Afatinib With Pembrolizumab for Treatment of Patients With Locally Advanced/Metastatic Squamous Cell Carcinoma of the Lung: The LUX-Lung IO/KEYNOTE 497 Study Protocol

Benjamin Levy,[1] Luis Paz-Ares,[2] Jaafar Bennouna,[3] Enriqueta Felip,[4] Delvys Rodríguez Abreu,[5] Dolores Isla,[6] Fabrice Barlesi,[7] Olivier Molinier,[8] Jeannick Madelaine,[9] Clarisse Audigier-Valette,[10] Sang-We Kim,[11] Hye Ryun Kim,[12] Mustafa Ozguroglu,[13] Mustafa Erman,[14] Firas Benyamine Badin,[15] Tarek M. Mekhail,[16] Ronald Scheff,[17] Michael J. Chisamore,[18] Behbood Sadrolhefazi,[19] Jonathan W. Riess[20]

Abstract

Background: Afatinib is a selective, irreversible ErbB family blocker that has shown survival benefit in lung squamous-cell carcinoma (SCC) patients. Pembrolizumab, a humanized immunoglobulin G4 monoclonal antibody to the programmed cell death 1 (PD-1) receptor, has also shown survival benefit in lung SCC. Concurrent inhibition of the PD-1 and epidermal growth factor receptor (EGFR) pathways represents a rational approach to improve responses and delay the onset of treatment resistance in lung SCC. **Trial Design:** This phase II, open-label, single-arm study (NCT03157089) is designed to assess the efficacy and safety of afatinib in combination with pembrolizumab in patients with stage IIIB/IV lung SCC that has progressed during/after first-line platinum-based chemotherapy. Eligible patients must have ≥1 target lesion (as per Response Evaluation Criteria in Solid Tumors version 1.1) and must have not received previous immune checkpoint inhibitor/EGFR-targeted therapy. The recommended phase II dose (RP2D) and safety profile will be determined during a safety run-in with oral afatinib (starting dose, 40 mg/d) with intravenous pembrolizumab (200 mg every 3 weeks). In the main study, all patients will receive afatinib at the RP2D with pembrolizumab until disease progression, unacceptable toxicity, or for up to 35 cycles. The primary end point is objective response (complete + partial response). Other end points include disease control, duration of objective response, progression-free survival, overall survival, tumor shrinkage, RP2D, and pharmacokinetics. Exploratory biomarker analysis will be performed. This study is being conducted in the United States, Spain, France, South Korea, and Turkey. Enrollment commenced in September 2017, with a target of 50 to 62 patients.

[1]Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital, Washington, DC
[2]Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain
[3]Department of Pneumology, Thoracic Oncology, University Hospital-Nantes, Nantes, France
[4]Medical Oncology Department, Vall d'Hebron Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain
[5]Department of Medical Oncology, Gran Canaria University Hospital, Las Palmas de Gran Canaria, Spain
[6]Department of Medical Oncology, University Hospital Lozano Blesa, Zaragoza, Spain
[7]Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France
[8]Pneumology, Centre Hospitalier Le Mans, Le Mans, France
[9]Pulmonology Department, Caen University Hospital, Caen, France
[10]Service de Pneumologie, Centre Hospitalier Sainte Musse, Toulon, France
[11]Asan Medical Center, Seoul, South Korea
[12]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea
[13]Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey
[14]Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey
[15]Hematology and Oncology, Baptist Health Medical Group, Lexington, KY
[16]Florida Hospital Cancer Institute, Orlando, FL
[17]Division of Hematology and Medical Oncology, Department of Medicine, Weill Cornell College of Medicine, New York, NY
[18]Merck & Co, Inc, Rahway, NJ
[19]Boehringer Ingelheim Canada Ltd, Burlington, Ontario, Canada
[20]UC Davis Comprehensive Cancer Center, Sacramento, CA

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Address for correspondence: Benjamin Levy, MD, Medical Oncology, Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital, 5255 Loughboro Rd NW, Building B, First Floor, Washington, DC 20016
Fax: 202-660-6501; e-mail contact: blevy11@jhmi.edu

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Afatinib With Pembrolizumab in Squamous Cell Lung Cancer

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Introduction

Squamous-cell carcinoma (SCC) of the lung accounts for approximately 20% of lung cancers in the United States, and often presents as advanced stage disease.[1] Relatively few treatments are currently available for advanced lung SCC after failure of first-line platinum-based chemotherapy and there remains a significant unmet need for improved treatment options, in the first-line and the relapsed/refractory settings.[2]

Although epidermal growth factor receptor (*EGFR*) mutations are rare in lung SCC, such tumors are characterized by EGFR protein overexpression.[3] EGFR-targeted drugs have been approved globally for patients with advanced lung SCC after failure of first-line treatment; these include the oral irreversible ErbB-family inhibitor, afatinib, which selectively inhibits homo- and heterodimers of EGFR, HER2, HER3, and HER4.[3,4] In the pivotal phase III LUX-Lung 8 study of lung SCC patients whose disease had progressed during platinum-based chemotherapy, afatinib significantly improved progression-free survival (PFS) and overall survival (OS) versus erlotinib.[5] Afatinib was well tolerated, with the most frequently occurring adverse events (AEs) being diarrhea, rash/acne, and stomatitis.[5] The anti-EGFR monoclonal antibody (mAb), necitumumab, has also been approved for the treatment of advanced SCC in combination with standard platinum-based chemotherapy.[6,7]

In recent years, there has been remarkable progress in the development of immunotherapies for the treatment of lung SCC, and most notably of immune checkpoint inhibitors that target the programmed cell death receptor 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway. The anti−PD-1 mAbs, pembrolizumab[8] and nivolumab,[9] are approved for second-line treatment of patients with advanced non−small-cell lung cancer (NSCLC), including those with squamous histology. Pembrolizumab is indicated for patients with PD-L1 expression in ≥1% of tumor cells (detected using the 22C3 anti-PD-L1 mAbs, ie, the Food and Drug Administration-approved companion diagnostic).[8,10,11]

The phase II/III KEYNOTE-010 study in patients with previously treated advanced NSCLC identified improved survival outcomes with pembrolizumab compared with docetaxel; this was confirmed in a subanalysis of lung SCC patients.[12] Although pembrolizumab was well tolerated, immune-related AEs were common,[12,13] but could potentially be managed by interrupting treatment and initiating corticosteroid therapy.

Although improvements in survival outcomes in lung SCC have been reported with afatinib and pembrolizumab monotherapy, they have been moderate in magnitude, and therefore more effective treatment options are still needed, such as combination therapies based on agents with complementary mechanisms of action. Preclinical studies suggest that *EGFR* mutations result in constitutive EGFR pathway activation and might lead to modulation of PD-L1 and the tumor immune microenvironment.[14,15] A recent report describing a luciferase-based screen of >200 compounds, developed to identify immunomodulatory compounds, showed that erlotinib augmented CD8+ T-cell killing of tumor cells. The results of the screen were validated in an ovarian carcinoma cell line and a lung adenocarcinoma cell line derived from $Kras^{G12D}$ $p53^{-/-}$ mouse, thus confirming the immunomodulatory potential of erlotinib, gefitinib, and afatinib, and their ability to enhance CD8+ T-cell killing with a potency approximately equivalent to their physiologic inhibitory $concentration_{50}$ values. Furthermore, a clustered regularly interspaced short palindromic repeats screen developed to identify genes that alter sensitivity to cytotoxic T lymphocyte-mediated killing showed that single guide RNAs, which target EGFR tumor cells to T-cell killing. In an MC38 colon cancer xenograft model, the combination of afatinib with anti−PD-1 therapy was shown to cause significantly greater inhibition of tumor growth, compared with afatinib or anti−PD-1 therapy alone.[16] Moreover, PD-L1 expression has been shown to increase after the development of resistance to gefitinib.[17] These findings provide evidence for the crossover between the EGFR and PD-1/PD-L1 pathways, and support concurrent inhibition of these pathways as a rational approach for treatment of SCC of the lung, with the aim of extending the duration of response and delaying the onset of resistance.

Results of a phase I clinical trial of the anti−PD-1 mAb, nivolumab, combined with erlotinib in *EGFR* mutation-positive NSCLC also support the use of combination therapy, because encouraging antitumor activity and manageable safety profiles were reported.[18] In another phase Ib trial, erlotinib in combination with the anti−PD-L1 mAb, atezolizumab showed an acceptable safety profile in patients with *EGFR* mutation-positive NSCLC.[19] Preliminary data from the phase Ib TATTON trial showed encouraging antitumor activity for the EGFR- tyrosine kinase inhibitor (TKI), osimertinib, with the anti−PD-1 mAb, durvalumab; however, there were reports of interstitial lung disease (ILD), and consequently, the safety profile of the combination requires further investigation.[20] The combination of afatinib with pembrolizumab is currently being studied in a phase I trial in patients with *EGFR*-mutant NSCLC whose disease progressed during erlotinib treatment (NCT02364609).

Safety factors to be considered when using EGFR-TKIs in combination with immune checkpoint inhibitors include the potential for increases in the incidence of severe ILD, pneumonitis, and elevated levels of alanine aminotransferase or aspartate aminotransferase, as reported with EGFR-TKIs such as osimertinib[21] and gefitinib.[22] Such effects could limit the use of these combination regimens.

Simultaneously targeting the EGFR and PD-L1 pathways might be a feasible therapeutic approach, and, as detailed previously, is supported by preclinical data, although relatively few studies have examined this approach in patients with lung SCC. The phase II LUX-Lung IO/KEYNOTE 497 trial is designed to assess treatment

outcomes of use of the combination of afatinib and pembrolizumab in patients with previously treated lung SCC.

Patients and Methods

Study Design and Objectives

The LUX-Lung IO/KEYNOTE 497 is a phase II, non-randomized, open-label, single-arm study (NCT03157089; 1200.283), designed to assess the efficacy and tolerability of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic lung SCC, after progression during or after first-line platinum-based chemotherapy. The trial comprises a "safety run-in," during which the overall safety profile and recommended phase II dose (RP2D) will be assessed, as well as the "main study" (Figure 1). During the safety run-in, 12 patients will receive afatinib (40 mg once daily [QD]) with pembrolizumab (200 mg every 3 weeks); on completion of the first cycle, the safety profile will be assessed and the RP2D will be determined by the safety monitoring committee (SMC).

If toxicities in the first safety run-in cohort are deemed unacceptable, then a second safety run-in will be conducted. Twelve patients will receive afatinib (starting dose, 30 mg QD); patients from the original safety run-in cohort who are still receiving afatinib 40 mg QD will have their dose reduced to 30 mg QD. If toxicities are deemed unacceptable in the second safety run-in cohort, the trial will be stopped. When the RP2D has been established, the main study will open for recruitment of 38 patients, who will receive afatinib (starting dose 30 or 40 mg QD) with pembrolizumab. Treatment with both afatinib (30 or 40 mg) and pembrolizumab (200 mg IV) will continue for up to 35 cycles, which is the approved treatment duration for pembrolizumab monotherapy, or until disease progression, unacceptable AEs, or other reasons for discontinuation; after study treatment completion, further therapy including continuation of afatinib treatment (using commercial batches), alternative therapy, or best supportive care will be decided by the investigator. After first documentation of progressive disease (PD), if the patient is clinically stable, treatment may continue (at the treating physician's discretion) until repeat imaging confirms PD.

Tolerability-based afatinib dose reductions will be permitted. In the event of Grade ≥3 drug-related AEs, Grade ≥2 drug-related diarrhea lasting ≥2 consecutive days, or reduced renal function due to dehydration (secondary to Grade ≥2 drug-related diarrhea), afatinib treatment will be suspended for ≤14 days. After recovery to Grade ≤1 or the baseline grade, afatinib may be resumed at a lower dose (reduced by 10 mg decrements to a minimum of 20 mg/d). In patients who do not recover to Grade ≤1 or the baseline grade, treatment will be permanently discontinued.

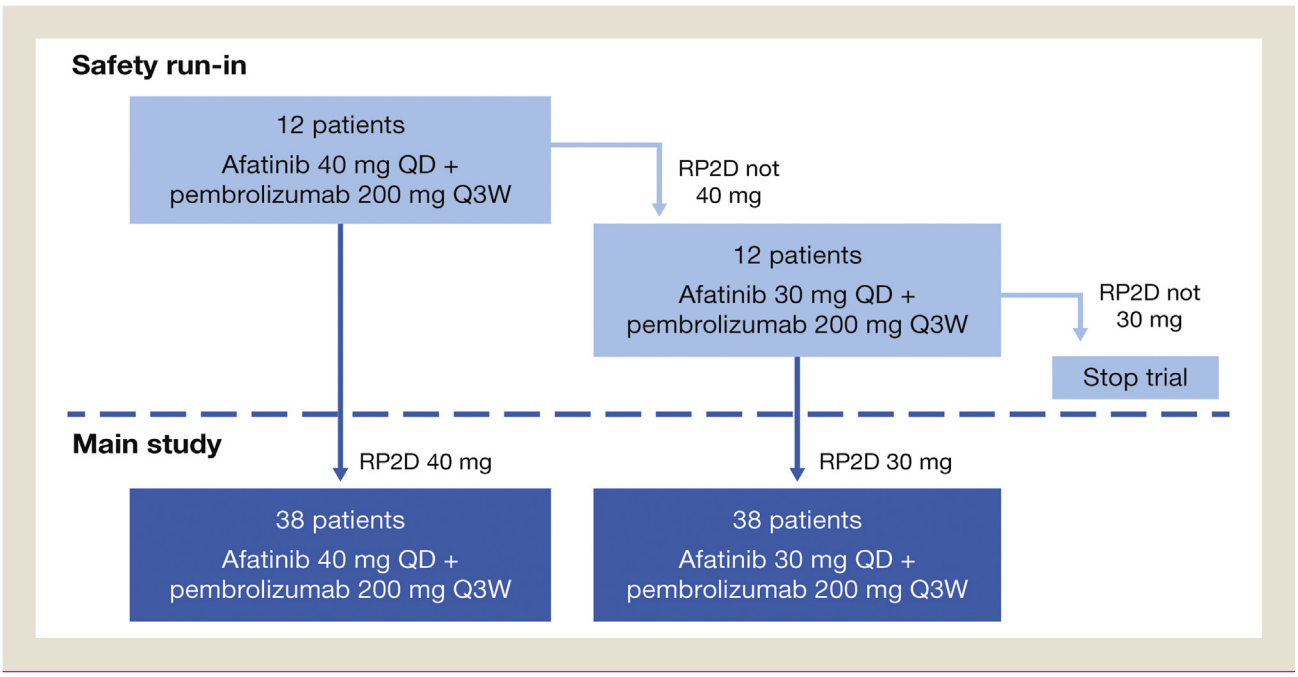
Key Eligibility Criteria

Patients with stage IIIB/IV squamous NSCLC, with an Eastern Cooperative Oncology Group performance status ≤1, adequate organ function, and no history of active autoimmune disease in the past 2 years, who have had disease progression during or after first-line platinum-based chemotherapy and have not received a previous immune checkpoint inhibitor or an EGFR-targeted therapy, are eligible for inclusion in the trial (full patient inclusion and exclusion criteria are detailed in Table 1).

Study End Points and Assessments

The primary end point is objective response (OR; complete response [CR] + partial response [PR]), assessed by the investigators, as defined by Response Evaluation Criteria in Solid

Figure 1 Study Design



Abbreviations: QD = once daily; Q3W = once every 3 weeks; RP2D = recommended phase II dose.

Table 1 Key Inclusion and Exclusion Criteria

Key Inclusion Criteria
Pathologically confirmed diagnosis of squamous NSCLC
Locally advanced (stage IIIB) or metastatic (stage IV) NSCLC not considered eligible for curative therapy
Documented disease progression or relapse during or after completion of at least 2 cycles of first-line platinum-based chemotherapy
Measurable disease, per RECIST version 1.1
Availability and willingness to provide a fresh tumor tissue sample obtained after relapse or progression during or after previous therapy
ECOG PS of 0 or 1
Adequate organ function (hematological, renal, hepatic, coagulation) within 10 days of treatment initiation
Recovered from major surgery or any previous anticancer- or radiation therapy-related toxicity to CTCAE grade ≤ 1[a]
Key Exclusion Criteria
Previous therapy with any immune checkpoint inhibitor or EGFR-targeted therapy[b]
Chemotherapy, non-EGFR targeted therapy, or anticancer hormonal treatment within 2 weeks of study initiation
History of (noninfectious) ILD/pneumonitis that required steroids, or current ILD/pneumonitis
History/presence of uncontrolled gastrointestinal disorders that could affect the intake and/or absorption of the study drug
Active autoimmune disease requiring systemic treatment in the past 2 years
Immunodeficiency, or receipt of systemic steroid therapy/immunosuppressive therapy within 7 days of the first dose of the study drug
Active infection requiring intravenous systemic therapy

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; ILD = interstitial lung disease; NSCLC = non–small-cell lung cancer; RECIST = Response Evaluation Criteria In Solid Tumors.

[a]Except for alopecia; stable sensory neuropathy must be CTCAE grade ≤ 2.

[b]Previous (neo)adjuvant checkpoint inhibitor or EGFR-targeted therapy is allowed if completed at least 12 months before relapse.

Tumors version 1.1 (RECIST). After the first radiologic evidence of PD, tumor assessments will be repeated every 4 weeks, until PD is confirmed by immune-related RECIST criteria.[23] Secondary end points are RP2D, disease control (CR + PR + stable disease), duration of OR, PFS, OS, and tumor shrinkage. Additional assessments include evaluation of efficacy according to PD-L1 expression status, exploratory assessment of biomarkers associated with immune status in tumor tissue (linked to the emergence of resistance), and assessment of the effect of pembrolizumab on the pharmacokinetic profile of afatinib.

Safety will be assessed on the basis of the incidence and severity of AEs, graded according to the Common Terminology Criteria for Adverse Events version 4.03; safety assessments will be overseen by the SMC. To assess the risk of excessive toxicity and confirm the RP2D, and to guide the recommendations of the SMC, a Bayesian logistic regression model (BLRM) will be applied. Determination of the RP2D will be on the basis of the dose-limiting toxicities (DLTs) during the first cycle of the safety run-in, but DLTs during all treatment cycles will be considered for confirmation of the RP2D using the BLRM.

Statistical Considerations

Because this is an exploratory study, evaluation of treatment efficacy will be on the basis of the scale of the response, rather than by testing a formal hypothesis. The primary analyses of efficacy and safety will include all patients who receive at least 1 dose of afatinib (at the starting RP2D) and/or pembrolizumab. Efficacy end points will be summarized using descriptive statistics, and Kaplan–Meier estimates will be determined for PFS, OS, and duration of OR. All efficacy end points will be repeated for the PD-L1 status subgroups, and for subgroups defined according to biomarkers related to immune status.

The expected objective response rates (ORRs) with single-agent afatinib and pembrolizumab are approximately 6% and 18%, respectively; consequently, it is anticipated that the combination will achieve an ORR of approximately 30% to 40%. With 50 evaluable patients, an ORR of $\geq$30% would be observed with a probability of approximately 81%, and assuming a true response rate of 35%; the probability of a false-positive signal is approximately 3%. It is therefore planned to treat 50 patients at the RP2D. If 40 mg QD is chosen as the starting RP2D, a total of 50 patients will be required, but if 30 mg QD is chosen, up to 62 treated patients might be required (12 at 40 mg QD and 50 at 30 mg QD [starting dose]).

The trial is being conducted in the United States, Spain, France, South Korea, and Turkey, in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice, and applicable region-specific requirements. The trial will be initiated only after approval by the respective institutional review boards/independent ethics committees at each center. All patients must provide written informed consent.

Discussion

Although genomic alterations have been identified in SCC of the lung, targeted therapies for actionable molecular aberrations are currently lacking. EGFR overexpression has a prominent role in the pathophysiology of squamous NSCLC; consequently EGFR-targeted therapy is a potential option for patients with lung SCC.[3] Moreover, inhibition of PD-1 leads to notable therapeutic benefit across different tumor types, including SCC of the lung.[13]

Preclinical evidence suggests that in *EGFR*-mutant NSCLC, antitumor immunity and tumor expression of PD-L1 might be driven by EGFR signaling[14,15]; therefore, concurrent inhibition of the EGFR and PD-1 pathways with afatinib and pembrolizumab represents a reasonable therapeutic approach to the treatment of lung SCC, because such tumors are often characterized by EGFR overexpression.[3]

Interim data from the KEYNOTE 407 trial showed that pembrolizumab with chemotherapy improved survival outcomes in patients with untreated metastatic squamous NSCLC,[24] whereas in the phase III IMpower131 trial, atezolizumab with chemotherapy was shown to reduce disease progression and deaths in patients with metastatic squamous NSCLC.[25] Despite the fact that pembrolizumab combined with platinum doublet chemotherapy is approved for use in treatment-naive SCC patients, there remains a need to explore combination strategies in the chemorefractory setting, particularly when a clear scientific rationale exists.

The known individual safety profiles of afatinib and pembrolizumab are generally more favorable than that of chemotherapy.[3,12] Importantly, in view of the nonspecific immune activation that occurs with pembrolizumab and other immunotherapies,[26] when initiating such therapies, physicians should consider the risk of immune-related AEs.

Conclusion

The LUX-Lung IO/KEYNOTE 497 trial will assess the combination of afatinib and pembrolizumab as a new treatment approach for SCC of the lung, with the aim to improve responses and to delay the onset of resistance.

If clinically meaningful efficacy results are observed, together with an acceptable safety and tolerability profile, further assessment of this treatment combination might be warranted.

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Disclosure

B. Levy has acted as a consultant/advisor to Celgene, Eli Lilly, Genentech, Pfizer, Merck Sharp & Dohme, AstraZeneca, Takeda, and Bristol-Myers Squibb, and has received research funding from Celgene and Boehringer Ingelheim. L. Paz-Ares has received honoraria from Eli Lilly, Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Amgen, Takeda, Boehringer Ingelheim, and AstraZeneca. J. Bennouna has acted as a consultant/advisor to

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