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

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Summary

Background Immunotherapy targeting the PD-1 axis has activity in several tumour types. We aimed to establish the activity and safety of the PD-1 inhibitor pembrolizumab in patients with untreated brain metastases from melanoma or non-small-cell lung cancer (NSCLC).

Methods In this non-randomised, open-label, phase 2 trial, we enrolled patients aged 18 years or older with melanoma or NSCLC with untreated brain metastases from the Yale Cancer Center. Patients had at least one untreated or progressive brain metastasis between 5 and 20 mm in diameter without associated neurological symptoms or the need for corticosteroids. Patients with NSCLC had tumour tissue positive for PD-L1 expression; this was not required for patients with melanoma. Patients were given 10 mg/kg pembrolizumab every 2 weeks until progression. The primary endpoint was brain metastasis response assessed in all treated patients. The trial is ongoing and here we present an early analysis. The study is registered with ClinicalTrials.gov, number NCT02085070.

Findings Between March 31, 2014, and May 31, 2015, we screened 52 patients with untreated or progressive brain metastases (18 with melanoma, 34 with NSCLC), and enrolled 36 (18 with melanoma, 18 with NSCLC). A brain metastasis response was achieved in four (22%; 95% CI 7–48) of 18 patients with melanoma and six (33%; 14–59) of 18 patients with NSCLC. Responses were durable, with all but one patient with NSCLC who responded showing an ongoing response at the time of data analysis on June 30, 2015. Treatment-related serious and grade 3–4 adverse events were grade 3 elevated aminotransferases (n=1 [6%]) in the melanoma cohort, and grade 3 colitis (n=1 [6%]), grade 3 pneumonitis (n=1 [6%]), grade 3 fatigue (n=1 [6%]), grade 4 hyperkalemia (n=1 [6%]), and grade 2 acute kidney injury (n=1 [6%]) in the NSCLC cohort. Clinically significant neurological adverse events included transient grade 3 cognitive dysfunction and grade 1–2 seizures (n=3 [17%]) in the melanoma cohort.

Interpretation Pembrolizumab shows activity in brain metastases in patients with melanoma or NSCLC with an acceptable safety profile, which suggests that there might be a role for systemic immunotherapy in patients with untreated or progressive brain metastases.

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Introduction

Substantial progress has been made in the treatment of patients with various cancers with immune checkpoint inhibitors. In this class, ipilimumab (anti-CTLA-4) gained approval for treatment of advanced melanoma based on improved survival compared with a peptide vaccine.[1] The second immune checkpoint to be assessed in clinical trials was the PD-1 axis. Two PD-1 inhibitors, pembrolizumab and nivolumab, have been approved for treatment of metastatic melanoma and non-small-cell lung cancer (NSCLC) after assessment in phase 3 trials that showed improvement in overall survival compared with standard of care in both diseases.[2–6]

In the USA, about 50 000 patients with metastatic melanoma or NSCLC develop brain metastases every year.[7] In particular, melanoma often metastasises to the brain; the incidence on autopsy is 70%.[8–10] At diagnosis, 10% of patients with metastatic NSCLC have brain metastases, and another 30% develop brain involvement during their illness.[11] Multifocal disease is common in both diseases; about half of patients with CNS involvement present with more than one brain lesion.[12]

Many effective drugs in development have not been well studied for CNS penetration, and patients with untreated brain metastases are excluded from most clinical trials. Trials often exclude patients with any history of brain metastasis—even if lesions have been irradiated and stable for a prolonged period, because of concerns about potential neurological sequelae.[13,14] More recently, clinical trials for patients with metastatic melanoma or NSCLC have allowed enrolment of patients with untreated brain metastases, but these are rare and typically local CNS treatment is needed before trial enrollment.[13,14]

With recent advances in local treatments, especially stereotactic radiosurgery, local control of brain metastases has improved with resultant prolongation of survival.[15]

Research in context

Evidence before this study

We searched PubMed through Jan 12, 2016, using the following terms: "Brain metastases" and "PD-1" or "PD-L1" and "melanoma" or "NSCLC". Although inhibitors of the PD-1 axis are being studied extensively in patients with various cancers with encouraging outcomes, little data are available for the activity in the CNS, because patients with untreated brain metastases have largely been excluded from these trials. The CTLA-4 inhibitor ipilimumab has shown activity in patients with untreated melanoma brain metastases, but no studies have been published on the activity of PD-1 or PD-L1 inhibitors in patients with untreated brain lesions.

Added value of this study

To our knowledge, this is the first study assessing the activity and safety of a PD-1 inhibitor in brain metastases from melanoma or non-small-cell lung cancer (NSCLC). Our findings showed that pembrolizumab is safe in patients with small, asymptomatic brain metastases, and has activity in the CNS that is similar to activity in systemic disease.

Implications of all the available evidence

Brain metastases from melanoma or NSCLC often present a clinical challenge, and very few trials focus on systemic treatments to control their disease. Previous findings have shown that pembrolizumab has clinical activity in patients with melanoma or NSCLC with a good toxicity profile. Our findings show that pembrolizumab has activity in the CNS in patients with small, asymptomatic, untreated brain metastases. Further studies are needed to confirm this activity and delineate the patient population in which pembrolizumab is most likely to be effective.

However, the use of stereotactic radiosurgery remains limited in the number of lesions that can be treated and long-term consequences can occur.[16] Whole brain radiotherapy is the main radiotherapy method for patients with more than four lesions or when stereotactic radiosurgery is not feasible, whereas surgery is typically reserved for haemorrhage, large lesions, and solitary brain metastases.[14] In view of the limitations of local treatments, systemic treatments might provide benefit for brain metastasis while simultaneously treating extracerebral disease.[17]

With the well documented systemic benefit from immunotherapy in patients with metastatic melanoma and NSCLC, we aimed to study the activity and safety of pembrolizumab in patients with untreated or progressive brain metastases. We present our initial results in this report.

Methods

Study design and participants

In this single institution, two cohort, phase 2 trial, we enrolled patients with melanoma or NSCLC and untreated or progressive brain metastases from the Yale Cancer Center. Key eligibility criteria were stage IV melanoma or NSCLC, age 18 years or older, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, life expectancy longer than 3 months, and adequate organ function (including absolute neutrophil count, haemoglobin, platelets, serum creatinine or creatinine clearance, serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, international normalized ratio or prothrombin time, and activated partial thromboplastin time). Patients had at least one brain metastasis between 5 mm and 20 mm that was untreated or that was unequivocally progressing after radiation as assessed by brain MRI; there was no maximum number of brain metastases allowed. Tumour tissue from a brain metastasis before enrolment was required for melanoma patients; use of archival tissue was allowed. Tumour PD-L1 positivity was required for enrolment of NSCLC patients only. We excluded patients with neurological symptoms attributable to brain metastases or who required corticosteroids to control neurological symptoms or perilesional oedema, and patients with leptomeningeal disease or significant autoimmune disease, or those who had previous treatment with agents targeting PD-1 or PD-L1. Previous surgical resection or radiotherapy for brain metastases was allowed, but lesions present at the time of whole brain radiotherapy or included in the stereotactic radiosurgery field were not considered assessable unless documented to have since progressed (defined as unequivocal growth of a metastatic lesion following radiotherapy as assessed by brain MRI). Any number of previous systemic therapies was allowed. A 2-week wash-out period for systemic treatments and radiotherapy was required before starting study treatment. We gave all patients prophylactic antiepileptics after seizure activity was noted in one patient early in the trial.

The study was approved by the Yale University Institutional Review Board; it is being done in accordance with international standards of good practice. All patients provide written informed consent at enrolment.

Procedures

We gave patients 10 mg/kg pembrolizumab intravenously every 2 weeks. Dose selection was based on data available when the protocol was written; subsequent findings showed that smaller doses are equally effective for systemic disease.[6,18] Dose reduction was not allowed but doses could be withheld for up to 12 weeks for toxic effects, at which time patients were discontinued from study. Treatment continued until disease progression, toxicity that precluded continuing study drug, withdrawal from