Phase IV study of afatinib as second-line therapy for patients with locally advanced or metastatic NSCLC harboring common *EGFR* mutations (Del19 and/or L858R)

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INTRODUCTION

- Afatinib, an oral, irreversible ErbB family blocker, is approved in many countries for the treatment of EGFR tyrosine kinase inhibitor (TKI)-naïve adult patients with locally advanced or metastatic NSCLC harboring activating *EGFR* mutations, including Del19 and L858R[1–3]
- This indication is based on the results of two large, randomized, Phase III studies that showed superior progression-free survival (PFS), objective response rate (ORR) and patient-reported outcomes in patients with *EGFR* mutation-positive NSCLC receiving first-line afatinib compared with standard platinum-doublet chemotherapy[4,5]
  - In more recent analyses, both trials also reported a substantial and significant benefit in overall survival (OS) with first-line afatinib versus chemotherapy in patients with NSCLC harboring *EGFR* Del19 mutations, with an improvement in median OS of 1 year[6]
- Some *EGFR* mutation-positive patients still receive first-line chemotherapy and there are limited data regarding the effect of afatinib in chemotherapy-pretreated *EGFR* mutation-positive patients
- This study was designed to evaluate the efficacy and safety of afatinib 40 mg/day in the second-line setting in a large cohort of these TKI-naïve patients[7]

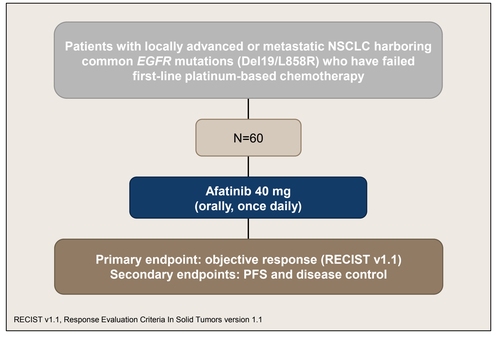
OBJECTIVE

- To assess the efficacy and safety of afatinib 40 mg/day as second-line treatment for patients with locally advanced or metastatic NSCLC harboring common *EGFR* mutations who have failed first-line platinum-based chemotherapy

TRIAL DESIGN

- Single-arm, open-label, Phase IV trial designed to evaluate the efficacy and safety of afatinib as second-line treatment in patients with locally advanced or metastatic NSCLC (Stage IIIB/IV) harboring common *EGFR* mutations (Del19 or L858R), following failure of first-line platinum-based chemotherapy (EudraCT2014-001077-14; NCT02208843; Figure 1)[7]
- Patient inclusion and exclusion criteria are shown in Table 1
- The presence of a documented common *EGFR* mutation (Del19 or L858R) is mandatory for study enrollment
- Patients without *EGFR* mutation status documentation will be asked to sign informed consent for *EGFR* mutation analysis prior to further screening for trial participation

Figure 1. Trial design



RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1

TREATMENT

- Eligible patients will receive once-daily treatment with afatinib (starting dose of 40 mg) until disease progression or study discontinuation due to intolerable adverse events (AEs)
- In accordance with afatinib dosing recommendations,[1,2] patients with drug-related grade ≥3 or selected prolonged grade 2 AEs will dose reduce by 10 mg decrements to a minimum dose of 20 mg; treatment will be discontinued if intolerable AEs are observed at the 20 mg dose

ENDPOINTS AND ASSESSMENTS

- The primary endpoint is objective tumor response (complete response [CR], partial response [PR])
- Secondary endpoints include PFS and disease control (CR, PR, stable disease); safety will also be assessed
- Tumor response and progression is evaluated according to RECIST v1.1
- Safety is evaluated by intensity and incidence of AEs, graded according to NCI CTCAE version 3.0

PATIENTS

Table 1. Patient eligibility criteria

Inclusion criteria	Exclusion criteria
Age ≥18 years	More than one line of prior therapy for disease (radiotherapy and radiosensitizers and/or intrapleural administration of anticancer agents is not counted as a line of therapy)
Pathologically confirmed diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung	Previously received <3 cycles of platinum-based chemotherapy due to toxicity and/or intolerance of treatment
Documented *EGFR* mutation (Del19 or L858R) with no other known *EGFR* mutation	Prior treatment with any EGFR-targeting TKI or antibody
Measurable disease according to RECIST v1.1	Treatment with chemotherapy, biological therapy or investigational agents within 3 weeks, hormonal therapy within 2 weeks, or radiotherapy (except palliative radiation) or major surgery within 4 weeks prior to start of study treatment
Radiologically confirmed progression or recurrence of disease during or following first-line therapy with a platinum-based chemotherapy regimen*	History or presence of cardiovascular abnormalities (uncontrolled hypertension, congestive heart failure New York Heart Association classification of 3, unstable angina or poorly controlled arrhythmia) or myocardial infarction within 6 months prior to start of study treatment
Eastern Cooperative Oncology Group performance status 0 or 1 at screening	Previous or concomitant malignancies with the exception of non-melanoma skin cancers, carcinoma *in situ* of the cervix, and ductal carcinoma *in situ* (malignancies must have been effectively treated)
Recovered from any previous therapy-related toxicity to NCI CTCAE grade ≤1 at study entry (except for alopecia and stable sensory neuropathy which must be grade ≤2)	Presence or history of brain or subdural metastases unless stable for at least 4 weeks
Adequate organ function and life expectancy ≥3 months	Known pre-existing interstitial lung disease, active infections, or history or presence of poorly controlled gastrointestinal disorders that could impact drug absorption

*The following prior therapies are also allowed: maintenance therapy (continuous or switch maintenance) following completion of first-line platinum-based therapy; platinum-based chemoradiotherapy with recurrence within 1 year of completing therapy, including patients receiving 2–3 cycles of further consolidation chemotherapy with the same or different agents if progression occurred within 1 year of completing consolidation treatment; and adjuvant/neoadjuvant platinum-based chemotherapy with recurrence within 1 year of completing chemotherapy
NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events

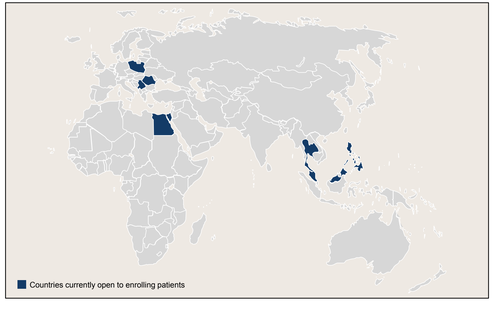
STATISTICAL ANALYSES

- Based on the confirmed ORR of 60% with afatinib in a previous Phase II trial in *EGFR* mutation-positive NSCLC patients following first-line chemotherapy,[8] a study of 60 patients is expected to provide a reasonable precision to the estimation of tumor response rate
- All patients receiving at least one dose of afatinib will be included in efficacy and safety analyses
- Efficacy and safety will be evaluated in a descriptive manner; there are no formal statistical hypotheses
  - Proportion of patients responding and 95% confidence intervals will be calculated for tumor response rates
  - Median PFS (defined as the time from the start of treatment to disease progression or death) and PFS probability will be derived from Kaplan–Meier curves

CURRENT STATUS

- This trial was initiated in October 2014 and is currently recruiting patients[7]
- Study locations include 22 trial sites in seven countries (Figure 2)
  - Trial sites are currently open to enrollment in all seven countries: Egypt, Romania, Serbia, Malaysia, The Philippines, Poland and Thailand

Figure 2. Participating countries



SUMMARY

- This single-arm, open-label, Phase IV trial is currently recruiting patients to evaluate the efficacy and safety of afatinib as second-line therapy in patients with locally advanced or metastatic NSCLC harboring common *EGFR* mutations (Del19 or L858R) who have failed treatment with first-line platinum-based chemotherapy
- The estimated completion date for the primary outcome is December 2016

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