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# Afatinib in EGFR TKI-Naïve Patients with Locally Advanced or Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer: A Pooled Analysis of Three Phase IIIb Studies

*Antonio Passaro[1]*, Filippo de Marinis[1], Hai-Yan Tu[2], Konstantin K. Laktionov[3], Jifeng Feng[4], Artem Poltoratskiy[5], Jun Zhao[6], Eng Huat Tan[7], Maya Gottfried[8], Victor Lee[9], Dariusz Kowalski[10], Cheng Ta Yang[11], BJ Srinivasa[12], Laura Clementi[13], Tejaswini Jalikop[14], Dennis Chin Lun Huang[15], Agnieszka Cseh[16], Keunchil Park[17] and Yi-Long Wu[2]*

[1] Division of Thoracic Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy, [2] Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China, [3] Russian Academy of Medical Sciences, Moscow, Russia, [4] Jiangsu Provincial Tumor Hospital, Nanjing, China, [5] Petrov Research Institute of Oncology, St Petersburg, Russia, [6] Peking University Cancer Hospital & Institute, Beijing, China, [7] National Cancer Centre, Singapore, Singapore, [8] Tel Aviv University, Tel Aviv, Israel, [9] Department of Clinical Oncology, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China, [10] Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland, [11] Chang Gung Memorial Hospital, Guishan, Taoyuan, Taiwan, [12] HCG Hospital, Bangalore, India, [13] Boehringer Ingelheim Italia S.p.A., Milan, Italy, [14] Syneos Health, Raleigh, NC, United States, [15] Boehringer Ingelheim Taiwan Limited, Taipei, Taiwan, [16] Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany, [17] Division of Hematology Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, South Korea

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**Edited by:**
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***Correspondence:**
*Antonio Passaro*
*Antonio.Passaro@ieo.it*

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**Background:** Afatinib is approved for first-line treatment of patients with epidermal growth factor receptor mutation-positive (*EGFR*m+) non-small-cell lung cancer (NSCLC). Here, we report findings from a combined analysis of three phase IIIb studies of afatinib in EGFR tyrosine kinase inhibitor (TKI)-naïve patients.

**Methods:** EGFR-TKI-naïve patients with *EGFR*m+ NSCLC received afatinib 40 mg/day. Dose reductions were permitted for adverse events (AEs). Efficacy endpoints included progression-free survival (PFS), time to symptomatic progression (TTSP), and tumor response. Subgroup analyses were performed by Eastern Cooperative Oncology Group performance status (ECOG PS), presence of brain metastasis, age and common/uncommon *EGFR* mutations (plus other factors).

**Results:** 1108 patients were treated. Median age was 61 years (range, 25–89); 19.2% had baseline brain metastases, 4.4% had ECOG PS ≥2, and 17.9% had tumors harboring uncommon mutations. Treatment-related AEs (TRAEs) were reported in 97.2%, most commonly diarrhea and rash. 41.6% had AEs leading to dose reduction. Median PFS was 13.0 months [95% confidence interval (CI): 12.0–13.8]; median TTSP was 14.8 months (95% CI: 13.9–16.1). Objective response rate (ORR) was 55.0%. Age, presence of baseline brain metastases, major (G719X, L861Q, S768I) or compound uncommon

mutations had little/no effect on PFS, TTSP, or ORR, while outcomes were poorer in patients with ECOG PS 2 or exon 20 insertion/T790M mutations.

**Conclusions:** Afatinib was tolerable with no new safety signals. Afatinib demonstrated encouraging efficacy in a broad patient population, including those with brain metastases or uncommon *EGFR* mutations.

**Keywords: afatinib, real world, safety, *EGFR* mutation, EGFR TKI-naïve, NSCLC**

## INTRODUCTION

Activating mutations in the epidermal growth factor receptor (*EGFR*) gene, leading to aberrant EGFR signaling, render non-small cell lung cancer (NSCLC) tumors highly sensitive to targeted treatment with EGFR tyrosine kinase inhibitors (TKIs) (1). Based on seminal randomized controlled trials (RCTs) (1), EGFR TKIs are the first-line treatment of choice in patients with advanced *EGFR* mutation-positive (EGFRm+) NSCLC, with five TKIs currently approved. These are: the first-generation reversible EGFR TKIs, gefitinib and erlotinib; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib; and the third-generation irreversible EGFR TKI, osimertinib (2–5).

As an ErbB family blocker, afatinib inhibits signaling *via* all hetero- and homodimers formed by ErbB1 (EGFR), ErbB2 [human epidermal growth factor receptor 2 (HER2)], ErbB3 (HER3), and ErbB4 (HER4) (6, 7). In RCTs, afatinib significantly improved progression-free survival (PFS) versus standard chemotherapy (8, 9). Furthermore, in the LUX-Lung 3 and 6 trials, afatinib significantly improved overall survival (OS) *versus* chemotherapy in patients with tumors harboring Del19 mutations (10). In LUX-Lung 7, afatinib conferred statistically significant improvement in PFS (although there was minimal difference in medians) and time-to-treatment failure versus gefitinib (11). There was no significant difference in OS (12). Across these RCTs, afatinib was tolerable, with few treatment discontinuations due to toxicity. Treatment-related adverse events (TRAEs) were managed effectively with tolerability-guided dose reductions.

RCTs are conducted under highly controlled settings, often with strict inclusion criteria. Consequently, certain patient subgroups are generally under-represented in clinical trials, such as the very elderly and patients with brain metastases, uncommon mutations, prior chemotherapy treatment, or Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2. Accordingly, the importance of assessing the efficacy and tolerability of recently developed drugs in 'real world' settings is becoming increasingly recognized (13). To date, available real-world evidence suggests that afatinib is effective and tolerable in diverse patient populations treated in routine clinical practice (14–18). Here, in order to assess outcomes in a larger cohort, we report a combined analysis of three phase IIIb studies of afatinib in EGFR TKI-naïve patients with *EGFR*m+ NSCLC treated in a setting similar to daily clinical practice (19, 20).

## METHODS

### Study Designs

Study 1200.55 (NCT01853826; conducted in Europe, Australia, Russia, and Israel), Study 1200.66 (NCT01953913; conducted in Asia), and Study 1200.193 (NCT01931306; conducted in South Korea) were all phase IIIb, open-label, multicenter, single-arm trials of afatinib in EGFR TKI-naïve patients with locally advanced or metastatic *EGFR*m+ NSCLC (**Supplementary Figure 1**). All studies were approved by the Institutional Review Board or Independent Ethics Committee of each participating center, and were carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and local laws. All patients provided written, informed consent.

### Patients and Treatment

Patients were aged ≥18 years with histologically-confirmed, locally advanced or metastatic *EGFR*m+ NSCLC, adequate organ function, and an ECOG PS of 0–2. Exclusion criteria included: previous use of an EGFR TKI; use of any anti-cancer treatment (or hormonal anti-cancer treatment for Study 1200.193) <2 weeks, radiotherapy (except palliative) <14 days (or <4 weeks for Study 1200.66), and major surgery <4 weeks before the first dose of afatinib; history or presence of cardiovascular abnormalities; pre-existing interstitial lung disease; and symptomatic brain metastases.

Patients received afatinib (starting dose 40 mg once daily) until disease progression, lack of tolerability or other reasons necessitating withdrawal. Investigators could continue afatinib beyond radiological progression for as long as they judged that the patient was benefiting. TRAEs were managed using tolerability-guided dose modifications. In the event of any drug-related grade ≥3 AE, persistent grade 2 diarrhea, or grade ≥2 renal dysfunction, treatment was paused until the severity recovered to grade ≤1 or baseline severity. Treatment could then be resumed at a lower dose (reduced by 10 mg decrements) to a minimum of 20 mg/day. If the patient could not tolerate 20 mg/day, or the patient did not recover to grade ≤1 or baseline within 6 weeks, treatment was discontinued.

### Endpoints and Assessments

The primary objective of each study was to evaluate the safety of afatinib; the secondary objective was to assess the efficacy of afatinib. AEs were graded using the National Cancer Institute

Common Terminology Criteria for Adverse Events version 3.0. Efficacy endpoints were chosen to reflect real-world clinical practice and current treatment guidelines, and included: PFS (defined as time from first administration of afatinib to the date of progression or to the date of death, whichever occurred first); time to symptomatic progression (TTSP; defined as the time from first administration of afatinib to the date of first documented clinically significant symptomatic progression); and tumor response. Efficacy analyses were based on the assessment of cancer-related symptoms and, if available, radiologic assessments as per standard of care at the participating institution and determined by Response Evaluation Criteria in Solid Tumors (RECIST). Tumor assessments, and the version of RECIST criteria used in the three studies were undertaken according to local standard of care at each participating site. PFS and ORR were judged by investigator. *EGFR* mutations were detected according to the methodology used at each participating institution.

## Statistical Analyses

All patients who received ≥1 dose of afatinib (treated set) were included in the safety and efficacy analyses. Subgroup analyses were conducted according to: *EGFR* mutation status (common/uncommon); presence of brain metastases at baseline (yes/no); age (<65 years/≥65 years and <75 years/≥75 years); ECOG PS (0–1/2); and line of therapy (first/second/>second). Patients with tumors harboring uncommon *EGFR* mutations were further subdivided into the following five groups: 1) T790M; 2) exon 20 insertions; 3) 'major' uncommon mutations (G719X, L861Q, and S768I, with or without any other mutation except T790M or exon 20 insertion); 4) compound mutations; and 5) other uncommon mutations. Outcomes were also assessed for compound mutations including major mutations. Descriptive statistics are presented; no hypotheses testing was planned, and all analyses were exploratory.

# RESULTS

## Patients, Disposition, and Treatment Exposure

Of the 1163 patients enrolled, 1109 entered and 1108 had been treated with afatinib (**Supplementary Figure 1**). Overall, 1081 (97.6%) patients discontinued treatment, the most common reason being progressive disease, in 739 (66.7%) patients. Median age was 61 years (range, 25–89), 38.2% of patients were aged ≥65 years, with 10.7% aged ≥75 years. Most patients (58.3%) were female and were predominantly either Asian (57.7%) or white (42.0%; **Table 1**). An ECOG PS of 2 was reported in 49 (4.4%) patients, and 213 (19.2%) patients had brain metastases. The most common histological classification was adenocarcinoma, in 95.8% of patients.

In total, 909 (82.0%) patients had tumors harboring common *EGFR* mutations, while 198 (17.9%) had tumors harboring uncommon mutations only; the most frequent uncommon *EGFR* mutations were insertions in exon 20, which were detected in 70 patients (6.3% overall). Nearly a third of patients (33.1%) had previously received systemic chemotherapy. The median duration of treatment across all lines of afatinib was 12.7 months (range, 0.07–56.1 months). Dose reductions from 40 mg/day to 30 mg/day were performed in 462 (41.7%) patients, 145 of whom (13.1% overall) had a further dose reduction to 20 mg/day.

## Safety

Most patients (1100; 99.3%) experienced an AE, and 620 (56.0%) patients experienced grade ≥3 AEs (**Table 2**). Any-grade TRAEs were reported in 1077 (97.2%) patients, and grade ≥3 TRAEs were reported in 412 (37.2%) patients. The most common TRAEs (any grade/grade ≥3) were diarrhea (89.1%/14.0%), rash (61.6%/9.1%), and paronychia (39.7%/3.6%; **Table 2**). Serious AEs (SAEs) were reported in 403 (36.4%) patients, the most common being malignant neoplasm progression in 53 (4.8%) patients, and pleural effusion in 38 (3.4%) patients; 81 (7.3%) patients had a treatment-related SAE, the most common being diarrhea in 28 (2.5%) patients. AEs leading to dose reduction of afatinib were reported in 461 (41.6%) of patients. The most common reasons for dose reduction were diarrhea in 199 (18%) patients, and rash in 108 (9.7%) patients. AEs leading to discontinuation of afatinib were reported in 160 (14.4%) patients, among whom 58 (5.2%) patients experienced TRAEs leading to drug discontinuation; the most frequent of these was diarrhea in 17 patients (1.5%). A total of 122 patients (11.0%) had an AE that led to death, including malignant neoplasm progression in 41 (3.7%) patients, and respiratory failure in 14 (1.3%) patients. There were five TRAEs resulting in death (decreased appetite, dyspnea, pneumonitis, respiratory failure, intestinal infarction).

## Efficacy

### PFS

Median PFS was 13.0 months overall and was 13.9 months among patients with tumors harboring common mutations (**Table 3**; **Figures 1A, B**). Median PFS was longer in patients with ECOG PS 0/1 compared to those with ECOG PS 2 (median: 13.4 and 7.7 months, respectively), and this was also the case among only those patients with tumors harboring common mutations (median, 14.1 and 8.8 months; **Table 3**; **Figures 1C, D**). Median PFS was slightly longer in patients without compared to those with brain metastases at baseline (median, 13.7 and 10.6 months; **Figure 1E**), and in patients treated with first-line afatinib compared to second- or later-line afatinib (median, 13.7, 12.9 and 8.3 months, respectively; **Figure 1F**), while age had little or no effect on PFS (**Table 3**; **Figures 1G, H**).

### TTSP

Median TTSP was 14.8 months overall and was 16.1 months in patients with tumors harboring common mutations (**Table 3**; **Supplementary Figures 2A, B**). Median TTSP was numerically longer in patients with ECOG PS 0/1 *versus* 2 (median, 15.2 and 9.9 months) including among only those with common mutations (median, 16.6 and 9.9 months; **Table 3**; **Supplementary Figures 2C, D**). Median TTSP was slightly longer in patients without baseline brain metastases compared

**TABLE 1** | Baseline demographics and disease characteristics in the treated set.

| Characteristic | Afatinib (n = 1108) |
|---|---|
| Sex, n (%) | |
| Female | 646 (58.3) |
| Median age, years (range) | 61 (25–89) |
| ≥65 years, n (%) | 423 (38.2) |
| ≥75 years, n (%) | 119 (10.7) |
| Race, n (%) | |
| Asian | 639 (57.7) |
| White | 465 (42.0) |
| Other[†] | 4 (0.4) |
| Smoking status, n (%) | |
| Never smoked | 735 (66.3) |
| Ex-smoker | 307 (27.7) |
| Current smoker | 66 (6.0) |
| Histological classification, n (%) | |
| Predominantly adenocarcinoma | 1061 (95.8) |
| Predominantly squamous cell carcinoma | 20 (1.8) |
| Large cell/undifferentiated carcinoma | 11 (1.0) |
| NOS/missing | 16 (1.4) |
| Prior therapy | |
| Any | 578 (52.2) |
| Chemotherapy/other systemic therapy | 373 (33.7) |
| Radiotherapy | 213 (19.2) |
| Surgery | 278 (25.1) |
| *EGFR* mutation, n (%) | |
| Common only (del19 and/or L858R) | 909 (82.0) |
| Del 19 | 556 (50.2) |
| L858R | 429 (38.7) |
| Uncommon only | 198 (17.9) |
| Missing | 1 (0.1) |
| Baseline ECOG PS, n (%) | |
| 0 | 285 (25.7) |
| 1 | 773 (69.8) |
| 2 | 49 (4.4) |
| Missing | 1 (0.1) |
| Baseline brain metastases,[‡] n (%) | 213 (19.2) |
| Prior systemic chemotherapy, n (%) | 367 (33.1) |

*ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NOS, not otherwise specified. [†]Other: one Native Hawaiian or other Pacific Islander; three Black/African American. [‡]Asymptomatic.*

to those with brain metastases at baseline (median, 15.5 and 13.7 months; **Supplementary Figure 1E**), and in patients treated with afatinib in first line compared with second or later lines (median, 16.0, 13.8 and 10.6 months, respectively; **Supplementary Figure 2F**). Age had little or no effect on TTSP (**Table 3** and **Supplementary Figures 2G, H**).

### Tumor Response

Overall, 609 of the 1108 treated patients (55.0%) had an objective response, including 40 (3.6%) complete responses and 569 (51.4%) partial responses. An additional 368 (33.2%) patients had stable disease, for a disease control rate of 88.2% (n=977). Median duration of objective response (DOR) in the overall treated set was 13.2 months (95% CI: 12.2–14.4), and median duration of disease control was 14.1 months (95% CI: 13.6–14.8; **Supplementary Table 1**).

### Patients with Uncommon Mutations

Baseline characteristics of patients with uncommon mutations were generally consistent with the overall treated set (**Table 4**).

**TABLE 2** | Overall summary of AEs, and most common TRAEs (occurring in ≥10% of patients).

| AE, n (%) | Treated set (n = 1108) | |
|---|---|---|
| Any AE | 1100 (99.3) | |
| Any grade ≥3 AE | 620 (56.0) | |
| Any TRAE | 1077 (97.2) | |
| Any grade ≥3 TRAE | 412 (37.2) | |
| Any SAE | 403 (36.4) | |
| AEs leading to dose reduction | 461 (41.6) | |
| AEs leading to discontinuation | 160 (14.4) | |
| TRAEs leading to discontinuation | 58 (5.2) | |
| AEs leading to death | 122 (11.0) | |
| Most common TRAEs | All grades | Grade ≥3 |
| Diarrhea | 987 (89.1) | 155 (14.0) |
| Rash | 683 (61.6) | 101 (9.1) |
| Paronychia | 440 (39.7) | 40 (3.6) |
| Stomatitis | 243 (21.9) | 27 (2.4) |
| Mucosal inflammation | 170 (15.3) | 20 (1.8) |
| Mouth ulceration | 149 (13.4) | 10 (0.9) |
| Dry skin | 144 (13.0) | 2 (0.2) |
| Pruritus | 135 (12.2) | 3 (0.3) |

*AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event.*

Compared with the T790M and exon 20 mutation subgroups (median PFS, 3.9 and 5.6 months, respectively), median PFS was longer in the compound, 'major' and 'other' mutation subgroups (11.0, 9.2, and 8.6 months, respectively), particularly in the subgroup with compound mutations with a 'major' uncommon mutation (15.6 months; **Figure 2A**). Median TTSP was also longest in the 'compound with major mutation' subgroup (18.5 months), followed by the compound mutation (13.9 months), 'major' mutation (11.1 months), 'other' mutation (9.7 months), exon 20 mutation (5.9 months), and T790M (3.8 months) subgroups (**Figure 2B**). Objective response rates were higher in the compound/'compound with major', and 'major' uncommon mutation subgroups compared with the exon 20 mutation and T790M subgroups, as was the corresponding DOR (**Supplementary Table 2**).

## DISCUSSION

This study was a combined analysis of three phase IIIb, open-label, multicenter, single-arm trials in which EGFR TKI-naïve patients with locally advanced or metastatic *EGFR*m+ NSCLC received afatinib. Patient characteristics were comparable to those previously reported in studies of EGFR TKIs used in routine clinical practice, both globally and in Asia (14–17). The patient population included subsets that are generally under-represented in clinical trials, including the elderly (38.2% aged ≥65 years; 10.7% aged ≥75 years), patients with brain metastases (19.2%), patients with ECOG PS 2 (4.4%), and those with tumors harboring uncommon *EGFR* mutations (17.9%).

In this diverse patient population, afatinib was generally tolerable with no new or unexpected safety findings. The most common AEs were EGFR TKI class-related toxicities (diarrhea, rash/acne, stomatitis, and paronychia) consistent with findings

**TABLE 3 |** Post-hoc analysis of TTSP and PFS for specified subgroups.

| Category | Patient subgroup | | |
|---|---|---|---|
| All patients | | | |
| N | 1108 | | |
| Median PFS, months (95% CI) | 13.0 (12.0–13.8) | | |
| Median TTSP, months (95% CI) | 14.8 (13.9–16.1) | | |
| *EGFR* mutation type[†] | Common[†] | | Uncommon[‡] |
| N | 909 | | 198 |
| Median PFS, months (95% CI) | 13.9 (13.2–14.7) | | 7.4 (6.0–9.0) |
| Median TTSP, months (95% CI) | 16.1 (14.8–17.7) | | 8.3 (7.2–11.0) |
| Common mutation type | Del19 | | L858R |
| N | 531 | | 378 |
| Median PFS, months (95% CI) | 14.5 (13.8–15.9) | | 12.6 (11.1–13.8) |
| Median TTSP, months (95% CI) | 17.2 (15.5–19.3) | | 14.5 (13.1–16.5) |
| ECOG PS | 0/1 | | 2 |
| N | 1058 | | 49 |
| Median PFS, months (95% CI) | 13.4 (12.4–14.1) | | 7.7 (5.7–11.6) |
| Median TTSP, months (95% CI) | 15.2 (14.1–16.6) | | 9.9 (7.6–13.9) |
| ECOG PS (patients with common mutations)[†] | 0/1 | | 2 |
| N | 869 | | 40 |
| Median PFS, months (95% CI) | 14.1 (13.5–14.8) | | 8.8 (5.7–13.9) |
| Median TTSP, months (95% CI) | 16.6 (15.1–18.1) | | 9.9 (7.6–14.5) |
| Afatinib line of therapy | First-line | Second-line | >Second-line |
| N | 770 | 261 | 77 |
| Median PFS, months (95% CI) | 13.7 (12.6–14.5) | 12.9 (11.3–13.8) | 8.3 (6.6–12.6) |
| Median TTSP, months (95% CI) | 16.0 (14.4–17.7) | 13.8 (12.7–15.4) | 10.6 (7.6–14.8) |
| Brain metastases at screening[§] | Yes | | No |
| N | 213 | | 894 |
| Median PFS, months (95% CI) | 10.6 (9.1–12.8) | | 13.7 (12.8–14.4) |
| Median TTSP, months (95% CI) | 13.7 (11.0–14.8) | | 15.5 (14.1–16.9) |
| Age, years | <75 years | | ≥75 years |
| N | 989 | | 119 |
| Median PFS, months (95% CI) | 13.0 (12.0–13.9) | | 13.0 (9.1–14.8) |
| Median TTSP, months (95% CI) | 14.8 (13.8–16.1) | | 14.8 (13.1–22.3) |
| Age, years | <65 years | | ≥65 years |
| N | 685 | | 423 |
| Median PFS, months (95% CI) | 12.6 (11.3–13.6) | | 13.9 (12.7–15.2) |
| Median TTSP, months (95% CI) | 13.8 (12.9–15.1) | | 17.5 (15.0–20.6) |

*CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NE, not evaluable; PFS, progression-free survival; TTSP, time to symptomatic progression. [†]Patients with EGFR mutation categories of Del19 only or L858R only. [‡]Patients with EGFR mutation categories other than Exon19 only and L858R only. [§]Asymptomatic.*

from the LUX-Lung 3, 6, and 7 studies (8, 9, 11). The overall rate of dose reductions due to AEs (41.6%) was similar to that reported in the LUX-Lung 3 and 7 studies (52% and 39%, respectively) (8, 11), but were more frequent than in LUX-Lung 6 (28%) (9), possibly reflecting differences in side effect management in different populations. However, consistent with RCT data (21, 22), and real-world studies (23), TRAEs rarely led to afatinib discontinuation in everyday clinical practice.

PFS and objective response rates (ORR) in this study are comparable to afatinib real-world studies (median PFS: 11.8–19.1 months; ORR: 67.1-76.5%) (14, 16, 17) and in the LUX-Lung trials, (median PFS 11.0–11.1 months; ORR: 56–70%) (8, 9, 11). At 14.8 months, median TTSP was almost 2 months longer than the median PFS, indicating that, following tumor progression, patients obtained clinical benefit from afatinib for another ~2 months on average, before clinically significant symptomatic progression was identified and treatment was suspended. Of note, the constituent studies in this analysis were largely undertaken before osimertinib was widely available as a second-line treatment option in patients with T790M-mediated acquired resistance to EGFR TKIs. Therefore, as it is estimated that 50–70% of patients treated with afatinib acquire the T790M mutation (24), the observation of widespread treatment beyond progression in this study probably does not reflect contemporary treatment practices, especially as tumor re-biopsies at the point of radiological progression are becoming more commonplace (25). In patients who acquire the T790M mutation, treatment with osimertinib should not be delayed. Nevertheless, in patients with *EGFR*m+ NSCLC and no obvious targeted second-line treatment options after failure of afatinib, continuing treatment beyond radiological progression could be an appropriate strategy in the absence of clinical deterioration.

Limited data are available to guide treatment choices in older patients with NSCLC, which can be complicated by age-related factors such as comorbidities and polypharmacy (26). Consistent with previous studies (26), afatinib appeared to be generally effective, and tolerable, in the elderly patients included in this analysis. Indeed, when using an age cut-off of 65 years, outcomes were actually slightly improved in older compared to younger patients, which is consistent with accumulating evidence that

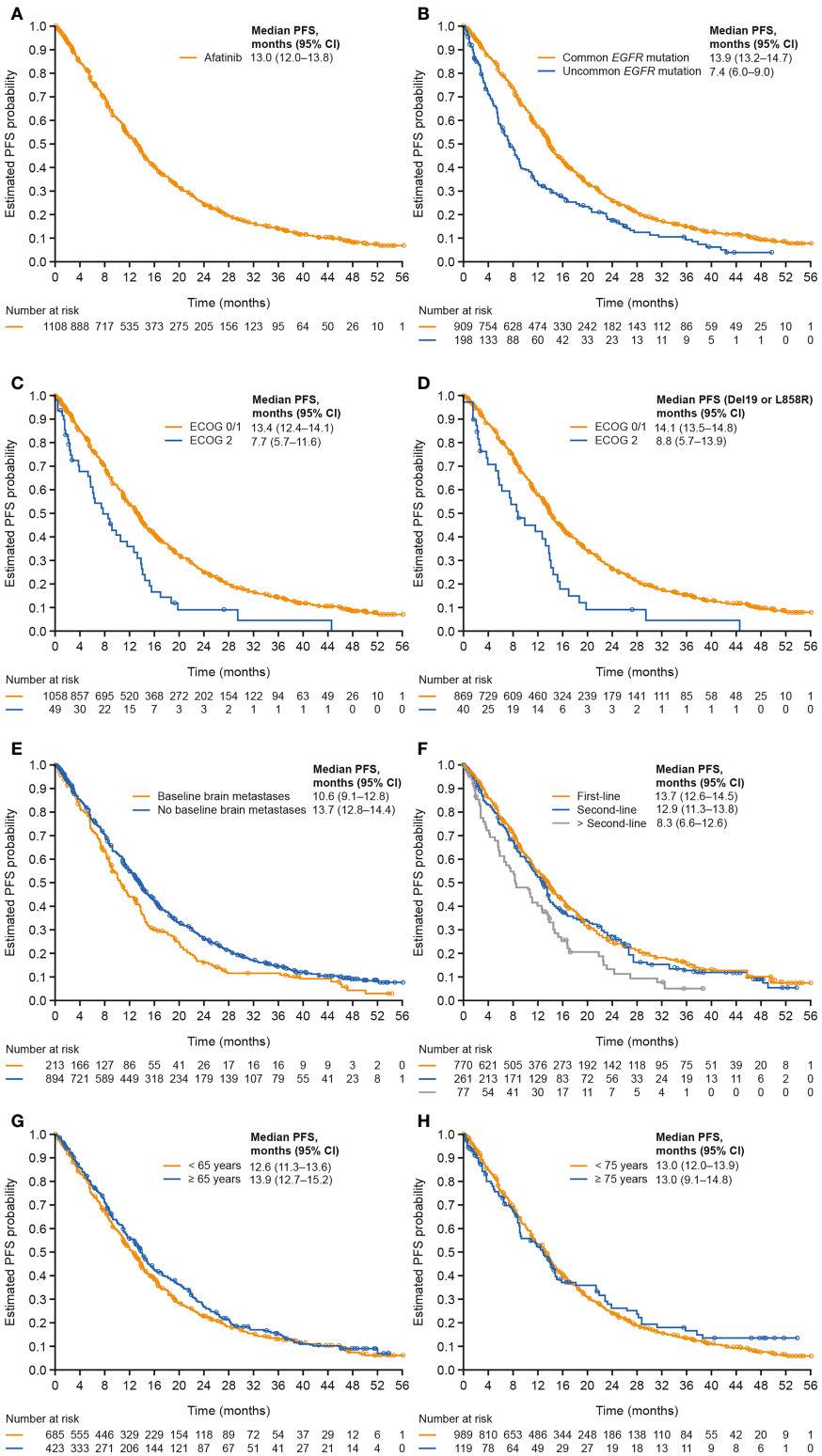


**FIGURE 1** | PFS in **(A)** all patients, **(B)** patients with tumors harboring common versus uncommon mutations, **(C)** patients with ECOG PS 0/1 versus 2, **(D)** patients with common mutations and ECOG PS 0/1 versus 2, **(E)** patients with versus without baseline brain metastases, **(F)** patients treated with afatinib in first, second and later lines of therapy, **(G)** patients aged <65 or ≥65 years, and **(H)** patients aged <75 or ≥75 years. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival.

**TABLE 4** | Baseline demographics and disease characteristics according to the type of uncommon *EGFR* mutation.

| Characteristic | T790M (n = 8) | Exon 20 (n = 36) | Major (n = 62) | Compound (n = 12) | Compound with major (n = 8) | Other (n = 5) |
|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | |
| Female | 3 (37.5) | 22 (61.1) | 31 (50.0) | 8 (66.7) | 5 (62.5) | 4 (80.0) |
| Race, n (%) | | | | | | |
| Asian | 1 (12.5) | 3 (8.3) | 41 (66.1) | 8 (66.7) | 6 (75.0) | 0 |
| White | 7 (87.5) | 33 (91.7) | 20 (32.3) | 4 (33.3) | 2 (25.0) | 5 (100) |
| Other[†] | 0 | 0 | 1 (1.6) | 0 | 0 | 0 |
| Prior lines of therapy | | | | | | |
| First | 6 (75.0) | 23 (63.9) | 43 (69.4) | 6 (50.0) | 5 (62.5) | 3 (60.0) |
| Second | 1 (12.5) | 6 (16.7) | 18 (29.0) | 6 (50.0) | 3 (37.5) | 1 (20.0) |
| Third | 0 | 5 (13.9) | 1 (1.6) | 0 | 0 | 1 (20.0) |
| ≥Fourth | 1 (12.5) | 2 (5.6) | 0 | 0 | 0 | 0 |
| Baseline ECOG PS, n (%) | | | | | | |
| 0 | 3 (37.5) | 15 (41.7) | 16 (25.8) | 3 (25.0) | 3 (37.5) | 1 (20.0) |
| 1 | 4 (50.0) | 9 (25.0) | 42 (67.7) | 8 (66.7) | 4 (50.0) | 4 (80.0) |
| 2 | 1 (12.5) | 1 (2.8) | 4 (6.5) | 1 (8.3) | 1 (12.5) | 0 |
| Missing | 0 | 1 (2.8) | 0 | 0 | 0 | 0 |
| Baseline brain metastases,[‡] n (%) | 0 | 8 (22.2) | 11 (17.7) | 1 (8.3) | 1 (12.5) | 1 (20.0) |

*ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor. [†]other: One Black/African American. [‡]Asymptomatic.*

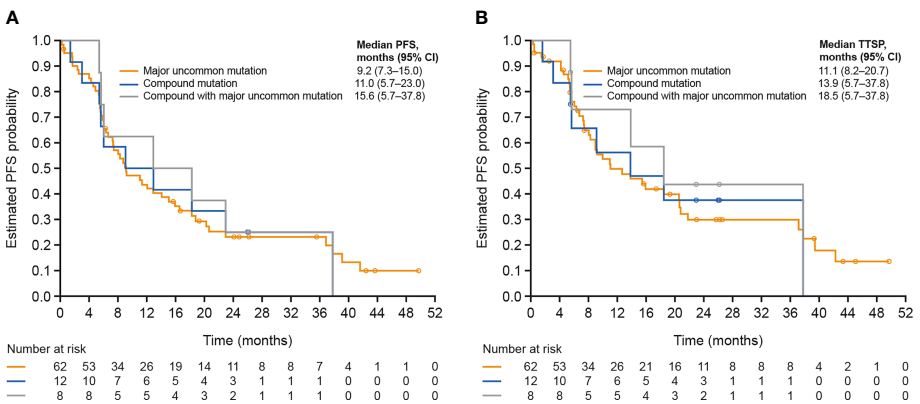


**FIGURE 2** | **(A)** PFS and **(B)** TTSP according to type of uncommon *EGFR* mutation. CI, confidence interval; EGFR, epidermal growth factor receptor; PFS, progression-free survival; TTSP, time to symptomatic progression.

EGFR TKIs may actually be more effective in prolonging PFS in older patients compared with younger patients (27, 28). We found that poor performance status (ECOG PS ≥2) was associated with worse efficacy outcomes with afatinib than in patients with ECOG PS 0/1; however, this analysis was based on only 4.4% of the patient population with ECOG PS 2, therefore limiting robust analysis of these findings. These findings illustrate that chronological age alone should not determine the choice of treatment in elderly patients with NSCLC, and that biological age is more relevant for predicting treatment efficacy and safety.

Patients with *EGFR*m+ NSCLC are particularly susceptible to developing brain metastases, both at diagnosis and during the disease course (15, 29). Consistent with previous studies (18, 30), the efficacy and safety of afatinib was not affected by the presence of stable brain metastases. Other studies have indicated that afatinib can cross the blood-brain-barrier, is active against symptomatic brain metastases and mitigates the risk of CNS progression (15, 31). Overall, therefore, afatinib appears to be a treatment option in patients with CNS involvement or at risk of CNS progression.

Consistent with previous findings (32, 33), this analysis demonstrated that afatinib was effective against 'major' uncommon mutations (G719, L761, and S768) and compound mutations. Contrary to results demonstrated in a previous study (34), efficacy was observed with afatinib across all treatment lines, including in patients with previous chemotherapy or EGFR TKI failure. Afatinib was also active in some patients with tumors harboring exon 20 insertions or 'other' *EGFR* mutations; however, novel therapies including mobocertinib (35), poziotinib (36) and the recently approved amivantamab (37) have shown promising activity in early phase clinical trials in tumors harboring exon 20 insertions, and may prove to be more effective for this subgroup of patients. Nevertheless, while new

effective treatment options are becoming available, it is unclear whether all exon 20 insertion mutations respond to amivantamab and other agents. More detailed data are therefore required to assess the sensitivity of individual mutations but it may be that EGFR TKIs could be an option in a subset of this highly heterogeneous group.

This broad activity reflects preclinical findings showing that many uncommon *EGFR* mutations, including compound and very rare mutations, are sensitive to afatinib (38). The finding that compound *EGFR* mutations (where an EGFR-TKI sensitizing or other mutation is identified together with a mutation of unknown clinical significance) (39) are particularly sensitive to treatment with afatinib is notable, as these mutations are identified in up to one quarter of *EGFR* mutation-positive NSCLC tumors and are associated with poor prognosis (39–41). Our findings suggest that afatinib may be considered as a treatment option if a compound mutation is detected, particularly for compound mutations that include a major mutation.

This study had several limitations. Its open-label design means that the results should be interpreted with caution, particularly regarding the impact of afatinib on survival outcomes. Additionally, next-generation sequencing was unavailable for all samples, therefore limiting the scope of analysis for known negative predictive factors such as concurrent non-*EGFR* co-mutations and the effect of allele frequency (42, 43). Furthermore, all radiological assessments and *EGFR* mutation detection were performed locally according to the methodology used at each participating institution. Finally, exploratory subgroup analyses were conducted post-hoc, meaning that no formal statistical comparisons could be conducted, thus limiting the strength of the conclusions

In summary, the safety and efficacy results from this combined analysis of three large phase IIIb studies are generally consistent with findings from subanalyses of previous RCTs and real-world studies of afatinib in *EGFR*m+ NSCLC. Afatinib was tolerable and demonstrated encouraging efficacy across different patient subgroups, including patients with brain metastases and those with tumors harboring uncommon *EGFR* mutations.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

All studies were approved by the Institutional Review Board or Independent Ethics Committee of each participating center, and were carried out in accordance with the Declaration of Helsinki, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and local laws. This is not a primary study but a pooled analysis of previous studies. All patients provided written, informed consent.

## AUTHOR CONTRIBUTIONS

APa: Formal analysis, investigation, resources, and manuscript writing. FdM: Formal analysis, investigation, resources, and manuscript writing. H-YT: Investigation and manuscript writing (review and editing). KKL: Formal analysis, investigation, resources, and manuscript writing (review and editing). JF: Investigation and manuscript writing (review and editing). APo: Formal analysis, investigation, resources, and manuscript writing (review and editing). JZ: Investigation and manuscript writing (review and editing). EHT: Investigation and manuscript writing (review and editing). MG: Manuscript writing (review and editing). VL: Conceptualization, methodology, validation, investigation, resources, and manuscript writing (original draft, review, and editing). DK: Formal analysis, investigation, data curation and manuscript writing (original draft, review, and editing). CY: Investigation and manuscript writing (review and editing). BS: Investigation and manuscript writing (review and editing). LC: Manuscript writing (review and editing). TJ: Investigation and manuscript writing (review and editing). DCLH: Investigation and manuscript writing (review and editing). AC: Conceptualization, methodology and manuscript writing (original draft, review, and editing). KP: Formal analysis, investigation, resources, and manuscript writing. Y-LW: Formal analysis, investigation, resources, and manuscript writing. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.709877/full#supplementary-material

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