Metastatic melanoma is a deadly disease. The frequency of brain metastases in patients with advanced melanoma ranges from 10% to 50%, with autopsy series suggesting that the rate could be as high as 75%. Prognosis for these patients remains poor, with a median overall survival of patients with brain metastases of only 2–5 months, with the shortest survival times noted for those with symptomatic metastases. Some studies show up to 8-month median survival with surgery, but, ultimately, brain metastases cause death in over 95% of these patients. Despite ongoing research and advancements in care, melanoma has typically been resistant to radiotherapy and cytotoxic chemotherapy. In the central nervous system (CNS), treatment options include surgery, stereotactic radiosurgery (SRS), and whole-brain radiation therapy (WBRT), depending on the size and number of lesions. Temozolomide has been the most widely used systemic treatment for brain metastases, with only 10% clinical response.

Recently, however, promising new therapies for advanced melanoma have emerged. Vemurafenib is an inhibitor of BRAF and is effective against tumors with the
**BRAF** V600E mutation, which is present in up to 60% of melanoma cases. After demonstration of improved progression-free and overall survival in these patients, FDA approval was granted in 2011. Immune checkpoint blockade is being increasingly validated as therapy for some patients with advanced melanoma. Ipilimumab is a monoclonal antibody that binds cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), a negatively regulatory co-stimulatory molecule that is expressed highly on activated T lymphocytes. Blockade of this molecule leads to enhanced and more durable activation of T cells and, thereby, a more vigorous antitumor immune attack. This antitumor effect has been demonstrated in a Phase III study, where ipilimumab treatment led to improved survival in patients with advanced systemic melanoma. Ipilimumab has also demonstrated activity in patients with brain metastases, with a prospective Phase II study finding the greatest effect when tumors are small and asymptomatic, and patients are not using corticosteroids. One major limitation of ipilimumab therapy, however, is the delayed onset of action. Responses are typically documented only after 3 months of therapy, and response following initial progression has been observed in a subset of patients who derive long-term benefit. Patients with large or symptomatic brain metastases represent a population that is perhaps the most vulnerable to small increments in tumor burden and most of these patients cannot maintain a performance status compatible with pursuing outpatient treatment for more than several weeks.

Ultimately, the emergence of new effective therapies like BRAF inhibitors and immune checkpoint inhibitors such as ipilimumab and nivolumab has allowed oncologists and neurosurgeons to be more aggressive with treatment for patients with advanced melanoma, particularly for those with multiple brain metastases. BRAF inhibitors may be efficacious against melanoma brain metastases—however, immunotherapy is the best approach for patients with BRAF wild-type disease. Neurosurgeons, neuroradiologists, and radiation oncologists are heavily engaged in the effort to control intracranial disease in these patients, and immune checkpoint blockade is becoming part of the armamentarium. There is increasing recognition that corticosteroids inhibit the impact of ipilimumab. Accordingly, a growing indication for craniotherapy in this patient population has been to address steroid dependence in patients who are receiving or are being considered for treatment with ipilimumab. In this report, we have analyzed the presenting features and the outcomes of melanoma patients who have undergone craniotherapy in temporal proximity to treatment with ipilimumab.

**Methods**

Institutional review board approval was obtained for this retrospective study. The study population included all patients with melanoma and brain metastases who received ipilimumab and underwent craniotherapy for tumor resection between 2008 and 2014 at the Massachusetts General Hospital. We restricted our final analysis to patients who underwent craniotherapy within 3 months prior to initiation of therapy or up to 6 months after cessation of ipilimumab administration. These selection criteria were based on evidence of sustained antitumor response after ipilimumab administration. The following information was obtained: date of birth; sex; date of primary melanoma diagnosis; number of cerebral metastases; date(s) of craniotherapy; date(s) and dose(s) of ipilimumab; radiation therapy type, dose(s), and date(s); neurological examination findings; operative note(s); pathology, including **BRAF** mutation status; and neurosurgical and oncological visit notes. Improvements in performance status were noted as “no change,” “improved,” or “worsened,” based on comparison of preoperative and postoperative notes. Corticosteroid dependence was determined by duration and magnitude of therapy. Many patients received an immediate preoperative dose and were placed on a postoperative 4-day Decadron taper, but only those who continued to require corticosteroids for symptom management were defined as corticosteroid users.

**Statistical Analysis**

Primary endpoints for this study were change in performance status, change in corticosteroid dosage, and survival, as measured from the time of first ipilimumab dose. Kaplan-Meier estimates were used to determine the median overall survival.

**Results**

A total of 20 patients with cerebral metastases who both received ipilimumab and also underwent craniotherapy for tumor were identified. Of this group, 12 patients fit the inclusion criteria based on timing of therapy (median age at surgery 59.2 years, range 39–72 years). Table 1 summarizes the patient and disease characteristics of each case. The median number of metastases at the time of craniotherapy was 2 (range 1 to > 20). The median number of ipilimumab doses was 4 (range 2–4). Nine of 12 patients received ipilimumab doses of 3 mg/kg, while 2 of the first patients treated under a compassionate-use protocol received doses of 10 mg/kg. Eleven of 12 courses of ipilimumab were stopped for disease progression, either systemically or intracranially, and 1 was stopped for the adverse event of colitis.

Table 2 demonstrates disease and treatment characteristics for all 12 patients. Of the 10 patients with known mutation status, half were **BRAF** mutant. Eight of 12 patients received other chemotherapy or immunotherapy in addition to ipilimumab. Ten of 12 patients underwent pre- or postoperative SRS to tumor regions.

As shown in Table 3, the study population included 6 patients who underwent surgery within 3 months of starting ipilimumab, 5 patients who underwent surgery during their course of ipilimumab, and 4 patients who underwent surgery within 6 months after their last dose of ipilimumab. There were no surgical complications related to the use of ipilimumab, regardless of whether surgery occurred during or following therapy. Three patients underwent craniotherapy twice, 2 having surgery both before and during ipilimumab treatment and another having surgery both before and after ipilimumab treatment. Symptomatic...
hemorrhagic tumor was the most common reason for surgery (6 of 14 cases).

Nine of 12 patients had qualitative improvement in their performance status following craniotomy. The status of 1 patient with multiple cerebral lesions deteriorated postoperatively in the context of progressive growth of 4 additional brain metastases. The status of 2 additional patients was unchanged postoperatively.

Of the 6 patients requiring corticosteroids prior to craniotomy, 3 patients tolerated corticosteroid dose reduction after surgery. Patients unable to tolerate tapering of their corticosteroid dosage had 3, 4, and more than 20 remaining tumors postoperatively. The patient in Case 2 tolerated a taper after his third and final craniotomy for metastasis, and the patients in Cases 3 and 6 tolerated tapers after the first of 2 craniotomies for dominant lesions.

Ten of 12 patients had died by the time of data collection, and 1 patient was lost to follow-up. The median survival after the start of ipilimumab treatment was 7 months, as shown in Fig. 1.

### Illustrative Cases

Cases 3 and 6 are representative examples of how an aggressive approach to local control of growing or symptomatic cerebral melanoma metastases can facilitate immunotherapy with checkpoint inhibitors.

**Case 3**

This patient had been treated for several years for metastatic melanoma and was found to have an initial brain metastasis (right temporal lobe) in July 2010. After this lesion was treated with stereotactic radiosurgery, a left parietal lobe lesion developed, causing intermittent right arm weakness. The patient was started on 4-mg twice-daily doses of Decadron. Due to progressive symptoms, the left parietal lobe tumor was resected in October 2010 (Fig. 2 left). The patient tolerated a short taper off of Decadron following this surgery. Shortly thereafter, the irradiated right temporal lobe lesion was found to have progressed and was resected (Fig. 2 right). With the patient completely off steroid medication, ipilimumab was started in February 2011, and 4 doses were administered. Although the systemic disease progressed, there was no recurrence of intracranial melanoma. The patient lived for 24 months after initiation of ipilimumab.

**Case 6**

This patient was initially diagnosed with Stage 1 melanoma and was found to have an initial brain metastasis (right temporal lobe) in July 2010. After this lesion was treated with stereotactic radiosurgery, a left parietal lobe lesion developed, causing intermittent right arm weakness. The patient was started on 4-mg twice-daily doses of Decadron. Due to progressive symptoms, the left parietal lobe tumor was resected in October 2010 (Fig. 2 left). The patient tolerated a short taper off of Decadron following this surgery. Shortly thereafter, the irradiated right temporal lobe lesion was found to have progressed and was resected (Fig. 2 right). With the patient completely off steroid medication, ipilimumab was started in February 2011, and 4 doses were administered. Although the systemic disease progressed, there was no recurrence of intracranial melanoma. The patient lived for 24 months after initiation of ipilimumab.
anoma in 2010 and was found to have metastasis to the colon in February 2014. In March 2014, due to progressive headaches and multiple falls, the patient underwent brain MRI and was found to have a 5 × 4–cm right frontal lobe lesion, a punctate posterior right frontal lobe lesion, and a 1.5 × 1.5–cm left temporal lobe lesion (Fig. 3 upper). Additionally, a PET scan showed multiple pulmonary and liver metastases. The patient started treatment with Decadron (4 mg 4 times a day) and underwent gross-total resection of a large right frontal metastasis in March 2014. Decadron treatment was tapered postoperatively. Ipilimumab treatment was started 2 weeks after surgery. The left temporal mass was seen to grow slightly. The decision to resect, rather than treat with stereotactic radiosurgery, was made so as to avoid the initiation of steroids that often occurs early after radiosurgery for mass lesions. One month later, the patient received stereotactic radiosurgery to a punctate posterior right frontal lobe lesion and fractionated stereotactic radiotherapy to both surgical cavities. Ipilimumab therapy was ultimately stopped after the third cycle because of severe colitis. Despite a heavy burden of systemic disease, the patient remains alive and clinically stable. Brain imaging 7 months after cessation of ipilimumab therapy and standard local treatments for metastases shows no evidence of recurrence or progression (Fig. 3 lower).

Discussion

The efficacy of resecting a single melanoma brain metastasis is clear. Oxford Centre for Evidence-Based Medicine Level 2 and 3 evidence supports craniotomy for resection in some cases of multiple brain metastases. The value of resection of melanoma metastasis in combination with ipilimumab therapy and standard local treatments for metastases shows no evidence of recurrence or progression (Fig. 3 lower).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Treatment Timing</th>
<th>Reason for Surgery</th>
<th>Performance Status</th>
<th>Corticosteroids</th>
<th>Systemic Progression</th>
<th>Survival After Ipi (mos), Status</th>
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</thead>
<tbody>
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<td>1</td>
<td>Surgery before Ipi</td>
<td>Dominant lesion, edema</td>
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<tr>
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<td>Yes</td>
</tr>
<tr>
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<td>Mass effect</td>
<td>Improved</td>
<td>Yes</td>
<td>Taper</td>
<td>Yes</td>
</tr>
<tr>
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<td>Hemorrhage</td>
<td>No change</td>
<td>None</td>
<td>Taper</td>
<td>Yes</td>
</tr>
<tr>
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<td>Hemorrhage</td>
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<td>Yes</td>
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<td>Weakness</td>
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<td>7</td>
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<td>Mass effect</td>
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<td>No</td>
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<td>Surgery during Ipi</td>
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<td>10</td>
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<tr>
<td>11</td>
<td>Surgery after Ipi</td>
<td>Solitary lesion, hemorrhage</td>
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</tr>
<tr>
<td>12</td>
<td>Surgery after Ipi</td>
<td>Solitary lesion</td>
<td>Improved</td>
<td>None</td>
<td>Taper</td>
<td>Yes</td>
</tr>
</tbody>
</table>

FIG. 1. Kaplan-Meier survival curve.

FIG. 2. Case 3. Axial T1-weighted gadolinium-enhanced MR images obtained in October 2010 (left) and December 2010 (right).
therapy for patients who would not otherwise be considered for surgery based on the number of lesions has not been established. This initial case series documents the characteristics of patients who underwent craniotomy for resection of brain metastases in temporal proximity to starting ipilimumab. Overall, surgery improved performance status in most cases, and there were no surgical complications related to the use of ipilimumab. Four of 6 patients who required corticosteroids prior to craniotomy continued to require them postoperatively; however, these patients were more likely to have high intracranial tumor burden. Ultimately, compared with the 6- to 8-month historical median survival rates for patients who undergo resection of melanoma brain metastases, our patient population did not appear to have a survival benefit, although the sample size was small.12,22

Traditionally, surgical intervention for melanoma of the CNS is viewed as having the greatest benefit for patients with a single brain lesion and a high preoperative performance status. For our population, surgery was chosen in many cases over radiosurgery because of hemorrhage, large lesion size causing mass effect, or tumor location in the posterior fossa. Yet, other factors may contribute to a decision for surgical intervention, particularly in the setting of ipilimumab treatment. In theory, there may be value in edema control and reduction in corticosteroid requirement for patients with single or multiple metastatic lesions. In a Phase II clinical study, Margolin et al. were the first group to demonstrate, prospectively, the activity of ipilimumab in patients with melanoma and brain metastasis. The response rate was greatest (24%) when patients had asymptomatic metastases that did not require corticosteroid treatment.14 These findings highlight the concern that the anti-inflammatory properties of corticosteroids may downregulate the response associated with checkpoint blockade. This appears to be true systemically as well as in the CNS.2,13 Steroid reduction is a reasonable goal for any patient being treated with cancer immunotherapy. However, the outcome for patients with symptomatic brain metastases who required steroids for symptom control was notably poor and apparently no different than for historical controls.

Another reason for surgical intervention may be for quality of life improvement, even without expected survival benefit. Resection of a large or hemorrhagic intracranial tumor may successfully palliate neurological symptoms and restore performance and independence in many patients. In our study, clinical neurological status and Karnofsky Performance Status improved or remained unchanged postoperatively in 11 of 12 patients in our study. Cases that may warrant surgical attention include brain tumors with mass effect, significant edema, hemorrhage, or impact on neurological function such as language, motor control, or level of arousal.

Our study is limited by the retrospective design, which includes an inherent selection bias, as well as the small number of patients and the heterogeneity of their clinical presentations and treatments. As a result, meaningful survival analyses could not be performed. Additionally, ipilimumab was administered in not the same manner in all cases.

Despite evidence in the literature of ipilimumab efficacy against melanoma brain metastases,2,15,19,23,26 none of the patients in our study demonstrated a radiographic response. The patient in Case 3, surviving 24 months, did not have any recurrence of intracranial disease following...
gross-total resection of metastases prior to ipilimumab, and it is conceivable that this patient’s lengthy overall survival and intracranial control were related to late and durable immune effects—off steroids. A larger study population with more clear responses to therapy might provide further evidence of the variability seen in response to these agents.

Many patients do not respond to immune checkpoint blockade. If craniotomy for cerebral metastases is to be justified by its ability to create a window of opportunity for patients to respond to immune checkpoint inhibition, patient selection would improve if reliable predictive patient characteristics or disease-related biomarkers for response existed. Some studies have indicated that factors such as an absolute lymphocyte count (ALC) > 1000 cells/μl, increases in ALC after 2 ipilimumab treatments, or maintained levels of inducible co-stimulator (ICOS) molecule correlated with clinical benefit from ipilimumab. In a study of 95 patients treated with ipilimumab, Simeone et al. reported that decreased levels of lactate dehydrogenase (LDH), c-reactive protein (CRP), and circulating regulatory T cells (Treg) were all significantly associated with a study of 95 patients treated with ipilimumab, Simeone et al. reported that decreased levels of lactate dehydrogenase (LDH), c-reactive protein (CRP), and circulating regulatory T cells (Treg) were all significantly associated with clinical response to ipilimumab and improved survival. Large multicenter studies will be required to validate these tests, and others, so that care for patients with advanced melanoma can be tailored appropriately.

Overall, even without intracranial response to ipilimumab, craniotomy for melanoma brain metastases, even when they are multiple, may improve quality of life. Ultimately, there must be continued study of predictive biomarkers that can determine which patients will respond to ipilimumab and, therefore, may achieve the greatest quality-of-life and survival benefits from surgery.

References


Author Contributions
Conception and design: Curry, Jones, Flaherty. Acquisition of data: Jones, Cahill, Brastianos, Flaherty. Analysis and interpretation of data: Curry, Jones, Cahill. Drafting the article: Curry, Jones. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Curry. Statistical analysis: Jones.

Correspondence
William T. Curry, Department of Neurosurgery, Stephen E. and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital, 55 Fruit St., YAW 9E-9026, Boston, MA 02114. email: wcurry@mgh.harvard.edu.