Case Report

Durable Response After 2 Doses of Pembrolizumab in a Patient With Non–Small-Cell Lung Cancer With an Isolated Brain Metastasis

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Clinical Practice Points

- More than two-thirds of patients with non–small-cell lung cancer have locally advanced or metastatic disease at presentation. Various targeted agents are approved for patients with a targetable driver mutation. However, most patients lack driver mutation and chemotherapy in the form of platinum doublet used to be the standard of care, with the response rate to cytotoxic chemotherapy at best approximately 30% and median survival less than a year.
- On the basis of recent data, combination chemoimmunotherapy is now the preferred first-line option for patients without a driver mutation. In patients with treatment-naive advanced non–small-cell lung cancer and high programmed death ligand 1 expression (≥50%) who lack an actionable driver mutation, single-agent pembrolizumab is another preferred treatment option.
- We report a case of a durable response in a patient with metastatic lung cancer after only 2 doses of pembrolizumab.
- In patients with metastatic non–small-cell lung cancer, a durable response can be achieved even with just 2 cycles of check point inhibitor.

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Introduction

More than two-thirds of patients with non–small-cell lung cancer (NSCLC) have locally advanced or metastatic disease at presentation.[1] Various targeted agents are approved for patients with a targetable driver mutation. However, most patients lack driver mutation and chemotherapy in the form of platinum doublet used to be the standard of care. The response rate with cytotoxic chemotherapy at best is approximately 30% and median survival is less than a year.[2,3] In addition, patients with advanced nonsquamous NSCLC, maintenance pemetrexed has improved survival compared with placebo.[4] Combination chemoimmunotherapy is now the preferred first-line option for patients without a driver mutation on the basis of the recent data from 3 phase III trials, KEYNOTE-189, KEYNOTE-407, and IMPower studies.[5-7] In patients with treatment-naive advanced NSCLC and high programmed death ligand 1 (PD-L1) expression (≥50%) who lack an actionable driver mutation, single-agent pembrolizumab is another preferred treatment option on the basis of the KEYNOTE-024 study.[8] In this article, we report a case of a durable response in a patient with metastatic lung cancer after only 2 doses of pembrolizumab.

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Case

A 65-year-old woman with no significant medical history and an active smoker was admitted with 6-week history of vertigo, headache, and vomiting. Computed tomography (CT) imaging of the head followed by magnetic resonance imaging (MRI) showed an isolated 2-cm mass in the right thalamus with extensive surrounding vasogenic edema. CT imaging of the chest, abdomen, and pelvis showed a right apical lung mass and metastatic adenopathy within

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the precarinal and right hilar regions with no other sites of metastasis (Figure 1A). The patient underwent surgical resection of this brain lesion. The surgical specimen was consistent with metastatic adenocarcinoma of the lung (Figure 2). The tumor had very high expression of PD-L1 at 95% and was negative for EGFR and ALK mutations. After surgery, the patient participated in inpatient rehabilitation for over 2 months with residual left-sided weakness. Because of her prolonged stay, pembrolizumab 200 mg intravenously was started while in rehabilitation, and a second dose given 3 weeks later in the outpatient clinic. Her clinical course was complicated with hospital admission for community acquired pneumonia. At this time the patient and her family decided against further cancer-directed treatments. However, over the course of the next 10 months, this patient clinically improved and she reconsidered this decision. Restaging studies were performed with MRI of the brain and CT imaging of the chest, abdomen, and pelvis, which showed no evidence of disease progression (Figure 1B). The patient wished to continue treatment with pembrolizumab monotherapy and has so far received 13 cycles of pembrolizumab. She continues to have stable disease on repeat imaging.

Discussion

Our case report highlights that a durable response can be achieved even with just 2 cycles of anti-programmed death 1 (PD-1) therapy. To the best of our knowledge, we have presented the first patient with metastatic lung carcinoma who achieved a durable response with 2 doses of pembrolizumab. Durable clinical response and preservation of response status after treatment discontinuation has not been traditionally seen with cytotoxic chemotherapy. Immunotherapy, in contrast, is known to produce durable clinical response even after treatment discontinuation. A meta-analysis of long-term overall survival data from trials that used ipilimumab in advanced or metastatic melanoma showed that the Kaplan–Meier overall survival curve began to plateau at around 3 year and extended up to 10 years in some patients.[9]

It has been hypothesized that a durable response to immunotherapy beyond treatment interruption is the result of restoration of T-cell function and immune adaptive endogenous memory. In our case, a durable response of 10 months was achieved with just 2 cycles of pembrolizumab. It is possible that the high PD-L1 expression of 95% might have played a significant role in the durability of response. Jimenez and colleagues recently reported on their retrospective study in which patients with PD-L1 expression of 90% to 100% had better clinical outcome compared with patients with 50% to 89% expression in terms of response rate and survival.[10] However, using PD-L1 expression as the only predictive marker of response to immunotherapy has its own limitations. The expression of PD-L1 is dynamic, in space and time, because of the constantly evolving immune response. Moreover, patients who lack PD-L1 expression can still have a durable response to immunotherapy. Rizvi and colleagues in their seminal study showed that in patients with NSCLC who are treated with pembrolizumab, durable clinical benefit can be seen in patients with nonsynchronous mutation burden.[11] Additionally, they reported that the clinical benefit correlated with a molecular signature specific to tobacco carcinogen-related mutagenesis and the burden of neoantigens. Also, in a systematic review, Norum and Nieder showed that response rate to immunotherapy was better among smokers than nonsmokers.[12] Smoking-related lung cancers, because of its chronic exposure to mutagens, carry a higher mutation burden compared with nonsmokers. Higher mutation burden results in higher expression of neoantigens. Hellmann and colleagues reported a significantly longer progression-free survival with ipilimumab and nivolumab than with the platinum-doublet chemotherapy among patients with treatment-naive metastatic NSCLC with a high tumor mutational burden irrespective of PD-L1 status.[13] Our patient's tumor mutation burden was not measured. However, she was an active smoker, suggesting that she might have a higher expression of neoantigens.

The optimal duration of treatment with PD-1 blockade in NSCLC is unknown. Forde and colleagues have shown a major pathological response in 45% of cases with surgically resectable early

Figure 1 Coronal View of Computed Tomography Images Obtained at (A) the Time of Diagnosis and (B) After 10 Months

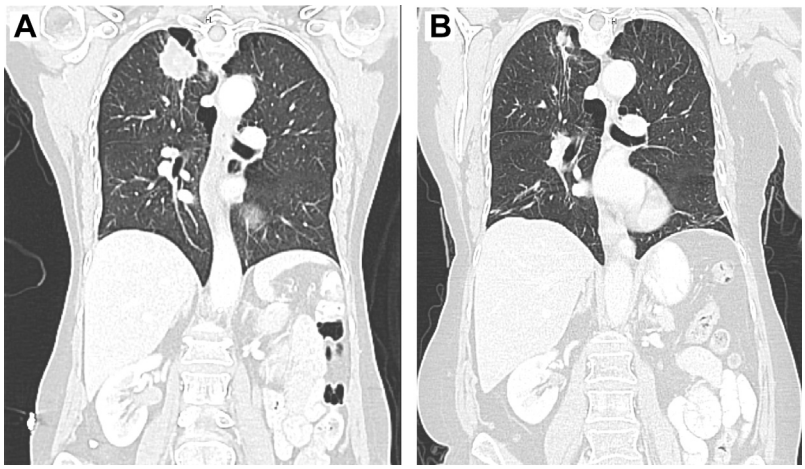
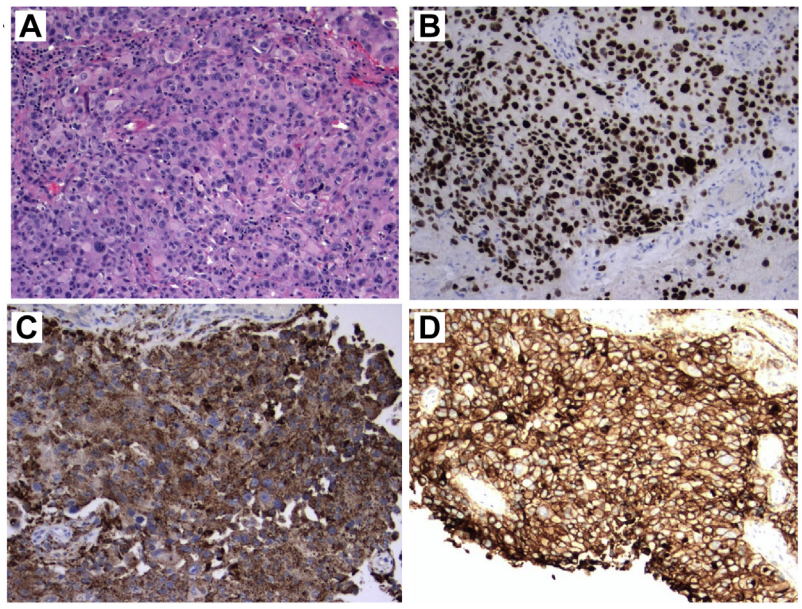


Figure 2 Metastatic Brain Lesion; Poorly Differentiated Adenocarcinoma, Consistent With Pulmonary Primary. The Biopsy Reveals a Solid Pattern of Malignant Large Cells Without Glandular Differentiation; Hematoxylin and Eosin (A). The Tumor Shows Strong Nuclear Expression of Thyroid Transcription Factor 1 (B), and Strong, Cytoplasmic Granular Expression of Napsin A (C). Immunohistochemical Stain for Programmed Death Ligand 1 22C3 FDA (Keytruda; Merck) Shows High Expression in Virtually 100% of the Tumor Cells With Strong Intensity (D). Magnification ×100, All Panels



NSCLC with just 2 doses of neoadjuvant nivolumab.[14] Major landmark clinical trials for advanced NSCLC with immunotherapy as a first-line treatment have used immunotherapy either alone or in combination with platinum doublet chemotherapy for up to 35 cycles or until disease progression.[5-8] These studies highlight the current lack of reliable information to guide the duration of immunotherapy.

Prospective studies to address the optimal duration of treatment with immunotherapy and predictive biomarkers to guide early discontinuation are needed. As patients live longer during immunotherapy treatment, it is important to find ways to reduce the financial burden and inconvenience.

Disclosure

The authors have stated that they have no conflicts of interest.

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