Global named patient use program of afatinib in advanced non-small-cell lung carcinoma patients who progressed following prior therapies

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Aim: A global afatinib named patient use program in non-small-cell lung carcinoma (NSCLC) commenced in 2010. **Materials & methods:** Eligible NSCLC patients had progressed after clinical benefit on prior erlotinib/gefitinib and/or had activating *EGFR/HER2* mutations, exhausted all other treatments, and were ineligible for afatinib trials. **Results:** Data, as of January 2016, were reported on 3966 heavily pretreated NSCLC patients (41 countries; six continents). Among 2595/3966 (65.4%) patients with tumor *EGFR* status, 2407 (92.8%) were *EGFR* mutation positive. Median time to treatment failure (2862/3966 [72.2%] patients with available data) was 4.4 months. Among 1141/2862 (39.9%) patients with response reported, objective response rate was 23.4% (267/1141). Safety findings were as expected. **Conclusion:** Time to treatment failure durations and objective response rates were encouraging.

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Afatinib is an orally available, irreversible ErbB family (*EGFR/Erbb1*; *HER2/Erbb2*; and *HER4/Erbb4*) blocker approved in the European Union, USA, Canada, Switzerland and several Asian, Latin American and Middle East countries for non-small-cell lung carcinoma (NSCLC) patients with certain sensitizing *EGFR* mutations [1,2]. In contrast to the reversible *EGFR* tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib, afatinib covalently binds to the ErbB receptor *in vitro*, irreversibly blocking signaling with sustained inhibition of mitogenic activity [3]. The global, Phase III LUX-Lung 3 (LL3) trial in metastatic *EGFR* mutation-positive NSCLC demonstrated a significant improvement in the primary end point of progression-free survival (PFS) with first-line afatinib 40 mg/day versus pemetrexed/cisplatin (11.1 vs 6.9 months; hazard ratio [HR]: 0.58; $p = 0.001$) for all patients with *EGFR* mutations [4]. A larger median PFS difference was noted for patients with common mutations of Del19

and L858R (13.6 months for afatinib vs 6.9 months for chemotherapy; HR: 0.47; $p < 0.001$) [5,6]. In a more recent analysis of the LL3 trial, first-line afatinib was shown to significantly prolong overall survival (OS) compared with chemotherapy in patients with Del19 mutation-positive NSCLC (33.3 vs 21.1 months; HR: 0.54; $p = 0.0015$) [6]. These outcomes were reproduced in the Phase III LUX-Lung 6 (LL6) trial, in which median OS in patients with Del19-positive tumors was 31.4 months with afatinib versus 18.4 months with gemcitabine/cisplatin (HR: 0.64; $p = 0.023$) [6]. Aside from enrolling only Asian patients, LL6 had an identical randomized trial design to LL3, comparing afatinib 40 mg/day to pemetrexed/cisplatin, and gave similar results to LL3 [6].

The LUX-Lung 1 (LL1) trial was a Phase IIb/III study in patients with chemotherapy and EGFR TKI-progressive NSCLC, in which afatinib 50 mg/day prolonged PFS versus placebo (3.3 vs 1.1 months; HR: 0.38; $p < 0.0001$) and increased investigator-assessed objective response rate (ORR: 11 vs 1%; $p = 0.0019$). There was no corresponding improvement in the primary end point of OS (10.8 vs 12.0 months; HR: 1.08; $p = 0.74$), although this was likely confounded by the receipt of subsequent cancer therapies in many patients [7]. Evidence has shown that EGFR TKIs can continue to benefit patients after disease progression, which is likely to be a key cause of this confounding effect [8,9]. The approved administration of afatinib is at the 40-mg dose level, to be given orally once daily [3].

An afatinib program was initiated in Germany and Australia in May 2010, when the results of the LL1 Phase III trial were reported [7,10]. Since then, this compassionate-use program has included 5622 patients from 49 countries on six continents. Here we present an analysis of the global named patient use (NPU) program. The results presented here do not include data from several expanded access programs, such as those in the USA. Furthermore, for some NPU programs, local restrictions preclude collection of patient data or use of collected data for a publication, or are limited to publication of basic patient characteristics only (e.g., Finland, Italy). These restrictions were based on our current knowledge obtained from the respective countries and resulted in the inclusion of 3966 patients from 41 countries in the analysis. It is important to note that this is the first complete report of the worldwide afatinib NPU data, as there were previous limited data reports published from individual countries, including Germany [11] and the UK [12].

Materials & methods

Patients

Patients were eligible for inclusion in the afatinib NPU program if they: had advanced/metastatic NSCLC; progressed after clinical benefit on erlotinib or gefitinib (with clinical benefit defined as complete response [CR], partial response [PR] or stable disease [SD] of at least 6 months) and/or had a mutation in *EGFR* or *HER2*; had exhausted all other treatment options; and were deemed ineligible to participate in an actively recruiting afatinib trial. Of note, chemotherapy-naïve patients were eligible if they were deemed unfit for chemotherapy.

Patients ($n = 3966$) were enrolled from the following 41 countries (on six continents): Africa: Egypt (4), South Africa (11); Australia: Australia (223); Eastern Asia: China (48), Hong Kong (302), Indonesia (18), Republic of Korea (377), Malaysia (96), Philippines (154), Singapore (145), Thailand (108); Europe: Austria (63), Belgium (115), Cyprus (4), Finland (9), France (14), Germany (575), Greece (28), Ireland (13), Italy (72), The Netherlands (85), Norway (51), Portugal (53), Slovakia (13), Slovenia (20), Spain (290), Sweden (64), Switzerland (65), UK (394); Latin America: Argentina (37), Chile (19), Colombia (13), Mexico (142), Nicaragua (1), Panama (3), Bolivarian Republic of Venezuela (13); Middle East and non-Eastern Asia: India (154), Israel (121), Lebanon (1), Saudi Arabia (3); North America: Canada (45).

Afatinib dose

The recommended starting dose for afatinib in this NPU program was continuous once daily oral treatment at the 50-mg dose level, as used in LL1. Lower starting doses of afatinib of 40 mg or 30 mg were allowed at the discretion of the treating physician. Dose modifications (10-mg steps; maximum dose of 50 mg/day; minimum dose of 30 mg/day) were allowed based on tolerability.

Ethics

The NPU program procedures, including enrollment criteria and treatment details, were approved by the responsible ethics committees, and the required country-specific and regional regulatory authorities were informed. As required by regulations, the NPU was stopped in each country once afatinib (GIOTRIF®; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) was available on the market. As of January 2016, the enrollment of NPU patients had ceased worldwide.

Data capture & analysis

Overall, the intention of the afatinib NPU program was to provide a compassionate treatment option for patients with no further established therapeutic option. Within the program, participating physicians were asked to provide an anonymized dataset for each patient, including age, gender, comorbidities, disease stage, prior therapies, *EGFR* mutation status and the specific mutations, if any. Only the reporting of adverse events (AEs), including tumor progression, was mandatory. Regarding the data on previous therapies, 'prior systemic therapy' included bevacizumab therapy and other antiangiogenesis agents while 'prior chemotherapy' did not. The safety and response data collection depended on local requirements and included, at a minimum, collection of all serious AEs (SAEs), AEs leading to afatinib discontinuation and AEs related to afatinib (according to the treating physician). As this was not a company-sponsored trial, it is important to note that this NPU program did not use case report forms that would readily allow capture of certain data such as AEs leading to dose discontinuation or reduction, and that there was no site monitoring with source verification, no site audits and no structured data collection. However, standard SAE forms and reporting were used.

Data were collected via request forms and, whenever possible, follow-up forms (which were provided after patient discontinuation). Most of the provided information was voluntary, not associated with program participation and entirely without compensation, resulting in incomplete data. The collected data were entered into a Microsoft Access® (Microsoft Corporation, WA, USA) database with a cut-off date of 18 January 2016 and were analyzed using SAS® software (Version 9.4, SAS Institute, Inc., NC, USA).

Time to treatment failure

Time to treatment failure (TTF) in months was calculated as the time from afatinib start date to the date of afatinib discontinuation, switch to another drug, death or end of available data, whichever occurred first; numbers of days were divided by 30.4375 for conversion to months.

Calculations of ORR & disease control rate

The ORR was calculated as the ratio of patients with a recorded PR or CR to the sum of patients with a PR, CR, SD, progressive disease (PD) or mixed response (MR). Disease control rate (DCR) was calculated by dividing the sum of patients categorized as PR, CR or SD by the sum of patients categorized as PR, CR, SD, PD or MR. There was no independent radiological verification of responses, SD or PD.

Results

Patient characteristics

NSCLC patients (n = 3966) were enrolled in this afatinib NPU program; 62.7% (n = 2389) were women (n = 154 [3.9%] had missing information) and the median age was 63 years (range: 24–94 years; 6.7% [n = 265] had missing information) (Table 1). Among patients with reported age, 28.1% (n = 1041) were at least 70 years of age and 6.2% (n = 229) were at least 80 years of age.

Histology

Histology was reported in 62.1% of all patients (n = 2461/3966). Of those with histology information, 90.9% were diagnosed with adenocarcinoma (n = 2236/2461), 2.6% (n = 64) with squamous cell carcinoma, 0.9% (n = 22) with large-cell carcinoma and 5.6% (n = 139) were reported as having 'other' carcinomas (Table 1).

Region

Approximately half (n = 1928; 48.6%) of the patients were from Europe and 31.5% (n = 1248) were from Eastern Asia, with smaller numbers from the Middle East and non-Eastern Asia, Latin America, Australia, North America and Africa (Table 1).

Starting dose

The afatinib starting dose was documented in 79.4% (n = 3149/3966) of all patients. More than half of the patients (53.6%, 1687/3149) used the recommended afatinib starting dose of 50 mg once daily. The starting dose for 40.2% (n = 1267/3149) of patients was 40 mg once daily, and 6.2% (n = 195/3149) started with 30 mg of afatinib (Table 1).

Table 1. Patient characteristics and enrollment by region (total N = 3966).[†]

Characteristic	N (%)
Median age, years (range)	63 (24–94)
Patients with age reported:	3701 (93.3 [‡])
– Patients with age ≥70 years	1041 (28.1)
– Patients with age ≥80 years	229 (6.2)
Gender	
Patients with gender reported:	3812 (96.1 [‡])
– Females	2389 (62.7)
– Males	1423 (37.3)
Histology	
Patients with histology reported:	2461 (62.1 [‡])
– Adenocarcinoma	2236 (90.9)
– Squamous cell carcinoma	64 (2.6)
– Large-cell carcinoma	22 (0.9)
– Other carcinomas	139 (5.6)
Enrollment by region	
Patients with region reported:	3966 (100 [‡])
– Europe	1928 (48.6)
– Eastern Asia	1248 (31.5)
– Middle East and non-Eastern Asia	279 (7.0)
– Latin America	228 (5.7)
– Australia	223 (5.6)
– North America	45 (1.1)
– Africa	15 (0.4)
Starting dose (daily)	
Patients with dose reported:	3149 (79.4 [‡])
– 50 mg	1687 (53.6)
– 40 mg	1267 (40.2)
– 30 mg	195 (6.2)
EGFR mutation status	
Patients with EGFR data reported:	2595 (65.4 [‡])
– Positive	2407 (92.8)
– Mutation-specific data reported	2080 (86.4 [§])
– Negative	188 (7.2)

[†]See the Methods section for included countries and exclusion/local restriction criteria.

[‡]Percentage of all patients.

[§]Percentage of EGFR mutation-positive patients.

EGFR & HER2 mutation status

Among patients with known EGFR status (n = 2595/3966; 65.4%), 92.8% (n = 2407) were reported as EGFR mutation positive (Table 1). More specific EGFR mutation information was provided in 86.4% (n = 2080) of EGFR mutation positive patients. A total of 16 (0.4%) patients had HER2 mutations.

Prior therapies

A total of 94.7% of patients had a prior treatment (n = 3756/3966). Of those, 97.9% (n = 3678/3756) received erlotinib and 9.0% (n = 329/3768) received both erlotinib and gefitinib (Table 2). The median number of lines of prior chemotherapy was 1 (interquartile range [IQR]: 1–2), with up to 11 lines being given. The median number of lines of prior systemic therapies was 2 (IQR: 2–3), with up to 15 lines being given. About half of all patients in the NPU program (48.6%) had received three or more lines of prior systemic therapy, meaning that afatinib was at least fourth-line therapy (Table 2).

Table 2. Previous therapies.

Characteristic	
Total number of patients, N (%)	3966 (100)
Patients with no prior treatment reported, N (%)	210 (5.3)
Patients with prior treatment reported, N (%)	3756 (94.7)
Prior TKI therapy, N (%)	
Prior erlotinib and/or gefitinib:	3678 (97.9 [†])
• Prior erlotinib only	2034 (55.3 [‡])
• Prior gefitinib only	1315 (35.8 [‡])
• Prior erlotinib and gefitinib	329 (8.9 [‡])
Prior treatment lines, median [IQR] (range):	
• Number of prior chemotherapy lines	1 [1–2] (0–11)
• Number of any prior systemic treatment lines	2 [2–3] (1–15)
Number of lines of previous chemotherapy [§] , %:	
• ≥3	16.7
• ≥2	45.4
• 1	36.2
• 0	18.4
Number of lines of previous systemic therapy [§] , %:	
• ≥4	19.3
• ≥3	48.6
• 2	34.2
• 1	17.3

[†]Percentage of subset with prior treatment reported.
[‡]Percentage of subset with any prior TKI treatment.
[§]Patient data from Canada and Italy excluded, since data on prior therapy were not reported.
IQR: Interquartile range; TKI: Tyrosine kinase inhibitor.

Table 3. Median time to treatment failure.

Population	N (%)	TTF, months; median (IQR)
Total number of patients	3966 (100)	
Patients with TTF reported	2862 (72.2 [†])	4.4 (1.9–11.8)
– EGFR mutation-positive patients	1823 (63.7 [‡])	4.3 (2.0–11.0)
– Specific mutation-positive information available	1562 (54.6 [‡])	4.3 (1.9–10.9)
– Common mutation (Del19 or L858R)	1434 (50.1 [‡])	4.3 (2.0–11.0)
– Uncommon (all)	254 (8.9 [‡])	4.3 (1.8–10.0)
• T790M positive	134 (52.8 [§])	4.5 (2.0–9.2)
• G719X, L861Q, S768I	77 (30.3 [§])	4.7 (1.8–9.5)
• Insertion in exon 20	57 (22.4 [§])	3.6 (1.8–10.3)
HER2 mutation positive	15 (93.8 [¶])	4.9 (1.7–13.0)

[†]Percentage of all patients.
[‡]Percentage of subset with TTF reported.
[§]Percentage of subset with any uncommon mutation.
[¶]Percentage of all HER2 mutation-positive patients.
IQR: Interquartile range; TTF: Time to treatment failure.

Previously administered systemic agents included chemotherapy drugs (e.g., cisplatin, carboplatin, gemcitabine, pemetrexed, paclitaxel and docetaxel), EGFR TKIs (e.g., erlotinib, gefitinib) and bevacizumab.

Time to treatment failure

The most frequently reported effectiveness parameter was TTF or the length of time patients were treated with afatinib in the NPU program. Median TTF (in months) for afatinib was calculated for 2862 patients (72.2% of all 3966 patients) based on available data; median TTF and IQR values are listed in Table 3. Median TTF was

Table 4. Response assessment.

Population	
Total number of patients, N (%)	3966 (100)
Patients with available TTF data, N (%)	2862 (72.2 [†])
Reported response assessment, N (%)	
– Patients with response assessment data reported:	1141 (39.9 [‡])
• CR	7 (0.6 [§])
• PR	260 (22.8 [§])
• MR	8 (0.7 [§])
• SD	506 (44.3 [§])
• PD	360 (31.6 [§])
DCR [¶] , n (%)	773 (67.7 [§])
ORR [#] , n/N (%)	
– All patients with response assessment reported:	267/1141 (23.4)
• <i>EGFR</i> mutation positive	181/723 (25.0)
– Common mutation positive – any	143/573 (25.0)
– Uncommon mutation positive – any:	26/100 (26.0)
– T790M	11/58 (19.0)
– G719X, L861Q, S768I	8/27 (29.6)
– Insertion in exon 20	7/20 (35.0)

[†]Percentage of all patients.
[‡]Percentage of subset with TTF reported.
[§]Percentage of subset with response assessment reported.
[¶]Patients with PR, CR or SD.
[#]Patients with PR or CR.
CR: Complete response; DCR: Disease control rate; MR: Mixed response; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease; TTF: Time to treatment failure.

4.4 months (IQR: 1.9–11.8) for all patients. Similar values were observed in patient subgroups: those reported as *EGFR* mutation positive (4.3 months), those with common *EGFR* mutations (4.3 months), those with uncommon *EGFR* mutations (4.3 months) and those with *HER2* mutations (4.9 months).

Response assessments including ORR & DCR

In this analysis, 2862/3966 (72.2%) were included. Of those patients, response assessments were reported in 39.9% (n = 1141/2862) of all patients. Of the total 1141 patients with response assessments, there were 260 PRs (22.8%), 7 CRs (0.6%), 8 MRs (0.7%), 506 SDs (44.3%) and 360 PDs (31.6%), for a DCR of 67.7% (Table 4).

The ORR was 23.4% (n = 267/1141) for all patients and 25.0% (n = 181/723) for those with any *EGFR* mutation (Table 4). Notably, a 26.0% (n = 26/100) ORR was reported in patients with uncommon *EGFR* mutations, including 19.0% (n = 11/58) in T790M mutation-positive patients and 35.0% (n = 7/20) in those with insertions in exon 20. In those with G719X, L861Q and S768I mutations, objective responses were seen in eight out of 27 patients (29.6%).

Safety

Table 5 displays the most common AEs for all 3966 patients. The most frequently reported AEs not related to disease progression included diarrhea, rash, paronychia, stomatitis and mucosal inflammation, all of which are believed to be due to inhibition of wild-type *EGFR* in normal tissues and have been previously reported in afatinib trials [5,7]. Rare cases of 'pneumonitis' were reported nine times and are a well-known risk with *EGFR* TKIs. Overall, no new or unexpected safety findings were observed.

Discussion

This global NPU program includes nearly 4000 patients from 41 countries on six continents. It therefore provides an important perspective and represents the first real-world evidence of afatinib use in clinical practice globally.

As might be expected with compassionate use, patients were heavily pretreated and had advanced disease. Among patients who received prior treatment, almost all (97.9%) had prior treatment with erlotinib and/or

Table 5. Most frequently reported adverse events (all grades).

Adverse event	Case count [†]
Diarrhea	1141
Malignant neoplasm progression	628
Rash	557
Paronychia	250
Stomatitis	224
Mucosal inflammation	218
Decreased appetite	185
Nausea	174
Fatigue	141
Neoplasm progression	141
Vomiting	134

[†]The denominators or the percentage for each adverse event per patient are not indicated because more than one case count for each adverse event occasionally occurred in a single patient (e.g., two separate episodes of diarrhea in one patient). Therefore, a frequency based on the number of patients would have been incorrect.

gefitinib (Table 2). The median number of prior lines of chemotherapy was one (maximum 11) with a median of two prior systemic therapies (maximum 15). Accordingly, 48.6% of all patients received afatinib as fourth or greater treatment line (Table 2).

The overall patient population was highly representative of the *EGFR* mutation-positive NSCLC patient population. Most patients were deemed *EGFR* mutation positive (92.8% of those with *EGFR* mutation analysis reported); entry of the remaining patients to the NPU program was heavily dependent on prior clinical benefit from prior erlotinib or gefitinib, a patient population known to have a high degree of enrichment for *EGFR* mutations [7]. A key exception was the small number of patients ($n = 16$) whose entry depended on *HER2* mutation positivity. As expected for a predominantly *EGFR* mutation-positive population, there was a predominance of females (62.7%). Most of the patients were from Europe (48.6%) or Eastern Asia (31.5%; Table 1).

The most frequently reported effectiveness parameter was TTF or the duration of treatment with afatinib ($n = 2862/3966$ patients, 72.2% of all). TTF provides an estimate of the time that investigators believe the patient may be benefiting while they are also still able to tolerate the treatment. TTF, therefore, incorporates both risk and benefit into a single practical parameter. It is important to note that there was no independent, central and blinded radiological confirmation on the lack of progression. The data, however, are useful in providing a real-world assessment of afatinib benefit. Median TTF was approximately 4.4 months in the following groups of patients: all patients, *EGFR* mutation-positive patients and common *EGFR* mutation-positive patients, and there was a trend toward longer TTF (median: 4.9 months) in the small number ($n = 16$) of *HER2* mutation-positive patients. A median TTF of more than 4 months in the setting of mostly third- to fourth-line NSCLC therapy is most encouraging. The results in patients with uncommon mutations were particularly noteworthy, with a median TTF of 4.3 months, which was similar even for those with T790M mutations (4.5 months) and insertions in exon 20 (3.6 months). These two types of uncommon mutations are well known to give rise to resistance to the reversible *EGFR* TKIs, erlotinib and gefitinib [13].

Although response assessments were reported in only 39.9% ($n = 1141/2862$) of patients and there was no independent radiological verification, the large 1141-patient database of response assessments provides a useful, real-world examination of responses as deemed by treating physicians globally. ORRs were consistent, ranging from 23 to 25% (Table 4) in all NSCLC patients, those with any *EGFR* mutation, and those with common *EGFR* mutations. ORRs of 23–25% in the setting of mainly third- to fourth-line NSCLC therapy are encouraging, given that second-line docetaxel showed a response rate of 15–18% in NSCLC patients with wild-type *EGFR* in the recent TAILOR and DELTA studies [14,15].

Since this study was initiated, progress has been made regarding the treatment of patients with *EGFR* mutation-positive NSCLC following acquired resistance to *EGFR* TKIs. The third-generation *EGFR* TKI, osimertinib, has recently been approved for the treatment of patients with an *EGFR* T790M mutation, the predominant mechanism of acquired resistance to erlotinib, gefitinib and afatinib (50–70% of cases) [16–18]. In this setting, osimertinib conferred an ORR of >60% and median PFS of approximately 8–12 months [16,19]. Furthermore, the recent Phase III FLAURA study positioned osimertinib as a first-line treatment option in patients with *EGFR* mutation-positive

NSCLC [20]. In this study, osimertinib achieved its primary end point of improved PFS versus erlotinib/gefitinib (median 18.9 vs 10.2 months; HR: 0.46 [95% CI: 0.37–0.57]) and was well-tolerated. Notably, afatinib was not included in the comparator arm and treatment options following failure currently remain uncertain [21].

Significant activity of afatinib in patients with uncommon *EGFR* mutations was reported in a *post hoc* analysis of several clinical trials [13]; this is supported by the current analysis in terms of both TTF and ORR. Particularly noteworthy was the number of responses in the 100 patients with uncommon mutations (ORR of 26.0%), including 11 responses in patients with T790M mutations (19.0%) and seven responses in patients with insertions in exon 20 (35.0%), two mutation types known to confer resistance to erlotinib and gefitinib.

As only six patients with *HER2* mutations had response assessments reported, the ORR in this population could not be accurately determined. It should be noted that there was also more uncertainty in the observed ORRs of the uncommon *EGFR* mutation subgroups as a result of the smaller numbers of patients involved.

In addition to enrichment for *EGFR* mutations and near-universal prior treatment with erlotinib and/or gefitinib, the patient population in this NPU program had another similarity with the patient populations of LL1 and LUX-Lung 4 (LL4): prior use of chemotherapy (1–2 lines in these LUX-Lung studies). In LL1, the median PFS for afatinib was 3.3 months, with an investigator response rate of 11% [7]. In LL4, the corresponding values were 4.4 months and 8%, respectively [22]. The activity of afatinib reported here in an even later line corroborates the results of LL1 and LL4, demonstrating activity of afatinib in this refractory setting. The activity seen here in the NPU program may have been related to the higher degree of enrichment for patients with *EGFR* mutations, a population known to be very sensitive to afatinib, and for which afatinib was approved in the first-line setting based on results from LL3 and LL6 [4,6].

In terms of safety, no new or unexpected patterns of AEs were observed in the afatinib NPU program. With consideration of the limitations of this program, the most common AEs were consistent with previous reports [5,7] for afatinib and with events associated with progression of lung cancer.

This NPU program provided simplified and expedited access to compassionate use of afatinib before drug approval for terminally ill, heavily pretreated, advanced NSCLC patients who were not eligible for afatinib clinical trials. Data were collected from oncologists on a voluntary basis without compensation, in line with local regulations and with limited but enough information to verify that afatinib can be used compassionately for patients with no other viable treatment alternatives. Consequently, there were no case report forms, no site monitoring with source verification and no audits. It is important to note these limitations, along with the lack of central testing for *EGFR* mutations and the lack of independent radiological review. However, standard SAE forms and reporting as in clinical trials were used.

Conclusion

In conclusion, this large global NPU program, including nearly 4000 heavily pretreated patients with *EGFR* mutation-positive NSCLC, provides the earliest real-world data available for afatinib globally. Although there have been recent advances in the treatment of specific patient sub-populations (including those harboring T790M mutation-positive disease), the efficacy observations such as TTF durations and response rates observed in this NPU program are encouraging. These data suggest that afatinib can provide clinical benefit in heavily pretreated NSCLC patients, including those with uncommon *EGFR* mutations. Furthermore, the safety profile of afatinib was as anticipated in this real-world setting.

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Ethical conduct of the research

The NPU program procedures, including enrollment criteria and treatment details, were approved by the responsible ethics committees, and the required country-specific and regional regulatory authorities were informed. As required by regulations, the NPU was stopped in each country once afatinib (GIOTRIF®; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) was available on the market. As of January 2016, the enrollment of NPU patients had ceased worldwide.

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Summary points

- A global afatinib named patient use (NPU) program in non-small-cell lung carcinoma (NSCLC) commenced in 2010, after LUX-Lung 1 demonstrated significantly improved progression-free survival and objective response rate (ORR) in patients with advanced NSCLC following failure of erlotinib/gefitinib and 1–2 chemotherapy lines.
- This NPU program provided compassionate treatment for NSCLC patients in countries that had no further established therapeutic options.
- The NPU program provided the earliest real-world data for afatinib in heavily pretreated patients with *EGFR* mutation-positive NSCLC.
- Data, as of January 2016, were reported on 3966 NSCLC patients from 41 countries.
- Median time to treatment failure (2862/3966 [72.2%] patients with available data) was 4.4 months.
- Among 1141/2862 (39.9%) patients with response assessments, ORR was 23.4% (267/1141); ORR for those with any *EGFR* mutation was 25.0% (181/723) and with uncommon *EGFR* mutations it was 26.0% (26/100), including 19.0% (11/58) in T790M-positive patients and 35.0% (7/20) in those with insertions in exon 20.
- Safety findings were as expected.
- Although there have been recent advances in the treatment of specific patient sub-populations (including those harboring T790M mutation-positive disease), the encouraging efficacy observed in this NPU program suggests that afatinib can provide clinical benefit in heavily pretreated NSCLC patients, including those with uncommon *EGFR* mutations.

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