		3 (1–16)	
Prior BM-directed treatment						
Intracranial radiation	41	71.9	0	0	41	85.4
Median number of prior rounds of radiation (range)	1 (1–6)					
Prior brain surgery	45	78.9	1[a]	11.1	44	91.7
Median number of prior surgeries (range)	2 (1–4)					
Prior systemic therapy	25	43.9	0	0	25	52.1
Median number of systemic therapies (range)	2 (1–15)					
Chemotherapy	21	36.8	0	0	20	41.7
Targeted therapy	16	28.1	0	0	16	33.3
Antibody–drug conjugate	9	15.8	0	0	9	18.8

[a]The one patient in cohort A who received prior brain surgery underwent a ventriculoperitoneal shunt and a craniotomy (for diagnostic purposes) and immediately afterwards, the patient enrolled onto the study for intracranial disease given multiple new untreated BMs. ACC, adenoid cystic carcinoma.

manageable adverse events (AEs)[7,11,12], we designed a prospective phase 2 study evaluating pembrolizumab in patients with treatment-naïve and recurrent BMs of diverse histologies.

Results

Trial

We conducted a phase 2 study to investigate the therapeutic effect of pembrolizumab in patients with CNS metastases. The trial included four cohorts: patients with previously untreated BMs (cohort A), recurrent BMs (cohort B), leptomeningeal carcinomatosis (cohort C) and those with 1–7 BMs undergoing stereotactic radiosurgery (cohort D). Per our prespecified analytic plan, cohorts A and B were combined for assessment of outcomes, and cohorts C and D were analyzed separately. The results of cohort C were previously reported and included patients with leptomeningeal carcinomatosis[13].

The primary endpoint for cohorts A and B was intracranial benefit combined for both cohorts, as defined by CR, partial response (PR) or stable disease (SD) by Response Assessment in Neuro-Oncology (RANO)[14] criteria for BMs. Secondary endpoints included OS, extracranial response (as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria[15]), time to intracranial progression (TTP_{CNS}), time to extracranial progression ($TTP_{extracranial}$) and toxicity. While these endpoints were assessed after combining cohorts A and B, the secondary endpoints of TTP_{CNS} and $TTP_{extracranial}$ were also reported on a per-cohort basis.

Patients

Between 6 October 2016 and 16 October 2018, 58 patients were enrolled (Fig. 1). Cohort A (untreated BMs) enrolled 10 patients, and cohort B (progressive BMs) enrolled 48 patients. For cohort A, patients treated with prior radiation, surgical resection or systemic therapy for their primary or extracranial disease were allowed if they had at least one BM that had not previously been treated with any modality. Cohort B enrolled patients with progressive brain metastases after CNS-directed therapy, such as radiation or surgery. Tumor histologies of enrolled patients are listed in Table 1. For the breast cancer cohort,

https://doi.org/10.1038/s41591-023-02392-7

Table 2 | Summary of response data for patients who experienced intracranial benefit (RANO and RECIST)

Case no.	Cohort	Primary tumor histology	Breast cancer subtype	Best overall response (RANO)	Best extracranial response (RECIST)	Reason off treatment
7	B	Breast	HR+HER2$^+$	SD	PD	PD
8	B	Melanoma		CR	PR	Toxicity
9	B	Breast	Triple-negative	SD	Unevaluable	PD
16	B	Pituitary		SD	Unevaluable	Withdrew consent
25	B	Breast	HR+HER2$^+$	SD	PD	PD
34	B	NSCLC		SD	SD	PD
40	B	Breast	HR+HER2$^+$	SD	SD	Toxicity
47	B	Pituitary		SD	SD	PD
50	A	Breast	Triple-negative	SD	PD	PD
51	B	Breast	HR+HER2$^-$	SD	SD	PD
56	A	NSCLC		PR—unsustained	PD	PD
57	B	NSCLC		CR	SD	Toxicity
58	B	Breast	Triple-negative	SD	PD	PD
62	B	Advanced sinonasal ACC		SD	Unknown	PD
63	B	Alveolar soft-part sarcoma		PR—sustained	SD	On treatment
66	B	Breast	HR+HER2$^-$	SD	SD	PD
67	B	Breast	HR+HER2 unknown	SD	SD	Withdrew consent
68	B	Breast	HR- HER2$^+$	SD	SD	PD
69	A	Ovarian		SD	PD	PD
70	B	Breast	Triple-negative	SD	PR	PD
71	B	Melanoma		SD	PD	PD
74	B	Breast	HR+HER2$^+$	SD	SD	PD
77	B	Breast	HR+HER2$^-$	SD	PD	PD
78	B	Prostate		PR—unsustained	SD	PD

16 patients had HER2-positive disease, 17 patients had hormone receptor (HR)-positive disease and 11 patients had the triple-negative subtype. For the 7 patients with NSCLC, two had *EGFR* mutations and one had an *ALK* rearrangement. For the 2 patients with melanoma, one had an activating *BRAF* mutation. The median time between initial cancer diagnosis and study enrollment was 36 months (range: 1–295 months) for the entire cohort, 23 months (range: 3–69 months) for cohort A and 38 months (range: 1–295 months) for cohort B. Fifty patients (87.7%) received systemic therapies before enrollment; 25 patients (43.9%) received CNS-specific systemic therapies following the initial diagnosis of BMs and before trial enrollment. The median number of prior CNS-specific systemic therapies was 2 (range: 1–15). Forty-one patients (71.9%) received prior intracranial radiation, with a median of one prior round of radiation (range: 1–6). Forty-five patients (78.9%) underwent prior brain surgery, with a median of 2 prior intracranial surgeries (range: 1–4) per patient. Patients were allowed to receive additional antitumor-directed therapy after stopping protocol treatment.

Primary endpoint

As one patient withdrew consent before receiving pembrolizumab, the sample size for efficacy and safety analyses was 57 patients. Twenty-four patients exhibited intracranial benefit from pembrolizumab (Table 2). The overall intracranial benefit rate was 42.1% (90% CI: 31–54%). Per prespecified criteria, the overall trial endpoint would be met if 8 or more patients had intracranial benefit; therefore, our study met its primary endpoint. In total, 3 of 9 (33.3%; 90% CI: 10–65%) patients in cohort A and 21 of 48 (43.8%; 90% CI: 31–57%) patients in cohort B had intracranial benefit. Intracranial efficacy was observed for diverse histologies, including breast, ovarian, pituitary and alveolar sarcoma (Extended Data Table 1). Thirty-seven percent of breast cancer patients (90% CI: 24–52%) and 43% of NSCLC patients (90% CI: 13–77%) had intracranial benefit. All four breast cancer subtypes were enrolled and derived efficacy from pembrolizumab; however, no significant relationship between clinical benefit with breast cancer subtype ($P = 0.55$), HER2 status ($P = 0.73$) or HR status ($P = 0.31$) was noted. No NSCLC patient with a known oncogenic driver had an intracranial response; however, our study only enrolled three patients meeting these criteria. Notably, five patients in our cohort (8.8%; 90% CI: 4–18%) had an intracranial response as defined by either PR or CR. The primary tumor histologies for these five patients were: NSCLC ($N = 2$), melanoma, alveolar sarcoma and prostate.

Secondary efficacy endpoints

Median OS was 8.0 months (90% CI: 5.5–8.7 months; Fig. 2). The median OS was 6.5 months (90% CI: 4.5–18.7 months) in cohort A and 8.1 months (90% CI: 5.3–9.6 months) in cohort B. The 1-year OS rate was 31% (90% CI: 19–44%) and 2-year OS rate was 14% (90% CI: 6–24%). The median TTP_{CNS} was 1.6 months (90% CI: 1.4–2.9 months; Fig. 3) for the entire cohort. The TTP_{CNS} was 1.6 months (90% CI: 1.2–4.5 months; Extended Data Fig. 1) in cohort A and 2.2 months (90% CI: 1.4–3.1 months; Extended Data Fig. 1) in cohort B. The median TTP_{CNS}, for the 24 patients with intracranial benefit, was 4.1 months (90% CI: 3.1–5.5 months). Notably, there were seven patients who survived for more than 2 years after

https://doi.org/10.1038/s41591-023-02392-7

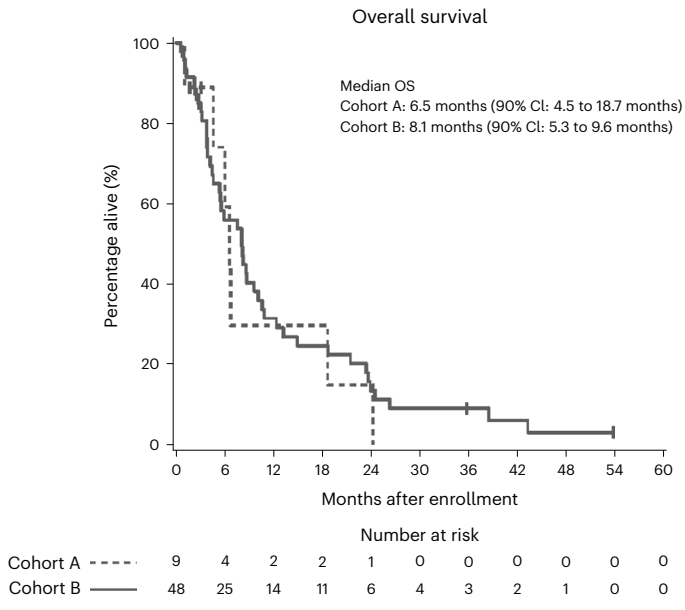


Fig. 2 | Kaplan–Meier estimates for overall survival. Kaplan–Meier estimates for all patients enrolled on trial. The median OS was 8.0 months (90% CI: 5.5–8.7 months). Cohort A (9 patients) is shown by the dashed line. Cohort B (48 patients) is shown by the bolded line.

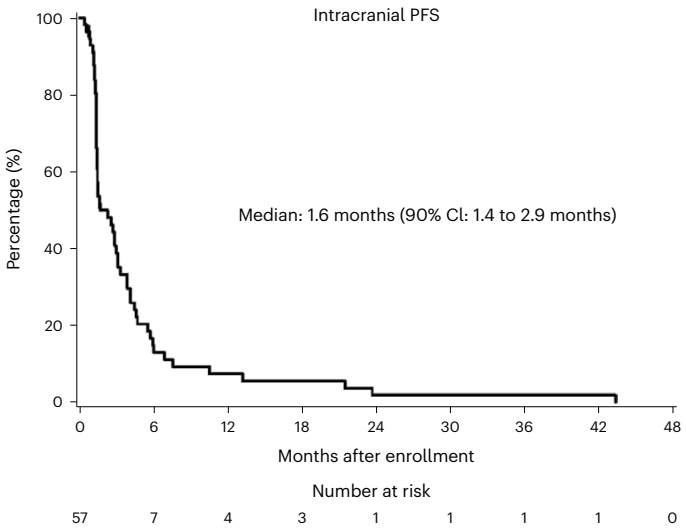


Fig. 3 | Kaplan–Meier estimate for intracranial progression-free survival. The median intracranial progression-free survival (PFS) was 1.6 months (90% CI: 1.4–2.9 months). Of 57 patients, 55 (96%) experienced an intracranial PFS event, and the remaining 2 patients were both lost to follow-up; 39 patients experienced CNS progression and 16 additional patients died without CNS progression. At 12 weeks, the intracranial PFS rate was 44% (90% CI: 31–57%), and at 18 weeks, the intracranial PFS rate was 26% (90% CI: 15–38%).

enrollment; primary tumor histologies included: breast ($N = 5$; two had HER2-positive and HR-positive disease, two had triple-negative disease and one had HER2-negative and HR-positive disease), melanoma and alveolar sarcoma. There was no significant difference ($P = 0.66$) in OS between patients with active extracranial disease and those without. All but one patient was off pembrolizumab at time of data lock; reasons for discontinuation included progressive disease (PD; $N = 45$), unacceptable toxicity ($N = 5$), subject withdrawal of consent ($N = 5$) and investigator decision ($N = 1$). For the 45 patients who stopped treatment due to intracranial PD, 10 patients (22.2%) had development of new BMs and 37 patients (82.2%) had progression of a known BM.

Seventeen patients did not have measurable extracranial disease at time of enrollment. For the remaining 40 patients, the extracranial disease RECIST RR was 7.5% (3/40; 90% CI: 2–18%) and extracranial benefit rate was 45% (18/40; 90% CI: 31–59%). Two patients in cohort A (25%; 90% CI: 5–60%) and 16 patients in cohort B (50%; 90% CI: 34–66%) had extracranial benefit. The median $TTP_{extracranial}$ was 4.5 months (90% CI: 2.7–8.0 months; Extended Data Fig. 2) for the entire cohort, 4.5 months (90% CI: 1.2–6.7 months; Extended Data Fig. 3) for cohort A and 4.6 months (90% CI: 2.7–8.1 months; Extended Data Fig. 3) for cohort B.

Safety and tolerability

The median number of cycles of pembrolizumab completed was 3 (range: 1–14). All patients reported at least one AE and 36 patients (63%; 90% CI: 51–74%) had one or more grade-3 or higher AE of any attribution. Thirteen patients required treatment delays due to AEs. Five patients had pembrolizumab discontinued due to unacceptable toxicity from transaminitis ($N = 4$) and adrenal insufficiency from hypophysitis ($N = 1$). Fifty patients had one or more AEs of any grade that were at least possibly related to pembrolizumab (Table 3). The most frequently occurring AEs deemed to be at least possibly treatment related were: fatigue ($N = 24$), nausea ($N = 15$), headache ($N = 12$), vomiting ($N = 10$) and transaminitis ($N = 10$). Neurologic AEs were mostly grade 1–2, with several instances of grade-3 or higher encephalopathy ($N = 4$), cerebral edema ($N = 3$) and headache ($N = 2$). Thirty patients (52%; 90% CI: 41–64%) had one or more grade-3 or higher AEs that were at least possibly treatment related. Two patients had a grade-4 AE at least possibly treatment related.

Discussion

While immune-based therapies, such as ICIs, have the potential to augment immune activity within the CNS[16–19], intracranial efficacy of ICI therapy outside of melanoma[6] and NSCLC BMs[7] is unknown as many immuno-oncology trials exclude patients with CNS disease. Consequently, there is considerable variability in physician practice for BMs as practice patterns are derived from post hoc analysis of prior studies, likelihood of ICIs exerting extracranial response and anecdotal experience. To our knowledge, this study is the first histology-agnostic trial dedicated specifically for the BM population evaluating intracranial efficacy of pembrolizumab. Our study met its primary endpoint, demonstrating a 42.1% intracranial benefit rate. These findings, combined with extracranial efficacy observed in diverse histologies[6,7,11], provide additional evidence that ICI deserves further investigation as first-line treatment paradigms for BMs. However, the high toxicity rate of ICI underscores the importance of identifying predictive biomarkers of response.

Consistent with prior trials evaluating intracranial efficacy of systemic agents[6,7,13,20], we chose intracranial benefit, which includes SD in addition to CR and PR, to screen for treatment efficacy. Given multi-institutional studies reporting median OS for patients with BMs at 4–6 months[21–24], prolonged stability for a disease entity with limited therapeutics is clinically meaningful. Our intracranial benefit rate of 42.1% is compelling, because most patients had multiple BMs and exhausted all conventional or off-label treatments before enrollment. The median OS was 8.0 months, which compares favorably to existing OS data for BM patients[21,22,24] and prior trials evaluating intracranial efficacy of systemic therapies[7,20]. The median TTP_{CNS}, for the 24 patients who experienced intracranial benefit, was 4.1 months. Seven of these patients derived durable benefit (OS > 2 years) from pembrolizumab, encompassing breast, melanoma and sarcoma histologies. Therefore, given limited effective systemic therapies for BMs of non-melanoma or NSCLC histologies, our study presents encouraging evidence of intracranial activity in histology-agnostic BMs with PD-1 blockade. We note that the toxicities of pembrolizumab were clinically noteworthy and exceeded those seen in other studies evaluating anti-PD-1 or anti-PD-L1 monotherapy[12,13,25–28], suggesting that further work is needed to optimize these promising treatments.

https://doi.org/10.1038/s41591-023-02392-7

Table 3 | Adverse events/toxicities new or worsening relative to enrollment, at least possibly related to treatment

		Toxicity grade CTCAE v4.0			
		01-Mild	02-Moderate	03-Severe	04-Life threatening
Toxicity category CTCAE v4.0	**Toxicity description CTCAE v4.0**	***N***	***N***	***N***	***N***
Blood and lymphatic system disorders	Anemia	2	2	–	–
	Elevated white blood cells	–	1	–	–
	Hepatotoxicity	–	1	–	–
Cardiac disorders	Ventricular tachycardia	1	–	–	–
Ear and labyrinth disorders	Vertigo	1	–	–	–
Endocrine disorders	Adrenal insufficiency	1	1	1	–
	Hyperthyroidism	1	–	–	–
	Hypophysitis	–	–	1	–
	Hypothyroidism	2	1	–	–
Eye disorders	Blurred vision	1	–	–	–
	Conjunctivitis	1	1	–	–
	Double vision	1	–	–	–
	Dry eye	1	–	–	–
	Itchiness, right eye	1	–	–	–
	Visual changes	–	1	–	–
	Watering eyes	1	–	–	–
Gastrointestinal disorders	Abdominal distension	–	–	1	–
	Abdominal pain	2	–	1	–
	Colitis	1	1	–	–
	Constipation	4	–	–	–
	Diarrhea	4	1	1	–
	Duodenal hemorrhage	1	–	–	–
	Dyspepsia	1	–	–	–
	Gastroesophageal reflux disease	1	–	1	–
	Mouth sore	1	–	–	–
	Nausea	8	6	1	–
	Vomiting	4	6	–	–
General disorders and admin site conditions	Chills	4	–	–	–
	Edema, limbs	1	1	–	–
	Facial numbness with lip tingling	1	–	–	–
	Fatigue	14	9	1	–
	Fever	2	1	–	–
	Gait disturbance	2	2	–	–
	Localized edema	1	–	–	–
	Malaise	4	1	–	–
	Night sweats	1	–	–	–
Infections and infestations	Infection, other; influenza B	–	1	–	–
	Oral Thrush	–	1	–	–
	Sinusitis	–	1	–	–
	Upper respiratory infection	–	1	–	–
Investigations	Alanine aminotransferase increased	6	1	1	–
	Alkaline phosphatase increased	–	1	1	–
	Aspartate aminotransferase increased	6	1	3	–
	Blood bilirubin increased	1	–	–	–
	Elevated thyroid-stimulating hormone	1	–	–	–
	Lymphocyte count decreased	1	–	1	–

https://doi.org/10.1038/s41591-023-02392-7

Table 3 (continued) | Adverse events/toxicities new or worsening relative to enrollment, at least possibly related to treatment

		Toxicity grade CTCAE v4.0			
		01-Mild	02-Moderate	03-Severe	04-Life threatening
Toxicity category CTCAE v4.0	**Toxicity description CTCAE v4.0**	***N***	***N***	***N***	***N***
	Platelet count decreased	1	2	–	–
	Weight gain	1	–	–	–
	Weight loss	1	–	–	–
	Decreased white blood cells	1	1	–	–
Metabolism and nutrition disorders	Anorexia	7	2	–	–
	Hyperglycemia	3	–	–	–
	Hypokalemia	–	–	2	–
	Hypomagnesemia	1	–	–	–
	Hyponatremia	4	–	1	–
	Hypophosphatemia	–	2	–	–
	Transaminitis	1	–	–	–
Musculoskeletal and connective tissue disorders	Arthralgia	3	–	–	–
	Back pain	–	2	–	–
	Body aches	1	–	–	–
	Bone pain	1	–	–	–
	Generalized muscle weakness	3	1	2	–
	Muscle cramps, back and legs	1	–	–	–
	Muscle weakness, left-sided	1	–	–	–
	Muscle weakness, lower limb	1	–	–	–
	Muscle weakness, right-sided	–	1	–	–
	Myalgia	5	–	–	–
	Myositis	–	1	–	–
	Neck pain	2	–	–	–
	Pain in extremity	1	–	–	–
Nervous system disorders	Cerebral edema	–	1	1	2
	Dizziness	4	1	–	–
	Dysarthria	–	1	–	–
	Dysgeusia	4	1	–	–
	Expressive aphasia	–	1	–	–
	Facial muscle weakness	1	–	–	–
	Headache	6	4	2	–
	Memory impairment	1	–	–	–
	Seizure	4	–	–	–
	Somnolence	–	1	–	–
	Syncope	–	–	1	–
Psychiatric disorders	Anxiety	1	–	–	–
	Confusion	2	–	4	–
	Delirium	–	–	1	–
	Depression	1	–	–	–
	Insomnia	5	–	–	–
Respiratory, thoracic and mediastinal disorders	Cough	3	1	–	–
	Dyspnea	3	–	–	–
	Pneumonitis	1	–	–	–
Skin and subcutaneous tissue disorders	Alopecia	1	–	–	–
	Dry skin	1	–	–	–

https://doi.org/10.1038/s41591-023-02392-7

Table 3 (continued) | Adverse events/toxicities new or worsening relative to enrollment, at least possibly related to treatment

		Toxicity grade CTCAE v4.0			
		01-Mild	02-Moderate	03-Severe	04-Life threatening
Toxicity category CTCAE v4.0	**Toxicity description CTCAE v4.0**	***N***	***N***	***N***	***N***
	Itchy skin	–	1	–	–
	Pruritus	3	–	–	–
	Rash, acneiform	2	–	–	–
	Rash, maculopapular	2	–	–	–
Vascular disorders	Hypertension	–	1	–	–
	Hypotension	–	1	–	–

CTCAE, Common Terminology Criteria for Adverse Events.

Given evidence of efficacy, a logical next step is to identify traits predictive of benefit from pembrolizumab. While one may expect that treatment-naïve BMs would have improved sensitivity to treatment compared to pretreated BMs, cohort A had a shorter OS than cohort B, although the numbers were small. One potential explanation is that pretreated tumors may possess a higher somatic mutation burden and immunogenic neoantigens from prior treatment, which may render susceptibility to ICIs. In addition, cohort A had a large proportion of patients with tumor histologies associated with ICI resistance and/or poor prognosis (for example, small-cell lung cancer, ovarian cancer, cancer of unknown primary). There was also no clear link between intracranial efficacy and histology. We observed efficacy for histologies responsive to ICIs, as well as those traditionally resistant to ICIs (for example, HR-positive breast cancer, prostate cancer). We did not identify a relationship between intracranial benefit and breast cancer subtype. Further investigation is needed to identify TME features that confer intracranial sensitivity to ICI.

While these results are promising, many questions remain. Although the intracranial benefit rate was 42.1%, the intracranial RR was only 8.8%. Biomarkers of intracranial activity are needed to inform precision-based approaches, given the risk for AEs in a frail patient population. Principled study focused on our trial's 'exceptional responders' is needed to identify specific facets of those patients' tumor or TME that mediate intracranial response. To build upon this and other studies leveraging ICIs in BMs, omics-based and functional studies evaluating mechanisms of intracranial immune escape and ICI resistance may identify new therapeutic targets. Additionally, we note multiple instances of divergent response between extracranial and intracranial disease burden with ICIs. This observation illustrates a clinical conundrum, where CNS disease may be adequately addressed at the cost of extracranial progression and vice versa. Given molecular and TME differences between BMs and ECMs, we encourage multiorgan TME-based studies to identify intracranial and extracranial mediators of metastasis and ICI sensitivity. These targets may serve as the basis for rationally designed pembrolizumab combination regimens that may result in synchronous extracranial and intracranial response. To facilitate evaluation and clinical translation of these therapeutic strategies, we urge planning of clinical trials with flexible inclusion criteria for patients with untreated or progressive BMs. To this end, the US Food and Drug Administration published recommendations for planning of future studies in light of the increasing incidence of BMs and an urgent need for therapeutics with intracranial activity[29]. Patient-derived samples (for example, pretreatment and posttreatment tissue, blood samples) from these trials are a valuable resource to identify potential biomarkers and mechanisms of resistance, which may then be used to propose new treatment strategies.

Our study had some limitations. First, our study did not possess a comparator arm through which to compare ICIs to best physician practice. Many patients had already exhausted conventional treatments and so there were no further feasible standard treatment options that could serve as an adequate control. Second, while our study had comparable results to prior BM trials, we found a limited overall OS and TTP_{CNS} benefit to pembrolizumab monotherapy. This phenomenon was likely due to the low intracranial RR and divergent responses observed between intracranial and extracranial tumor burden. Additionally, we note that our results were obtained in a population weighted toward heavily pretreated patients in a tertiary referral center and therefore may not be generalizable for the general oncology population. Nonetheless, our data suggest promising intracranial efficacy of pembrolizumab in diverse histologies, as heavily pretreated tumors often exhibit lower RRs to systemic therapies compared to treatment-naïve tumors. In addition, there are few therapeutic options with intracranial efficacy for patients with tumor histologies that do not commonly spread to the CNS. This clinical scenario is increasing in incidence, and a pembrolizumab-based regimen may be a consideration for such patients. Next, we did not obtain health-related quality-of-life measures, which are an important future direction to measure the day-to-day impact that treatment-induced functional impairments have on quality of life.

Finally, our cohort contained a heterogeneous mix of histologies, including some that do not commonly spread to the CNS or respond to ICIs. Our study was initially planned in 2014, before studies demonstrating intracranial efficacy of ICIs for melanoma and NSCLC. As these patients more commonly received ICIs as standard-of-care treatment, our study population was enriched with patients with breast cancer, a tumor type in which ICI monotherapy is not generally effective, and other tumor histologies with minimal therapeutics with intracranial efficacy. Nonetheless, we identified a subset of patients with durable intracranial stability, illustrating the promise of PD-1 blockade as the backbone of future therapeutic strategies for BMs, and warranting further evaluation in larger studies. In addition, our results suggest that the decision to administer pembrolizumab should not be based on solely tumor histology, but perhaps a yet-to-be-determined facet of a patient's tumor genome or TME. Further investigation into biomarkers of response and mechanisms of ICI resistance is needed. We also encourage further study of combination immunotherapy approaches for BM patients, such as using PD-1 blockade in the neoadjuvant setting or in combination with radiation or a systemic therapy targeting a germane feature of the TME. These studies will be instrumental to build upon this study's promise to maximize efficacy and minimize toxicity. Finally, determining the effect of prior treatment (for example, radiation or targeted therapy) of BMs on intracranial efficacy of ICI therapy is an important area of future study to help guide stratification of patients in future trials.

In summary, we conducted a phase 2 trial evaluating efficacy of pembrolizumab in a BM cohort of diverse histologies. Our results suggest that pembrolizumab exerts promising activity in a subset of these tumors and results in improved outcomes compared to historical controls. We also demonstrate durable antitumor activity and manageable

toxicity with pembrolizumab in a subset of patients. These results, combined with prior studies[6,7], illustrate a potential paradigm shift in integrating immune-based therapies for BM treatment regimens, which have traditionally been centered around surgical resection and radiotherapy. However, this promising efficacy will need to be carefully balanced with the risk of toxicity. Therefore, while our trial met its primary endpoint, additional study regarding molecular or TME facets of BMs is needed to identify biomarkers of response or mechanisms of resistance. Those studies can be applied to enhance the therapeutic benefit of PD-1 blockade in rationally designed combinatorial regimens.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02392-7.

References

1. Gradishar, W. J. et al. Clinical practice guidelines in oncology. *J. Natl Compr. Cancer Netw.* **16**, 310–320 (2018).
2. Brastianos, P. K. et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov.* **5**, 1164–1177 (2015).
3. Chen, G. et al. Molecular profiling of patient-matched brain and extracranial melanoma metastases implicates the PI3K pathway as a therapeutic target. *Clin. Cancer Res.* **20**, 5537–5546 (2014).
4. Fischer, G. M. et al. Molecular profiling reveals unique immune and metabolic features of melanoma brain metastases. *Cancer Discov.* **9**, 628–645 (2019).
5. Kim, N. et al. Single-cell RNA sequencing demonstrates the molecular and cellular reprogramming of metastatic lung adenocarcinoma. *Nat. Commun.* **11**, 2285 (2020).
6. Tawbi, H. A. et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N. Engl. J. Med.* **379**, 722–730 (2018).
7. Goldberg, S. B. et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. *Lancet Oncol.* **21**, 655–663 (2020).
8. Tawbi, H. A. et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. *Lancet Oncol.* **22**, 1692–1704 (2021).
9. Long, G. V. et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol.* **19**, 672–681 (2018).
10. Sundermeyer, M. L., Meropol, N. J., Rogatko, A., Wang, H. & Cohen, S. J. Changing patterns of bone and brain metastases in patients with colorectal cancer. *Clin. Colorectal Cancer* **5**, 108–113 (2005).
11. Powles, T. et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol.* **21**, 1563–1573 (2020).
12. Brastianos, P. K. et al. Phase 2 study of pembrolizumab in patients with recurrent and residual high-grade meningiomas. *Nat. Commun.* **13**, 1325 (2022).
13. Brastianos, P. K. et al. Single-arm, open-label phase 2 trial of pembrolizumab in patients with leptomeningeal carcinomatosis. *Nat. Med.* **26**, 1280–1284 (2020).
14. Lin, N. U. et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol.* https://doi.org/10.1016/S1470-2045(15)70057-4 (2015).
15. Eisenhauer, E. A. et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* https://doi.org/10.1016/j.ejca.2008.10.026 (2009).
16. Taggart, D. et al. Anti–PD-1/anti–CTLA-4 efficacy in melanoma brain metastases depends on extracranial disease and augmentation of CD8$^+$T cell trafficking. *Proc. Natl Acad. Sci. USA* **115**, E1540–E1549 (2018).
17. Thomas, D. L., Kranz, D. M. & Roy, E. J. Experimental manipulations of afferent immune responses influence efferent immune responses to brain tumors. *Cancer Immunol. Immunother.* **57**, 1323–1333 (2008).
18. Sasaki, K. et al. Preferential expression of very late antigen-4 on type 1 CTL cells plays a critical role in trafficking into central nervous system tumors. *Cancer Res.* **67**, 6451–6458 (2007).
19. Masson, F. et al. Brain microenvironment promotes the final functional maturation of tumor-specific effector CD8$^+$T cells. *J. Immunol.* **179**, 845–853 (2007).
20. Brastianos, P. K. et al. Palbociclib demonstrates intracranial activity in progressive brain metastases harboring cyclin-dependent kinase pathway alterations. *Nat. Cancer* **2**, 498–502 (2021).
21. Brastianos, P. K., Curry, W. T. & Oh, K. S. Clinical discussion and review of the management of brain metastases. *JNCCN J. Natl Compr. Canc. Netw.* **11**, 1153–1164 (2013).
22. Sperduto, P. W. et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2011.38.0527 (2012).
23. Sperduto, P. W., Berkey, B., Gaspar, L. E., Mehta, M. & Curran, W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int. J. Radiat. Oncol. Biol. Phys.* https://doi.org/10.1016/j.ijrobp.2007.06.074 (2008).
24. Gaspar, L. et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int. J. Radiat. Oncol. Biol. Phys.* https://doi.org/10.1016/S0360-3016(96)00619-0 (1997).
25. Weber, J. et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N. Engl. J. Med.* **377**, 1824–1835 (2017).
26. Harrington, K. J. et al. Efficacy and safety of nivolumab plus ipilimumab vs nivolumab alone for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck: the phase 2 CheckMate 714 randomized clinical trial. *JAMA Oncol.* https://doi.org/10.1001/JAMAONCOL.2023.0147 (2023).
27. Wakelee, H. A. et al. IMpower010: primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (NSCLC). *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2021.39.15_suppl.8500 (2021).
28. Goldberg, S. B. et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol.* **17**, 976–983 (2016).
29. US Food and Drug Administration. Cancer clinical trial eligibility criteria: brain metastases. Guidance for industry. https://www.fda.gov/media/121317/download (2020).

https://doi.org/10.1038/s41591-023-02392-7

[1]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA. [2]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA, USA. [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA. [4]Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. [5]Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA. [6]These authors contributed equally: Priscilla K. Brastianos, Albert E. Kim. [7]These authors jointly supervised this work: Elizabeth R. Gerstner, Ryan J. Sullivan. ✉e-mail: pbrastianos@mgh.harvard.edu

Methods

Study oversight

The study (Clinicaltrials.gov identifier NCT02886585) was designed by the principal investigators and conducted in accordance with the provision of the Declaration of Helsinki and Good Clinical Practice guidelines. The Dana-Farber Harvard Cancer Center (DF/HCC) Institutional Review Board approved the protocol. All patients provided signed informed consent. Funding was provided by Merck. The clinical trial protocol is included in the Supplementary Information.

Patients

Eligible patients had histologically confirmed disease from any metastatic solid tumor and measurable disease in the CNS, defined as at least one metastasis that could be measured in at least one dimension as ≥5 mm. For cohort A (10 patients), patients must have had previously untreated BM. Patients with newly diagnosed, treatment-naïve primary tumors who presented with BMs were not allowed to forego available therapy that demonstrated a definitive OS benefit as first-line therapy. Therefore, the following diagnoses in the treatment-naïve setting were excluded: HER2-positive breast cancer, small-cell lung cancer and an oncogene-addicted NSCLC (for example, an *EGFR* or *ALK* mutation). In cases of treatment-naive systemic tumors, only patients for whom there was no available therapy with a definitive OS benefit were permitted. Otherwise, enrolled patients in cohort A had to progress on at least one line of prior therapy for their primary tumor.

For cohort B (48 patients), patients must have had progressive BMs immediately before enrollment. Any number of BM-directed therapies, such as surgery, radiation and systemic therapies with CNS penetration, were allowed. For patients with prior intracranial radiation, there must have been unequivocal evidence of progression of at least one lesion treated by radiation (for example, tissue confirmation or discussion in a multidisciplinary tumor board). Participants who had chemotherapy, targeted therapy, immunotherapy or radiotherapy within 2 weeks before trial enrollment were excluded. To minimize the risk of enrolling patients with pseudo-progression, patients with prior intracranial radiation must have unequivocal evidence of progression (for example, biopsy). Concurrent radiation or systemic therapy, other than aromatase/hormone inhibition or ovarian suppression, were not allowed. Other key inclusion criteria included the following: age ≥ 18 years, ECOG performance status ≤ 2 and stable dose of dexamethasone at 2 mg or less for at least 7 d before start of trial. Key exclusion criteria included leptomeningeal involvement of cancer and prior treatment with an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent.

Study design, treatment and endpoints

The Dana-Farber/Harvard Cancer Center Data and Safety Monitoring Committee reviewed all toxicity and accrual data. Pembrolizumab was administered intravenously at 200 mg every 3 weeks until disease progression, death or unacceptable toxicity. Dose reductions were not permitted; however, dose interruptions of up to 12 weeks were allowed for AEs. Treatment was resumed once AEs improved to grade 0–1 and corticosteroids (if started) were reduced to ≤10 mg of prednisone or equivalent.

Brain magnetic resonance imaging and computed tomography of the chest, abdomen or pelvis was obtained every 8 weeks for re-staging. Intracranial and extracranial efficacy was assessed centrally via blinded review by the Massachusetts General Hospital (MGH) Tissue Imaging Metrics Core using RANO[14] and RECIST (v1.1) (ref. 15) criteria for CNS and extracranial disease, respectively. The primary endpoint was intracranial benefit, defined as a best response of CR, PR or SD during treatment. Under these criteria, CR is defined as the disappearance of all CNS target lesions. PR is a ≥30% decrease in the sum of longest diameters (LDs) in CNS target lesions, relative to the baseline or nadir sum LDs, without new CNS lesions. This response must be sustained for at least 4 weeks, while on a stable corticosteroid dose. SD is defined as a <30% decrease and a <20% increase in the sum LDs of target lesions relative to baseline/nadir LDs, without new CNS lesions. Secondary endpoints include extracranial RR (defined as CR or PR, per RECIST), intracranial PFS, extracranial PFS, OS and toxicity using CTCAE v4.0.

Statistical analysis

This study was designed as an open-label, single-stage, single-arm phase 2 clinical trial with a target accrual of 58 patients to achieve at least 52 evaluable patients (that is, received at least one dose of pembrolizumab). The population comprised two cohorts that were combined for analysis: cohort A (untreated BMs) and cohort B (treatment-refractory BMs). The primary efficacy endpoint was the intracranial benefit rate based on RANO criteria. The study design compared a null intracranial benefit rate of 10% against an alternative of 24%. This null intracranial benefit rate was selected based upon recent clinical studies evaluating intracranial efficacy of systemic therapies in BM[7,30–33]. If at least 8 patients among the total of 52 had intracranial benefit, the primary efficacy endpoint would be met and pembrolizumab would be considered worthy of further study in this patient population. This design has a type-I error of 10% and power of 89% (target type-II error of 15%).

Intracranial and extracranial benefit rates were summarized with 90% exact binomial CIs. Toxicities that were new or worsening relative to baseline were summarized according to the worst grade occurring for each patient. The distributions of OS and PFS were presented using the method of Kaplan–Meier with 90% CI estimates using log(−log) methods. Clinical data were collected with InForm Software (version 6.2). Data analysis was performed using SAS 9.4 (SAS Institute). No data were excluded from the analyses. As this was a non-blinded, non-randomized study, the investigators were not blinded to allocation during experiments and outcome assessment.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The raw clinical and imaging data are protected due to patient privacy laws. Information is taken directly from the electronic medical record or original source generated by treating investigators (for example, email confirmations, AE logs). This is stored on a secured network drive to which only appropriately trained and delegated staff have access to. Lesion measurements are obtained from the Tumor Metrics Imaging Core online portal that uses a secure server to which only appropriately trained and delegated staff are granted access to. Any requests for raw and analyzed data should be sent in writing to P.B. and will be reviewed by the DF/HCC Institutional Review Board in an expeditious fashion (for example, approximately 6 months). Patient-related data not included in the paper were generated as part of a clinical trial and are subject to patient confidentiality. Any data and materials (for example, study protocol, clinical data or imaging data) that can be shared will require approval from the DF/HCC Institutional Review Board and a material transfer agreement. De-identified data then will be transferred to the inquiring investigator in an expeditious fashion over secure file transfer. The study protocol and statistical analysis plan are included with the submission.

References

30. Freedman, R. A. et al. TBCRC 022: a phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J. Clin. Oncol.* **37**, 1081–1089 (2019).
31. Margolin, K. et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol.* **13**, 459–465 (2012).

32. Lin, N. U. et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J. Clin. Oncol.* **26**, 1993–1999 (2008).
33. Lin, N. U. et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin. Cancer Res.* **15**, 1452–1459 (2009).

Acknowledgements

Funding for this trial was provided by Merck Sharp & Dohme, a subsidiary of Merck & Co. (to MGH), Damon Runyon Cancer Research Foundation (to P.K.B.), Ben and Catherine Ivy Foundation (to P.K.B.). P.K.B. also receives support from Breast Cancer Research Foundation, Hellenic Women's Club Demetra Fund, Terry and Jean de Gunzburg MGH Research Scholar Fund and the National Institutes of Health (1R01CA227156-01 and 1R01CA244975-01). A.E.K. is supported by an American Brain Tumor Association Basic Research Fellowship In Honor of P. Fabbri, the William G. Kaelin, Jr., Physician-Scientist Award of the Damon Runyon Cancer Research Foundation, American Association for Cancer Research Breast Cancer Research Fellowship and the American Society of Clinical Oncology Young Investigator Award. E.R.G. is supported by the National Cancer Institute (R01CA211238 and R01CA244975). Most importantly, we thank the patients and their families for contributing to research efforts.

Author contributions

P.K.B. and R.J.S. conceived the study and wrote the protocol with input from E.R.G., D.P.C., F.G.B. and A.G.-H. P.K.B., A.E.K., E.Q.L., N.U.L., B.O., P.Y.W., L.N., J.V.C., J.D., A.E., R.S.H., I.K., D.L., E.M., E.W., M.M., K.O., H.A.S., D.P.C., E.R.G., M.M. and R.J.S. supported the clinical trial, including recruitment and/or management of patients in the trial. A.G.-H. performed the statistical analysis. A.E.K., B.B., M.A.S., N.I., J.M.L., B.M., S.N., N.M., S.R. and E.J.S. helped collect data and samples. E.R.G. was the imaging chair of the study. A.E.K., P.K.B., E.R.G. and R.J.S. wrote the manuscript. All the authors interpreted the data, reviewed the manuscript and approved the final version.

Competing interests

P.K.B. consulted for Tesaro, Angiochem, Genentech-Roche, ElevateBio, Eli Lilly, SK Life Sciences, Pfizer, Voyager Therapeutics, Sintetica, MPM, Advise Connect Inspire, Kazia and Dantari, received institutional research funding (to MGH) from Merck, Mirati, Eli Lilly, Kinnate, BMS and Pfizer and has received honoraria from Merck, Medscape, Pfizer, and Genentech-Roche. B.O. has received clinical trial support from Incyte and Eisai. J.D. has served as a consultant for Amgen, Blue Earth Diagnostics and Unum Therapeutics and received research support (to MGH) from Novartis and Eli Lilly. R.S.H. consulted for AbbVie, Daichii Sankyo, EMD Serono, Lilly, Novartis, Regeneron, and Sanofi; and received institutional research funding (to MGH) from Abbvie, Agios, Corvus, Daichii Sankyo, Erasca, Exelixis, Lilly, Mirati, Novartis and Turning Point. P.Y.W. received institutional research funding (to DF/HCC) from AstraZeneca/Medimmune, Beigene, Celgene, Chimerix, Eli Lilly, Erasca, Genentech/Roche, Kazia, MediciNova, Merck, Novartis, Nuvation Bio, Puma, Servier, Vascular Biogenics and VBI Vaccines, and has served on the scientific advisory board for AstraZeneca, Bayer, Black Diamond, Celularity, Chimerix, Day One Bio, Genenta, Mundipharma, Novartis, Novocure, Nuvation Bio, Prelude Therapeutics, Sapience, Servier, Sagimet, Vascular Biogenics and VBI Vaccines. H.A.S. has served on the scientific advisory board for Advanced Accelerator Applications, and received institutional research funding (to MGH) from AbbVie. R.J.S. consulted for Novartis, BMS and Pfizer, and received institutional research funding (to MGH) from Merck. The remaining authors declare no competing interests.

Additional information

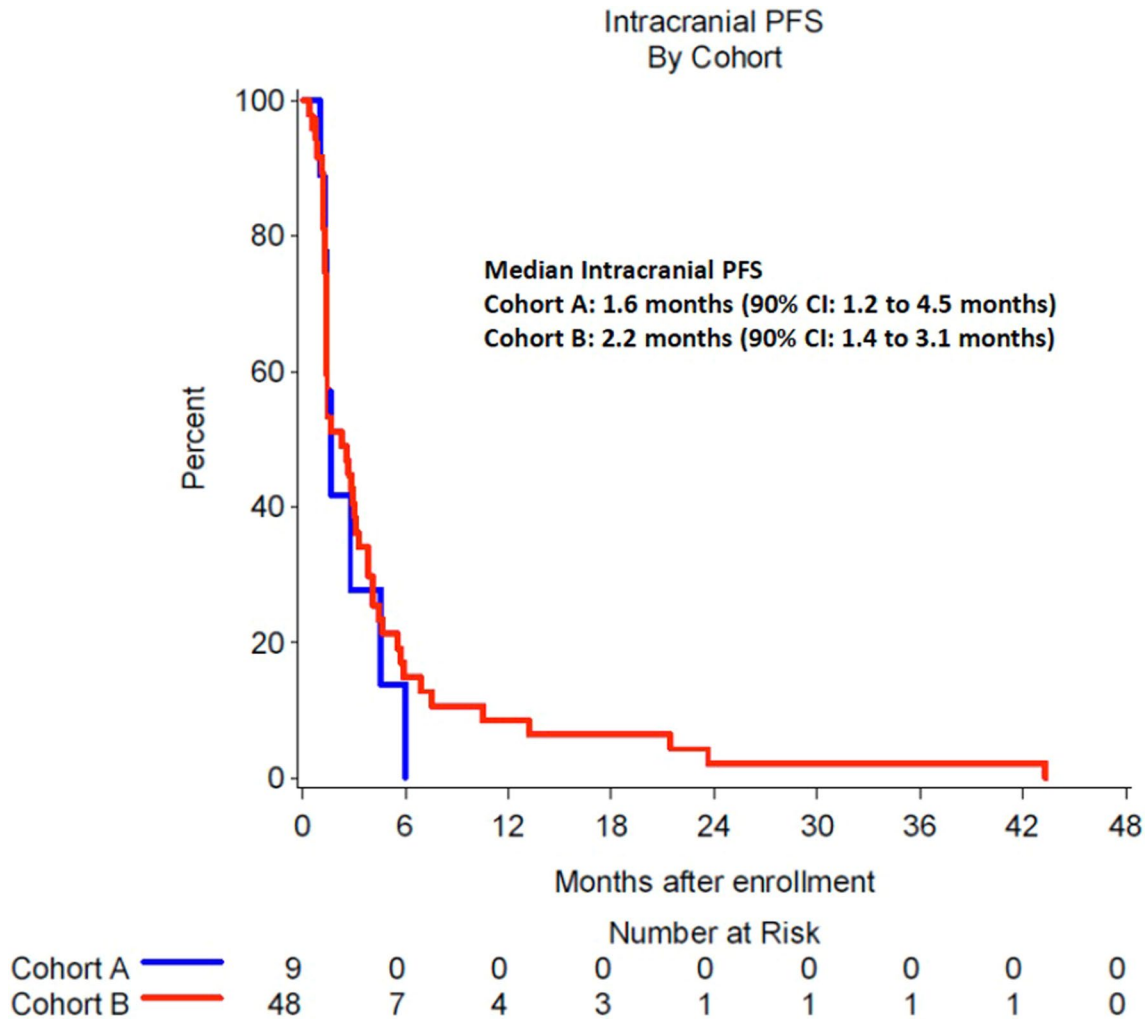
Extended data is available for this paper at https://doi.org/10.1038/s41591-023-02392-7.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-023-02392-7.

Correspondence and requests for materials should be addressed to Priscilla K. Brastianos.

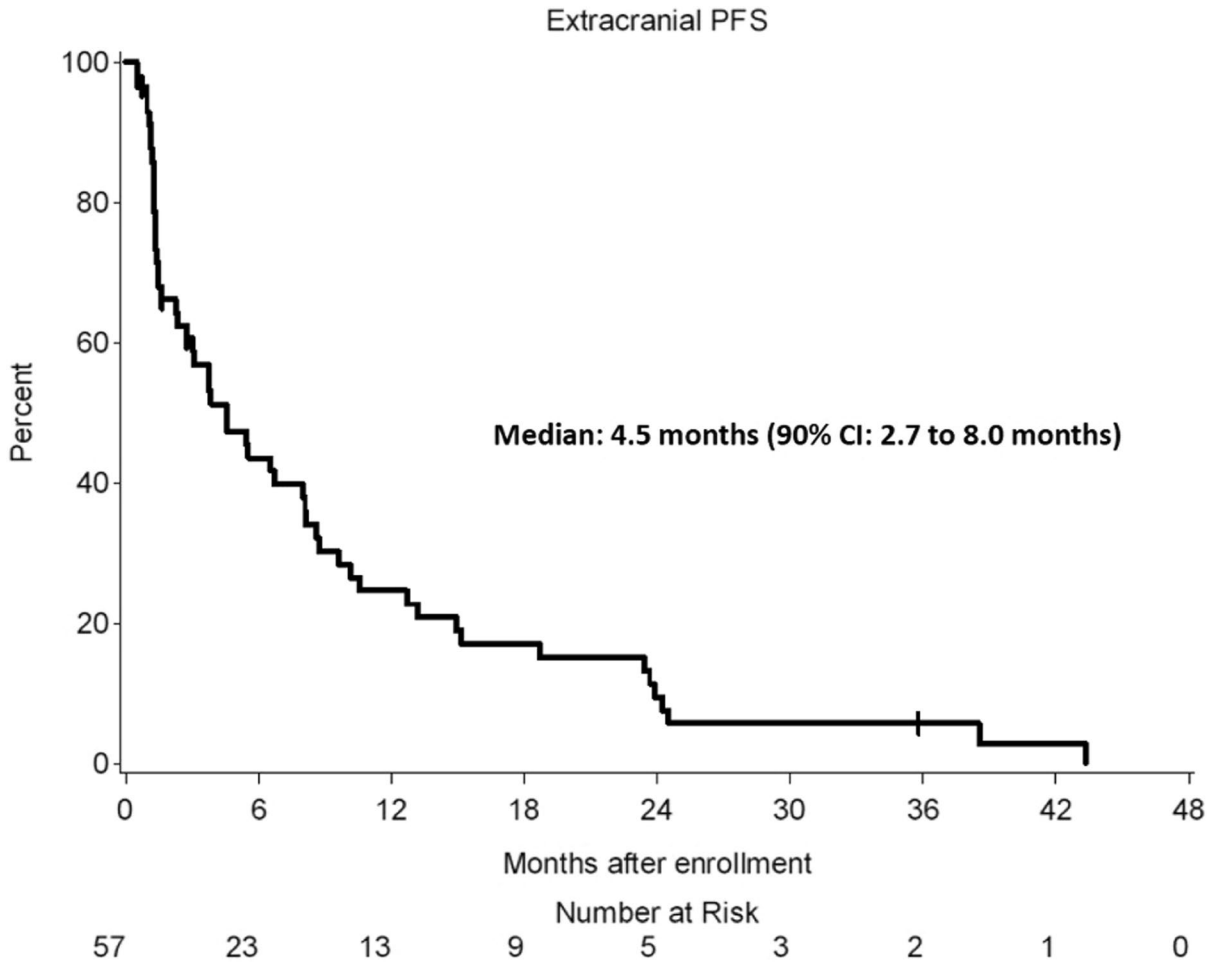
Peer review information *Nature Medicine* thanks Annette Molinaro, Carey Anders and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Saheli Sadanand, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-023-02392-7



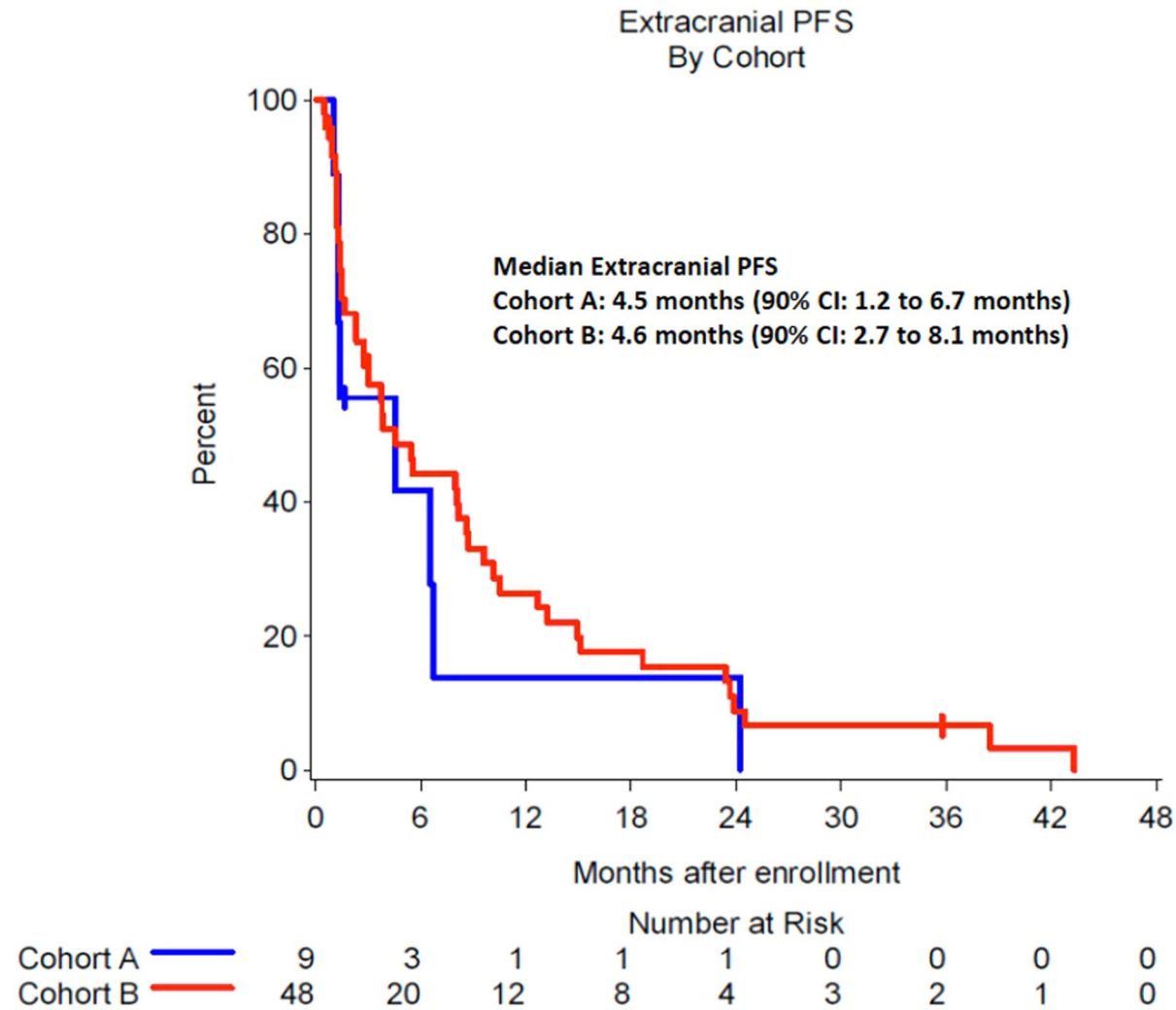
Extended Data Fig. 1 | Kaplan-Meier Estimate for Intracranial Progression-free Survival, by Cohort. The median intracranial PFS was 1.6 months for cohort A (blue line - 90% CI: 1.2-4.5 months) and 2.2 months for cohort B (red line - 90% CI: 1.4-3.1 months).

https://doi.org/10.1038/s41591-023-02392-7



Extended Data Fig. 2 | Kaplan-Meier Estimate for Extracranial Progression-Free Survival. The median extracranial PFS was 4.5 months (90% CI: 2.7-8.0 months). Extracranial PFS was defined as the time of enrollment until the earlier of RECIST-defined disease progression or death. Patients who neither progressed nor died have follow-up that is censored at the date of last visit. CNS progression events are ignored. 53 of 57 patients (93%) experienced an extracranial PFS event. 18 patients experienced systemic progression and 35 additional died without systemic progression.

https://doi.org/10.1038/s41591-023-02392-7



Extended Data Fig. 3 | Kaplan-Meier Estimate for Extracranial Progression-Free Survival, by Cohort. The median time to extracranial progression was 4.5 months (blue line - 90% CI: 1.2-6.7 months) for cohort A and 4.6 months (red line - 90% CI: 2.7-8.1 months) for cohort B.

https://doi.org/10.1038/s41591-023-02392-7

Extended Data Table 1 | Intracranial benefit by histology of primary tumor

	Clinical benefit (RANO)			
	No		Yes	
	N	%	N	%
All	33	57.9	24	42.1
Initial Primary Tumor Diagnosis				
Breast	22	62.9	13	37.1
HR+ HER2+	5	55.6	4	44.4
HR+ HER2-	4	57.1	3	42.9
HR+ HER2 Unknown	-	-	1	100.0
HR- HER2+	6	85.7	1	14.3
Triple Negative	7	63.6	4	36.4
Extraosseous osteosarcoma	1	100.0	-	-
Melanoma	-	-	2	100.0
Esophageal	1	100.0	-	-
Neuroendocrine Carcinoma	1	50.0	1	50.0
Non-Small Cell Lung Cancer NOS	4	57.1	3	42.9
Ovarian	-	-	1	100.0
Pituitary carcinoma	-	-	1	100.0
Prostate	-	-	1	100.0
Renal Cell Carcinoma	1	100.0	-	-
Small Cell Lung Cancer	2	100.0	-	-
Adenocarcinoma of unknown primary	1	100.0	-	-
Advanced sino-nasal ACC	-	-	1	100.0
Alveolar soft part sarcoma	-	-	1	100.0

A summary of intracranial benefit according to primary diagnosis is presented. Clinical benefit occurred in 37% (13/35) of patients with breast cancer and 43% (3/7) of patients with NSCLC. Both patients with melanoma BMs achieved intracranial benefit. For patients with breast cancer, summaries according to cancer subtype are provided. Using a Fisher's exact test with a two-sided *P* value, there was no significant relationship between clinical benefit and either breast cancer subtype ($P=0.55$) or HR status ($P=0.31$). No adjustment was made for multiple comparison.

nature portfolio

Corresponding author(s): Brastianos

Last updated by author(s): May 2, 2023

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Clinical data were collected with InForm Software (Version 6.2). Intracranial and extracranial efficacy was assessed centrally via blinded review by the MGH Tissue Imaging Metrics Core using Response Assessment in Neuro-Oncology (RANO) for brain metastases and Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Toxicity was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
Data analysis	Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data Availability Statement: The raw clinical and imaging data are protected due to patient privacy laws. Information is taken directly from the electronic medical

record or original source generated by treating investigators (e.g. email confirmations, Adverse Event logs). This is stored on a secured network drive to which only appropriately trained and delegated staff have access to. Lesion measurements are obtained from the Tumor Metrics Imaging Core online portal that uses a secure server to which only appropriately trained and delegated staff are granted access to. Any requests for raw and analyzed data should be sent in writing to Priscilla Brastianos (pbrastianos@mgh.harvard.edu) and will be reviewed by the DF/HCC Institutional Review Board (IRB) in an expeditious fashion (e.g. approximately six months). Patient-related data not included in the paper were generated as part of a clinical trial and are subject to patient confidentiality. Any data and materials (e.g. study protocol, clinical data, or imaging data) that can be shared will need approval from the DF/HCC IRB and a Material Transfer Agreement in place. Deidentified data then will be transferred to the inquiring investigator in an expeditious fashion over secure file transfer. The study protocol and statistical analysis plan are included with the submission.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The study recruited male and female adult patients. Most patients in our study were female (46/57; 80.7%). No other gender specific analyses were done.
Reporting on race, ethnicity, or other socially relevant groupings	Demographic information and baseline characteristics was collected at the baseline visit. Standard demographic parameters include age, sex, and race/ethnicity (recorded in accordance to prevailing regulations). These data were collected from the electronic medical record, which is typically collected at the time that the patient registers to become a patient.
Population characteristics	Eligible patients had histologically confirmed disease from any metastatic solid tumor and measurable disease in the CNS, defined as at least one metastasis that could be measured in at least one dimension as > 5 mm. For cohort A (10 patients), patients must have had previously untreated asymptomatic BM. Patients with newly-diagnosed, treatment-naïve primary tumors that presented with BM were not allowed to forego available therapy that demonstrated a definitive overall survival (OS) benefit as first-line therapy. Therefore, the following diagnoses in the treatment-naïve setting were excluded: HER-2 positive breast cancer, small-cell lung cancer, and an oncogene-addicted non-small cell lung cancer (e.g. EGFR, ALK mutation). In cases of treatment-naive systemic tumors, only patients for whom there was no available therapy with a definitive OS benefit were permitted. Otherwise, enrolled patients in cohort A had to progress on at least one line of prior therapy for their primary tumor. For cohort B (48 patients), patients must have had progressive BM immediately prior to enrollment. Any number of BM-directed therapies, such as radiation and systemic therapies with CNS penetration, were allowed. For patients with prior intracranial radiation, there must be unequivocal evidence of progression of at least one lesion treated by radiation (e.g. tissue confirmation or discussion in a multi-disciplinary tumor board). Participants who had chemotherapy, targeted therapy, immunotherapy, or radiotherapy within 2 weeks prior to trial enrollment were excluded. To minimize the risk of enrolling patients with pseudo-progression, patients with prior intracranial radiation must have unequivocal evidence of progression (e.g. biopsy). Concurrent radiation or systemic therapy, other than aromatase/hormone inhibition or ovarian suppression, were not allowed. Other key inclusion criteria included the following: age > 18 years, ECOG performance status < 2, and stable dose of dexamethasone at 2 mg or less for at least 7 days prior to start of trial. Key exclusion criteria included leptomeningeal involvement of cancer and prior treatment with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. Some factors may have led to inadvertent bias and could impacted the study results. First, the majority of patients were female (80.7%). Second, prior treatment may impact the study results. Finally, we had a heterogenous cohort comprised of 14 different tumor histologies - and different histologies may have varied responses to treatment.
Recruitment	Patients were identified and recruited through the Massachusetts General Hospital Pappas Center for Neuro-Oncology (MGH) and Dana-Farber Center for Neuro-Oncology (DFCI). The treating physician explained the clinical trial to the patient, and provided them with a copy of the trial protocol was provided after signing consent. In addition, the MGH and DFCI have a large referral base encompassing the New England area through which eligible patients were referred and recruited to our study. As a result, our study population was heavily based from the Massachusetts/New England area. We do not expect this location bias to affect our results. The majority of enrolled patients were heavily pre-treated and were referred for trial enrollment after they had progressed through conventional lines of therapy (e.g. radiation, other systemic therapies). With this highly selected patient group, we would expect our results to be affected such that overall survival/patient outcomes on the study drug would be adversely affected. We plan to validate our results through future prospective studies.
Ethics oversight	The Dana-Farber Harvard Cancer Center (DF/HCC) Institutional Review Board approved the protocol.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	This study was designed as an open-label, single-stage, single-arm phase 2 clinical trial with a target accrual of 58 patients to achieve at least 52 evaluable patients (i.e., received at least one dose of pembrolizumab). The population is comprised of two cohorts that were combined for analysis: cohort A (untreated BM) and cohort B (treatment-refractory BM). The primary efficacy endpoint was the intracranial benefit rate based on RANO criteria. The study design compared a null intracranial benefit rate of 10% against an alternative of 24%. If at least 8 patients among the total of 52 had intracranial benefit, the primary efficacy endpoint would be met and pembrolizumab would be considered worthy of further study in this patient population. This design has a type-I error of 10% and power of 89% (target type-II error of 15%).
Data exclusions	No data was excluded.
Replication	Replication of findings could not be performed, as this was a clinical trial that required Dana-Farber/Harvard Cancer Center Institutional Review Board approval. Here, we are reporting pre-specified analysis of a phase II clinical trial. Replication of this study would entail another trial and IRB approval. We aim to prospectively validate this work in future studies.
Randomization	There was no randomization of patients in our study, as this was a single arm phase II study.
Blinding	Blinding was not possible for our study, as this was a single arm phase II study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Clinicaltrials.gov identifier NCT02886585
Study protocol	The full clinical trial protocol was provided with manuscript submission.
Data collection	Study data files for all patients were retrieved for this report on July 21, 2022. The first patient was enrolled on October 6, 2016 and the last patient for this analysis was enrolled on October 16, 2018. Clinical research coordinators and physicians collected salient clinical information for each patient at the Massachusetts General Hospital Cancer Center - Pappas Center of Neuro-Oncology (Yawkey Center, Suite 9E; 55 Fruit Street, Boston, MA 02114). Information was taken directly from the electronic medical record or original source generated by treating investigators (e.g. email confirmations, Adverse Event logs). This data was then stored on a secured network drive and the Inform Database (Oracle; version 6.2) to which only appropriately trained and delegated staff have access to. Lesion measurements on MRI are obtained from the Tumor Metrics Imaging Core online portal that utilizes a secure server to which only appropriately trained and delegated staff are gained access to. All collected data were then sent to the Dana-Farber/Harvard Cancer Center Office of Data Quality for quality control before analysis.
Outcomes	The primary endpoint was intracranial benefit, defined as a best response of complete response (CR), partial response (PR), or stable disease (SD) during treatment, as per RANO criteria for BM. Under these criteria, CR is defined as the disappearance of all CNS target lesions. PR is a ≥30% decrease in the sum of longest diameters (LD) in CNS target lesions, relative to the baseline or nadir sum LD, without new CNS lesions. This response must be sustained for at least four weeks, while on a stable corticosteroid dose. SD is defined as <30% decrease and <20% increase in the sum LD of target lesions relative to baseline/nadir LD, without new CNS lesions. Secondary endpoints include extracranial response rate (defined as CR or PR, per RECIST version 1.1 criteria), intracranial progression-free survival (PFS), extracranial PFS, overall survival (OS), and toxicity using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Of note, intracranial and extracranial efficacy was assessed centrally via blinded review by the MGH Tissue Imaging Metrics Core using RANO and RECIST 1.1 criteria for CNS or extracranial disease, respectively.