Aftatinib in combination with pembrolizumab in patients with Stage IIIB/IV squamous cell carcinoma of the lung

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Introduction
Rationale for dual inhibition
- EGFR overexpression is more common in squamous tumors than adenocarcinomas, which may explain the sensitivity of some patients with SCC to EGFR-targeted treatments. 1
- Blockade of PD-1 induces notable responses across different tumor types, including SCC of the lung. 2
- Preclinical evidence suggests that both the immune microenvironment and tumor expression of PD-L1 are altered in SCC of the lung. 3

Concurrent inhibition of the EGFR and PD-1
- EGFR overexpression is more common in squamous tumors than adenocarcinomas, which may explain the sensitivity of some patients with SCC to EGFR-targeted treatments. 1
- Blockade of PD-1 induces notable responses across different tumor types, including SCC of the lung. 2
- Preclinical evidence suggests that both the immune microenvironment and tumor expression of PD-L1 are altered in SCC of the lung. 3

Endpoint variety
- PFS, OS, and DCR
- Secondary endpoints:
  - Objective response
  - Duration of response

Study design
- Phase II, open-label, non-randomized single-arm study with a safety run-in
- Target enrollment is 50–60 patients
- The study will be conducted in the USA, Spain, France, and Denmark
- Enrollment will open in October 2017

Objectives
- To assess the efficacy and safety profile and confirm the RP2D of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic NSCLC who progressed during or after first-line platinum-based treatment

Study design
- Phase II, open-label, non-randomized, single-arm study with a safety run in (NCT03157091: 2283; LUX-Lung IO/KEYNOTE 497)

Patient eligibility criteria
Key inclusion criteria
- Pathologically confirmed diagnosis of Stage IIIB/IV NSCLC of squamous/mixed histology, not eligible for curative therapy
- Progressed on/after ≥2 cycles of first-line platinum-based CT
- ErbB2, ErbB3, and ErbB4 formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4

Key exclusion criteria
- History/presence of uncontrolled symptomatic CNS metastases or symptomatic leptomeningeal disease
- History/presence of uncontrolled gastrointestinal disorders
- Progression on or after ≥2 cycles of first-line platinum-based CT
- Pathologically confirmed diagnosis of Stage IIIB/IV NSCLC of squamous/mixed histology, not eligible for curative therapy

Endpoints
Primary endpoint
- OR

Secondary endpoints
- Disease control
- Duration of objective response
- OS

Further endpoints
- Safety analyses and exploratory biomarker analyses will also be performed

Mechanism of action: afatinib and pembrolizumab
- Afatinib
  - A small molecule, selective, and irreversible EGF family blocker
  - Effectively inhibits signaling from all homo- and heterodimers formed by the EGF family members EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4
  - Improved PFS, OS, and DCR versus erlotinib in a Phase III study in previously treated patients with advanced SCC of the lung

- Pembrolizumab
  - Humanized immunoglobulin G4 (IgG4) mAb
  - High affinity and potent receptor-blocking activity for PD-1
  - Has shown an encouraging PFS advantage versus CT in previously untreated SCC of the lung, and prolonged OS versus docetaxel in the second-line setting following CT

References
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Introduction

Rationale for dual inhibition

• Genomic alterations in SCC of the lung have been characterized; however, molecularly targeted therapies for this disease are currently lacking

• EGFR overexpression is more common in squamous tumors than adenocarcinomas, which may explain the sensitivity of some patients with SCC to EGFR-targeted treatments

• Blockade of PD-1 induces notable responses across different tumor types, including SCC of the lung

• Preclinical evidence suggests that both the immune microenvironment and tumor expression of PD-L1 may be modulated by EGFR signaling in EGFR-mutant NSCLC

• Concurrent inhibition of the EGFR and PD-1 pathways using the combination of afatinib and pembrolizumab represents a rational and promising approach for treatment of SCC of the lung, to improve responses and delay the onset of resistance

PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SCC, squamous cell carcinoma
Mechanism of action: afatinib

**Afatinib**

- A small molecule, selective, and irreversible ErbB family blocker
  - Effectively inhibits signaling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4\(^6\)
- Improved PFS, OS, and DCR versus erlotinib in a Phase III study in previously treated patients with advanced SCC of the lung\(^7\)

![Diagram of afatinib mechanism](image)

DCR, disease control rate; OS, overall survival; PFS, progression-free survival
Mechanism of action: pembrolizumab

**Pembrolizumab**
- Humanized immunoglobulin G4 (IgG4) mAb
- High affinity and potent receptor-blocking activity for PD-1
- Has shown an encouraging PFS advantage versus CT in previously untreated SCC of the lung, and prolonged OS versus docetaxel in the second-line setting following CT\textsuperscript{3,8}

CT, chemotherapy; mAb, monoclonal antibody
Study design

Objectives
• To assess the efficacy and safety profile and confirm the RP2D of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous NSCLC who progressed during or after first-line platinum-based treatment

Study design
• Phase II, open-label, non-randomized, single-arm study with a safety run in (NCT03157089; 1200.283; LUX-Lung IO/KEYNOTE 497)
Study design (cont’d)

Safety run-in

12 patients
Afatinib 40 mg QD + pembrolizumab 200 mg Q3W

RP2D not 40 mg

12 patients
Afatinib 30 mg QD + pembrolizumab 200 mg Q3W

RP2D not 30 mg

Stop trial

Main study

38 patients
Afatinib 40 mg QD + pembrolizumab 200 mg Q3W

RP2D 40 mg

38 patients
Afatinib 30 mg QD + pembrolizumab 200 mg Q3W

RP2D 30 mg

QD, once daily; Q3W, every 3 weeks
Endpoints

Primary endpoint

OR†

Disease control†

Duration of objective response†

PFS†

OS

Tumor shrinkage

RP2D

Secondary endpoints

Further endpoints

Pharmacokinetics

Safety analyses and exploratory biomarker analyses will also be performed

†By investigator assessment according to RECIST v1.1
OR, objective response; RECIST, Response Evaluation Criteria in Solid Tumors
Patient eligibility criteria

Key inclusion criteria

Pathologically confirmed diagnosis of Stage IIIB/IV NSCLC of squamous/mixed histology, not eligible for curative therapy

Progressed on/after ≥2 cycles of first-line platinum-based CT

≥18 years

Measurable disease

ECOG PS 0–1

Adequate organ function

Recovered from major surgery or any previous anticancer- or radiation therapy-related toxicity to CTCAE grade ≤1‡

‡Except for alopecia; stable sensory neuropathy must be ≤CTCAE grade 2

CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status;
### Patient eligibility (cont’d)

**Key exclusion criteria**

<table>
<thead>
<tr>
<th>Previous treatments:</th>
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<tbody>
<tr>
<td>Immune checkpoint inhibitor therapy</td>
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<tr>
<td>EGFR inhibiting drugs</td>
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<tr>
<td>Immunosuppressive therapy within 7 days prior to study initiation</td>
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<tr>
<td>CT, non-EGFR targeted therapy, or anticancer hormonal treatment within 2 weeks prior to study initiation</td>
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<table>
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<tr>
<th>Patients with:</th>
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<tbody>
<tr>
<td>Symptomatic CNS metastases or carcinomatous meningitis</td>
</tr>
<tr>
<td>History/presence of ILD/pneumonitis</td>
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<tr>
<td>History/presence of uncontrolled gastrointestinal disorders</td>
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<tr>
<td>Immunodeficiency</td>
</tr>
<tr>
<td>Active autoimmune disease that has required systemic treatment within 2 years</td>
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CNS, central nervous system; ILD, interstitial lung disease
Key findings and conclusions

Objectives:
• To assess the efficacy and safety and confirm the RP2D of afatinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous NSCLC who progressed during or after first-line platinum-based treatment

Study design:
• Phase II, open-label, non-randomized single-arm study

Endpoints:
• Primary endpoint: OR
• Secondary and further endpoints: antitumor activity, RP2D, pharmacokinetics
Current status

- Enrollment will open in October 2017
- The study will be conducted in the USA, Spain, France, South Korea, and Turkey
- Target enrollment is 50–60 patients
References


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Corresponding author email address: jwriess@ucdavis.edu. Data were previously presented: Levy, et al. IASLC Chicago Multidisciplinary Symposium in Thoracic Oncology, poster #19.

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