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A phase Ib trial of continuous once-daily oral afatinib plus sirolimus in patients with *epidermal growth factor receptor* mutation-positive non-small cell lung cancer and/or disease progression following prior erlotinib or gefitinib☆

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ABSTRACT

Objectives: Dysregulation of the downstream PI3K/AKT/mTOR signaling pathway is a proposed mechanism of resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). We investigated safety and antitumor activity of afatinib plus sirolimus as a potential combination to reverse acquired resistance to EGFR-TKIs in a phase IB trial in patients with *EGFR* mutation-positive non-small-cell lung cancer (*EGFR* mut NSCLC) and/or disease progression following prior erlotinib/gefitinib.
Materials and methods: Patients with *EGFR* mut NSCLC and/or disease progression following at least prior erlotinib/gefitinib were included in the trial. The primary endpoint was incidence of dose-limiting toxicities (DLT) to determine the maximum tolerated dose (MTD). Four initial dose cohorts were proposed to evaluate DLTs. Other endpoints included tumor response, safety, progression-free survival (PFS) and pharmacokinetics.

Abbreviations: AE, adverse events; Afa, afatinib; AR, acquired resistance; AUC, area under curve; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CTP, clinical trial protocol; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; G, grade; KM, Kaplan–Meier; MTD, maximum tolerated dose; mTOR, mammalian target of rapamycin; mut, mutation; N, number of patients; NSCLC, non-small cell lung cancer; OS, overall response; PI3K, Phosphoinositide 3-kinase; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; RECIST, response evaluation criteria in solid tumors; RR, response rates; SD, stable disease; Siro, sirolimus; TKI, tyrosine kinase inhibitor.

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Results: Thirty-nine patients received afatinib and sirolimus. Additional dose cohorts were added since the second cohort (afatinib 40 mg/day and sirolimus 5 mg/day) was considered to have excessive toxicity. All patients experienced adverse events (AE) [grade 3: 66.7%; serious AE: 56.4%]. The most frequent AEs were diarrhea (94.9%), mucosal inflammation (64.1%), asthenia (53.8%) and rash (53.8%). Discontinuations and dose reduction due to AEs occurred in 23.1% and 25.6% of patients. MTD was determined as afatinib 30 mg and sirolimus 1 mg. Responses were observed in 5 patients (12.8%) [2 (5.1%) with confirmed partial response (PR); 3 (7.7%) with unconfirmed PR], and stable disease in 18 patients (46.2%). Four of the 5 responses were at doses above MTD. PFS at 6 months was estimated in 33.3% (median PFS 3.4 months). Pharmacokinetic parameters of afatinib and sirolimus were similar after single administration or in combination.
Conclusion: The combination of afatinib and sirolimus showed lower responses than expected. Together with increased AEs and poor tolerability, this precludes clinical use and further clinical development of this combination. No pharmacokinetic interactions were observed.
ClinicalTrials.gov Identifier: NCT00993499.

1. Introduction

The landscape of cancer therapy has undergone substantial changes since the advent of tyrosine kinase inhibitor (TKI) therapy. Effective agents against different types of tumors are now available in the clinical setting, including epidermal growth factor receptor (EGFR) inhibitors in lung cancer [1–4].

Up to 80% of lung cancers express EGFR [5] and *EGFR* mutations (mut) are associated with increased sensitivity and improved outcome to the EGFR-TKIs gefitinib and erlotinib [6,7]. The pivotal study in unselected, advanced non-small-cell lung cancer (NSCLC) patients showed a progression-free survival (PFS) and overall survival (OS) advantage for erlotinib over placebo [7]. A more recent study demonstrated no OS advantage of afatinib, but PFS results suggest a potential role in patients with advanced NSCLC previously treated with EGFR-TKIs [8]. However, patients harboring *EGFR* mut consistently attain better outcome when treated with erlotinib or gefitinib upfront [9–11]. Afatinib, an irreversible oral drug that selectively blocks signaling from all ErbB family receptors [12], has demonstrated similar benefit to other TKIs for upfront treatment of these patients [13,14].

Despite high initial response rates (RR) to EGFR-TKIs, all *EGFR*-mut NSCLC patients ultimately develop resistance, attributable to multiple mechanisms with the acquisition of a secondary *EGFR* mut (T790M) being the most common [15,16]. The T790M mut has also been identified prior to EGFR-TKI treatment, contributing to primary resistance [17]. Dysregulation of the downstream PI3K/AKT/mTOR signaling pathway has also been implicated as a mechanism of acquired resistance (AR) to EGFR-TKIs in preclinical models [18,19]. This pathway mediates NSCLC cell proliferation and survival and has been implicated in lung cancer development and metastasis [20,21].

Sirolimus is a macrolide antibiotic inhibitor of mTOR that blocks several signal transduction pathways leading to cell cycle arrest [22]. Sirolimus also potently inhibits angiogenesis and endothelial cell proliferation in vitro and in vivo [23,24]. Preclinical data showed that the combination of afatinib with sirolimus resulted in almost complete tumor regression in mice with *EGFR* L858R/T790M tumors, with dramatic downregulation of S6 phosphorylation, a biomarker of mTOR signaling [25].

We hypothesized that concurrent inhibition of signal transduction through EGFR and PI3K/AKT/mTOR may achieve additive or synergistic antitumor activity in patients with advanced NSCLC progressing to EGFR-TKIs. The present phase IB trial therefore tested the combination of afatinib and sirolimus in NSCLC patients who had progressed after one or more lines of treatment and who had developed resistance to prior EGFR-TKIs.

2. Patients and methods

2.1. Patient population

Advanced NSCLC patients who had progressed to previous treatment and who were either *EGFR* mut-positive, or *EGFR* mut-negative/unknown, with disease progression following response or stable disease (SD) for ≥6 months after erlotinib or gefitinib treatment were eligible; this was amended from "patients with EGFR negative disease but who progressed after achieving clinical benefit for ≥12 weeks from erlotinib". Complete eligibility criteria are detailed in Appendix A.

2.2. Study design and treatments

BI1200.70 (NCT00993499) was an uncontrolled phase Ib, open-label, 3 + 3 design, dose-escalation, multicenter trial (conducted in eight centers in Spain from October 2009 to February 2014). Primary endpoint was to determine the maximum tolerated dose (MTD) with the combination of afatinib and sirolimus based on dose-limiting toxicities (DLTs). Secondary endpoints included overall safety, pharmacokinetics (PK) and antitumor efficacy.

Eligible patients underwent an 8-day run-in period, during which they were treated with sirolimus monotherapy before combination therapy. Four cohorts of combination therapy with 30–50 mg of afatinib and 5–10 mg of sirolimus were initially planned (Table 1). However, treatment at lower doses was associated with high DLT frequencies and two Protocol Amendments removed the options for dosing in cohorts 3 and 4 and introduced five additional cohorts with sirolimus at lower doses. Once MTD was identified, 12 additional patients were recruited into that

Table 1
Planned and actual dose cohorts following protocol amendments.

Cohort	Afatinib, mg/day	Sirolimus, mg/day(except for cohort −1)
−1[a,b]	30	1 every other day
0a[c]	30	1
0b[c]	40	1
0c[c]	30	3
0d[a,b]	40	3
1	30	5
1a	30	10
2	40	5
3[b,d]	40	10
4[b,d]	50	10

[a] New cohorts added after amendment 3.
[b] Cohorts without dosing.
[c] New cohorts added after amendment 2.
[d] Cohorts removed after amendment 2.