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BRIEF REPORT

Efficacy and Safety Results of the Afatinib Expanded Access Program

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ABSTRACT

Introduction: Afatinib is an oral, irreversible ErbB family blocker approved for first-line treatment of metastatic epidermal growth factor receptor (*EGFR*) mutation–positive non–small cell lung cancer (NSCLC). The expanded access program (EAP) allowed early access to afatinib and provided additional data on its safety, tolerability, and efficacy.

Methods: The afatinib EAP was an open-label, multicenter, single-arm program in the United States that treated and followed patients with locally advanced or metastatic NSCLC harboring *EGFR* mutations. Afatinib 40 mg was administered orally once daily until discontinuation due to disease progression, adverse events (AEs), or transition to commercially available drug.

Results: Three hundred twenty-two patients received ≥1 dose of afatinib. Most patients had received prior therapies. Drug-related AEs occurred in 89.4% of patients, including 7.8% with serious AEs. The most common afatinib-related AEs (all grades) were diarrhea

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(77.0%) and rash (36.0%). Dose reductions occurred in 31.1% of patients. Discontinuation rates due to diarrhea (1.6%) or rash/acne (0.3%) were low. Efficacy data were collected and analyzed when available, with 17.1% and 69.9% of patients achieving objective response and disease control, respectively, in this highly pretreated population.

Conclusions: No additional or unexpected safety concerns were revealed, and afatinib demonstrated antitumor activity in a heavily pretreated NSCLC patient population in a routine clinical setting.

Trial Registration: ClinicalTrials.gov Identifier: NCT01649284.

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Keywords: Afatinib; EGFR; Expanded access program; Non–small cell lung cancer; Safety

INTRODUCTION

Afatinib (GILOTRIF®, Boehringer Ingelheim; Ingelheim, Germany) is an oral, irreversible ErbB family blocker approved by the US Food and Drug Administration (FDA) for first-line treatment of metastatic non–small cell lung cancer (NSCLC) in patients whose tumors harbor epidermal growth factor receptor (*EGFR*) mutations, specifically exon 19 deletions (Del19) or exon 21 (L858R) substitutions, as identified by an FDA-approved test [1]. Afatinib is also approved for the treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy [1]. It has been evaluated in several NSCLC clinical trials, including tyrosine kinase inhibitor (TKI)–naïve and TKI-exposed patients [2–4]. Results from two global phase 3 trials, LUX-Lung 3 and LUX-Lung 6, demonstrated significant progression-free survival (PFS) benefit with afatinib versus cisplatin/pemetrexed and cisplatin/gemcitabine, respectively, as first-line therapy among patients with common *EGFR* mutations (Del19/L858R) [5, 6]. In both studies, a significant overall survival (OS) benefit was also observed with afatinib in patients with Del19 mutations [7].

Expanded access, or "compassionate use," makes investigational drugs available to patients in the United States who are ineligible for ongoing clinical trials [8]. This expanded access program (EAP) was developed to provide afatinib access before FDA approval for patients with locally advanced or metastatic NSCLC harboring *EGFR* mutations, regardless of the line of therapy (not limited to Del19 or L858R mutations in the first-line setting, as currently indicated). The aim of this study was to collect additional information on afatinib safety, tolerability, and efficacy in a real-world clinical setting.

METHODS

Patients/Program Design

The afatinib EAP was an open-label, multicenter, single-arm program conducted at 66 US sites. Adult patients with locally advanced or metastatic NSCLC harboring *EGFR* mutations (identified per the institution's testing methodology), adequate organ function, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 were eligible regardless of line of therapy. Patients with symptomatic brain metastases were excluded from participation, but patients with previously treated asymptomatic brain metastases were eligible, provided they had stable disease for ≥4 weeks on stable doses of medication.

Patients were instructed to take a single oral dose of afatinib 40 mg with a glass of water at approximately the same time each day, with no food for ≥3 h before and ≥1 h after taking afatinib. Dose escalation was prohibited. Dose reductions in 10-mg steps were allowed based on tolerability. Adverse events (AEs) were categorized and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. For patients with any grade ≥3 treatment-related AEs, prolonged grade 2 diarrhea (≥48 h), grade ≥2 worsening renal function, or acute onset and/or unexplained worsening of pulmonary symptoms, afatinib treatment was withheld while supportive care was administered or clinical

assessment was completed. After the AE fully resolved, returned to baseline, or improved to grade 1, afatinib was reinstituted at a dose reduced by 10 mg; the dose could not be increased. For unrelated AEs, the treating physician could pause medication for ≤14 days without dose reduction. Patients were discontinued from the EAP if afatinib was paused >6 weeks.

Patients were followed monthly until discontinuation due to disease progression, unacceptable AEs, or transition to commercially available drug. The EAP was stopped when afatinib became commercially available. Palliative radiation therapy was permitted for symptom control.

The protocol received institutional review board approval, and the study was conducted in accordance with the principles of the Declaration of Helsinki of 1964, as revised in 2013 and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent.

Assessments

The primary objective was to provide afatinib access to patients who might benefit from it. There were no primary or secondary efficacy objectives, but disease assessments were performed per local standard of care. Safety was assessed descriptively.

Statistical Analysis

Exploratory, descriptive analyses of demographic, safety, and efficacy data were planned based on the treated set (all patients who were dispensed medication and were documented to have taken ≥1 afatinib dose), with two subgroups divided by previous TKI exposure.

RESULTS

Patients

From July 2012 to March 2014, 371 patients were enrolled and 322 patients were treated with ≥1 afatinib dose (Fig. 1). Common reasons for discontinuation were disease progression (53.4%) and EAP completion (28.3%). After the EAP was stopped, patients were transitioned to commercial product, if appropriate. Baseline demographic characteristics were generally representative of NSCLC patients with *EGFR* mutations (Table 1); most (82.9%) had common *EGFR* mutations (Del19/L858R). T790M mutation or exon 20 insertion was present in 25 (7.8%) and 22 (6.8%) patients, respectively; 23/25 patients with T790M mutations also had other *EGFR* mutations. The mean age was 64.6 years, and most patients were female (68.6%), white (73.6%), and had an ECOG PS of 0 or 1 (87.0%). Most patients received prior therapy, with 87.3% of patients previously exposed to a TKI (primarily erlotinib), 67.1% to systemic chemotherapy, and 8.7% to another anticancer therapy. Afatinib was first-line therapy for 23 (7.1%) patients, second-line therapy for 85 (26.4%) patients, third-line therapy for 71 (22.0%) patients, and later-line therapy for 143 (44.4%) patients. A total of 86 (26.7%) patients had brain metastases present at screening.

Exposure

Median treatment duration was 86 days (maximum, 393 days). Nearly half of the patients (48.1%) received afatinib for ≥90 days. Dose reductions occurred in 100 (31.1%) patients, with 98 patients reduced from 40 to 30 mg (including 30 patients subsequently reduced to 20 mg) and two patients reduced from 40 to 20 mg.

Safety

Most patients (96.3%) experienced an AE, with 89.4% experiencing ≥1 drug-related AE (Table 2). Serious AEs occurred in 33.9% of patients, with 7.8% considered related to afatinib. Treatment discontinuation due to AEs was reported for 12.1% of patients; 5.3% discontinued due to afatinib-related AEs.

The most common drug-related AEs were diarrhea (77.0%) and rash (36.0%); the majority were grade 1 or 2. Afatinib-related grade 3 AEs occurred in 18.0% of patients, including

diarrhea (9.9%); rash (1.9%); dehydration (1.6%); stomatitis, mucosal inflammation, and fatigue (each 1.2%); and acute renal failure (0.9%). Grade 4 afatinib-related AEs occurred in 4 (1.2%) patients (peripheral edema, multi-organ failure, dehydration, and acute renal failure; $n = 1$ each), but only one required discontinuation (peripheral edema).

The majority of afatinib-related serious AEs were grade 3, with diarrhea ($n = 9$), dehydration ($n = 6$), and acute renal failure ($n = 3$) the most common. Disease progression was responsible for most fatal events; no fatal event was considered related to afatinib.

Supportive care measures were implemented for 66.8% of patients with diarrhea and 33.9% with rash. Dose reductions occurred in 31.1% of patients: 16.8% due to diarrhea, and 3.7% due to rash. With dose reduction and treatment, few patients discontinued because of diarrhea (1.6%) or rash (0.3%).

Efficacy

While no efficacy objectives were prespecified, data were collected and analyzed where possible. Afatinib demonstrated antitumor activity in this heavily pretreated population in which 44.4% of patients had received ≥3 prior therapies. The population included patients with common and non-sensitizing *EGFR* mutations. Overall, 69.9% of patients achieved disease control (Table 3). Although subgroup comparisons must be interpreted cautiously due to small sample sizes and patient heterogeneity, TKI-naïve patients generally experienced better efficacy versus TKI-exposed patients. Most responses (89.1%) were observed within the first 16 weeks from start of treatment, and median duration of tumor response (4.1 months) was similar for TKI-naïve and TKI-exposed patients. Although many patients (28.3%) transitioned to commercial drug and were not fully

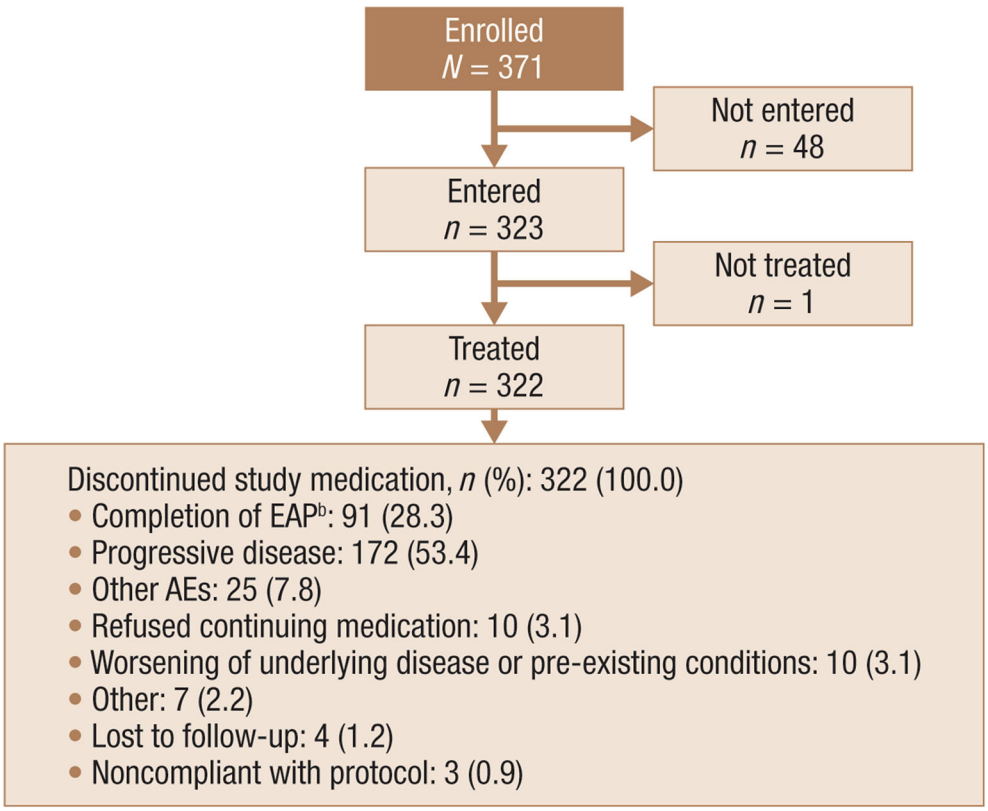

Fig. 1 Disposition of patients (enrolled set).[a] *EAP* expanded access program, *AE* adverse event. [a] Enrolled set included all patients who signed the informed consent. [b] Transition to commercially available drug

Table 1 Demographic Data (Treated Set)

Characteristic	Afatinib 40 mg, $N = 322$
Gender, *n* (%)	
Female	221 (68.6)
Male	101 (31.4)
Race, *n* (%)[a]	
White	237 (73.6)
Asian	56 (17.4)
Black/African American	24 (7.5)
Native Hawaiian/Pacific Islander	2 (0.6)
American Indian/Alaska Native	2 (0.6)
Age, mean (SD), years	64.6 (12.1)
Min; max	35; 94
Smoking status, *n* (%)	
Never smoked	201 (62.4)
Ex-smoker	113 (35.1)
Currently smokes	8 (2.5)
Baseline ECOG score, *n* (%)	
0	112 (34.8)
1	168 (52.2)
2	42 (13.0)
TKI status, *n* (%)	
Exposed[b]	281 (87.3)
Naïve	41 (12.7)
First-line afatinib	23 (7.1)
Common *EGFR* mutation, *n* (%)	267 (82.9)
Uncommon *EGFR* mutation, *n* (%)[c]	55 (17.1)
T790M	25 (7.8)
Exon 20 insertions	22 (6.8)
G719S, G719A, G719C	20 (6.2)
L861Q	13 (4.0)
S768I	4 (1.2)
Other—not specified	13 (4.0)
Time since first diagnosis, mean (SD), months	32.8 (28.0)
Min; max	1; 152
Histologic classification, *n* (%)	
Predominantly adenocarcinoma	303 (94.1)
NOS	8 (2.5)
Predominantly squamous cell carcinoma	7 (2.2)
Large cell/undifferentiated carcinoma	4 (1.2)
Clinical stage at initial diagnosis, *n* (%)[d]	
0–IIB	54 (16.8)
IIIA	24 (7.5)
IIIB	23 (7.1)
IV	218 (67.7)

SD standard deviation, *ECOG* Eastern Cooperative Oncology Group, *TKI* tyrosine kinase inhibitor, *EGFR* epidermal growth factor receptor, *NOS* not otherwise specified

[a] Data missing for one patient

[b] All except two patients received erlotinib

[c] Patients can appear in ≥1 category

[d] Data missing for three patients

documented until disease progression, median PFS was 3.6 months and was longer among TKI-naïve patients. Due to early censoring, OS data were immature.

DISCUSSION

This EAP provided early access to afatinib and collected additional prospective safety and efficacy information. Despite most patients being heavily pretreated, the safety profile was consistent with earlier trials of afatinib monotherapy, with no new safety concerns [2, 5, 6]. The most common AEs were gastrointestinal and dermatologic, which is

Table 2 AE Overall Summary (Treated Set)

Number of patients, *n* (%)	Afatinib 40 mg, *N* = 322
Any AE	310 (96.3)
Drug-related AEs[a]	288 (89.4)
AEs reported in >10% of treated patients (all grades; grade 3/4)[b]	
Diarrhea	248 (77.0); 32 (9.9)
Rash	116 (36.0); 6 (1.9)
Mucosal inflammation	54 (16.8); 4 (1.2)
Stomatitis	43 (13.4); 4 (1.2)
Nausea	41 (12.7); 1 (0.3)
Dry skin	40 (12.4); 2 (0.6)
Fatigue	36 (11.2); 4 (1.2)
Paronychia	34 (10.6); 0
AEs leading to discontinuation	39 (12.1)
Drug-related AEs leading to discontinuation	17 (5.3)
AEs leading to dose reduction	69 (21.4)
Serious AEs[c]	109 (33.9)[d]
Required hospitalization	89 (27.6)
Resulted in death[e]	48 (14.9)
Prolonged hospitalization	15 (4.7)
Life threatening	6 (1.9)
Persistent/significant disability	4 (1.2)
Other	4 (1.2)

AE adverse event

[a] Investigator defined

[b] Grade 4 drug-related AEs occurred in four patients, including one patient each with peripheral edema, multi-organ failure, dehydration, and acute renal failure; no grade 5 AEs were reported

[c] A patient may be counted in ≥1 seriousness criterion

[d] Afatinib-related serious AEs occurred in 7.8% of patients

[e] No deaths were considered by the investigators to be related to afatinib. Most deaths were due to disease progression

similar to those reported for other EGFR-targeted therapies. Most cases of diarrhea and rash/acne were adequately managed by pausing treatment, dose reduction, and supportive treatment and infrequently required discontinuation. These findings suggest that, with proper dose optimization and diarrhea and rash/acne management, patients can remain on afatinib treatment.

Although this EAP was not designed with specific efficacy aims, afatinib demonstrated antitumor activity, with disease control achieved in 69.9% of patients and objective tumor response in 17.1%. This response rate is slightly higher compared to the LUX-Lung 1 trial of afatinib after failure of erlotinib, gefitinib, or both [2]. PFS durations were shorter compared to LUX-Lung 3 (11.1 months) and LUX-Lung 6 (11.0 months) [5, 6]; however, only 7.1% of patients in this EAP received afatinib as first-line treatment, and many patients were not fully documented until disease progression. Patients also had an extensively longer time since first diagnosis in this EAP.

Findings of this EAP must be tempered against several limitations. Subgroup analyses must be interpreted with caution due to small sample size and widely different durations of drug exposure. *EGFR* mutation testing was not standardized across sites, which may have resulted in varying sensitivity levels for identification of mutations between sites. Lastly, although the majority of patients were alive at the end of the program, the EAP was not designed to follow patients through death, and OS data are immature and not reliably interpretable.

CONCLUSION

The results of the afatinib EAP confirm that, in a broad patient population, afatinib is not associated with unexpected safety signals and has safety and antitumor activity profiles similar to those observed in earlier clinical trials.

Table 3 Efficacy End Points (Treated Set)

	Overall, $N = 322$	TKI-naïve,[a] $n = 41$	TKI-exposed, $n = 281$
Response,[b] *n* (%) [95% CI]			
Disease control[c]	225 (69.9)	34 (82.9)	191 (68.0)
	[64.5–74.8]	[67.9–92.8]	[62.2–73.4]
Objective response[d]	55 (17.1)	14 (34.1)	41 (14.6)
	[13.1–21.6]	[20.1–50.6]	[10.7–19.3]
Stable disease	170 (52.8)	20 (48.8)	150 (53.4)
	[47.2–58.4]	[32.9–64.9]	[47.4–59.3]
Median duration of objective response,[d] months [95% CI]	4.1 [3.4–5.3]	3.4 [2.1–NE]	4.2 [3.0–5.8]
Median duration of disease control,[c] months [95% CI]	4.7 [4.4–5.2]	5.9 [3.5–NE]	4.6 [4.2–5.0]
Median PFS, months [95% CI]	3.6 [3.1–4.2]	5.8 [3.4–8.1]	3.6 [2.9–3.9]

TKI tyrosine kinase inhibitor, *CI* confidence interval, *NE* not estimable, *PFS* progression-free survival

[a] Includes 23 patients treated with first-line afatinib

[b] Tumor response is based on clinical, radiologic, or other assessment

[c] Disease control included complete response + partial response + stable disease

[d] Objective response included complete response + partial response

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Compliance with Ethics Guidelines. The protocol received institutional review board approval, and the study was conducted in accordance with the principles of the Declaration of Helsinki of 1964, as revised in 2013 and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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