original report

Long-Term Survival of Patients With Melanoma With Active Brain Metastases Treated With Pembrolizumab on a Phase II Trial

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abstract

PURPOSE Pembrolizumab is active in melanoma, but activity in patients with untreated brain metastasis is less established. We present long-term follow-up of pembrolizumab-treated patients with new or progressing brain metastases treated on a phase II clinical trial (ClinicalTrials.gov identifier: NCT02085070).

PATIENTS AND METHODS We enrolled 23 patients with melanoma with one or more asymptomatic, untreated 5- to 20-mm brain metastasis not requiring corticosteroids; 70% of patients had prior systemic therapy. Pembrolizumab was administered for up to 24 months. Brain metastasis response, the primary end point, was assessed by modified Response Evaluation Criteria in Solid Tumors (RECIST). Pretreatment tumors were analyzed for T-cell infiltrate and programmed death ligand 1.

RESULTS Six patients (26%) had a brain metastasis response. Eight patients (35%) did not reach a protocol evaluation scan and were unevaluable for brain metastasis response as a result of progression or need for radiation. Brain metastasis and systemic responses were concordant, with all ongoing at 24 months. The median progression-free and overall survival times were 2 and 17 months, respectively. Eleven patients (48%) were alive at 24 months. This included three unevaluable patients. One of these three patients had hemorrhaged, and two had symptoms from perilesional edema requiring radiosurgery, but all three patients remained on commercial pembrolizumab more than 24 months later. None of the 24-month survivors received subsequent *BRAF* inhibitors. Neurologic adverse events occurred in 65% of patients; all adverse events but one were grade 1 or 2. Three patients had seizures, which were treated with anticonvulsants. Most responders had higher pretreatment tumor CD8 cell density and programmed death ligand 1 expression, whereas all nonresponders did not.

CONCLUSION Pembrolizumab is active in melanoma brain metastases with acceptable toxicity and durable responses. Multidisciplinary care is required to optimally manage patients with brain metastases, including consideration of radiation to large or symptomatic lesions, which were excluded in this trial. Two-year survival was similar to patients without brain metastasis treated with anti–programmed cell death 1 agents. Concordant brain and extracerebral responses support use of pembrolizumab to treat small, asymptomatic brain metastases.

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ASSOCIATED CONTENT

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Immune checkpoint inhibitors have revolutionized cancer care. Ipilimumab, the first approved checkpoint inhibitor for melanoma, inhibits cytotoxic T-cell lymphocyte-4.[1] Inhibitors of programmed cell death 1 (PD-1) or its ligand (PD-L1) were approved for multiple tumor types based on randomized trials.[2-7] Randomized trials, however, excluded patients with untreated brain metastases from melanoma or non–small-cell lung cancer (NSCLC), which occur in more than 50,000 patients per year in the United States.[8]

Melanoma is the solid tumor with the highest propensity for dissemination to the CNS; the incidence at autopsy is up to 70%.[9,10] Brain metastases occur in 30% of patients with metastatic NSCLC, and multifocal disease is common in both malignancies.[11] Although local therapies, particularly surgery and stereotactic radiosurgery (SRS), are effective for isolated lesions, they do not prevent regional or distant recurrences. Whole-brain radiation is typically ineffective for melanoma.[9,10] Therefore, systemic therapies require additional exploration, particularly because many patients have extracerebral disease as well.

Clinical trials have typically excluded patients with brain metastases because of concerns regarding CNS penetration and historically poor prognosis. Landmark trials for melanoma using recently approved drugs enrolled more than 6,000 patients, none with active

brain metastasis; brain metastasis–specific trials only enrolled 234 patients (4.1%).[10] Some studies even excluded patients with previously irradiated, stable brain metastases because of concerns about neurologic sequelae.

Given the dramatic responses in melanoma and NSCLC in extracerebral disease, we initiated a phase II trial of pembrolizumab in patients with NSCLC or melanoma and untreated brain metastases (ClinicalTrials.gov identifier: NCT02085070). This trial was initiated before US Food and Drug Administration approval of pembrolizumab with the goal of determining the activity and safety in patients with CNS involvement. Given the importance of the study, we published interim findings from the first 36 patients (18 patients with each disease).[12] Here, we present the final results and long-term follow-up for the full melanoma cohort and tumor-based correlative studies.

PATIENTS AND METHODS

Study Design

This was a two-cohort phase II trial approved by the Yale University Institutional Review Board. This description focuses solely on the melanoma cohort. Pembrolizumab 10 mg/kg was administered intravenously every 2 weeks for up to 24 months. Subsequent studies have shown that smaller doses are equally effective. Treatment continued until progression of disease (PD), toxicity precluding continuing pembrolizumab, withdrawal from study, or death. Patients deriving clinical benefit could continue on trial despite PD; local therapy was allowed for progressing lesions, in the CNS or systemically.

A safety brain magnetic resonance imaging (MRI) scan was obtained at 4 weeks. Response evaluation was conducted every 8 weeks using gadolinium-enhanced brain MRI and computed tomography of the chest, abdomen, and pelvis or positron emission tomography–computed tomography. Cerebral metastases were assessed by unidimensional evaluation using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 modified to allow target lesions in the CNS 5 mm or greater (or at least twice the slice thickness if 2.5 mm or greater), permitting up to five target brain metastases (modified RECIST).[13] Systemic response was measured using standard RECIST version 1.1. The primary end point was brain metastasis response rate (RR). Secondary end points included extracerebral and overall RR, progression-free survival (PFS), and overall survival (OS). Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 4.0.

Patients

Key eligibility criteria included stage IV melanoma, age older than 18 years, Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, and at least one 5- to 20-mm brain metastasis untreated or unequivocally progressing radiographically after local therapy. Equivocal lesions were biopsied. We enrolled patients with either archival tumor tissue from a CNS metastasis or requiring biopsy or debulking for diagnosis or disease control. Exclusion criteria included symptomatic brain metastases, corticosteroid requirement for perilesional edema, leptomeningeal disease, autoimmune disease, or prior anti–PD-1/PD-L1 therapy. Prior resection or radiation of brain metastases was allowed, but lesions present during whole-brain radiotherapy or included in the SRS field were considered unevaluable, unless unequivocally progressing since radiation.

Correlative Studies

CNS or extracerebral tumor tissues were cored to generate a tissue microarray and stained for quantitative immunofluorescence measures of PD-L1 expression and tumor-infiltrating lymphocyte (TIL) content using previously described methods.[14,15] Image capturing and quantification of target expression were conducted as described.[14-16]

Statistical Analysis

We hypothesized that activity of pembrolizumab in brain metastases is similar to that in extracerebral sites. When the protocol was written, the RR to pembrolizumab in melanoma was estimated at 38%. The study was designed for 86% power to demonstrate a brain metastasis RR greater than 10% at an overall one-sided 10% α level, if the true best brain metastasis RR is 38%. Analyses, including the primary end point of brain metastasis RR, included patients who received at least one dose of pembrolizumab. A sequential monitoring procedure was used (Data Supplement) to evaluate efficacy and futility based on brain metastasis response. Pembrolizumab would have been deemed futile and the trial halted if none of the first eight patients, less than two of the first 13 patients, less than three of the first 17 patients, or less than four of the first 20 patients responded. Median PFS and OS times were estimated using the Kaplan-Meier method, with patients censored at data cutoff on January 5, 2018.

RESULTS

Patient Characteristics

We enrolled 23 patients with melanoma between March 2014 and August 2015. Clinical characteristics are listed in Table 1. Eighteen patients (78%) had prior local CNS therapy, as described.[12] The number of brain metastases was one to 81 metastases. Untreated or progressive brain metastases were 20 mm or less; lesions that were larger, located in an eloquent area of the brain, or otherwise concerning were treated with local therapy before initiation of pembrolizumab.

Clinical Activity in Brain Metastases and Extracerebral Metastases

The primary end point was brain metastasis response by modified RECIST. Six patients achieved a confirmed, objective CNS response (two partial responses [PRs] and four

TABLE 1. Baseline Characteristics of All Treated Patients

Characteristic	No. of Patients (N = 23)	%
Age, years		
Median	65	
Range	40-84	
Sex		
Male	15	65
Female	8	35
ECOG PS		
0	10	43
1	13	57
Elevated LDH	9	39
Mutation*		
BRAF	9	41
NRAS	5	23
No. of prior systemic therapy regimens		
0	7	31
1	9	39
2	4	17
≥ 3	3	13
Prior ipilimumab	13	57
Prior *BRAF* inhibitors	4	17
Prior CNS therapy†		
None	5	22
Surgical resection	12	52
Whole-brain radiotherapy	5	22
Stereotactic radiosurgery	12	52

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

**BRAF* and *NRAS* status were unknown for one patient.

†Some patients had more than one CNS therapy modality.

complete responses [CRs]). One patient had stable disease (SD) as his best response, and eight patients had PD. Brain metastasis RR was defined as the percentage of patients with confirmed PR or CR of the total number of patients treated (23 patients). The brain metastasis RR was 26% (95% CI, to 10% to 48%).

Eight (35%) of the 23 treated patients were unevaluable for brain metastasis response (Data Supplement); three of these patients had rapid extracerebral PD without confirmation of PD in the brain as a result of clinical deterioration, one developed biopsy-proven pseudoprogression, and one died after the second cycle of unknown causes. Notably, one patient had hemorrhage in all measurable lesions requiring emergent SRS, but this patient remains on commercial pembrolizumab and without new lesions at 41 months. Moreover, two unevaluable patients developed neurologic symptoms from perilesional edema requiring transient corticosteroids and SRS to measurable lesions and similarly remain free of progression in both the body and brain at 34 and 31 months, respectively, with one patient off therapy and one on commercial pembrolizumab. This suggests that the antitumor activity of pembrolizumab might be underestimated by the RR.

Eight patients were unevaluable for extracerebral response (Data Supplement); three of these patients had no extracerebral disease, four had clinical deterioration without documenting progression, and one died of unknown causes. The two patients unevaluable for cerebral response as a result of edema requiring SRS had extracerebral responses. The 15 patients evaluable for extracerebral response included four patients with CRs, three with PRs, one with SD, and seven with PD. All four patients treated with *BRAF* inhibitors as their most recent therapy had PD. Notably, all patients with extracerebral response also responded in the CNS.

Changes in sums of diameters of target lesions are depicted in Figure 1A. Time to response and duration of treatment are depicted in Figure 1B and the Data Supplement.

Survival Analyses

Patients were observed until death, except for one patient with a confirmed PR who was lost to follow-up after 38 months while off therapy and progression free. The median PFS time was 2 months (95% CI, 2 months to not reached). The median OS time was 17 months (95% CI, 10 months to not reached). Figure 2 shows Kaplan-Meier curves depicting PFS and OS. Patients were continued on study drug for up to 24 months. Once pembrolizumab became commercially available, it was offered to patients coming off study. All six intracranial responses (100%) were ongoing at 24 months. One patient developed PD intra- and extracranially at 30 months and died at 34 months after experiencing disease progression on ipilimumab and nivolumab, and one patient developed extracranial progression at 37 months and is responding to experimental immunotherapy. At 24 months of follow-up, 11 patients (48%) remained alive (95% CI, 31% to 73%); at data lock, the median follow-up time for these 11 patients was 34 months (range, 28 to 43 months).

Safety

Pembrolizumab was well tolerated (Table 2). Most treatment-related adverse events (AEs) were grade 1 to 2. Grade 3 AEs affecting one patient each included hepatitis, hyponatremia, acidosis, and rash. Most neurologic toxicities were grade 1 or 2. Three patients developed grade 1 or 2 seizure activity controlled by antiepileptics and transient corticosteroids. Four patients developed other neurologic symptoms from perilesional edema, resulting in removal from study, one with PD and one with inflammation and minimal tumor cells, which were histologically documented in both patients. Two additional patients with symptomatic perilesional edema, described earlier, did not have CNS

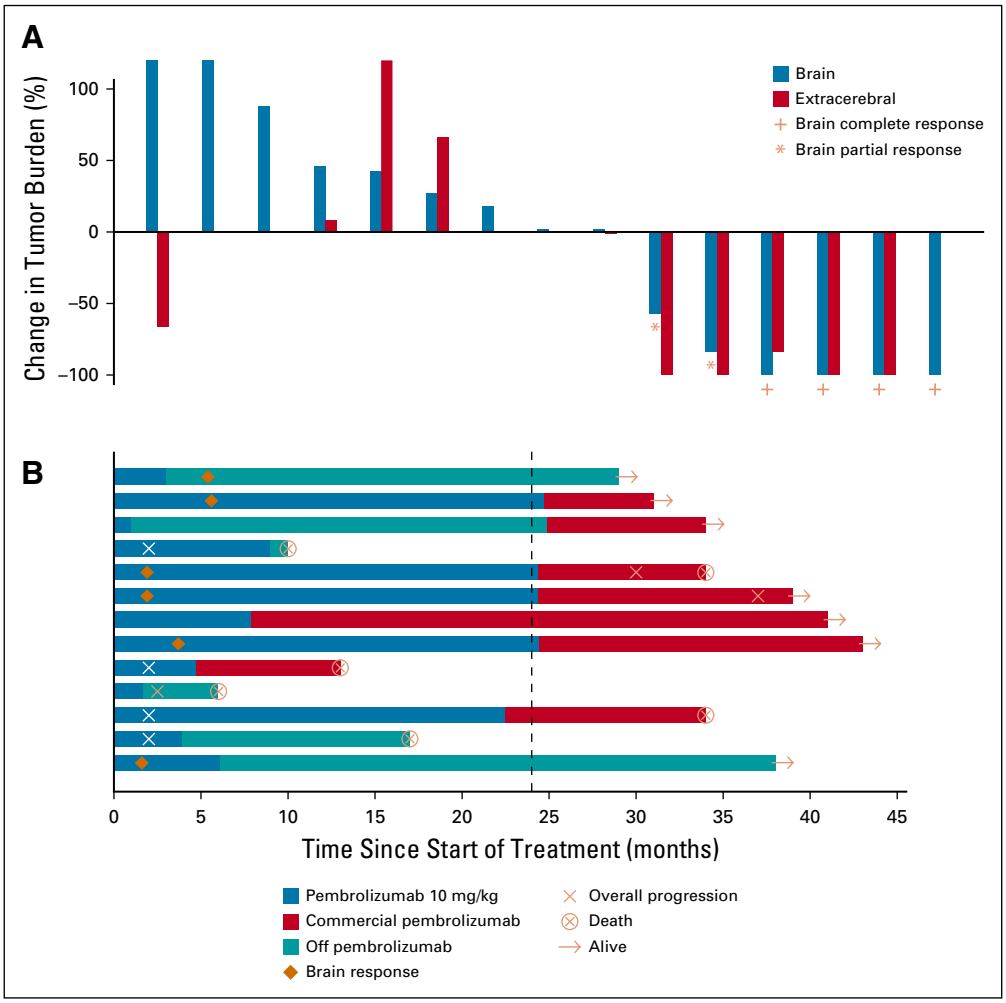

FIG 1. Characteristics of responses in the brain and extracerebral metastasis sites. (A) Best brain metastasis response by modified Response Evaluation Criteria in Solid Tumors (RECIST) and extracerebral response by RECIST version 1.1 in evaluable patients. Bars represent individual patients; blue bars and red bars represent changes in evaluable brain and extracerebral lesions, respectively. The amplitude of the bars demonstrates the percent change in tumor burden from baseline to the best response. We note that the patient on the left had progression in the brain and a mixed response in extracerebral sites with unequivocal progression of nontarget lesions. (B) Horizontal bars represent individual patients (evaluable or unevaluable) who remained on trial for ≥ 4 months. Bars are partitioned and color coded to indicate the time that patients were on study drug (pembrolizumab 10 mg/kg every 2 weeks), commercial pembrolizumab (2 mg/kg or 200 mg every 3 weeks), or off pembrolizumab. The timing of brain metastasis response, overall progression, death, or censoring is marked on the corresponding position of the bars. The dashed line represents the time the study ended (24 months).

progression, but given the location of their lesions and concerns for worsening symptoms, they were treated with SRS and a brief course of corticosteroids with no recurrence of neurologic symptoms. The most common neurologic AEs included gait disturbance (22%) and headache (17%), both of which were grade 1 or 2.

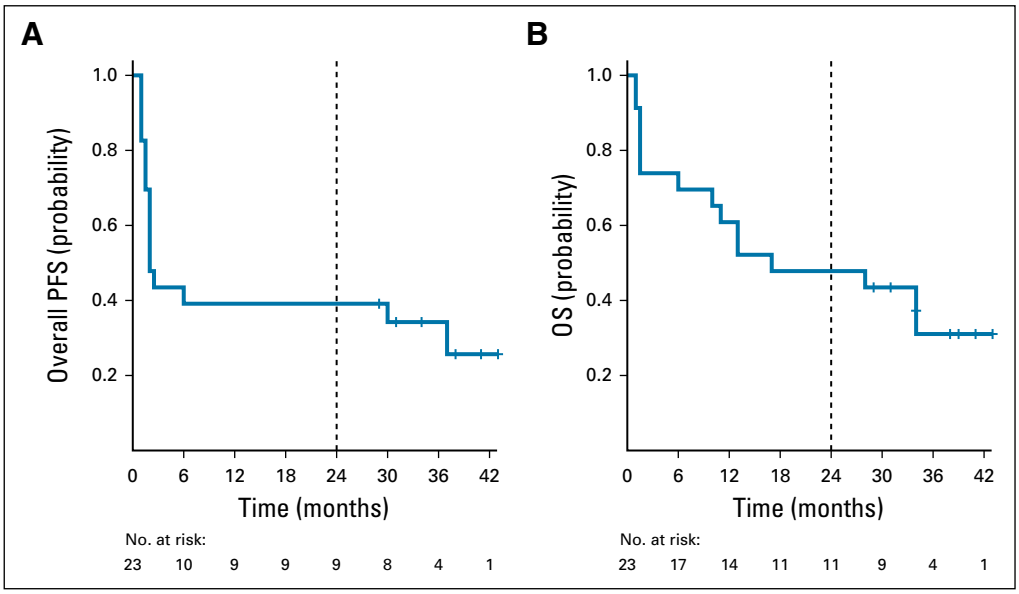

FIG 2. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS). The dashed lines represent the time when the study ended at 24 months.

TABLE 2. Neurologic Adverse Events and Treatment-Related Non-Neurologic Adverse Events in All Treated Patients

	Melanoma Patients (N = 23)			
	Grade 1-2		Grade 3-4	
Adverse Event	No.	%	No.	%
Neurologic adverse events*				
Ataxia	5	22	0	0
Headache	4	17	0	0
Cognitive dysfunction	3	13	1	4
Seizure	3	13	0	0
Dizziness	2	9	0	0
Dysgeusia	2	9	0	0
Dysphagia	2	9	0	0
Neuropathy	2	9	0	0
Somnolence	1	4	0	0
Treatment-related non-neurologic adverse events				
Constitutional symptoms	13	57	0	0
Dermatologic				
Rash	5	22	1	4
Pruritis	5	22	0	0
Arthralgias	4	17	0	0
Endocrinopathies	3	13	0	0
GI disorders				
Diarrhea	2	9	0	0
Dry mouth	1	4	0	0
Respiratory disorders				
Nasal congestion	2	9	0	0
Metabolic disorders				
Acidosis	0	0	1	4
Hyponatremia	0	0	1	4
Elevated transaminases	0	0	1	4

*Regardless of attribution to study drug.

Four-week safety scans were performed to verify lack of new lesions in critical sites requiring immediate SRS. Many responses occurred after 4 weeks (Fig 1B), and no responders had PD at 4 weeks. Safety scans did not result in management changes; all early interventions were based on symptoms.

Radiation necrosis was seen in seven patients (30.4%) in previously irradiated lesions, one with cystic changes. Radionecrosis was determined radiographically in two patients, defined as lesions with growth and subsequent shrinkage,[17] whereas five patients had biopsy-confirmed radionecrosis. The mean time from SRS to radionecrosis was 19.4 ± 8.5 months. The mean time from initiating pembrolizumab to radionecrosis was 18.3 ± 9.6 months.

Correlative Studies

We previously showed that PD-L1 expression in stromal inflammatory cells is a better predictor of tumor shrinkage than expression in tumor cells.[14] Therefore, we assessed the association between stromal PD-L1 and response. We also measured CD8-positive TILs by percentage of CD8-positive area, which correlated with PD-L1 (r = 0.787), assessing continuous values rather than an arbitrary cut-point. In Figure 3A, we show the distribution of CD8 cells and stromal PD-L1 expression among patients. Given the concordant responses in cerebral and extracerebral sites and because of the high percentage of unevaluable patients and patients lacking viable tumor for analysis in the brain or extracerebral sites, we considered response from either site (brain or body) for this analysis. Among nine evaluable patients with PD, all had lower PD-L1 expression and lower CD8-positive TILs, whereas of patients who achieved a PR, CR, or SD (eight patients, including three who were unevaluable for brain response but who responded in the body), six had higher values for both variables and two did not. Conversely, no patient with overall PD had higher PD-L1 and CD8. The association between PD-L1 and CD8 content and 24-month survival is less clear (Fig 3B). Examples of a PD-L1–staining tumor with higher CD8 content corresponding to a responder and lower PD-L1 and CD8 TIL content in a nonresponder are shown in Figure 4.

DISCUSSION

We present long-term follow-up and final results of the melanoma cohort on a phase II trial of pembrolizumab in patients with untreated or progressing brain metastases. To the best of our knowledge, these are the most mature data on PD-1 inhibitors in this population. We enrolled 23 patients, and although the brain metastasis RR was only 26%, three patients who were unevaluable for CNS response remained alive and progression free at 24 months. All patients who responded systemically also responded in the CNS, and all responses were ongoing for the 24-month duration of the study. The median OS time was 17 months, and 48% of patients were alive at 2 years. The safety profile was acceptable; most neurologic toxicities were grade 1 or 2 and typically responsive to transient corticosteroids. Complications unique to this population included perilesional edema and radionecrosis.

Clinical trials specific for patients with active brain metastasis are relatively rare, yet RRs in the brain using newer, active drugs are similar to responses seen in extracerebral sites.[10] Although the RR in this trial was lower than that seen in studies with PD-1 inhibitors in the front-line setting in patients without active brain metastases,[2,3] 70% of our patients had prior systemic therapies. Comparing our results to extracerebral disease in the second-line setting, the results are similar. For example, in a landmark study comparing nivolumab to investigators' choice in the

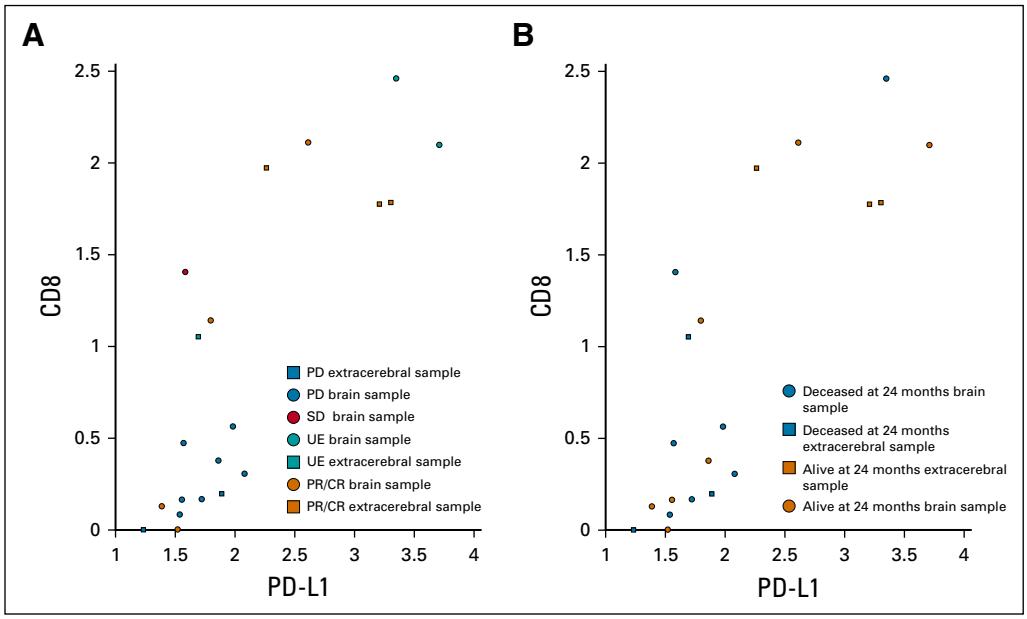

FIG 3. Scatter plot of programmed death ligand 1 (PD-L1) levels versus CD8-positive area for individual patients. Values presented are the log transformation of 1 plus the value. Patients with biopsies from extracerebral sites are denoted by squares, and patients with brain biopsies are denoted by circles. Seventeen of the 20 specimens were collected before therapy. (A) Patients with progressive disease (PD) are denoted in blue, those with stable disease (SD) in red, and responders (either complete response [CR] or partial response [PR]) in orange, and three unevaluable (UE) patients are denoted in teal. Note that overall response is depicted in this figure given the small number of patients with evaluable specimens, including two patients who had response in extracerebral sites but were unevaluable for CNS response. (B) Patients alive at 24 months are denoted in orange, and patients dead at 24 months are denoted in blue.

second-line setting, the RR was 27%.[18] In a trial of previously treated patients with melanoma comparing pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, and chemotherapy, the RRs in the pembrolizumab arms were 22% and 28%, respectively, consistent with our study.[19] Neither of these studies specifies the RR among patients with M1C disease.

The brain metastasis RR should be further interpreted in the context of trials specific to this patient population. Brain metastasis RRs greater than 50% have been observed in *BRAF*-mutant melanoma, treated with *BRAF*/MEK inhibitors, although the duration of response tends to be shorter.[20] Ipilimumab, administered in 51 patients with untreated brain metastases, was less active than PD-1 inhibitors, similar to extracerebral disease.[21] This trial enrolled a similar population; 78% of patients had prior systemic therapies. The median OS was 7 months, and only 29% of patients completed 12 weeks of therapy, likely because of the lower RR to ipilimumab than PD-1 inhibitors. Long et al[22] conducted a trial of nivolumab or nivolumab plus ipilimumab in patients with brain metastasis; the RRs to monotherapy and combination therapy were 20% and 42%, respectively, in asymptomatic patients. Notably, patients previously treated with *BRAF*/MEK inhibitors had a worse outcome. In our study, no patients previously treated with *BRAF*/MEK inhibitors responded to pembrolizumab. Tawbi et al[23] presented early results of a trial of ipilimumab and nivolumab in patients with untreated with brain metastasis, demonstrating a brain metastasis RR of 55%. Notably, 88% of patients were previously untreated. This suggests that despite the toxicities from dual immune checkpoint inhibitors, combination therapy should be considered for robust patients with brain metastases.

All patients in our study who achieved an objective response remained in response at 24 months, which is longer than the CNS response in patients treated with *BRAF*/MEK inhibitors.[20] The previously mentioned studies of immune therapy in this patient population are less mature,[22,23] and our study represents the first report of long-term survival in patients with active brain metastases treated with anti–PD-1 therapy.

The concordance between cerebral and extracerebral response suggests similarity in tumor biology in the different anatomic sites. This suggests that brain metastases, particularly when small and not located in critical sites (eg, brainstem or motor strip), can safely be treated with systemic therapy or systemic therapy combined with local therapy.

The unexpectedly high percentage of patients (35%) unevaluable for CNS response indicates that benefit from pembrolizumab might be underestimated by the RR. Three of the eight patients unevaluable for intracranial response remain progression free at 41, 34, and 31 months; two of these patients are on commercial pembrolizumab, and one is off therapy. Two patients were removed from study as a

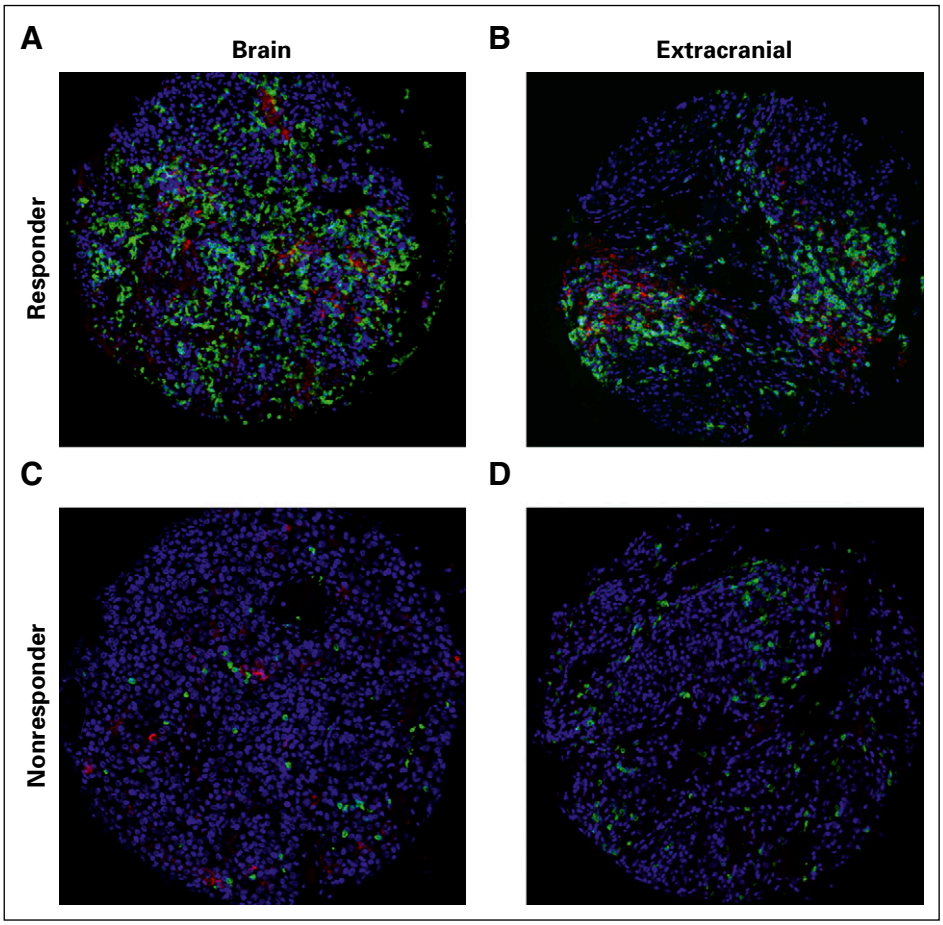

FIG 4. Quantitative immunofluorescent staining of programmed death ligand 1 (red) and CD8-positive T-cell infiltrating lymphocytes (green) in matched brain and extracranial sites in both (A and B) a responder and (C and D) a nonresponder, respectively. Nuclear compartment staining was defined by 4′,6-diamidino-2-phenylindole signal (blue).

result of symptomatic perilesional edema from pembrolizumab (the lesions were not clearly growing) requiring SRS, and one patient was removed as a result of intralesional hemorrhage requiring SRS. This suggests that salvage SRS significantly contributes to survival.

Our study was not designed to replace unevaluable patients, but rather to determine the RR in the intent-to-treat population. Our experience suggests that alternative trial end points and designs should be considered, such as the RR among evaluable patients, preplanned replacement of unevaluable patients, and use of brain metastasis PFS or OS as a primary end point. Moreover, this underscores the need for multidisciplinary management of these patients, because anti–PD-1 treatment in the absence of local interventions should only be used for selected patients who are closely monitored.

We treated patients with pembrolizumab for up to 2 years. At 2 years, 48% of patients were alive, similar to the reported 2-year survival rate of 43% in the phase I trial of nivolumab for patients without brain metastases and the 36% to 38% 2-year survival rate in patients receiving pembrolizumab in the second-line setting, many with advanced disease and a history of brain metastases.[19,24]

Non-neurologic toxicities were not severe. One patient died of unknown causes after two cycles. Neurologic toxicities attributable to edema were managed with a brief course of corticosteroids. After the first patient had a seizure, prophylactic antiepileptics were prescribed. We recommend this practice for patients with untreated brain metastases treated with immune therapy. We also recommend evaluation by a multidisciplinary team to determine the best strategy for managing these complex patients. The incidence of radionecrosis (30.4%) was higher than expected based on historical observations. It is unclear whether this is a result of immune therapy, improved longevity, or both.

One patient presented with mental status changes after one cycle. MRI showed growth in all lesions, and biopsy showed inflammation, indicating that tumor growth in this setting might not always represent progression.[25] Similar findings have been demonstrated in other patients with brain metastasis treated with anti–PD-1 therapy after prior radiation.[26] Alternative positron emission tomography and/or MRI modalities are needed to better determine disease status in this population.

Interestingly, edema was less common in the study using ipilimumab and nivolumab by Tawbi et al.[23] Although it is plausible that ipilimumab mitigated edema, the difference is more likely a result of patient selection; most of our patients had received prior lines of systemic and local

therapy. We are conducting a trial of pembrolizumab in combination with bevacizumab (ClinicalTrials.gov identifier: NCT02681549), both to mitigate edema and radionecrosis and to enhance antigen-specific T-cell migration, as described.[27]

Pretreatment cerebral and/or extracerebral samples were available in 20 patients. The number of patients with paired cerebral and extracerebral samples was too small to compare. Consistent with other studies, there is no clear threshold for PD-L1 positivity and TIL content below which responses are not seen. Most responders had higher tumor PD-L1 expression and TIL content than nonresponders, as seen in trials for patients with extracerebral melanoma, but these biomarkers remain insufficiently robust for patient selection, and with the small number of patients in this study, these results need to be interpreted with caution.

Limitations of this study include the small sample size, use of historical controls,[28] the large number of unevaluable patients, and the single-institution nature. Moreover, this study was not designed to assess activity of pembrolizumab on larger brain metastases. However, the survival data are, to the best of our knowledge, the most mature, and our study demonstrates that survival in this population is similar to that of patients with extracerebral metastasis treated with PD-1 inhibitors. Additional studies of PD-1 inhibitors, including the addition of vascular endothelial growth factor inhibitors to decrease edema and radionecrosis, are warranted in patients with brain metastasis.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABLITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.00204.

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Final approval of manuscript: All authors

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REFERENCES

1. Hodi FS, O'Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711-723, 2010
2. Robert C, Schachter J, Long GV, et al: Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 372:2521-2532, 2015
3. Robert C, Long GV, Brady B, et al: Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372:320-330, 2015
4. Borghaei H, Paz-Ares L, Horn L, et al: Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373:1627-1639, 2015
5. Brahmer J, Reckamp KL, Baas P, et al: Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373:123-135, 2015
6. Garon EB, Rizvi NA, Hui R, et al: Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 372:2018-2028, 2015
7. Rittmeyer A, Barlesi F, Waterkamp D, et al: Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255-265, 2017
8. Davis FG, Dolecek TA, McCarthy BJ, et al: Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data. Neuro-oncol 14:1171-1177, 2012
9. Flanigan JC, Jilaveanu LB, Faries M, et al: Melanoma brain metastases: Is it time to reassess the bias? Curr Probl Cancer 35:200-210, 2011
10. Cohen JV, Tawbi H, Margolin KA, et al: Melanoma central nervous system metastases: Current approaches, challenges, and opportunities. Pigment Cell Melanoma Res 29:627-642, 2016
11. Gavrilovic IT, Posner JB: Brain metastases: Epidemiology and pathophysiology. J Neurooncol 75:5-14, 2005
12. Goldberg SB, Gettinger SN, Mahajan A, 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

13. Qian JM, Mahajan A, Yu JB, et al: Comparing available criteria for measuring brain metastasis response to immunotherapy. J Neurooncol 132:479-485, 2017
14. Kluger HM, Zito CR, Turcu G, et al: PD-L1 studies across tumor types, its differential expression and predictive value in patients treated with immune checkpoint inhibitors. Clin Cancer Res 23:4270-4279, 2017
15. Kluger HM, Zito CR, Barr ML, et al: Characterization of PD-L1 expression and associated T-cell infiltrates in metastatic melanoma samples from variable anatomic sites. Clin Cancer Res 21:3052-3060, 2015
16. Baine MK, Turcu G, Zito CR, et al: Characterization of tumor infiltrating lymphocytes in paired primary and metastatic renal cell carcinoma specimens. Oncotarget 6:24990-25002, 2015
17. Colaco RJ, Martin P, Kluger HM, et al: Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases? J Neurosurg 125:17-23, 2016
18. Larkin J, Minor D, D'Angelo S, et al: Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: A randomized, controlled, open-label phase III trial. J Clin Oncol 36:383-390, 2018
19. Hamid O, Puzanov I, Dummer R, et al: Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma. Eur J Cancer 86:37-45, 2017
20. Davies MA, Saiag P, Robert C, et al: Dabrafenib plus trametinib in patients with $BRAF^{V600}$-mutant melanoma brain metastases (COMBI-MB): A multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol 18:863-873, 2017
21. Margolin K, Ernstoff MS, Hamid O, et al: Ipilimumab in patients with melanoma and brain metastases: An open-label, phase 2 trial. Lancet Oncol 13:459-465, 2012
22. Long GV, Atkinson V, Lo S, 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
23. Tawbi HA-H, Forsyth PAJ, Algazi AP, et al: Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204. J Clin Oncol 35, 2017 (suppl 15; abstr 9507)
24. Topalian SL, Sznol M, McDermott DF, et al: Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 32:1020-1030, 2014
25. Cohen JV, Alomari AK, Vortmeyer AO, et al: Melanoma brain metastasis pseudoprogression after pembrolizumab treatment. Cancer Immunol Res 4:179-182, 2016
26. Alomari AK, Cohen J, Vortmeyer AO, et al: Possible interaction of anti-PD-1 therapy with the effects of radiosurgery on brain metastases. Cancer Immunol Res 4: 481-487, 2016
27. Wallin JJ, Bendell JC, Funke R, et al: Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nat Commun 7:12624, 2016
28. Cannistra SA: Phase II trials in *Journal of Clinical Oncology*. J Clin Oncol 27:3073-3076, 2009

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Survival of Patients With Melanoma With Active Brain Metastases Treated With Pembrolizumab on a Phase II Trial

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