ORIGINAL ARTICLE

Phase II Study of Maintenance Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC)

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ABSTRACT

Objective: The aim of this study was to assess the efficacy of maintenance pembrolizumab in patients with extensive-stage SCLC after treatment with platinum and etoposide.

Methods: Patients with extensive-stage SCLC with a response or stable disease after induction chemotherapy were eligible. Pembrolizumab at a dose of 200 mg administered intravenously every 3 weeks was initiated within 8 weeks of the last cycle of chemotherapy. The primary end point of the study was progression-free survival (PFS) from study registration, with overall survival (OS) as a key secondary end point. Available tumor tissue was assessed for expression of programmed death ligand 1 (PD-L1) both in the tumor cells and in the surrounding stroma. Blood for circulating tumor cells was collected before the first, second, and third cycles of pembrolizumab.

Results: Of the 45 patients enrolled, 56% were male and 22% had treated brain metastases. The median PFS was 1.4 months (95% confidence interval [CI]: 1.3–2.8), with a 1-year PFS of 13%. The median OS was 9.6 months (95% CI: 7.0–12), with a 1-year OS of 37%. Of the 30 tumors that could be assessed, three had PD-L1 expression ($\geq$1%) in the tumor cells. A total of 20 tumors could be assessed for PD-L1 expression in the stroma. The median PFS in the eight patients with tumors positive for expression of PD-L1 at the stromal interface was 6.5 months (95% CI: 1.1–12.8) compared with 1.3 months (95% CI: 0.6–2.5) in 12 patients with tumors negative for this marker. No unexpected toxicities were observed.

Conclusion: Maintenance pembrolizumab did not appear to improve median PFS compared with the historical data. However, the 1-year PFS rate of 13% and OS rate of 37% suggest that a subset of patients did benefit from pembrolizumab.

Keywords: SCLC; Maintenance; Pembrolizumab; Metastatic

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Introduction

More than 30,000 new cases of SCLC are diagnosed each year in the United States, and most of these patients have extensive-stage disease at diagnosis.[1] Despite a high response rate with platinum-etoposide combination therapy, the median progression-free survival (PFS) after completion of initial chemotherapy is only 2 months and the median overall survival (OS) is about 10 months.[2] Therefore, there remains a need to evaluate novel agents for the management of these patients.

Recently, immune checkpoint inhibitors, specifically, drugs targeting the programmed cell death protein 1 (PD-1) pathway in T cells, have shown clinical benefit in several tumor types.[3] Pembrolizumab, which is an antibody targeting programmed cell death protein 1 (PD-1) is approved for several tumor types, including advanced NSCLC, in both the frontline and recurrent settings.[4] Available data suggest that immune checkpoint inhibitors are more likely to benefit patients with NSCLC who are smokers and whose tumors have a high mutational burden.

SCLC occurs almost exclusively in patients who are smokers, and generally these tumors have a high mutational burden. Therefore, there is an expectation that immune checkpoint inhibitors will be beneficial in these patients. We speculated that immunotherapy may be better tolerated and more effective in patients after completion of chemotherapy because these patients are likely to have better performance status and fewer symptoms than at the time of disease progression. In addition, clinical and preclinical data suggest that chemotherapy may enhance the susceptibility of the tumor to immunotherapy.[5,6]

Therefore, we conducted a single-arm phase II study to evaluate the ability of maintenance pembrolizumab to improve PFS and OS in patients with extensive-stage SCLC.

Methods

Study Population

Patients with extensive-stage SCLC were eligible if they were at least 18 years of age and had a response or stable disease after four to six cycles of platinum-etoposide chemotherapy. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate hematologic, hepatic, and renal function. Patients with treated brain metastases were eligible. Patients were excluded if they had autoimmune disease, including a paraneoplastic disorder of autoimmune nature that required systemic treatment (disease-modifying agents, corticosteroids, or other immunosuppressive drugs) within the previous 3 months or active interstitial lung disease or pneumonitis. Prior therapy with immune checkpoint inhibitors was not allowed. Prophylactic cranial radiation and thoracic radiation were permitted.

The study procedures were approved by the institutional review boards at each participating institution. Good Clinical Practice guidelines, Declaration of Helsinki ethical standards, and all local and national regulations were followed. All patients provided written informed consent before participation.

Study Design and Assessments

Imaging studies, including brain scans confirming response or disease stability, had to be done no more than 3 weeks before the patient started treatment with pembrolizumab. Patients treated with brain radiation, either prophylactic or therapeutic, or radiation to any other site, were required to have completed radiation therapy at least 7 days before starting treatment with pembrolizumab.

All eligible patients were treated with pembrolizumab at a dose of 200 mg intravenously every 3 weeks. Pembrolizumab had to be started within 8 weeks of the start of the last cycle of chemotherapy. Therapy was continued for a total of 2 years unless disease progression or unacceptable toxicity developed or the patient withdrew consent. A patient could continue to receive pembrolizumab despite progression defined on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 if it was determined that the patient was deriving clinical benefit. However, if there was further RECIST-defined progression after two more cycles, pembrolizumab was discontinued. Adverse events were assessed according to National Cancer Institute Common Toxicity Criteria version 4.0. Treatment delays or discontinuations were defined for drug-related toxicities, including immune-related adverse events. No modification of the pembrolizumab dose was permitted.

Patients underwent imaging studies to assess disease status after every two cycles for the first six cycles and then at the discretion of the treating physician, but no less than every four cycles. Retrieval of pretreatment biopsy specimens for assessment of PD-L1 expression in tumor cells and stromal tissue was conducted by Qualtek Clinical Laboratories (Newton, PA). Assessment of tumor PD-L1 level was conducted by using the DAKO 22C3 antibody (Dako, Carpinteria, CA). A sample was considered adequate for PD-L1 assessment only if there were at least 50 viable tumor cells or five viable tumor cells with PD-L1 staining. A modified proportion score was used to assess PD-L1 expression in tumor cells. The modification in modified proportion score is that mononuclear cells within the tumor cell nests staining for PD-L1 were counted in combination with tumor cells positive for PD-L1. In addition to PD-L1 expression in the