Afatinib in combination with pembrolizumab in patients with Stage IIIIB/IV squamous cell carcinoma of the lung

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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 treatments1,2
- Blockade of PD-1 induces notable responses across different tumor types, including SCC of the lung3,4
- Preclinical evidence suggests that both the immune microenvironment and tumor expression of PD-L1 may be modulated by EGFR signaling in EGFR-mutant NSCLC5,6
- 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 resistance7

EGFR, epidermal growth factor receptor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; NSCLC, non-small-cell lung carcinoma; SCC, squamous cell carcinoma

Mechanism of action

Afatinib
- 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 Erbb48
- Improved PFS, OS, and DCR versus erlotinib in a Phase III study in previously treated patients with advanced SCC of the lung6

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 previously treated NSCLC (of mixed histology) following CT3,4

Key inclusion criteria
- Pathologically confirmed diagnosis of Stage IIIIB/IV NSCLC of squamous/mixed histology, not eligible for curative therapy
- Progressed on/after ≥2 cycles of first-line platinum-based CT
- Measurable disease
- ECOG PS 0–1
- Adequate organ function
- Recovered from surgery or any previous anticancer- or radiation-related toxicity to CTCAE grade ≤1
- Provision of a tumor tissue sample

Key exclusion criteria
- Previous treatments: Immune checkpoint inhibitor therapy
- EGFR inhibiting drugs
- Immunosuppressive therapy within 7 days prior to study initiation
- CT, non-EGFR targeted therapy, or anticancer hormonal treatment within 2 weeks prior to study initiation
- Patients with: Symptomatic CNS metastases or carcinomatous meningitis
- History/presence of I/LD pneumonitis
- History/presence of uncontrolled gastrointestinal disorders
- Immunodeficiency
- Active autoimmune disease that has required systemic treatment within 2 years

Study design

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

Safety run-in
- 12 patients
- Afatinib 40 mg QD + pembrolizumab 200 mg Q3W
- RP2D not 40 mg

Main study
- 38 patients
- Afatinib 40 mg QD + pembrolizumab 200 mg Q3W
- RP2D 40 mg

Objective and endpoints

Objective
- 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

Primary endpoint
- Objective response

Secondary endpoints
- Disease control
- Duration of objective response
- OS
- PFS
- Tumor shrinkage
- RP2D

Further endpoints
- Pharmacokinetics
- Safety
- Biomarker and pharmacogenetic analyses will include:
  - PD-L1 protein expression
  - Immune system-related gene expression
  - Evaluation of immune status by determination of tumor infiltrating cells (e.g., CD8+ cells) or TH1-type cytokines
  - Blood biomarkers related to the emergence of resistance at progression

References


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