Overview

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Title: Phase II Study of Afatinib as Third-Line Treatment for Patients in Korea With Stage IIIB/IV Non-Small Cell Lung Cancer Harboring Wild-Type *EGFR*

Authors: Myung-Ju Ahn,[a] Sang-We Kim,[b] Byoung-Chul Cho,[c] Jin Seok Ahn,[a] Dae Ho Lee,[b] Jong-Mu Sun,[a] Dan Massey,[d] Miyoung Kim,[e] Yang Shi,[f] Keunchil Park[a]

[a]Samsung Medical Center, Seoul, Republic of Korea; [b]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [c]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [d]Boehringer Ingelheim Ltd. UK, Bracknell, United Kingdom; [e]Boehringer Ingelheim Korea, Seoul, Republic of Korea; [f]Boehringer Ingelheim China, Beijing, China

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Keunchil Park: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Roche (C/A); AstraZeneca (RF); AstraZeneca, Eli Lilly, Roche (H); **Dan Massey:** Boehringer Ingelheim (E); **Yang Shi:** Boehringer Ingelheim (E); **Miyoung Kim:** Boehringer Ingelheim (E). The other authors indicated no financial relationships.

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Author Summary: Abstract and Brief Discussion

Background

This phase II single-arm trial evaluated afatinib, an irreversible inhibitor of the ErbB receptor family as third-line treatment of Korean patients with advanced non-small cell lung cancer (NSCLC) and tumors with wild-type *EGFR*. Currently, no standard therapy exists for these patients.

Methods

Eligible patients had stage IIIB/IV wild-type *EGFR* lung adenocarcinoma and had failed to benefit from two previous lines of chemotherapy but had not received anti-EGFR treatment. Patients received oral afatinib at 40 mg per day until disease progression or occurrence of intolerable adverse events (AEs). The primary endpoint was confirmed objective tumor response (OR) rate (confirmed complete response [CR] or partial response [PR]). Secondary endpoints included disease control rate (DCR; OR or stable disease for ≥6 weeks), progression-free survival (PFS), and safety.

Results

Forty-two patients received afatinib treatment, and 38 of those were included in efficacy analyses. No confirmed CRs or PRs were reported. DCR was 24% (9 of 38 patients), with a median disease control duration of 19.3 weeks. Median PFS was 4.1 weeks (95% confidence interval: 3.9–8.0). Frequently reported AEs (mainly grades 1 and 2) were rash/acne (88%), diarrhea (62%), and stomatitis (57%).

Conclusion
Heavily pretreated patients with wild-type *EGFR* NSCLC treated with afatinib monotherapy did not experience an objective response and only 24% had disease stabilization lasting more than 6 weeks. AEs were manageable and consistent with the expected safety profile.

Discussion
Although well established for lung cancer patients with molecular targets such as activating *EGFR* mutations or *ALK* rearrangement, there is no standard targeted therapy for those patients without identified molecular drivers. In these patients, there are no standard treatment options following failure of two previous lines of standard chemotherapy.

Preclinical studies demonstrated that afatinib conferred greater antitumor activity than reversible EGFR tyrosine kinase inhibitors in wild-type *EGFR* cancer models. Hence, this study was designed to investigate the efficacy of afatinib monotherapy in heavily pretreated NSCLC patients whose tumors have wild-type *EGFR.* Overall, 9 of 38 evaluable patients (24%) experienced stabilization of their disease for ≥6 weeks with afatinib monotherapy for a median duration of 19.3 weeks (range: 11.6–28.0 weeks), whereas no patients achieved an objective tumor response (Fig. 1). Median progression-free survival, a secondary endpoint, was 4.1 weeks (95% confidence interval: 3.9–8.0) (Fig. 2). These limited efficacies in this population are consistent with existing evidence.

All treated patients had at least one AE, the majority of which were mild (grade 1) or moderate (grade 2). The most common AEs were rash/acne (37 patients, 88%), followed by diarrhea (26 patients, 62%) and stomatitis (24 patients, 57%)—all known characteristics of EGFR inhibition and consistent with the known safety profile of afatinib. Seventeen patients (40%) had at least one serious AE (SAE); nine had fatal events, but none of the SAEs was considered to be treatment related. There were no events of interstitial lung disease or pneumonitis.

The absence of a comparator arm restricts, to some extent, the conclusions that can be drawn from this study. Because tissue samples were available from only 19 patients, the central laboratory was unable to confirm wild-type *EGFR* status for the total population, although eligible patients should have been identified as wild-type *EGFR* by a local laboratory. Four patients were excluded from the efficacy analysis because they tested positive for *EGFR* mutations by the central laboratory; three of these derived benefit (two with partial response and one with stable disease).

In conclusion, 24% of heavily pretreated NSCLC patients experienced disease stabilization for ≥6 weeks with afatinib. Third-line afatinib was tolerable, and AEs were manageable.

Trial Information

Disease	Lung cancer – NSCLC
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	2 prior regimens
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Confirmed Objective Tumor Response Rate
Secondary Endpoint	Progression Free Survival
Additional Details of Endpoints or Study Design	A two-stage design was adopted, with an early-stopping rule after 15 evaluable patients had completed at least one course (defined as 28 days) of afatinib (or progressed during the first course). Progression to the second stage was allowed if one or more of the 15 patients achieved an unconfirmed complete (CR) or partial response (PR), or, in the absence of response, a DCR of ≥30% was observed. Up to an additional 25 evaluable patients (40 patients in total) could be treated in the second stage. Sample size calculations were based on the assumption that the underlying response rate for the selected patient population would be 10%. With this response rate, one responder of the 15 patients in the initial stage gave a 79% probability of continuing with the trial. For the second stage, 40 patients would be expected to provide >90% probability of observing an OR rate of ≥5% (i.e., more than two responders). All patients who received at least one dose of afatinib were included in the safety analysis, while those with laboratory-confirmed EGFR mutations were excluded from the efficacy analysis. Exploratory

	efficacy analyses were performed in patients grouped by baseline ECOG PS, gender, and smoking history. An exact 95% Clopper-Pearson CI was calculated for the proportion of responders, with similar point estimates and exact CIs calculated for CR, PR, and SD. Descriptive statistics were produced for the duration of OR and disease control. Kaplan-Meier estimates and 95% CIs, using Greenwood's standard error estimate, were tabulated for PFS
Investigator's Analysis	Correlative endpoints not met but clinical activity observed

Drug Information

Drug 1 **Generic/Working name**	Afatinib
Trade name	Giotrif
Company name	Boehringer Ingelheim
Drug type	Small molecule
Drug class	ErbB receptor family
Dose	40 mg (mg) per flat dose
Route	oral (po)
Schedule of Administration	28-day treatment course. Afatinib was taken at the same time each day on an empty stomach

Patient Characteristics

Number of patients, male	33
Number of patients, female	9
Stage	Stage IIIB (2 patients), stage IV (40 patients)
Age	Median (range): 58.0 years (range 40–75)
Number of prior systemic therapies	2
Performance Status:	ECOG • 0 — 1 • 1 — 38 • 2 — 3 • 3 — 0 • unknown — 0
Other	Patients were required to have progressed following two lines of chemotherapy (at least one of which was a platinum-containing doublet regimen), with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Patients were excluded if they had received prior treatment with EGFR-targeting small molecules or antibodies
Cancer Types or Histologic Subtypes	• Advanced NSCLC with wild-type EGFR

Primary Assessment Method

Experimental Arm: Advanced NSCLC With Wild-Type EGFR

Number of patients screened:	47
Number of patients enrolled:	43
Number of patients evaluable for toxicity:	42
Number of patients evaluated for efficacy:	38
Evaluation method:	RECIST 1.1

Response assessment CR:	0%
Response assessment PR:	0%
Response assessment SD:	24%
Response assessment PD:	63%
Response assessment other:	13%
(Median) duration assessments PFS:	4.1 weeks, CI: 3.9–8.0
(Median) duration assessments OS:	31.4 weeks, CI: 14.4–49.9
(Median) duration assessments disease control duration (range):	19.3 weeks (11.6–28.0)
(Median) duration assessments duration of treatment (range):	4.3 weeks (1.4–54.4)

Adverse Events

Name	NC/NA	1	2	3	4	5	All Grades
Rash/Acne[a]	12%	38%	45%	5%	0%	0%	88%
Diarrhea	38%	50%	12%	0%	0%	0%	62%
Stomatitis[a]	43%	38%	17%	2%	0%	0%	57%
Decreased appetite	57%	38%	5%	0%	0%	0%	43%
Nail effect[a]	67%	19%	10%	5%	0%	0%	33%
Pruritus	71%	26%	2%	0%	0%	0%	29%
Cough	79%	10%	12%	0%	0%	0%	21%
Nausea	81%	17%	2%	0%	0%	0%	19%
Fatigue[a]	83%	12%	5%	0%	0%	0%	17%
Dry skin	86%	14%	0%	0%	0%	0%	14%
Dyspnea	88%	10%	0%	0%	0%	2%	12%
Headache	88%	2%	7%	0%	0%	2%	12%
Myalgia	88%	10%	2%	0%	0%	0%	12%
Pneumonia	88%	0%	0%	0%	0%	12%	12%
Abdominal pain	90%	7%	2%	0%	0%	0%	10%
Back pain	90%	2%	7%	0%	0%	0%	10%
Chest pain	90%	5%	2%	2%	0%	0%	10%
Hemoptysis	90%	2%	5%	0%	0%	2%	10%
Productive cough	90%	2%	7%	0%	0%	0%	10%
Pyrexia	90%	5%	5%	0%	0%	0%	10%

[a]Represents a grouped category in which patients experienced specific AEs within each group: rash/acne (rash, acne, skin exfoliation, skin fissures, dermatitis acneiform, drug eruption, erythema, exfoliative rash, folliculitis, rash pustular, skin disorder, skin ulcer); stomatitis (stomatitis, mucosal inflammation, dry mouth, glossitis, glossodynia, mouth ulceration); nail effect (paronychia, nail disorder, nail infection, onychoclasis); and fatigue (fatigue, asthenia).
Most frequently reported adverse events (10% of patients or above).
Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion:	Study completed
Pharmacokinetics / Pharmacodynamics:	Not Collected
Investigator's Assessment:	Correlative endpoints not met but clinical activity observed

Discussion

Currently, no standard therapy is available for non-small cell lung cancer (NSCLC) patients without *EGFR* mutations whose disease has progressed after two previous lines of standard chemotherapy. Afatinib has demonstrated greater antitumor activity than reversible EGFR tyrosine kinase inhibitors (TKIs) in in vitro wild-type *EGFR* lung cancer models [1]. The present study aimed to investigate the efficacy of afatinib in patients with wild-type *EGFR* NSCLC and included 42 heavily pretreated Korean patients (Table 1).

Thirty-eight patients were included in the efficacy analysis; four patients were excluded because central laboratory analysis found their tumors to harbor an *EGFR* mutation. The results demonstrate that although no patients achieved an objective response, the disease control rate was 24% (nine patients with stable disease [SD] for ≥6 weeks), and the median duration of disease control was 19.3 weeks (Table 2). The maximum change from baseline in tumor size is shown in Figure 1. The sum of longest diameters of target lesions increased during treatment (mean maximum change from baseline of +15%). At the time of data cutoff, nearly all patients had progressed (37 of 38 patients [97%]). Median progression-free survival (PFS) was 4.1 weeks (95% confidence interval [CI]: 3.9–8.0) (Fig. 2A). As shown in Figure 2B, median overall survival (OS) was 31.4 weeks (95% CI: 14.4–49.9). Median follow-up time for OS was 56.2 weeks, and 28 patients (74%) had died by the cutoff for the primary data analysis. Although no patient achieved an objective response, our results indicate some limited clinical activity of afatinib in patients with wild-type *EGFR*.

Median treatment time with afatinib was 4.3 weeks (range: 1.4–54.4 weeks). All treated patients had at least one adverse event (AE) during the study, but AEs were manageable and consistent with the known safety profile of afatinib [2–6]. Rash/acne, diarrhea, and stomatitis are expected consequences of EGFR inhibition [7, 8] and these events were the most common in this study (Table 3). Episodes of rash/acne, diarrhea, or stomatitis were generally not serious and were manageable. Nine patients (21%) experienced AEs of grade 3, and one patient had grade 4 neutropenia that was considered unrelated to afatinib. Treatment-related AEs experienced by patients in this study were generally of CTCAE grade 1 or 2. Thirty-eight of 42 patients (90%) reported at least one AE that the investigator considered to be treatment related, and these occurred at similar frequencies to the overall AEs. AEs led to discontinuation of afatinib in seven patients (17%); two patients discontinued afatinib because of AEs that were deemed treatment related. Six patients (14%) had dose reductions of afatinib because of AEs. Seventeen patients (40%) had at least one serious AE (SAE); nine of those had fatal events (dyspnea, gastrointestinal obstruction, hemoptysis, headache, pneumonia and vomiting). None of the SAEs was considered related to afatinib treatment. There were no events of interstitial lung disease or pneumonitis.

The limited efficacy shown with targeted EGFR inhibition using afatinib in this heavily pretreated patient population with wild-type *EGFR* is consistent with existing evidence. Several small studies have previously shown that patients who have been previously treated and whose tumors have a wild-type *EGFR* may derive some clinical benefit from reversible EGFR TKIs, such as erlotinib or gefitinib [9–16], as well as from the irreversible investigational agent dacomitinib [17]. The rate of disease control observed in this study is of a magnitude reported in previous evaluations of erlotinib [13, 18], and the median PFS seen in this study is generally comparable with previous studies of EGFR TKIs.

Given the lack of salvage therapy options with proven efficacy in these difficult-to-treat third-line patients with wild-type *EGFR* status, a recent focus in treating this group of patients has turned toward investigation of EGFR inhibition in the second-line setting. Results of ongoing studies are awaited with interest; however, interim results from the phase III TAILOR study show superior PFS with docetaxel over second-line erlotinib in NSCLC patients without *EGFR* mutations [19].

The absence of a comparator arm restricts, to some extent, the conclusions that can be drawn from this study. Another consideration is that wild-type *EGFR* status could not be confirmed for the whole population. Only 19 samples were available, and, of these, tumors from four patients were found to harbor *EGFR* mutations and were excluded from the efficacy analysis. Of note, three of these patients (two with partial response [PR] and one with stable disease) appeared to have benefited from treatment. Heterogeneity of the study population with respect to first- and second-line treatments and variable responses to these treatments may also have affected the overall results. Conversely, a strength of this study is that response rates were based on confirmed response, as opposed to the less stringent criterion of "best response."

Although direct sequencing is considered a gold standard for *EGFR* mutation detection, the method may be associated with a higher false-negative rate than real-time quantitative polymerase chain reaction [18]. Consequently, we sought to confirm the wild-type status of the tumors of the enrolled patients (who underwent direct sequencing at a local laboratory) using the Therascreen *EGFR* mutation test (Qiagen, Manchester, U.K., http://www.qiagen.com) at a central laboratory. Interestingly, the only patients who achieved a PR in this study had their tumors subsequently identified as *EGFR* mutation-positive by Therascreen. Consequently, the use of a validated test with high sensitivity and specificity is one of the elements to be considered in the clinical setting to give patients the best chance of treatment with a targeted therapy.

Our findings of some, albeit limited, clinical benefit of afatinib in a proportion of NSCLC patients with wild-type *EGFR* in this setting highlights the need to investigate further the opportunities for biomarker-driven therapy in wild-type *EGFR* patients. KRAS status, and ALK, ROS, and RET rearrangements are possible targets [20]. In addition, having considered modest clinical

benefit, the potential for combination therapy with afatinib and other novel agents (e.g., anti-insulin-like growth factor 1 receptor monoclonal antibodies) in heavily pretreated patients with NSCLC merits investigation.

In conclusion, patients among this difficult-to-treat, heavily pretreated population of patients with wild-type *EGFR* NSCLC derived no or very modest benefit from afatinib. Third-line afatinib was tolerable, and AEs were manageable. In the absence of established third-line treatments, the role of afatinib for advanced NSCLC patients with wild-type *EGFR,* previously treated with platinum-containing doublet chemotherapy, may warrant further investigation within biomarker-driven or combination strategies.

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Figures and Tables

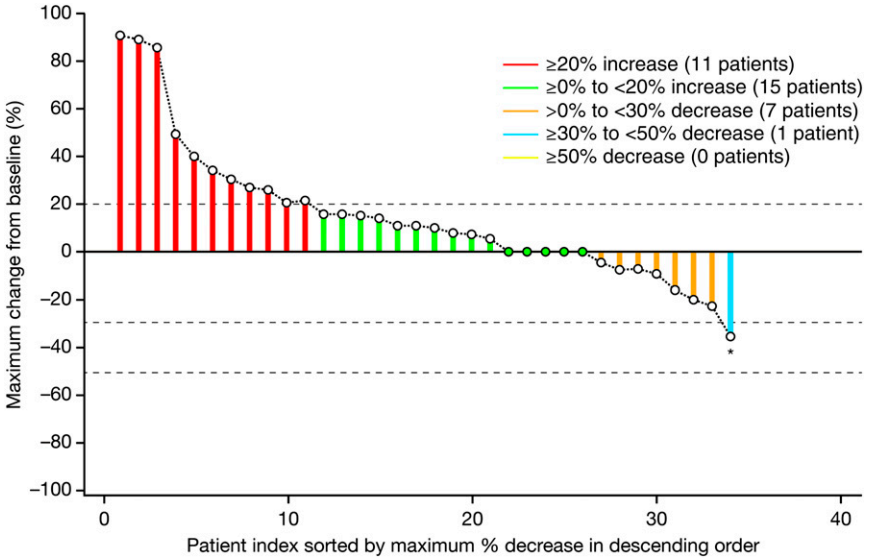

Figure 1. Maximum change in tumor size (target lesions) from baseline in patients with wild-type epidermal growth factor receptor ($n = 34$). The maximum mean change from baseline is +15% (range: −35 to 91). *This patient had a partial response after 3.7 weeks; however, the response was not confirmed at the subsequent scan (week 8), which showed progressive disease.

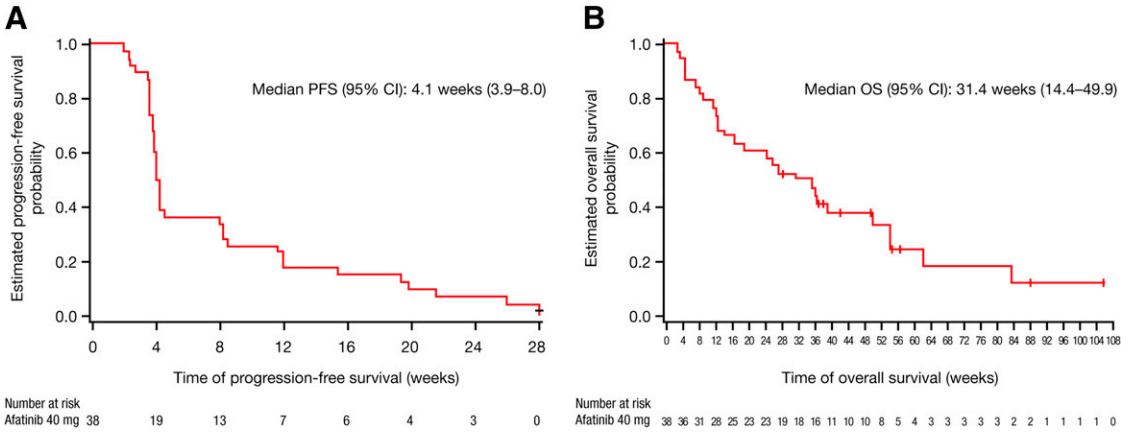

Figure 2. Progression-free survival **(A)** and overall survival **(B)**.
Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Table 1. Patient demographics, characteristics, and disease status at baseline

Characteristic/disease status	Number of patients ($N = 42$)
Sex, *n* (%)	
Male	33 (79)
Female	9 (21)
Asian race, *n* (%)	42 (100)
Age, years	
Median (range)	58.0 (40–75)
≥65 years, *n* (%)	7 (17)
Smoking status, *n* (%)	
Never smoked	14 (33)
Former smoker	27 (64)
Current smoker	1 (2)
ECOG PS, *n* (%)	
0	1 (2)
1	38 (90)
2	3 (7)
Time from first histologic diagnosis, months	
Median (range)	11.1 (0.5–49.2)
Histological classification, *n* (%)	
Adenocarcinoma	40 (95)
Mixed histology[a]	1 (2)
Basaloid squamous	1 (2)
Clinical stage at screening, *n* (%)	
IIIB	2 (5)
IV	40 (95)
Metastases present at screening, *n* (%)	
Any	39 (93)
Bone	14 (33)
Brain	6 (14)
Liver	12 (29)
Pleural effusion	10 (24)
Other	30 (71)
Number of metastatic sites, *n* (%)	
0	3 (7)
1	13 (31)
2	11 (26)
≥3	15 (36)
Baseline sum of target lesions, mm	
Median (range)	60.6 (18.0–209.0)

[a]Adenocarcinoma and bronchioloalveolar carcinoma.
ECOG PS = Eastern Cooperative Oncology Group performance status.

Table 2. Best overall response according to Response Evaluation Criteria in Solid Tumors assessed by investigator review

Best overall confirmed response	Number of patients ($N = 38$),[a] *n* (%)
Disease control	9 (24)
Objective response	0 (0)
Complete response	0 (0)
Partial response[b]	0 (0)
Stable disease	9 (24)
Progressive disease	24 (63)
Unknown	5 (13)

[a]Four patients were excluded from the efficacy analysis because central laboratory analysis detected an *EGFR* gene mutation.
[b]One patient had an unconfirmed partial response.

Table 3. Most frequently reported adverse events (≥10% of patients)

AE category	All AEs ($N = 42$), *n* (%)	Grade ≥3 ($N = 42$), *n* (%)
Rash/acne[a]	37 (88)	2 (5)
Diarrhea	26 (62)	0
Stomatitis[a]	24 (57)	1 (2)
Decreased appetite	18 (43)	0
Nail effect[a]	14 (33)	2 (5)
Pruritus	12 (29)	0
Cough	9 (21)	0
Nausea	8 (19)	0
Fatigue[a]	7 (17)	0
Dry skin	6 (14)	0
Dyspnea	5 (12)	1 (2)
Headache	5 (12)	1 (2)
Myalgia	5 (12)	0
Pneumonia	5 (12)	5 (12)
Abdominal pain	4 (10)	0
Back pain	4 (10)	0
Chest pain	4 (10)	1 (2)
Hemoptysis	4 (10)	1 (2)
Productive cough	4 (10)	0
Pyrexia	4 (10)	0

[a]Represents a grouped category in which patients experienced specific AEs within each group: rash/acne (rash, acne, skin exfoliation, skin fissures, dermatitis acneiform, drug eruption, erythema, exfoliative rash, folliculitis, rash pustular, skin disorder, skin ulcer); stomatitis (stomatitis, mucosal inflammation, dry mouth, glossitis, glossodynia, mouth ulceration); nail effect (paronychia, nail disorder, nail infection, onychoclasis); and fatigue (fatigue, asthenia).
Abbreviation: AE, adverse event.