BRIEF REPORT

Phase 1b Open-Label Trial of Afatinib Plus Xentuzumab (BI 836845) in Patients With *EGFR* Mutation-Positive NSCLC After Progression on EGFR Tyrosine Kinase Inhibitors

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ABSTRACT

Introduction: Insulin-like growth factor signaling has been implicated in acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) in NSCLC. This phase 1 trial (NCT02191891) investigated the combination of xentuzumab (an insulin-like growth factor-ligand neutralizing monoclonal antibody) and afatinib (an EGFR TKI) in patients with previously treated *EGFR* mutation-positive NSCLC.

Methods: The trial comprised dose escalation (part A) and expansion (part B). Patients had advanced or metastatic NSCLC that had progressed on EGFR TKI monotherapy or platinum-based chemotherapy (nonadenocarcinoma only, part A) or irreversible EGFR TKI monotherapy (part B). Absence of *EGFR* T790M mutation was required in part B. Part A used a 3 + 3 design, with a starting dose of xentuzumab 1000 mg/wk (intravenous) and afatinib 30 mg/d (oral). Primary endpoints were the maximum tolerated dose of the combination (part A) and objective response (part B).

Results: A total of 16 patients each were treated in parts A and B. Maximum tolerated dose was xentuzumab 1000 mg/wk plus afatinib 40 mg/d. No patients in part B had an objective response, but 10 had stable disease (median [range] duration of disease control: 2.3 [0.8–10.9] mo). The most common drug-related adverse events were diarrhea (75 %), paronychia (69 %), and rash (69 %) in part A and diarrhea (31 %), rash (19 %), paronychia (19 %), and fatigue (19 %) in part B.

Conclusions: There were no new safety issues; xentuzumab and afatinib could be safely coadministered. Nevertheless, the combination revealed only modest activity in patients with *EGFR* mutation-positive, T790M-negative NSCLC after progression on afatinib.

Keywords: Afatinib; EGFR tyrosine kinase inhibitor; IGF; NSCLC; Xentuzumab

Introduction

EGFR tyrosine kinase inhibitors (TKIs) are approved for first-line treatment of advanced *EGFR* mutation-positive NSCLC (*EGFR*m+ NSCLC).[1] Despite achieving initial responses, acquired resistance inevitably develops. The predominant resistance mechanism for first- and second-generation EGFR TKIs is the *EGFR* T790M mutation.[2] Although osimertinib is active against *EGFR*-sensitizing and T790M mutations,[3] there are no approved targeted therapies after progression on EGFR TKIs without T790M mutation.

Signaling by means of the insulin-like growth factor (IGF) axis has been implicated in acquired resistance to EGFR TKIs, in the absence of other known mechanisms (including T790M),[4,5] providing a rationale for combining an EGFR TKI with an IGF inhibitor.

Xentuzumab, a humanized monoclonal antibody that targets IGF ligands, IGF-1 and IGF-2, is found to have tolerability and preliminary efficacy in two phase 1 studies.[6] This trial evaluated xentuzumab plus afatinib in patients with previously treated *EGFR*m+ NSCLC.

Material and Methods

Study Design and Patients

This open-label, phase 1 trial (NCT02191891) comprised two sequential parts: dose escalation and confirmation (part A) and dose expansion (part B) (Fig. 1). Eligible patients were aged more than or equal to 18 years with pathologically confirmed advanced or metastatic, stage IIIb or IV and measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1. In part A, patients had *EGFR*m+ adenocarcinoma that had progressed on EGFR TKI monotherapy or squamous cell carcinoma that had progressed on platinum-based chemotherapy. In part B, patients had *EGFR*m+ (T790M-negative) NSCLC that had progressed on irreversible EGFR TKI monotherapy. Patients were excluded if their disease had progressed on an insufficient dose of EGFR TKI (in the opinion of the investigator), or, for part B, if they had received more than two previous EGFR TKI regimens for relapsed or metastatic NSCLC. For part A only, patients who had previously received afatinib were excluded if their assigned treatment dose exceeded their last afatinib dose. Chemotherapy, biological therapy, or investigational agents (except EGFR TKIs) were not permitted within 4 weeks before starting the study treatment.

Dose escalation used a 3 + 3 design, with starting doses of xentuzumab 1000 mg/wk (intravenous) and afatinib 30 mg/d (oral). After determination of maximum tolerated dose (MTD), six additional patients were included at that dose level to evaluate the recommended phase 2 dose (RP2D). In part B, the starting dose was the MTD or RP2D; however, for patients with disease progression on afatinib less than 40 mg/d, starting dose was the last dose of afatinib. Treatment continued until disease progression, intolerable

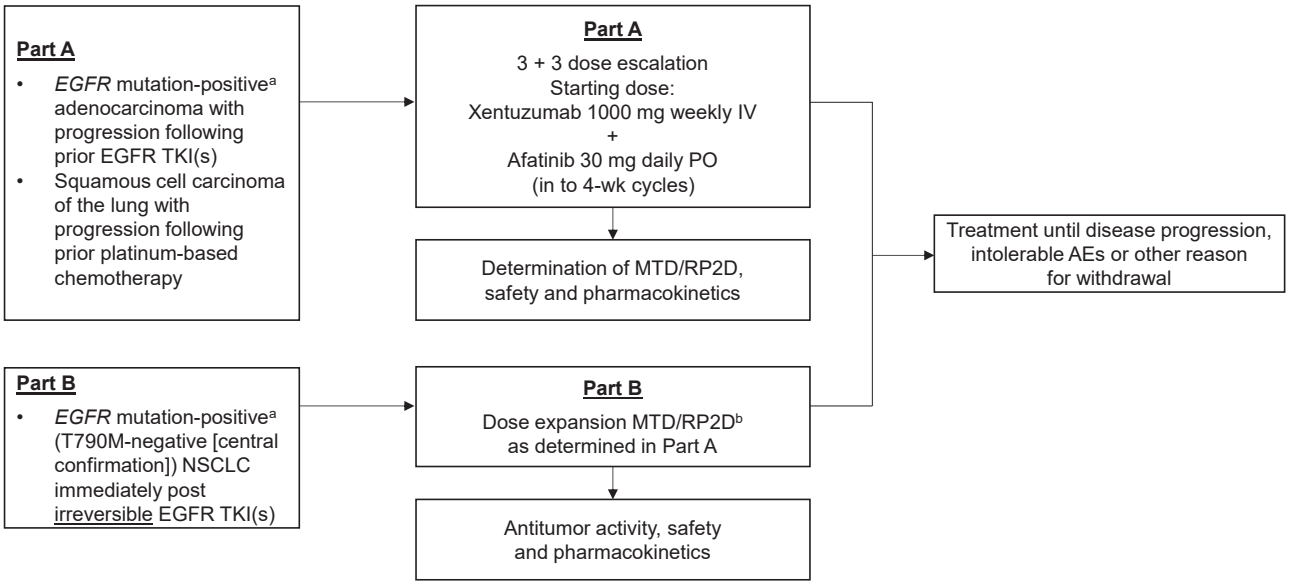

Figure 1. Study design. [a]Documented activating *EGFR* mutation (del19, L858R, G719X, L861X). [b]Part B only: For patients with disease progression while on afatinib less than 40 mg/d, the starting dose was the last dose of afatinib. Any alternative starting dose of afatinib was discussed and agreed with the sponsor. AE, adverse event; del19, exon 19 deletion; IV, intravenously; MTD, maximum tolerated dose; PO, orally; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

adverse events (AEs), consent withdrawal, or noncompliance.

NCT02191891 was performed in accordance with the Declaration of Helsinki, the International Council on Harmonisation Good Clinical Practice, and local laws. All local ethics committees approved the trial. All patients provided written, informed consent.

End Points and Assessments

The primary end points were MTD (on the basis of dose-limiting toxicities during cycle 1) in part A and objective response (OR; best overall response of complete response or partial response [PR] per Response Evaluation Criteria in Solid Tumors version 1.1) in part B. Part B secondary end points were disease control (best overall response of complete response, PR, or stable disease), time to OR, and duration of OR. Further end points included progression-free survival (PFS). Tumor assessment was performed every 4 weeks for the first 8 weeks, in 8-week intervals thereafter, and in 12-week intervals after cycle 16. As the first assessment was at 4 weeks, stable disease was unconfirmed. AEs were graded according to Common Terminology Criteria for Adverse Events version 4.03. Blood and tumor samples were collected for analysis of single-gene mRNA expression as markers of efficacy and for biomarker evaluation (including free and total IGF-1 and IGF-2 and bioactive IGF). Gene expression analysis was conducted using a custom-designed panel of probes targeting 58 genes.

Statistical Analysis

All analyses were descriptive and exploratory. An estimated nine to 18 patients were deemed necessary to establish the MTD. In part B, assuming a true response rate of 20 %, a sample size of 18 patients had a 73 % probability of observing more than or equal to three patients with OR.

Results

Patients and Treatment

In part A (conducted October 2014–October 2016), 28 patients were screened at six sites in South Korea, Singapore, and Taiwan and 16 were treated (xentuzumab 1000 mg/wk plus afatinib 30 mg/d [Xe1000 + Af30], n = 4 [one patient was replaced owing to missing >5 afatinib doses in cycle 1]; Xe1000 + afatinib 40 mg/d [Af40], n = 12). In addition, 14 patients (88 %) discontinued owing to progressive disease, one (6 %) owing to AEs, and one (6 %) withdrew consent.

In part B (conducted June 2016–March 2018), 39 patients were screened at 10 sites in South Korea, Singapore, Taiwan, and Japan and 16 were treated (Xe1000 + Af20, n = 4; Xe1000 + Af30, n = 2; Xe1000 +

Table 1. Baseline Characteristics in Part A and Part B

	Part A			Part B
Parameters	Xe1000 + Af30 (n = 4)	Xe1000 + Af40 (n = 12)	Total (N = 16)	Total (N = 16)
Median age, y (range)	60.5 (52-74)	57.0 (48-77)	60.0 (48-77)	59.5 (41-76)
Male, n (%)	2 (50)	7 (58)	9 (56)	6 (38)
Asian race, n (%)	4 (100)	12 (100)	16 (100)	16 (100)
Smoking status, n (%)				
Never smoked	3 (75)	7 (58)	10 (63)	11 (69)
Exsmoker	1 (25)	5 (42)	6 (38)	5 (31)
Histological subtype (%)				
Adenocarcinoma	3 (75)	10 (83)	13 (81)	16 (100)
Squamous cell carcinoma	0	2 (17)	2 (13)	0
Mixed subtype, predominantly adenocarcinoma	1 (25)	0	1 (6)	0
Median time since first diagnosis, mo (range)	12.9 (7.1-17.6)	23.8 (10.2-46.6)	18.9 (7.1-46.6)	14.6 (3.5-83.0)
ECOG PS score, n (%)				
0	1 (25)	7 (58)	8 (50)	3 (19)
1	3 (75)	5 (42)	8 (50)	13 (81)
Brain metastases at screening, n (%)	0	4 (33)	4 (25)	3 (19)
Previous systemic chemotherapy in metastatic setting, n (%)	1 (25)	4 (33)	5 (31)	0
Previous EGFR TKI therapy, n (%)	4 (100)	10 (83)	14 (88)	16 (100)
Number of previous EGFR TKIs, n (%)				
0	0	2 (17)	2 (13)	0
1	3 (75)	5 (42)	8 (50)	15 (94)
2	1 (25)	4 (33)	5 (31)	1 (6)
3	0	1 (8)	1 (6)	0
Type of last EGFR TKI therapy, n (%)				
Reversible	3 (75)	5 (42)	8 (50)	0
Irreversible	1 (25)	5 (42)	6 (38)	16 (100)
Missing	0	2 (17)	2 (13)	0
EGFR mutation-positive at screening, n (%)	4 (100)[a]	10 (83)[a,b]	14 (88)[a,b]	16 (100)
Del19 at screening, n (%)				
Positive	2 (50)	4 (33)[b]	6 (38)[b]	11 (69)
Negative	2 (50)	6 (50)[b]	8 (50)[b]	5 (31)
L858R at screening, n (%)				
Positive	1 (25)	6 (50)[b]	7 (44)[b]	4 (25)
Negative	3 (75)	4 (33)[b]	7 (44)[b]	12 (75)
G719X at screening, n (%)				
Positive	1 (25)	1 (8)[b]	2 (13)[b]	0
Negative	3 (75)	9 (75)[b]	12 (75)[b]	16 (100)
T790M at screening, n (%)				
Positive	0	3 (25)[b]	3 (19)[b]	0
Negative	4 (100)	7 (58)[b]	11 (69)[b]	16 (100)
L861X at screening, n (%)				
Positive	0	0	0	1 (6)
Negative	4 (100)	10 (83)[b]	14 (88)[b]	15 (94)

[a]In part A, four patients had multiple mutations, three patients had Del19 + T790M, and one patient had L858R + G719X.
[b]*EGFR* mutation status was missing for two patients in the Xe1000 + Af40 group.
Af30, afatinib 30 mg/d; Af40, afatinib 40 mg/d; Del19, exon 19 deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor; Xe1000, xentuzumab 1000 mg/wk.

Af40, n = 10). A total of 13 patients (81 %) discontinued owing to progressive disease, two (13 %) owing to AEs, and one (6 %) withdrew consent. Planned enrollment was 18 patients; however, owing to slow recruitment, the recruitment period was not extended.

Baseline characteristics are summarized in Table 1. Median treatment duration was 3.3 months (range: 0.7–13.0) in part A and 1.8 months (range: 0.4–11.1) in part B. Xentuzumab and afatinib exposures were similar in each part.

Table 2. Drug-Related AEs Reported in More Than or Equal to Two Patients in Either Part A or Part B of the Study

	Part A (N = 16)		Part B (N = 16)	
AEs (Preferred Term)	All Grades	Grade 3	All Grades	Grade 3
Any AE	16 (100)	2 (13)	9 (56)	1 (6)
Diarrhea	12 (75)	0	5 (31)	0
Paronychia	11 (69)	0	3 (19)	0
Rash	11 (69)	0	3 (19)	1 (6)
Pruritus	7 (44)	0	0	0
Stomatitis	6 (38)	1 (6)	0	0
Mucosal inflammation	4 (25)	0	1 (6)	0
Decreased appetite	3 (19)	0	2 (13)	0
Fatigue	0	0	3 (19)	0
Dry skin	3 (19)	0	0	0
Folliculitis	2 (13)	0	0	0
Xerosis	2 (13)	0	0	0

AE, adverse event.

Maximum Tolerated Dose

No patient had a dose-limiting toxicity during cycle 1 or the "on-treatment" period. MTD and RP2D was Xe1000 + Af40 (highest protocol-defined dose).

Safety

All patients in part A and 14 of 16 patients (88 %) in part B had at least one AE (three grade 5 events; all others were grade ≤3 intensity). Serious AEs were reported in seven patients (44 %) in part A and three patients (19 %) in part B. Among the three patients with fatal AEs (all considered unrelated), one patient (part A) died owing to dyspnea and two patients (part B) died owing to intestinal perforation and respiratory failure.

All patients in part A and nine of 16 patients (56 %) in part B had at least one investigator-defined drug-related AE (all grade ≤3 intensity; Table 2).

Two patients in part A (with pathologic fracture and peritoneal hemorrhage) and two in part B (peripheral edema and pleural effusion) discontinued both study drugs owing to AEs. No patient had dose reductions.

One patient each in part A and part B (both Xe1000 + Af40) had possibly clinically relevant high glucose levels (11.0–14.5 mmol/liter and intermittent 13.3–18.9 mmol/liter). Aside from one patient in part A (Xe1000 + Af30) with grade 1 drug-related hyperglycemia, none had AEs indicative of abnormal glucose metabolism.

Efficacy

No patient in part B had an OR; 10 of 16 patients had a best overall response of stable disease (Xe1000 + Af20, n = 2; Xe1000 + Af30, n = 2; Xe1000 + Af40, n = 6). Disease control was achieved in 63 % of patients; median duration was 2.3 months (range: 0.8–10.9). Median PFS was 1.8 months (95 % confidence interval: 0.9–3.6).

In a planned analysis of patients in part B plus the RP2D-treated set in part A (Xe1000 + Af40 [excluding squamous carcinoma]), one of 26 patients (4 %) had a PR after 0.7 month (PR duration: 4.6 mo). This 54-year-old female patient had an *EGFR* T790M mutation and exon 19 deletions and previous best response of PR to erlotinib. A total of 19 patients (73 %) had disease control; median duration was 3.5 months (range: 0.8–12.9). Median PFS in the part B plus RP2D-treated set was 2.8 months (95 % confidence interval: 1.7–3.6).

Tissue and Circulating Biomarker Analyses

In the part B plus RP2D-treated set, high baseline mRNA expression of *AKT1* and *CCND3* and low expression of *CCNB1*, *ETS1*, *IGFBP6*, and *MET* were associated with longer PFS (Supplementary Table 1). For disease control, odds ratios could not be estimated reliably for several genes owing to low patient numbers; for all other genes, there were no statistically significant findings.

There was a numerical increase in mean total IGF-1 and IGF-2 from baseline, and a numerical decrease in bioactive IGF and free IGF-1 was observed and broadly sustained in parts A and B.

Discussion

The RP2D was determined as xentuzumab 1000 mg/wk plus afatinib 40 mg/d. Safety findings were consistent with the known safety profile of afatinib[7–9]; drug-related AEs were most often diarrhea, paronychia, and rash. Two abdominal serious AEs occurred: peritoneal hemorrhage (part A) and intestinal perforation (a fatal AE in part B). Peritoneal hemorrhage was considered related to treatment. Both study drugs were discontinued, and the patient recovered. Intestinal perforation occurred approximately two weeks after discontinuation of the study drugs after disease

progression and was not considered related to the treatment. Hyperglycemia was of interest because IGF-1 receptor-targeted agents have been linked to hyperglycemia, owing to cross-reactivity with insulin-receptor isoform-B[10]; however, only one patient had drug-related hyperglycemia (grade 1).

No patient in part B had an OR; 10 (63 %) achieved disease control. In the pooled part B plus RP2D-treated set cohort, one patient (4 %) had an OR and 73 % had disease control. The lack of ORs in this study is discordant with preclinical findings in NSCLC models, which revealed additive antitumor effects and sensitization of afatinib-resistant cells with combined afatinib and linsitinib (an IGF-1R and IR TKI).[11] Changes in IGF-axis biomarkers (total IGF-1 and IGF-2, bioactive IGF, and free IGF-1) were consistent with the mechanism of xentuzumab and previous reports.[6]

Overall, xentuzumab and afatinib could be safely coadministered, although the combination did not reveal substantial clinical activity in patients with *EGFR*m+ T790M-negative NSCLC after progression on afatinib. We suggest that such "reversal of resistance" trials represent a novel concept to avoid larger randomized trials for signal detection of rare resistance mechanisms, such as IGF-axis dependency. This trial design was chosen to minimize the number of patients enrolled to evaluate the suitability of treatment combinations that could overcome EGFR TKI-resistant NSCLC.

CRediT Authorship Contribution Statement

Keunchil Park: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing—original draft, Writing—review and editing, Visualization, Supervision.

Daniel Shao Weng Tan: Conceptualization, Methodology, Data Curation, Writing—review and editing.

Wu-Chou Su: Investigation, Data Curation, Writing—review and editing.

Byoung Chul Cho: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing—review and editing.

Sang-We Kim: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing—review and editing.

Ki Hyeong Lee: Investigation, Resources, Writing—review and editing.

Chin-Chou Wang: Investigation, Resources, Data Curation, Writing—review and editing.

Takashi Seto: Data Curation, Writing—review and editing.

Dennis Chin-Lun Huang: Conceptualization, Methodology, Writing—original draft, Writing—review and editing, Supervision.

Helen Hayoun Jung: Project administration and Writing—review and editing.

Ming-Chi Hsu: Methodology, Formal analysis, Writing—review and editing.

Thomas Bogenrieder: Conceptualization, Methodology, Formal analysis, Writing—review and editing, Supervision, Project administration.

Chia-Chi Lin: Conceptualization, Formal analysis, Data Curation, Writing—review and editing.

Availability of Data and Materials

To ensure independent interpretation of the clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g., study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html.

Prior to providing access, documents will be examined, and, if necessary, redacted, and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can be requested through the following link: https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html.

All such requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the data sets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended on request.

Researchers should use https://trials.boehringer-ingelheim.com to request access to the study data.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jto.org and at https://doi.org/10.1016/j.jtocrr.2021.100206.

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