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

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Atafinib and pembrolizumab represent a rational and promising approach for treatment of SCC of the lung, to improve survival, proliferation, invasion, and cytotoxicity. Pembrolizumab 200 mg Q3W may be modulated by EGFR signaling in EGFR-mutant NSCLC.

Key inclusion criteria
- Pathologically confirmed diagnosis of Stage IIIB/IV NSCLC of squamous/mixed histology, not eligible for curative treatment
- Progressed on/after ≥2 cycles of first-line platinum-based CT
- ECOG PS 0–1
- Adequate organ function
- Measurable disease
- Pembrolizumab 200 mg Q3W
- Safety run-in

Key exclusion criteria
- Immune checkpoint inhibitor therapy
- Previous treatments: EGFR inhibiting drugs
- Uncontrolled carcinomatous meningitis
- Symptomatic CNS metastases or history/presence of uncontrolled CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events

Endpoints
- Primary endpoint: OR
- Secondary endpoints: antitumor activity, RP2D, pharmacokinetics
- Further endpoints: Safety analyses and exploratory biomarker analyses will also be performed

References

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 550-660 patients

Atafinib
- Small molecule, selective, and irreversible EGFR family blocker
- Effectively inhibits signaling from all homo- and heterodimers formed by the EGFR 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

Rationale for dual inhibition
- EGFR overexpression is more common in squamous 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 different tumor types, including SCC of the lung

Objectives
- To assess the efficacy and safety profile and confirm the RP2D of atafinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous NSCLC who progressed during or after first-line platinum-based treatment
- Phase II, open-label, non-randomized single-arm study with a safety run in (NCT03157089; 1200.283; University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA; Institut de Cancérologie de l’Ouest, Nantes, France; Boehringer Ingelheim Danmark A/S, Copenhagen, Denmark; Boehringer Ingelheim Canada Ltd, Mississauga, Ontario, Canada; Juthe Hospitaler/University School of Medicine, Riyadh; Korona Comprehensive Cancer Center, Riyadh; Mater Hospitaler, Washington, D.C., USA)

Study design
- Phase II, open-label, non-randomized single-arm study with a safety run in (NCT03157089; 1200.283; University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA; Institut de Cancérologie de l’Ouest, Nantes, France; Boehringer Ingelheim Danmark A/S, Copenhagen, Denmark; Boehringer Ingelheim Canada Ltd, Mississauga, Ontario, Canada; Juthe Hospitaler/University School of Medicine, Riyadh; Korona Comprehensive Cancer Center, Riyadh; Mater Hospitaler, Washington, D.C., USA)

Endpoints
- Primary endpoint: OR
- Secondary and further endpoints: antitumor activity, RP2D, pharmacokinetics

Key findings and conclusions
- To assess the efficacy and safety and confirm the RP2D of atafinib in combination with pembrolizumab in patients with locally advanced or metastatic squamous NSCLC who progressed during or after first-line platinum-based treatment
- Phase II, open-label, non-randomized single-arm study

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

Mechanism of action: atafinib and pembrolizumab
- Atafinib: Selective, irreversible EGFR family blocker
- Pembrolizumab: Humanized IgG4 mAb that binds to PD-1

Safety run-in
- 12 patients
- Afatinib 40 mg QD + pembrolizumab 200 mg Q3W
- RP2D 40 mg
- 12 patients
- Afatinib 30 mg QD + pembrolizumab 200 mg Q3W
- RP2D not 30 mg

Secondary endpoints
- Disease control rate (DCR), disease control rate; OS, overall survival; PFS, progression-free survival

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

Patient eligibility criteria
- Pathologically confirmed diagnosis of Stage IIIB/IV NSCLC of squamous/mixed histology, not eligible for curative treatment
- Progressed on/after ≥2 cycles of first-line platinum-based CT
- 2+ years
- Adequate organ function
- Recovered from major surgery or any previous anticancer- or radiation-related toxicity to CTCAE grade ≥1

Study population
- 120 patients
- 38 patients

Study population
- 120 patients
- 38 patients

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