BRIEF REPORT

Checkpoint Inhibitors in Metastatic *EGFR*-Mutated Non–Small Cell Lung Cancer—A Meta-Analysis

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ABSTRACT

Introduction: We performed a meta-analysis to assess the role of immune checkpoint inhibitors as second-line therapy in *EGFR*-mutant advanced NSCLC.

Methods: Randomized trials comparing immune checkpoint inhibitors against chemotherapy were identified. We retrieved the hazard ratio (HR) and 95% confidence interval (CI) for overall survival (OS) of the intention-to-treat population and *EGFR* mutation–defined subgroups. We used the fixed-effects inverse variance–weighted method to pool estimates of treatment efficacy. Statistical tests were two sided.

Results: In the three included studies that compared immune checkpoint inhibitors (nivolumab [n = 292], pembrolizumab [n = 691], and atezolizumab [n =144]) against docetaxel (n = 776), immune checkpoint inhibitors significantly prolonged OS over that with docetaxel overall (n = 1903, HR = 0.68, 95% CI: 0.61–0.77, $p < 0.0001$) and in the *EGFR* wild-type subgroup (n = 1362, HR = 0.66, 95% CI: 0.58–0.76, $p < 0.0001$) but not in the *EGFR*-mutant subgroup (n = 186, HR = 1.05, 95% CI: 0.70–1.55, $p < 0.81$; treatment-mutation interaction $p = 0.03$).

Conclusion: In *EGFR*-mutant advanced NSCLC, immune checkpoint inhibitors do not improve OS over that with docetaxel. Mechanisms of acquired resistance to first-line tyrosine kinase inhibitor therapy should be elucidated to guide selection of second-line treatment for these patients.

Keywords: NSCLC; *EGFR* mutation; Immune checkpoint inhibitors; Predictive biomarker

Introduction

Small molecule EGFR tyrosine kinase inhibitors (TKIs) are a highly effective treatment for advanced NSCLC with activating mutations of the *EGFR* gene. Despite an initial response, most of these patients experience disease progression approximately 10 to 13 months after first-line TKI therapy. Selection of optimal salvage therapy for some of these patients remains an ongoing challenge.

Several mechanisms of acquired resistance to TKI therapy have been reported: new *EGFR* T790M mutation,[1,2] transformation to a small cell histological type,[1] and activation of alternative antiapoptosis signaling pathways.[1–4] Third-generation TKIs are potent oral irreversible inhibitors of sensitizing *EGFR* mutations and the T790M resistance mutation. Third-generation TKIs can be effective salvage therapy for patients in whom T790M mutation develops and whose disease progresses during treatment with earlier-generation TKIs.[5]

Novel immunotherapy agents, nivolumab[6] and pembrolizumab,[7] which are programmed death 1 (PD-1) immune checkpoint inhibitors, are potential alternative salvage treatments. Both prolong overall survival (OS)

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compared with docetaxel and have been approved by the U.S. Food and Drug Administration as a new standard of care for second-line treatment of advanced NSCLC.

Evidence to support the role of immune checkpoint inhibitors in *EGFR*-mutated lung cancers is conflicting. Murine models have demonstrated significant response to the treatment with anti–PD-1 antibody in *EGFR*-mutant but not *KRAS*-driven lung tumors[8]; however, in a retrospective analysis of 58 patients with advanced NSCLC treated with PD-1/programmed death ligand 1 (PD-L1) inhibitors, only 4% of patients harboring *EGFR* mutations or anaplastic lymphoma receptor tyrosine kinase gene (*ALK)* rearrangements were tumor responders and 23% of patients with *EGFR* wild-type and *ALK*-negative or unknown tumors were responders.[9] We performed this meta-analysis to better assess the role of immune checkpoint inhibitors in *EGFR*-mutated advanced NSCLC.

Methods

Eligible randomized trials that compared immune checkpoint inhibitors against chemotherapy in the second-line setting were identified from MEDLINE, EMBASE, PubMed, and the Cochrane Central Register of Controlled Trials databases for articles published in English between January 1996 and July 2016 by using the following terms: *advanced/metastatic lung neoplasm/cancer/carcinoma*, *checkpoint inhibitor*, *cytotoxic T-lymphocyte associated protein 4*, *PD-1*, *PD-L1*, *ipilimumab*, *nivolumab*, *pembrolizumab*, and *randomized/controlled clinical trial*. To identify unpublished studies, we also searched abstracts from proceedings of the American Society of Clinical Oncology and European Society for Medical Oncology conferences and proceedings of the World Lung Cancer Conference.

For each included trial, we extracted study and patient characteristics and retrieved the hazard ratio (HR) and 95% confidence interval (CI) for OS of the intention-to-treat population and subgroups defined by *EGFR* mutation status. Data were extracted independently by two authors (C. L. and J. M.), with discrepancies resolved by consensus.

We used the fixed-effects inverse variance–weighted method to pool results to estimate the size of the benefit of treatment. A test for treatment-mutation interaction was used to assess differences in treatment effect across *EGFR*-defined subgroups. All statistical tests were two sided.

Results

We identified three eligible trials[6,7,10,11] (Table 1 and Fig. 1). In total, 1903 patients were randomized to receive an immune checkpoint inhibitor (nivolumab [n = 292], pembrolizumab [n = 691], and atezolizumab

Table 1. Characteristics of Patients in Constituent Trials

Study Name, Year (Reference)	Treatment Comparison	Median Overall Survival[a] (mo)	n	*EGFR* Mutation[b] (%)	*EGFR* Wild Type[b] (%)	Age <65 y (%)	ECOG PS 0 (%)	Women (%)	Never-Smoker (%)	Adenocarcinoma (%)	Only 1 Prior Line of Therapy (%)
Checkmate 057, 2015[6]	Nivolumab vs. docetaxel	12.2 vs. 9.4	582	14	58	58	31	45	20	93	88
Keynote 010, 2015[7]	Pembrolizumab vs. docetaxel	10.4[c] vs. 12.7[d] vs. 8.5	1034	8	85	58	34	39	18	68	69
POPLAR, 2016[11]	Atezolizumab vs. docetaxel	12.6 vs. 9.7	287	6	51	61	33	41	20	66	66

[a]Median overall survival as reported for each treatment arm of the intention-to-treat population.
[b]The percentages do not add up to 100% because of missing *EGFR* status.
[c]Pembrolizumab, 2 mg/kg, arm.
[d]Pembrolizumab, 10 mg/kg, arm.
EGOG PS, Eastern Cooperative Oncology Group performance status.

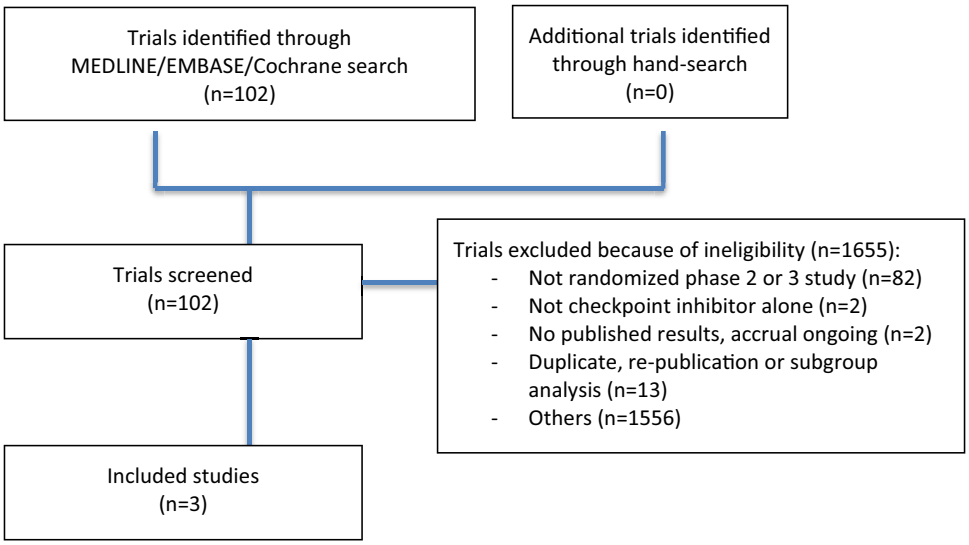

Figure 1. Flow diagram showing inclusion and exclusion of studies.

[n = 144]) or docetaxel (n = 776). *EGFR* mutation status was known for 1548 patients (81%). Treatment with an immune checkpoint inhibitor, compared with docetaxel, was associated with a 32% reduction in the risk for death in the intention-to-treat population (HR = 0.68, 95% CI: 0.61–0.77, $p < 0.0001$; heterogeneity $p = 0.67$). In the *EGFR* wild-type subgroup (n = 1362), the pooled HR was 0.66 (95% CI: 0.58–0.76, $p < 0.0001$; heterogeneity $p = 0.96$). In the *EGFR*-mutant subgroup (n = 186), the pooled HR was 1.05 (95% CI: 0.70–1.55, $p < 0.81$; heterogeneity $p = 0.80$). There was a statistically significant treatment-mutation interaction ($p = 0.03$) (Fig. 2). Among the *EGFR*-mutant subgroup, there was no significant statistical heterogeneity in treatment effect: $\chi^2 = 0.46$ ($p = 0.42$) and $I^2 = 0\%$.

Discussion

In this hypothesis-generating study, meta-analysis has demonstrated that *EGFR* mutation status is a potential predictive biomarker for OS in advanced NSCLC treated with an immune checkpoint inhibitor versus with docetaxel. There was no OS advantage in the

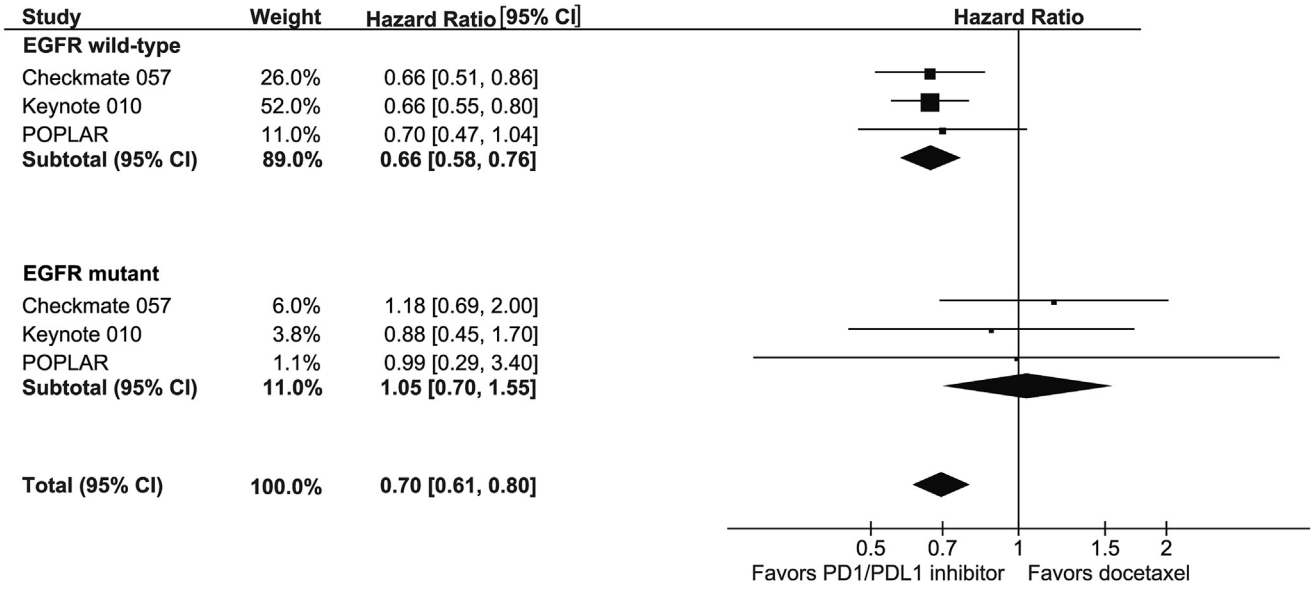

Figure 2. Forest plot of hazard ratios comparing overall survival in the *EGFR* gene wild-type and mutated subgroups in patients who received programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) immune checkpoint inhibitors versus docetaxel. Hazard ratios for each trial are represented by the squares, and the horizontal line crossing the squares represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two sided.

EGFR-mutant subgroup, but there was a 34% reduction in the risk for death in the *EGFR* wild-type subgroup.

Reliable biomarkers that could be used to select patients with a higher likelihood of benefit from immune checkpoint inhibitors remain vital in second-line treatment of advanced NSCLC. *EGFR* mutation has not been examined as a biomarker for this purpose. Current research has focused on PD-L1 overexpression as a predictive biomarker for checkpoint inhibition.[6,10–12] In one study of patients with PD-L1 overexpression, defined as PD-L1 expression in more than 50% of tumor cells (i.e., tumor proportional score [TPS] $>$ 50%), patients with *EGFR*-mutant tumors had significantly shorter OS than those who had *EGFR* wild-type tumors (median OS = 6.5 vs. 15.7 months) when treated with pembrolizumab.[12] In fact, OS did not differ significantly according to PD-L1 expression in the *EGFR*-mutant (TPS $>$ 50% vs. $<$1%: median OS = 6.5 vs. 5.7 months). In the *EGFR* wild-type subgroup (TPS $>$ 50% vs. $<$1%: median OS = 15.7 vs. 9.1 months). The predictive value of PD-L1 overexpression, particularly for the *EGFR*-mutant subgroup, remains unclear. Further, the concordance of PD-L1 expression with *EGFR* status and variation in PD-L1 expression with different types of *EGFR* mutations are also unknown. Another vital unanswered research question is whether the different mutations of the *EGFR* gene have different immunogenicity and hence result in different tumor responses to immune checkpoint inhibition.

Mutation burden in lung and other cancers is also considered predictive of benefit for checkpoint inhibition. Among patients with NSCLC treated with pembrolizumab, higher nonsynonymous mutation burden in tumors has been associated with greater clinical benefit.[13] Interestingly, *EGFR*-mutated lung cancer was shown to have low mutation burden in another study using next-generation sequencing,[14] providing a plausible biological explanation for the finding of our meta-analysis. Immunogenicity of *EGFR*-mutant tumors could be increased with combination treatments including PD-1 and cytotoxic T-lymphocyte associated protein 4 inhibitors, as demonstrated by significant response over that with PD-1 monotherapy (50% vs. 14%) in a small study.[15] Further trials are required to confirm this finding.

The major strength of this study is the inclusion of the most up-to-date data from all relevant trials, which overcomes the problem of inadequate power of individual trials to compare *EGFR* subgroups to assess a mutation-treatment interaction. The major limitation of our retrospective analysis is that *EGFR* status was not assessed in 19% of patients. We also acknowledge that the *EGFR* subgroup comprised only 186 patients and the different types of *EGFR* mutations were unknown. Nevertheless, we believe that these data provide useful exploratory information. Other limitations are that *EGFR* status was not determined universally by means of centralized testing in the included studies. The number of lines of TKI therapies received and whether patients who received multiple lines were equally distributed between randomized arms was also unknown. The impact of these factors on our analyses is unknown. Given these limitations, prospectively designed and adequately powered randomized trials will be required to confirm the value of *EGFR* mutation to predict OS benefit with immune checkpoint inhibitor treatment over docetaxel.

Future research should compare, in a head-to-head randomized trial, a T790M inhibitor against a combination of different immune checkpoint inhibitors or a combination of an immune checkpoint inhibitor with a T790M inhibitor for the majority of patients who acquired a new *EGFR* T790M mutation[1,2] after progression from first-line TKI therapy. For those patients without T790M mutation or those who had a T790M mutation but progressed after T790M inhibitor therapy, the role of immune checkpoint agents also warrants further investigation.

In conclusion, an immune checkpoint inhibitor as second-line therapy did not improve OS over that with docetaxel therapy in *EGFR*-mutated advanced NSCLC. This finding should be considered as hypothesis-generating and interpreted cautiously. For patients with *EGFR*-mutated advanced NSCLC, mechanisms of acquired resistance to first-line TKI therapy should be elucidated to guide second-line treatment selection.

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