ORIGINAL ARTICLE

A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC

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ABSTRACT

Background: Despite the significant antitumor activity of pembrolizumab in NSCLC, clinical benefit has been less frequently observed in patients whose tumors harbor *EGFR* mutations compared to *EGFR* wild-type patients. Our single-center experience on the KEYNOTE-001 trial suggested that pembrolizumab-treated EGFR-mutant patients, who were tyrosine kinase inhibitor (TKI) naïve, had superior clinical outcomes to those previously treated with a TKI. As TKI naïve EGFR-mutants have generally been excluded from pembrolizumab studies, data to guide treatment decisions in this patient population is lacking, particularly in patients with programmed death ligand 1 (PD-L1) expression $\geq$50%.

Methods: We conducted a phase II trial (NCT02879994) of pembrolizumab in TKI naive patients with *EGFR* mutation–positive, advanced NSCLC and PD-L1–positive ($\geq$1%, 22C3 antibody) tumors. Pembrolizumab was administered 200 mg every 3 weeks. The primary endpoint was objective response rate. Secondary endpoints included safety of pembrolizumab, additional pembrolizumab efficacy endpoints, and efficacy and safety of an *EGFR* TKI after pembrolizumab.

Results: Enrollment was ceased due to lack of efficacy after 11 of 25 planned patients were treated. Eighty-two percent of trial patients were treatment naïve, 64% had sensitizing *EGFR* mutations, and 73% had PD-L1 expression $\geq$50%. Only 1 patient had an objective response (9%), but repeat analysis of this patient's tumor definitively showed the original report of an *EGFR* mutation to be erroneous. Observed treatment-related adverse events were similar to prior experience with pembrolizumab, but two deaths within 6 months of enrollment, including one attributed to pneumonitis, were of concern.

Conclusions: Pembrolizumab's lack of efficacy in TKI naïve, PD-L1+, EGFR-mutant patients with advanced NSCLC, including those with PD-L1 expression $\geq$50%, suggests that it is not an appropriate therapeutic choice in this setting.

Keywords: NSCLC; programmed death 1 (PD-1); *EGFR*; tumor immunology; pembrolizumab; programmed death ligand 1

Introduction

Programmed death 1 (PD-1) axis inhibition has resulted in durable responses in NSCLC patients whose tumors harbor mutations in the *EGFR* gene. However, data to date suggests that responses are considerably

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less frequent in this patient population compared to *EGFR* wild type (WT) patients.[1-4]

Approximately 10% of patients in North America and approximately 30% to 50% of patients of East Asian descent have mutations in the *EGFR* gene, of which 90% have sensitizing mutations.[5] Although tumors with *EGFR* sensitizing mutations are generally responsive to tyrosine kinase inhibitors (TKIs) directed against *EGFR*,[5-9] the benefits are transient, and recurrence inevitably occurs. As patients with *EGFR* mutations are typically younger than *EGFR* WT patients,[10] this population would derive particular benefit from the durable responses seen with PD-1 axis inhibitors.[3]

There has been much speculation regarding the limited benefit of PD-1 axis inhibitors in EGFR-mutant NSCLC.[2,11] Higher nonsynonymous tumor mutational burden is associated with improved benefit from anti–PD-1 therapy,[12] and tumors from EGFR-mutant patients have less mutations than those in *EGFR* WT patients.[13] Whereas PD-1 axis inhibitors have shown greater benefit among patients with high expression of programmed death ligand 1 (PD-L1), *EGFR* TKIs downregulate PD-L1 expression in a laboratory setting.[14-19] The relevance of this finding is unclear as tumor PD-L1 expression levels in some clinical series have been largely unaffected by TKI administration.[2]

The limited benefit of PD-1 axis inhibitors in EGFR-mutant patients has led to alternate approaches, including combining agents targeting both pathways. Yet synergy has not been observed between *EGFR* TKIs and anti–PD-1 therapy in a peripheral blood mononuclear cell co-culture system.[16] Clinical trials evaluating concurrent administration of an *EGFR* TKI and a PD-1 axis inhibitor in EGFR-mutant NSCLC patients have been conducted (NCT02364609, 02630186, 02039674, 02013219, 02088112, and 02143466). A number of these studies have run into concerns related to toxicity. Specifically, grade 3 or higher adverse events (AEs) were observed in more than 50% of patients receiving combination therapy in two phase I studies, with interstitial lung disease (ILD) occurring in 38% of patients receiving both durvalumab and osimertinib.[20,21] Further, on Arm E of CheckMate-012, which evaluated the combination of nivolumab and erlotinib, the observed clinical outcomes were not clearly superior to what would be expected with erlotinib alone.[22] Because of the high response rate with *EGFR* TKIs in EGFR-mutant patients,[23] PD-1 axis inhibition has not been formally evaluated before TKI administration.

We previously reported our single-center experience on the KEYNOTE-001 trial at the University of California, Los Angeles (UCLA). Four EGFR-mutant patients that had not received an *EGFR* TKI before pembrolizumab had improved clinical outcomes (objective response rate [ORR] = 50%, median progression-free survival (PFS) = 157.5 days, median overall survival (OS) = 559 days) compared to the 26 EGFR-mutant patients with a history of TKI therapy before pembrolizumab (ORR = 4%, median PFS = 56 days, median OS = 120 days), with a median follow-up for surviving patients of 42.4 months.[24,25] That experience was limited by small patient numbers, but formed the basis for a trial (NCT02879994) to evaluate the hypothesis that pembrolizumab before *EGFR* TKI therapy in patients with advanced NSCLC whose tumors harbored an *EGFR* mutation and were PD-L1 positive ($\geq$1% 22C3 antibody) would be superior to the current strategy in which PD-1 axis inhibitors are used after failure of an *EGFR* TKI. We were reassured by the typical rapid efficacy of *EGFR* TKIs, which we anticipated could quickly salvage patients who were progressing on pembrolizumab. The planned enrollment was 25 patients.

Methods

Patients

Eligible patients (18 years of age or older) had advanced NSCLC, adequate organ function, and an Eastern Cooperative Oncology Group performance status of $\leq$1. Key inclusion criteria included the following two tumor-specific factors (identified in a Clinical Laboratory Improvement Amendments–certified lab): (1) *EGFR* mutation positive (sensitizing or nonsensitizing); and (2) PD-L1–positive, defined as $\geq$1% tumor membranous staining by immunohistochemistry using the 22C3 pharmDx test. Key exclusion criteria included prior therapy with an *EGFR* TKI, prior PD-1 axis inhibitor therapy or any other drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, active autoimmune disease, or history of ILD or pneumonitis (Supplementary Data 1 NCT02879994 Protocol).

Study Oversight

As the study was conducted at a single center, the protocol and its amendments were approved by the UCLA Institutional Review Board, Internal Scientific Peer Review Committee, and the Medical Radiation Safety Committee. The study was monitored by the Jonsson Comprehensive Cancer Center Data Safety and Monitoring Board. Good Clinical Practice guidelines were followed throughout the study. Patients were required to provide written informed consent before all study-related activities.

Study Design and Treatment

The primary endpoint of the study was ORR to pembrolizumab, per modified Response Evaluation Criteria in Solid Tumors 1.1. Secondary objectives included safety of pembrolizumab and additional efficacy endpoints (PFS and OS). Patients received pembrolizumab 200 mg by intravenous infusion every 3