ORIGINAL ARTICLE

Nivolumab Plus Erlotinib in Patients With *EGFR*-Mutant Advanced NSCLC

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ABSTRACT

Introduction: This phase I study evaluated nivolumab combined with erlotinib in patients with advanced *EGFR*-mutant NSCLC.

Methods: Patients with advanced *EGFR*-mutant NSCLC who were EGFR tyrosine kinase inhibitor (TKI)–naive or TKI-treated but had not received chemotherapy were treated with nivolumab 3 mg/kg every 2 weeks and erlotinib 150 mg/d until disease progression or unacceptable toxicity. The primary objective was safety and tolerability.

Results: Twenty patients with TKI-treated and one with TKI-naive *EGFR*-mutant NSCLC were treated with nivolumab

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Drs. Gettinger and Hellmann contributed equally to this work.

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plus erlotinib. Treatment-related grade 3 toxicities occurred in five patients (liver enzyme elevations, n = 2; diarrhea, n = 2; weight loss, n = 1), with no grade ≥4 toxicities. In the TKI-treated population, the objective response rate was 15% (3 of 20, including one complete response), and the 24-week progression-free survival rate was 48%. Responses lasted 13.8, 17.6, and 38.2 months per investigator records. A fourth patient had a nonconventional immune-related response lasting 12.5 months. Among these four patients, two were never-smokers and one each had 35– and <1-pack-year histories. Post-EGFR TKI pre-trial tumor biopsy specimens from these patients detected *EGFR* T790M mutations in two patients and MNNG HOS Transforming gene (*MET)* amplification in a third; two patients each had primary *EGFR* exon 19 deletions or L858R mutations. The TKI-naive patient, who had compound *EGFR* mutations (L858R and S768I) and ultimately achieved a complete response, had an ongoing response lasting more than 5 years based on investigator records.

Conclusions: Nivolumab plus erlotinib was tolerable, with durable responses in patients with *EGFR*-mutant, TKI-treated NSCLC.

Keywords: Nivolumab; Programmed death 1 axis inhibitor; Erlotinib; Combination therapy; *EGFR*-mutant NSCLC

Introduction

Activating *EGFR* mutations are found in approximately 15% of adenocarcinomas of the lung in White populations. In Asian populations, *EGFR* mutations can be identified in 50% or more of adenocarcinomas of the lung.[1] Currently, erlotinib, gefitinib, and afatinib—small-molecule EGFR tyrosine kinase inhibitors (TKIs)—are approved for first-line use in patients with *EGFR*-mutant lung cancer in numerous countries, with objective response rates (ORRs) of 56% to 83%, median progression-free survival (PFS) of 9.5 to 13.6 months, and median overall survival (OS) of 19.3 to 30.5 months.[2–8] On the emergence of resistance to EGFR TKIs, a second *EGFR* mutation in exon 20, T790M, can be found in resistant tumor biopsy specimens from approximately half of patients, where it is believed to be the primary mediator of such resistance (other potential mediators of acquired resistance to EGFR TKIs include histologic transformation to small cell carcinoma and MNNG HOS Transforming gene [*MET*] amplification).[9,10] If *EGFR* T790M is detected at the time of resistance to first-line EGFR TKI treatment, either in tumor cells or as free circulating mutant DNA in blood, osimertinib, a third-generation *EGFR* mutation-specific TKI, is indicated. ORR with osimertinib in this setting was 71%, with a median PFS of 10.1 months.[11] Recently, osimertinib was granted priority review in the United States as frontline therapy for advanced *EGFR*-mutant NSCLC. This was based on a phase III trial that showed a PFS benefit in EGFR TKI-naive patients compared with either erlotinib or gefitinib (median PFS of 18.9 months versus 10.2 months; hazard ratio = 0.46, 95% confidence interval [CI]: 0.37–0.57, $p < 0.001$).[12]

Data evaluating standard chemotherapy after the development of resistance to first-line EGFR TKI treatment are limited. One phase III trial reported a median PFS and OS of 5.4 months and 17.2 months with platinum-doublet chemotherapy, respectively, regardless of T790M status; ORR was 34% with chemotherapy in this study.[13] Another trial found median PFS and ORR to be 4.4 months and 31% with chemotherapy, respectively, in patients with T790M-positive disease.[11]

Three programmed death-1 (PD-1) axis inhibitor antibodies have been approved in the United States, Canada, and Europe for use in patients with advanced NSCLC. Nivolumab, a fully human PD-1 immune checkpoint inhibitor antibody, is indicated following disease progression on first-line platinum-based chemotherapy, irrespective of tumor programmed death-ligand 1 (PD-L1) expression. Relatively few patients with *EGFR* mutations were included in the trials establishing the use of PD-1 axis inhibitors in advanced NSCLC. A meta-analysis evaluating this population suggested little benefit with PD-1 axis inhibitor therapy over standard second-line chemotherapy with docetaxel.[14]

CheckMate 012 (NCT01454102) is a multiarm phase I study evaluating nivolumab in combination with different agents including erlotinib, bevacizumab, ipilimumab, or platinum-doublet chemotherapy in advanced NSCLC. Herein we present the safety and efficacy of nivolumab combined with erlotinib in a cohort of patients with chemotherapy-naive *EGFR*-mutated advanced NSCLC.

Material and Methods

Study Design and Treatment

CheckMate 012 was approved by local institutional review boards, and all patients provided written informed consent before enrollment. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonisation. The primary objective was the safety and tolerability of nivolumab plus erlotinib, measured by the frequency of adverse events (AEs) and serious AEs, including laboratory abnormalities occurring up to 100 days after the last dose of study drug. The secondary objective was antitumor activity of nivolumab combined with erlotinib, measured by ORR and