Phase Ib trial of afatinib and BI 836845 in advanced non-small cell lung cancer

#479TiP

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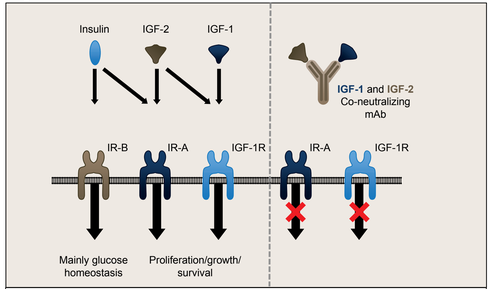
INTRODUCTION

- Epidermal growth factor receptor (*EGFR*) mutations have been found in approximately 10% of Caucasian patients with non-small cell lung cancer (NSCLC) and 40–50% of East Asian patients with NSCLC[1]
- Monotherapy with EGFR tyrosine kinase inhibitors (TKIs) has been established as standard first-line treatment for patients with advanced *EGFR*-mutated NSCLC; however, despite an initial response or disease stabilization, patients invariably develop acquired resistance[2]
- In preclinical studies, insulin-like growth factor (IGF) signaling has been implicated in acquired resistance to EGFR TKIs in the absence of other known mechanisms including *EGFR* T790M mutation[3–5]
  - This finding provides a supportive rationale to investigate whether an EGFR TKI combined with an IGF inhibitor may overcome this resistance
- BI 836845 is a humanized monoclonal antibody of the IgG1 isotype that binds to human IGF-1 and IGF-2 and neutralizes their growth-promoting activities (Figure 1)

Figure 1. BI 836845 mechanism of action



IGF, insulin-like growth factor; IR, insulin receptor; mAb, monoclonal antibody; R, receptor

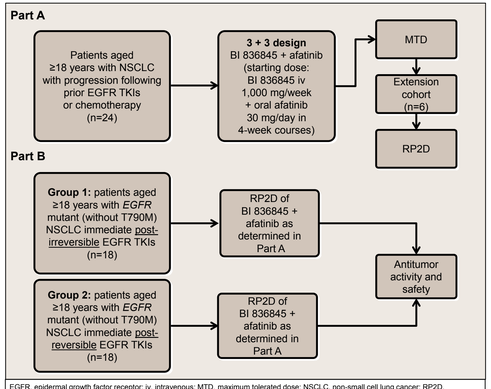
- Preliminary results from two Phase I studies of BI 836845 in patients with advanced solid tumors have shown a tolerable safety profile and signs of antitumor activity[6,7]
- This trial was designed to evaluate the safety and early antitumor activity of BI 836845 combined with the EGFR TKI inhibitor afatinib in patients with *EGFR*-mutated NSCLC progressing following prior treatment (EGFR TKIs or platinum-based chemotherapy)

TRIAL

Design

- This is a multicenter, open-label, Phase I clinical trial to evaluate the safety, tolerability and antitumor activity of the combination of BI 836845 and afatinib (NCT02191891; Study 1280.16)
  - The trial consists of two sequential parts: a dose confirmation part (Part A) followed by an expansion part (Part B; Figure 2)

Figure 2. Study design



EGFR, epidermal growth factor receptor; iv, intravenous; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; RP2D, recommended Phase II dose; TKIs, tyrosine kinase inhibitors

Objective

- Part A: to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of BI 836845 in combination with afatinib in patients with NSCLC with progression following prior treatment (EGFR TKIs or platinum-based chemotherapy)
- Part B: to evaluate the early antitumor activity of BI 836845 in combination with afatinib in patients with *EGFR*-mutated NSCLC with progression following prior EGFR TKIs

Sample size

- Up to 60 patients will be entered; eligibility criteria are shown in Tables 1 and 2
  - Part A: approximately nine to 18 patients will be enrolled to determine the MTD (three to six patients per cohort), followed by an extension cohort of six patients to evaluate the safety of the MTD and determine the RP2D
  - Part B: 18 patients in each of two expansion cohorts to determine the safety and antitumor activity of the RP2D

Table 1. Key inclusion criteria

Inclusion criteria
Age ≥18 years with pathologic confirmation of advanced and/or metastatic Stage IIIb/IV NSCLC
Documented activating *EGFR* mutation (exon 19 deletion, L858R, G719X, L861X). Exception: patients with squamous cell predominant histology in Part A
Presence of *EGFR* activating mutation and absence of *EGFR* T790M mutation in the tumor associated with the latest disease progression (Part B only)
Adequate fresh or archival tumor tissue at the latest disease progression, immediately prior to the study entry for central *EGFR* mutation test and/or resistance analysis
Progression of disease while on continuous treatment with single-agent EGFR TKI or, for histology other than adenocarcinoma and without prior EGFR TKI treatment, progression of disease on platinum-based chemotherapy (Part A only). Progression of disease while on continuous treatment with single-agent EGFR TKI (e.g. erlotinib or gefitinib or afatinib) with TKI-free period ≤30 days prior to study treatment (Part B only). Patients whose disease progresses only in the CNS are not eligible
No intervening systemic therapy between cessation of EGFR TKI and initiation of the treatment in the study. Exception: patient with squamous cell predominant histology in Part A
Measurable disease presented after tumor biopsy for the latest disease progression
ECOG performance score 0 or 1
Fasting plasma glucose <8.9 mmol/L (<160 mg/dL) and HbA1C <8%
Life expectancy of ≥3 months in the opinion of the investigator
Recovery from any previous therapy-related toxicity to grade ≤1 at study entry (except for stable sensory neuropathy grade ≤2 and alopecia)
Written informed consent that is consistent with ICH-GCP guidelines and local regulation

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ICH-GCP, International Conference on Harmonization-Good Clinical Practice; NSCLC, non-small cell lung cancer

Table 2. Key exclusion criteria

Exclusion criteria
For patients who have been treated with afatinib: last treatment at reduced dose below the assigned dose level (for Part A only) or last treatment at reduced dose below 30 mg/day (for Parts A and B)
Patients whose disease progressed on insufficient dose of EGFR TKI immediately prior to study in the opinion of the investigator
More than two (Part B) prior EGFR TKI treatment regimens for relapsed or metastatic NSCLC
Chemotherapy, biological therapy or investigational agents (except EGFR TKIs) within 4 weeks prior to the start of study treatment
Use of previous EGFR TKIs except afatinib within 3 days of initiation of treatment
Radiotherapy within 4 weeks prior to the start of study treatment, except palliative radiation to target organs other than chest up to 2 weeks prior to the start of study treatment, and/or single dose palliative treatment for symptomatic metastasis to be discussed with sponsor prior to enrolling
Active brain or subdural metastases, unless local therapy is completed and the use of corticosteroids was discontinued or is at a stable dose for ≥4 weeks before starting study treatment; symptoms attributed to brain metastases must be stable for ≥4 weeks

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer

Endpoints

Primary

- Part A: MTD and/or RP2D of BI 836845 in combination with afatinib and dose-limiting toxicities during the first treatment course
- Part B: objective response (defined as a complete response [CR] or partial response [PR] according to the Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1)

Secondary (Part B only)

- Disease control (defined as CR, PR or stable disease)
- Time to objective response
- Duration of objective response

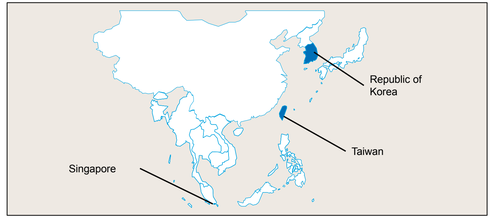
Other (Part B only)

- Progression-free survival
- Overall survival

CURRENT STATUS

- The trial was initiated in October 2014 and is currently recruiting patients
- Patients are being enrolled at nine trial sites in three countries (Figure 3)

Figure 3. Study sites



SUMMARY

- This open-label, Phase I clinical trial is currently recruiting patients in three Asian countries to evaluate the safety, tolerability and early antitumor activity of BI 836845 combined with afatinib in patients with *EGFR*-mutated NSCLC progressing following prior treatment with reversible or irreversible EGFR TKIs and in patients with squamous cell histology

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