ORIGINAL ARTICLE

Activity of Afatinib in Heavily Pretreated Patients With *ERBB2* Mutation–Positive Advanced NSCLC: Findings From a Global Named Patient Use Program

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ABSTRACT

Introduction: Approximately 1% to 4% of NSCLC tumors harbor erb-b2 receptor tyrosine kinase 2 (*ERBB2*) mutation; there is no approved targeted treatment for this subgroup.

Methods: Patients with stage IV NSCLC that progressed after clinical benefit on erlotinib/gefitinib and/or had activating *EGFR* or *ERBB2* mutations, had exhausted other treatments, and were ineligible for afatinib trials were enrolled in a named patient use program, receiving afatinib 30 to 50 mg/d on a compassionate basis within routine clinical practice. Efficacy and safety were retrospectively assessed in the subgroup with *ERBB2* mutation-positive NSCLC.

Results: Twenty-eight heavily pretreated patients in the named patient use program had a documented *ERBB2* mutation by local testing. Median time-to-treatment failure

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(TTF; time from treatment initiation to discontinuation for any reason) was 2.9 months; eight patients (29%) had TTF greater than 1 year. Objective response rate was 19% (3 of 16 patients with response data achieved partial response) and disease control rate (DCR) was 69% (11 of 16). Among 12 patients for whom type of *ERBB2* mutation was specified, 10 had a p.A775_G776insYVMA insertion in exon 20, four of whom (40%) remained on afatinib for more than 1 year. This subgroup had median TTF of 9.6 months, objective response rate of 33% (two of six), and disease control rate of 100% (six of six).

Conclusions: This analysis of patients treated in clinical practice provides further evidence of the activity of afatinib in *ERBB2* mutation-positive NSCLC, and suggests that identification of specific subgroups with certain mutations, such as p.A775_G776ins/YVMA insertion in exon 20, could help optimize outcomes with ErbB2-targeted treatment.

Keywords: Afatinib; NSCLC; *ERBB2* mutation

Introduction

Driven by the identification of specific genomic aberrations that underlie oncogenic molecular abnormalities, targeted therapy has significantly enhanced outcomes for patients with NSCLC carrying activating mutations in the *EGFR* gene, or translocations in the ALK receptor tyrosine kinase (*ALK*) gene or *ROS1*.[1,2] Recently, the first targeted treatment was approved for NSCLC harboring the BRAF V600E mutation.[3] However, several other oncogenic drivers have been identified in NSCLC that do not yet have approved targeted treatments; these include mutations in *KRAS*, MET proto-oncogene receptor tyrosine kinase (*MET*), ret proto-oncogene (*RET*), phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), and erb-b2 receptor tyrosine kinase 2 (*HER2*) genes.[1,2]

Erb-b2 receptor tyrosine kinase 2 (ErbB2 [HER2]) is a member of the ErbB family of tyrosine kinases, which also includes EGFR (ErbB1), ErbB3, and ErbB4.[4] Approximately 1% to 4% of NSCLC tumors harbor mutations in the *ERBB2* gene, and in *EGFR*/*KRAS*/*ALK*-negative adenocarcinoma specimens, the frequency of *ERBB2* mutations was found to be 6%.[5,6] In adenocarcinoma, the occurrence of *ERBB2* mutations appears to be almost mutually exclusive to other oncogenic drivers, and although such mutations were initially thought to occur predominantly in this type of NSCLC, they have more recently been observed in squamous cell carcinoma of the lung.[5,7,8] *ERBB2* mutations are more commonly found in women and never-smokers than in men and former- or current-smokers, but their prognostic implication is unknown.[9] There is increasing evidence that the use of anti-ErbB2 agents (such as afatinib, dacomitinib, neratinib, trastuzumab, and the antibody-drug conjugate trastuzumab emtansine [T-DM1]) may elicit objective responses in *ERBB2* mutation–positive NSCLC.[9-15] In addition, the pan-ErbB tyrosine kinase inhibitor (TKI) poziotinib is currently being investigated in a phase II clinical trial of patients with advanced NSCLC, including those with insertion mutations in exon 20 of *ERBB2* (clinical trials no. NCT03318939).

Afatinib is a selective inhibitor of the ErbB protein family, which irreversibly blocks signaling of all homodimers and heterodimers formed by these proteins.[16,17] Having been approved in the United States and European Union in 2013 for the treatment of *EGFR* mutation–positive NSCLC (and subsequently in several other regions), afatinib has more recently been approved for the treatment of metastatic squamous NSCLC that has progressed after platinum-based chemotherapy. Initial results for the treatment of *ERBB2* mutation–positive NSCLC with afatinib have been encouraging, with objective response or disease control observed in two case series.[7,18] In addition, in a recent independent analysis presented while this manuscript was in preparation, among 27 patients with metastatic *ERBB2* mutation–positive NSCLC treated with afatinib, the objective response rate (ORR) was 15%, with partial responses (PRs) lasting 5 to 10 months.[19] Similarly, of 13 pretreated patients with *ERBB2* mutation–positive NSCLC who were enrolled in the phase II NICHE trial, 1 (8%) achieved a PR and 7 (54%) achieved disease control after 12 weeks of afatinib treatment.[20] These findings, although modest and limited by low patient numbers, confirm that afatinib has clinical activity in some patients with *ERBB2* mutation–positive NSCLC.

A large pool of data is available for heavily pretreated patients who received afatinib under a named patient use (NPU) program. The program was initiated after the results of the phase IIb/III LUX-Lung 1 trial were reported; in LUX-Lung 1, afatinib (50 mg/d) improved progression-free survival and ORR versus placebo in patients with advanced NSCLC who had failed previous treatment with the EGFR TKIs erlotinib or gefitinib and at least one line of chemotherapy.[21] Under the NPU program, afatinib was made available on a compassionate use basis to patients with no remaining established treatment option who were ineligible for participation in afatinib trials; this included patients with activating *EGFR* or *ERBB2* mutations, with or without a history of failed erlotinib or gefitinib treatment. The afatinib NPU program is therefore a global source of real-world data. Between May 2010 and January 2016, more than 5600 patients with NSCLC received afatinib under the NPU program, and almost 4000 patients were

eligible for inclusion in an analysis of the efficacy and safety of afatinib in this setting; among those for whom response data were available, 23.4% achieved an objective response.[22] Here, we report treatment outcomes for the subset of patients with *ERBB2* mutation–positive NSCLC who were treated as part of the NPU program.

Materials and Methods

Patient Enrollment

Patients were eligible to enroll in the afatinib NPU program if they had pathologically confirmed stage IV adenocarcinoma of the lung; had progressed after clinical benefit on erlotinib or gefitinib ("clinical benefit" being defined as stable disease [SD] for at least 6 months, or a complete response [CR] or PR) and/or had an activating mutation in *EGFR* or *ERBB2*; had exhausted all other treatment options (chemotherapy-naïve patients were eligible if they had been deemed unfit for chemotherapy); and were deemed ineligible to participate in an actively recruiting afatinib trial.

The NPU program procedures (including enrollment criteria and treatment details) were adapted locally and approved in each region according to local regulations. Written informed consent was obtained from each patient before participation. Enrollment into the NPU program was stopped in each country once afatinib (GIOTRIF, Boehringer Ingelheim Pharma GmbH & Co., KG, Ingelheim am Rhein, Germany) became available on the market; enrollment had ceased worldwide by January 2016.

Afatinib Treatment

The recommended starting dose for afatinib was 50 mg once daily, as in the LUX-Lung 1 trial.[21] Lower starting doses of 40 mg or 30 mg once daily were allowed if deemed necessary by the treating physician. Dose modifications were permitted based on tolerability (10-mg steps; maximum dose of 50 mg/d; minimum dose of 30 mg/d). Combination treatment with other anticancer therapies was allowed if deemed necessary by the treating physician and in accordance with local regulations.

Data Reporting

The purpose of the NPU program was to provide early access to afatinib for patients with no other treatment option, while also generating additional safety information on afatinib. Participating physicians were requested to report all serious adverse events (AEs), AEs leading to afatinib dose reduction or discontinuation, and AEs assessed as causally related to afatinib. Standard serious AE forms and reporting procedures were used to record safety data, and local regulations on safety reporting had to be followed. Additional data, provided as anonymized datasets, included age, sex, *EGFR* and *ERBB2* mutation status and the nature of the specific mutations, disease stage, prior therapies, and comorbidities. Some datasets relating to patient characteristics and efficacy outcomes were incomplete because they were collected via request forms and, whenever possible, follow-up forms were been completed after discontinuation of afatinib. In some countries, local restrictions did not allow collection of patient data, or precluded or limited the use of such data in a publication.

ERBB2 Mutation-Positive Subgroup Analyses

Among patients for whom genotype information was available, those with an activating *ERBB2* mutation were included in these retrospective analyses. In accordance with the inclusion criteria, these patients were not required to have received prior erlotinib or gefitinib. Outcomes (as of April 2017) were evaluated for patients with any *ERBB2* mutation (the overall group), and according to *ERBB2* mutation type.

Time to treatment failure (TTF) was defined as the time from the start of afatinib treatment to the date afatinib was discontinued for any reason (including switching to another drug, death, or end date of available data, whichever occurred first). TTF was calculated in months by dividing the number of days from start to discontinuation of treatment by 30.417.

The ORR was calculated as the sum of patients with a recorded CR or PR, as a proportion of the total number of patients with available response data (those with CR, PR, SD, progressive disease [PD], or mixed response). Disease control rate (DCR) was calculated as the sum of patients categorized as PR, CR, and SD, as a proportion of all patients with available response data (PR + CR + SD + PD + mixed response). There was no independent radiological verification of responses, SD, or PD, so all such response assessments were made by each individual investigator at their discretion as appropriate for a real-world setting. Also, as in a real-world setting, scan frequency and scan methodology were not mandated but left to the discretion of the investigator.

Results

Patient Characteristics

Of 5650 patients with NSCLC from 49 countries enrolled in the NPU program, 3966 patients from 41 countries were included in the overall analysis.[22] A total of 28 patients were documented as having *ERBB2* mutation–positive NSCLC (16 patients with *ERBB2* mutations were identified in the original analysis of the overall NPU program population[22]; an additional 12 patients have since been identified and were included in the present analysis). These patients were enrolled in Europe (8 in Switzerland, 2 in Spain, 1 each in Belgium,

Germany, The Netherlands, and Slovenia), Taiwan (11 patients), Israel (2 patients), and Argentina (1 patient). Characteristics of the *ERBB2* mutation–positive patients in the NPU program are summarized in Table 1; the median age was 55 years (range: 39 to 93 years), 16 patients (57%) were female, and all had adenocarcinoma histology.

Treatment history was recorded for all 28 patients. Overall, this was a heavily pretreated population; most patients had received at least one prior systemic therapy (n = 26; 93%), and 16 (57%) had received three or more prior systemic therapies (Table 1). Ten patients (36%) had received first-generation EGFR TKIs (erlotinib and/or gefitinib in any treatment line), with only one having a concurrent EGFR mutation (an exon 19 deletion). Seven patients (25%) had received previous anti-ErbB2 treatment, four with trastuzumab only, and three with both trastuzumab and lapatinib.

Treatment with afatinib was initiated at 50 mg once daily in 11 patients (39%) and 40 mg once daily in 17 patients (61%) (Table 1).

ERBB2 Mutation Type

Information on the specific *ERBB2* mutation type was available for 12 patients; all mutations were in exon 20. Among these 12 patients, the most frequently reported *ERBB2* mutation, occurring in 10 patients (83%), was a p.A775_G776insYVMA insertion in exon 20 (Fig. 1).[19] This insertion occurs at amino acids 776–779 and may alternatively be referred to as 2325/YVMA, Y772-A775dup, p.A771-M774dup, ErbB2 G776-YVMA, and ErbB2^{YVMA}.[4]

Table 1. Characteristics of Patients With Confirmed *ERBB2* Mutation-Positive NSCLC in the Afatinib NPU Program (N = 28)

Age, y; median (range)	55 (39-93)
Gender, female/male	16 (57) / 12 (43)
Prior systemic treatment	
No. of lines	
0	2 (7)
1	6 (21)
2	4 (14)
3	8 (29)
4	6 (21)
≥5	2 (7)
Prior first-generation EGFR TKI[a]	10 (36)
Prior anti-ErbB2 treatment	7 (25)
Trastuzumab only	4 (14)
Trastuzumab and lapatinib	3 (11)
Afatinib starting dose	
40 mg	17 (61)
50 mg	11 (39)

Values are n (%) unless otherwise stated.
[a]Erlotinib/gefitinib in any line.
ErbB2, erb-b2 receptor tyrosine kinase 2; NPU, named patient use; TKI, tyrosine kinase inhibitor.

The other reported mutation was the M774 duplication, which occurred in two patients (17%) (Fig. 1).

Efficacy

Overall *ERBB2* mutation–positive group. Median TTF in all patients with any *ERBB2* mutation (N = 28) was 2.9 months. Eight patients (29%) remained on afatinib for more than 1 year (Table 2). Tumor response data were available for 16 patients (57%). In those patients, the ORR was 19% (three patients achieved PR) and the DCR was 69% (eight patients with SD plus the three patients with PR) (Table 2).

Efficacy by *ERBB2* mutation type. In the subgroup analysis conducted according to *ERBB2* mutation type, patients with the p.A775_G776insYVMA insertion mutation (n = 10; the most common type of *ERBB2* mutation in this study population) had a median TTF of 9.6 months, and four patients (40%) remained on afatinib for more than 1 year. Tumor response data were available for six patients (60%) with the p.A775_G776insYVMA insertion; in those patients, the ORR was 33% (two patients achieved a PR; see patient cases 1 and 2, below) and the DCR was 100% (four patients with SD plus the two patients with a PR) (Table 2).

Neither of the two patients with other specified *ERBB2* mutations (both duplication mutations of M774) remained on afatinib for more than a year; the median TTF was 1.9 months. Response data were unavailable for both of these patients, meaning that the ORR and DCR could not be calculated (Table 2).

Examples of Patients Who Derived Clinical Benefit From Afatinib

A Taiwanese patient with a p.A775_G776insYVMA insertion in exon 20 who achieved PR on afatinib. This patient was a 67-year-old male ex-smoker from Taiwan with stage IV lung adenocarcinoma, wild-type for *EGFR* and *ALK*, with a *ERBB2* mutation of p.A775_G776insYVMA insertion in exon 20. He had received first-line chemotherapy with cisplatin/pemetrexed; following failure of first-line chemotherapy, afatinib was then initiated at 40 mg upon entering the NPU program. He achieved a PR due to afatinib monotherapy and remained on afatinib monotherapy for 236 days before disease progression was detected (7.8 months' progression-free survival on afatinib monotherapy). Following progression, he was maintained on afatinib, having experienced clear benefit (PR [Fig. 2]), with the addition of other anticancer agents in an attempt to produce a greater degree of response through combination therapy. He received paclitaxel plus afatinib for 172 days. Paclitaxel was then discontinued and gemcitabine initiated while continuing afatinib; only one dose of gemcitabine was

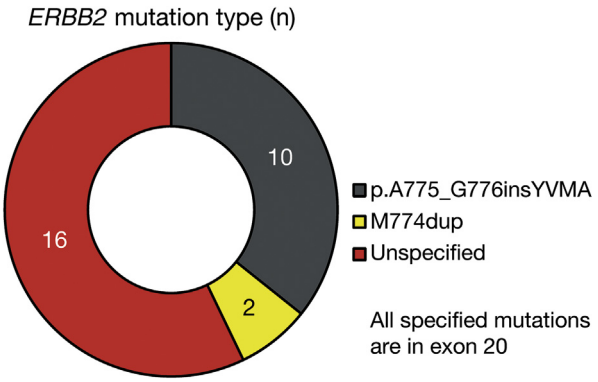

Figure 1. *ERBB2* mutation types identified in patients participating in the NPU program.

administered due to poor tolerability. The patient subsequently received afatinib monotherapy. He remained on afatinib for a total of 508 days (including all periods of monotherapy and combination therapy), constituting a TTF of 16.7 months. Figure 2 shows computed tomography scans at baseline (Fig. 2*A*, after failing first-line chemotherapy and before afatinib monotherapy) and after 6 weeks of afatinib monotreatment (Fig. 2*B*), and shows the PR observed during afatinib monotreatment.

A European patient with a p.A775_G776insYVMA insertion in exon 20 who achieved PR on afatinib. This patient was a 60-year-old female with stage IV adenocarcinoma of both lungs; *ERBB2* genotyping showed duplication of A771-M774 in exon 20, which was later identified as being synonymous to the p.A775_G776insYVMA insertion in exon 20. Before entering the NPU program, the patient had received four cycles of chemotherapy with cisplatin plus gemcitabine, followed by five cycles of chemotherapy with pemetrexed plus carboplatin, and then erlotinib for 2 months. Afatinib was initiated at 40 mg, as fourth-line systemic therapy, upon entering the NPU program, and a PR was achieved. The patient remained on afatinib monotherapy for 360 days (TTF 11.8 months). Figure 3 shows positron-emission tomography scans taken before initiation of afatinib and after ~3 months of treatment, confirming the PR and showing the reduced activity of metastases after treatment.

Safety

The most common AEs reported to us were diarrhea/gastrointestinal toxicity and skin disorders, which were reported in 10 and eight patients, respectively. Reported AEs (excluding disease progression, metastases, and death unrelated to afatinib and due to disease progression) are presented in Table 3.

Discussion

Real-world data on the use of afatinib were available from the NPU program for 28 heavily pretreated patients with documented *ERBB2* mutation–positive NSCLC. Median TTF for these patients was 2.9 months, and 29% remained on afatinib treatment for more than 1 year. Of the 16 patients for whom tumor response data were available, 19% had an objective response and 69% achieved disease control. There were no unexpected safety findings.

According to the literature, most *ERBB2* mutations are located in exon 20, which encodes part of the kinase

Table 2. Time to Treatment Failure and Tumor Responses in *ERBB2* Mutation-Positive Patients Receiving Afatinib in the NPU Program

	All *ERBB2* Mutation-Positive Patients	Patients With p.A775_G776insYVMA in Exon 20	Patients With M774dup in Exon 20
n (%)	28 (100)	10 (36)	2 (7)
TTF			
Median TTF, months	2.9	9.6	1.9
TTF > 1 year	8 (29)	4 (40)	0 (0)
Tumor responses			
Patients with response data available	16 (57)	6 (60)	0 (0)
ORR[a]	3 (19)	2 (33)	ND[c]
DCR[b]	11 (69)	6 (100)	ND[c]
PR	3 (19)	2 (33)	ND[c]
SD	8 (50)	4 (67)	ND[c]

Values are n (%) unless otherwise stated.
[a]ORR = proportion of patients with CR or PR.
[b]DCR = proportion of patients with CR, PR, or SD.
[c]ND = not determined as no response assessments were available.
CR, complete response; DCR, disease control rate; ND, not determined; *ERBB2*, erb-b2 receptor tyrosine kinase 2; NPU, named patient use; ORR, objective response rate; PR, partial response; SD, stable disease; TTF, time to treatment failure.

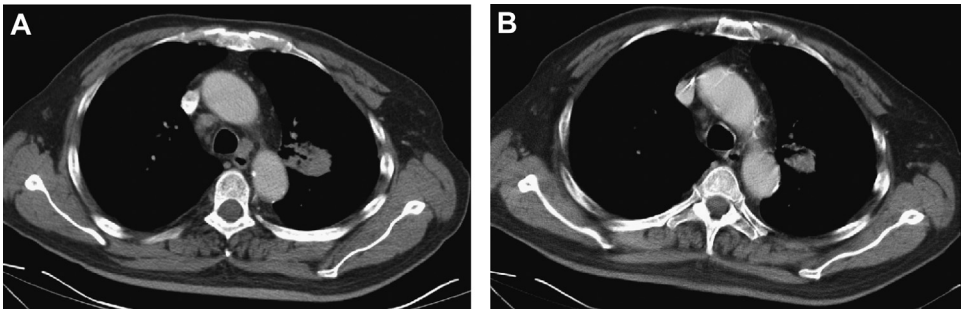

Figure 2. Computed tomography scans at baseline (*A*) and after 6 weeks of afatinib treatment (*B*) in a Taiwanese patient with a p.A775_G776insYVMA insertion in exon 20 who achieved a PR.

domain; these mutations occur with a frequency of 1% to 4% in NSCLC.[4,6,23,24] In the current analysis, *ERBB2* mutation type was specified for 12 patients; all mutations were in exon 20, and the p.A775_G776insYVMA insertion was the most common, occurring in 10 patients (83%). Two patients (17%) had another specified mutation, the M774 duplication mutation in exon 20. These findings are consistent with a previous report based on 11 patients with *ERBB2* mutation–positive NSCLC, in which all *ERBB2* mutations were insertions or duplications in exon 20, with YVMA insertions being the most common, occurring in 6 patients (55%).[4] In the current analysis, patients with a p.A775_G776insYVMA insertion in exon 20 (n = 10) appeared to derive the greatest benefit from afatinib treatment (median TTF 9.6 months, compared with 1.9 months in patients with the M774 duplication mutation), although inferences are limited by the small sample size as well as the absence of data for patients with mutations other than p.A775_G776insYVMA insertion or M774 duplication in exon 20.

The findings of this analysis are consistent with previous observations in patients with *ERBB2* mutation–positive NSCLC who received afatinib within a clinical trial setting. For example, in a recent analysis of data from 27 patients with metastatic *ERBB2* mutation–positive lung cancer who participated in an international, multicenter clinical trial between 2009 and 2016, the ORR was 15% (four PRs), compared with 19% in the current analysis.[19] YVMA insertion in exon 20 was the most common *ERBB2* mutation type in the clinical trial population (59%), and the three patients who achieved the longest lasting PRs (5 to 10 months) had this mutation.[19] In the NICHE trial, a single-arm phase II study of afatinib in pretreated patients with advanced NSCLC harboring *ERBB2* mutations in exon 20 (n = 13), 7 patients (54%) achieved disease control at 12 weeks.[20] Although lack of activity in the other 6 patients meant that the pre-specified criteria for proceeding to further clinical testing were not met, descriptive molecular analysis suggested that prolonged disease stabilization

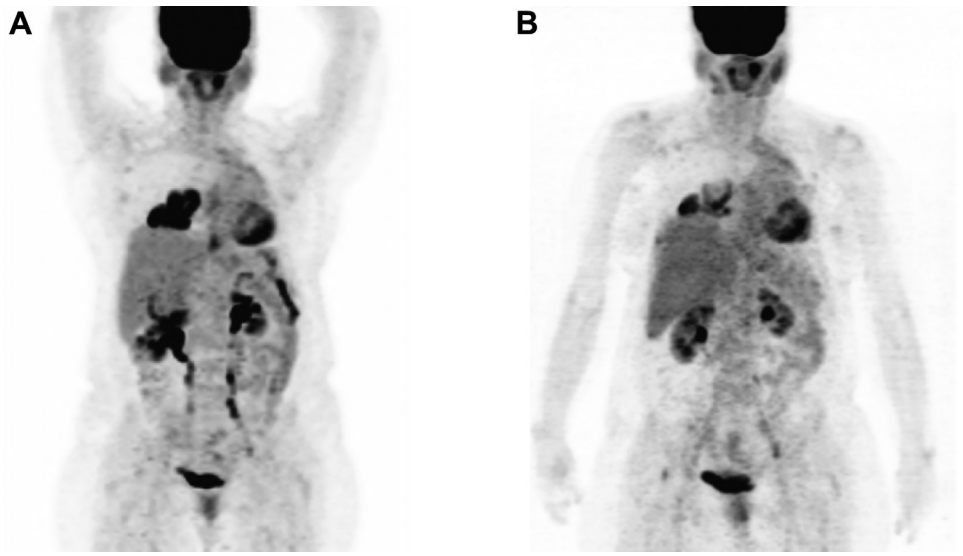

Figure 3. Positron-emission tomography scans taken (*A*) before initiation of afatinib and (*B*) after ~3 months of treatment in a European patient with a p.A775_G776insYVMA insertion in exon 20 who achieved a PR.

Table 3. Adverse Events of Any Grade Reported in *ERBB2* Mutation-Positive Patients Receiving Afatinib in the NPU Program (N = 28)

Event	n
Diarrhea/gastrointestinal toxicity	10
Skin disorders[a]	8
Stomatitis/mucositis/mouth ulceration	4
Respiratory disorders[b]	3
Paronychia	2
Nausea/vomiting	2
Depressed consciousness	1
Septic shock	1
Leukocytosis	1
Paralysis	1

Excludes disease progression, metastases, and deaths unrelated to afatinib and due to disease progression.
[a]Skin disorders = acne, dermatitis, dermatosis, pruritus, rash, skin toxicity.
[b]Respiratory disorders = Adult Respiratory Distress Syndrome, dyspnea, lung infection, respiratory failure, respiratory insufficiency.
NPU, named patient use; *ERBB2*, erb-b2 receptor kinase 2.

occurred in some patients with YVMA insertions. Therefore, despite the challenges of evaluating larger cohorts of patients with rarer *ERBB2* mutations, there is accumulating evidence that the presence of YVMA insertions in exon 20 identifies a subgroup of patients with *ERBB2* mutation–positive NSCLC for whom afatinib may be a treatment option.

Oncogenic activation of ErbB2 may result from protein overexpression, gene copy number gain (due to gene amplification or chromosome 17 polysomy), and gene mutations that lead to molecular alterations in the ErbB2 receptor; limited emerging data suggest that *ERBB2* gene mutations may be more relevant in lung carcinogenesis than *ERBB2* overexpression or amplification.[25] Consequently, to optimize outcomes with ErbB2-targeted therapies in NSCLC, it may be necessary to define the treatment population more precisely. The distinction between *ERBB2* mutation and *ERBB2* amplification is fundamental because these appear to be mutually exclusive forms of *ERBB2* alteration that define distinct clinical entities and represent different therapeutic targets.[26] For example, in a phase II study of the irreversible pan-ErbB TKI dacomitinib in patients with *ERBB2*-mutant or amplified lung adenocarcinomas, PRs (lasting 3+, 11, and 14 months) were seen in 12% of patients with *ERBB2* exon 20 mutations, but not in patients with *ERBB2* amplifications.[13] Further research is required to better understand the biology of the exon 20 YVMA mutation, as well as that of rare *ERBB2* mutations, and to further explore ErbB2-related biomarkers that may help to define patient groups and optimize identification of patients most likely to respond to different forms of ErbB2-targeted therapy.

The importance of precisely defining oncogenic driver *ERBB2* alterations (overexpression or amplification, as well as nonsynonymous *ERBB2* mutations) is further illustrated by the limited efficacy of established anti-ErbB2 therapies in NSCLC, despite their proven efficacy in *ERBB2*-positive breast cancer. For example, studies of trastuzumab in *ERBB2*-positive NSCLC have yielded disappointing results.[27-29] Potential benefit was only observed in a small subgroup of patients whose tumors expressed high levels of ErbB2 (immunohistochemistry level 3+) or who had *ERBB2* amplification detected by fluorescence in situ hybridization.[27,28] By contrast, in a case study of a patient with an *EGFR* exon 21 mutation and a *ERBB2* exon 20 mutation, treatment with trastuzumab and paclitaxel elicited a PR.[11] In a recent phase II study of T-DM1 in ErbB2-overexpressing NSCLC, objective response was only seen in immunohistochemistry level 3+ patients (ORR 20%).[30] In other phase II studies, T-DM1 was active in patients with *ERBB2* mutation–positive NSCLC with an ORR of 44% (8 of 18 patients) in one study and an ORR of 14% (one of seven patients) in another study.[14,31]

The safety profile of afatinib has been well established, with diarrhea, rash, and stomatitis being among the most common side effects.[21,32] Cardiotoxicity is a potential safety concern for all agents targeting ErbB2 because ErbB2 is expressed in the heart and is thought to play a role in normal cardiac function.[33] Heart failure and increased risk of cardiac dysfunction have been reported as AEs in patients treated with trastuzumab.[34,35] However, there is no evidence of cardiac dysfunction from afatinib clinical trials to date, and there were no heart failure AEs reported in patients with *ERBB2* mutation–positive NSCLC treated with afatinib in this NPU program.[36]

The NPU program provides a large pool of patients who have received afatinib in "real life" conditions in clinical practice. However, missing information is an inherent limitation in this type of analysis. It is likely that the analysis did not include all patients harboring *ERBB2* mutations, given that genotyping information was not available for all patients; indeed, the frequency of *ERBB2* mutations (28 of 3966 [0.7%]) was slightly lower than the 1% to 4% range reported previously.[4,5] Other missing information included *ERBB2* mutation type for 16 patients (57%) identified as having *ERBB2* mutation–positive NSCLC, tumor response data for 12 patients (43%), and details of the number of patients who received other anticancer therapies in combination with afatinib. AEs may have been under-reported in this real-world setting compared to clinical trials. Another limitation was that there was no independent, central radiological confirmation of reported responses or disease progression. Survival data were not available for the *ERBB2* mutation–positive patient group; however, interpretation of survival data would be confounded by

the high number of prior therapies received by many patients, and the large variability in the treatment line in which patients received afatinib.

Despite the limitations of this small, retrospective analysis, these data show that afatinib provides clinical benefit for patients with *ERBB2* mutation–positive NSCLC, in particular those harboring the most common *ERBB2* mutation found in lung adenocarcinomas, the p.A775_G776insYVMA insertion in exon 20. This may suggest that, in addition to those with sensitizing *EGFR* mutations, a broader group of patients could benefit from targeted treatment with afatinib. Prospective evaluation of afatinib in *ERBB2* mutation–positive NSCLC patients is therefore warranted, and one phase II study is currently recruiting participants (clinical trial no. NCT02597946).

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