Lung Cancer 152 (2021) 127–134

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Afatinib in EGFR TKI-naïve patients with locally advanced or metastatic *EGFR* mutation-positive non-small cell lung cancer: Interim analysis of a Phase 3b study

Filippo de Marinis [a,*], Konstantin K. Laktionov [b], Artem Poltoratskiy [c], Inna Egorova [d], Maximilian Hochmair [e], Antonio Passaro [a], Maria Rita Migliorino [f], Giulio Metro [g], Maya Gottfried [h], Daphne Tsoi [i], Gyula Ostoros [j], Simona Rizzato [k], Guzel Z. Mukhametshina [l], Michael Schumacher [m], Silvia Novello [n], Rafal Dziadziuszko [o], Wenbo Tang [p], Laura Clementi [q], Agnieszka Cseh [r], Dariusz Kowalski [s]

[a] *European Institute of Oncology IRCCS, Milan, Italy*
[b] *Federal State Budgetary Institution "N.N.Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russia*
[c] *Petrov Research Institute of Oncology, St Petersburg, Russia*
[d] *Clinical Oncology Dispensary, St Petersburg, Russia*
[e] *Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Vienna, Austria*
[f] *San Camillo-Forlanini Hospital, Rome, Italy*
[g] *Santa Maria della Misericordia Hospital, Perugia, Italy*
[h] *Tel Aviv University, Tel Aviv, Israel*
[i] *St John of God Murdoch Hospital, Murdoch, WA, Australia*
[j] *National Korányi Institute for Pulmonology, Budapest, Hungary*
[k] *Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy*
[l] *Ministry of Health of the Republic of Tatarstan, Kazan, Russia*
[m] *Ordensklinikum Elisabethinen, Linz, Austria*
[n] *University of Turin, AOU San Luigi, Orbassano, Italy*
[o] *Medical University of Gdansk, Gdansk, Poland*
[p] *Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA*
[q] *Boehringer Ingelheim Italia S.p.A., Milan, Italy*
[r] *Boehringer Ingelheim International, Ingelheim, Germany*
[s] *Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

ARTICLE INFO

Keywords:
Afatinib
Safety
EGFR mutation
EGFR TKI-naïve
NSCLC

ABSTRACT

Objectives: Randomized controlled trials have demonstrated that afatinib is a suitable treatment option for patients with epidermal growth factor receptor mutation-positive (*EGFR*m +) non-small cell lung cancer (NSCLC). However, such studies often exclude patients treated in routine clinical practice. We report interim results from a Phase 3b, open-label, multicenter, single-arm, exploratory trial, in which afatinib was investigated in a real-world setting.

Materials and methods: Patients with *EGFR*m + tyrosine kinase inhibitor (TKI)-naïve NSCLC received afatinib 40 mg orally, once-daily, until disease progression, or voluntary withdrawal. Primary objective was safety.

Results: Overall, 479 patients received afatinib: median age 65 years, 8 % of patients had an ECOG performance status ≥ 2, 17 % had brain metastases, and 13 % had tumors containing uncommon mutations only. All but one patient (99.8 %) had an adverse event (AE). Treatment-related AEs (TRAEs; any/grade ≥ 3) occurred in 97 %/44 % of patients; most common were diarrhea (87 %/16 %) and rash (51 %/11 %). AEs leading to afatinib dose-reduction were reported in 258 patients (54 %), and 37 patients (8 %) discontinued treatment due to a TRAE. Objective response rate was 45.5 %, median duration of response was 14.1 months (95 % CI: 12.2–16.4). Overall median time to symptomatic progression and progression-free survival were 14.9 months (95 % CI: 13.8–17.6) and 13.4 months

* Corresponding author at: Filippo de Marinis, European Institute of Oncology IRCCS, Via G. Ripamonti 435, 20141 Milan, Italy.
E-mail address: Filippo.DeMarinis@ieo.it (F. de Marinis).

https://doi.org/10.1016/j.lungcan.2020.12.011
Received 15 September 2020; Received in revised form 7 December 2020; Accepted 12 December 2020
Available online 17 December 2020

(95 % CI: 11.8–14.5), respectively, in the overall population and 19.3 months (95 % CI: 15.6–21.8) and 15.9 months (95 % CI: 13.9–19.1) in patients with *EGFR* exon 19 deletions.
Conclusions: Afatinib administration in routine clinical practice was well tolerated with no new safety signals and demonstrated promising efficacy in patients with *EGFR*m + NSCLC. TRAEs were generally manageable with tolerability-guided dose reductions. Overall, these data independently support findings from randomized controlled trials of afatinib in *EGFR*m + NSCLC.

1. Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality globally, accounting for approximately 1.7 million deaths in 2018 [1]. Despite advances in the treatment of NSCLC in recent decades, current therapy options are still associated with poor survival [2]. Chemotherapy, the historical standard of care, typically delays NSCLC disease progression by only a few months and can be associated with considerable toxicity [3]. However, the identification of numerous oncogenic driver mutations in recent years has allowed the development of targeted therapies based on the molecular characteristics of individual tumor types. Immune checkpoint inhibitors are now the standard of care, either alone or with chemotherapy, in patients with tumors harboring no epidermal growth factor receptor (*EGFR*), *ALK*, or other molecular aberrations [4].

Up to 50 % of Asian [5] and 10–15 % of Caucasian patients [6] with NSCLC have tumors that harbor mutations in the *EGFR* gene [7]. The most common mutations within this gene are exon 19 deletions (Del19) and the L858R point mutation (L858R), which account for approximately 90 % of all *EGFR* mutations [8,9]. First-, second-, and third-generation EGFR tyrosine kinase inhibitors (TKIs) are available as first-line treatment options for patients with *EGFR* mutation-positive (*EGFR*m +) NSCLC tumors [10–14].

Unlike first-generation (erlotinib or gefitinib) EGFR TKIs, second-generation (afatinib and dacomitinib) ErbB family inhibitors bind irreversibly to EGFR, ErbB2 and ErbB4, and block transphosphorylation of ErbB3 to inhibit all ErbB family signaling [15,16]. Randomized controlled trials (RCTs) have demonstrated that second and third-generation EGFR TKIs have improved efficacy, compared with first-generation TKIs in this setting [17–19]. In Phase 3 RCTs (LUX-Lung 3 and 6) [20], treatment with afatinib resulted in a significant improvement in overall survival (OS) vs chemotherapy in patients whose tumors harbored Del19 mutations (LUX-Lung 3: 33.3 vs 21.1 months; LUX-Lung 6: 31.4 vs 18.4 months) [21]. Furthermore, treatment with afatinib, compared with treatment with standard chemotherapy, improved PFS in the overall population (LUX-Lung 3: median: 11.1 vs 6.9 months, HR: 0.58; LUX-Lung 6; median: 11.0 vs 5.6 months, HR: 0.28), including those with uncommon mutations [22]. In the randomized Phase 2b LUX-Lung 7 trial [19], afatinib significantly improved progression-free survival (PFS; median: 11.0 vs 10.9 months, HR: 0.73, p = 0.017), objective response rate (ORR; 70 % vs 56 %, odds ratio 1.873, p = 0.0083) and time-to-treatment failure (TTF; median: 13.7 vs 11.5 months, HR: 0.73, $p = 0.0073$) compared with gefitinib in patients with Del19/L858R *EGFR*m + NSCLC. However, no significant difference in OS was observed with afatinib vs gefitinib (27.9 vs 24.5 months; HR: 0.86, p = 0.26) [23]. Across these RCTs, patients treated with afatinib experienced EGFR TKI class-related toxicities (diarrhea, rash/acne, stomatitis, nail effects), which were successfully managed with tolerability-guided dose reductions [19,20].

RCTs are conducted with strict inclusion criteria that often exclude patients with certain characteristics commonly observed in the routine clinical practice (real-world), such as older age, brain metastases, uncommon mutations, prior chemotherapy treatment, or Eastern Cooperative Oncology Group performance status (ECOG PS) $\geq$ 2. Real-world studies, which include patients with a range of characteristics, including those excluded from clinical trials, can generate additional data to help clinicians make evidence-based treatment decisions for a wider range of patients than traditional RCTs. This is particularly important as the treatment landscape for *EGFR*m + NSCLC evolves, with greater focus on determining the optimal treatment sequence [24].

The current study is a real-world study of afatinib in patients with *EGFR*m + NSCLC. The aim was to evaluate the safety and efficacy of afatinib in EGFR TKI-naïve patients with locally advanced or metastatic NSCLC harboring *EGFR* mutation(s), who are reflective of everyday clinical practice. We present here an interim analysis, conducted 4 years after recruitment was completed.

2. Materials and methods

2.1. Study design

This is a Phase 3b, open-label, multicenter, single-arm, exploratory trial of afatinib in EGFR TKI-naïve patients with locally advanced or metastatic *EGFR*m + NSCLC. The trial was conducted at 119 sites within Europe, Australia, Russia and Israel (see Supplementary material A for all enrolling countries). The protocol was updated after recruitment was completed to specify that an interim analysis could be conducted once patient recruitment was complete. The study was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant Boehringer Ingelheim Standard Operating Procedures (SOPs). Patients were required to give written informed consent, prior to admission into the trial.

The study is registered at Clinical trials.gov number NCT01853826 and the European Union Clinical Trials register EudraCT number 2009-017661-34.

2.2. Patients and treatment

The study enrolled patients (aged $\geq$ 18 years) with histologically confirmed, locally advanced or metastatic *EGFR*m + (locally assessed) NSCLC, with an ECOG PS of $\leq$ 2, adequate organ function and no prior use of EGFR TKI treatment. Patients were excluded if they had received anti-cancer treatment within 2 weeks prior to start of trial treatment, or had symptomatic brain metastases. All *EGFR* mutation types were permitted (see Supplementary material B for additional criteria).

Patients received oral afatinib 40 mg, once-daily, until disease progression, lack of tolerability or other reasons necessitating withdrawal. Study treatment could be continued beyond radiological progression only (without symptomatic progression) until clinical progression, if it was deemed in the patient's benefit following a careful risk-benefit assessment and confirmation of clinical benefit by the investigator. Treatment-related adverse events (TRAEs) were managed by tolerability-guided dose modifications. In the event of any drug related AE of grade $\geq$ 3, or persistent grade 2 diarrhea, or grade $\geq$ 2 renal dysfunction, treatment was paused until the patient recovered to grade $\leq$ 1 or baseline, before treatment was resumed with dose reduction of 10 mg decrements. If the patient could not tolerate 20 mg/day, or the patient did not recover to grade $\leq$ 1 or baseline within 6 weeks, treatment was discontinued. Concomitant therapies, including anesthetic agents, vitamins, homeopathic/herbal remedies and nutritional supplements, were allowed and were recorded from the date of informed consent to the follow-up visit.

2.3. Endpoints and assessments

The primary objective was to evaluate safety. Primary endpoints included AEs, coded according to Medical Dictionary for Drug Regulatory Activities (MedDRA version 21.0) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, evaluated by investigator assessment. Safety evaluation visits were conducted after administration, and every 28 (-7/+2) days until withdrawal. The secondary objective was to determine the efficacy of afatinib. Secondary endpoints included: time to symptomatic progression (TTSP; defined as the time from first administration of afatinib to the date of first documented clinically significant symptomatic progression [symptoms get worse or disease spreads to other parts of the body]), PFS, ORR and duration of response, disease control rate (DCR) and duration of disease control, as judged by the investigator. 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).

EGFR mutations were detected according to the *EGFR* mutation testing methodology used in each participating institution.

2.4. Statistical analyses

All patients who received at least one dose of afatinib (treated set) were included in the safety and efficacy analyses. Subgroup analysis of TTSP and PFS was conducted according to ECOG PS, brain metastases at baseline (presence/absence), line of therapy and *EGFR* mutation type (Del19/L858R/uncommon). Descriptive statistics are presented; no hypotheses testing was planned, and all analyses were exploratory.

3. Results

3.1. Patients, disposition, and treatment exposure

At data cut-off for the interim analysis (30th July 2018), 479 patients had received afatinib. Patient baseline characteristics are shown in Table 1. Most patients were Caucasian (97 %) and the median age was 65 years (range: 25–89) with 50 % of patients aged ≥ 65 years. An ECOG PS of 2 was reported in 36 (8 %) patients and 83 (17 %) patients had brain metastases. The most common histological classification was adenocarcinoma in 95 % of patients. In total, 416 (87 %) had NSCLC harboring common *EGFR* mutations, and 62 (13 %) patients had tumors containing uncommon mutations only, the most frequent of which were insertions in *EGFR* exon 20, which were detected in 37 of 62 (60 %) of these tumors. Afatinib was most commonly used as a first-line therapy (78 %) and 126 (26 %) patients had previously received systemic chemotherapy.

Overall, 452 (94 %) patients discontinued treatment; the most common reason for treatment discontinuation was progressive disease in 331 (69 %; Fig. 1) patients. The median duration of treatment across all lines of afatinib was 11.8 months (range: 0.07–55.4 months).

Table 1
Baseline demographics and disease characteristics.

Characteristic	Afatinib (n = 479)
Sex, n (%)	
Female	314 (65.6)
Median age, years (range)	65 (25–89)
≥ 65 years, n (%)	241 (50.3)
≥ 75 years, n (%)	92 (19.2)
Race, n (%)	
White	465 (97.1)
Asian	10 (2.1)
Other[a]	4 (0.8)
Smoking status, n (%)	
Never smoked	305 (63.7)
Ex-smoker	143 (29.9)
Current smoker	31 (6.5)
Baseline ECOG PS, n (%)	
0	171 (35.7)
1	271 (56.6)
2	36 (7.5)
Missing	1 (0.2)
Histological classification, n (%)	
Predominantly adenocarcinoma	457 (95.4)
Predominantly squamous cell carcinoma	7 (1.5)
Large cell/undifferentiated carcinoma	9 (1.9)
Missing	3 (0.6)
Not otherwise specified	3 (0.6)
Clinical stage at diagnosis, n (%)	
I–II	49 (10.2)
IIIA	39 (8.1)
IIIB	33 (6.9)
IV	357 (74.5)
Missing	1 (0.2)
Prior lines of therapy	
First	374 (78.1)
Second	81 (16.9)
Third	18 (3.8)
≥ Fourth	6 (1.3)
EGFR mutation category, n (%)	
Exon 19 deletions only[b]	232 (48.4)
L858R only[b]	162 (33.8)
Any uncommon[c]	84 (17.5)
Exon 20 insertions[d]	37 (7.7)
G719S, G719A, G719C[d]	12 (2.5)
T790M[d]	12 (2.5)
L861Q[d]	10 (2.1)
S768I[d]	9 (1.9)
Other[d]	18 (3.8)
Number of metastatic sites, n (%)	
0	17 (3.5)
1	121 (25.3)
2	136 (28.4)
≥ 3	204 (42.6)
Missing	1 (0.2)
Metastases at screening, n (%)	
Brain	83 (17.3)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.
[a] Other: 1 Native Hawaiian or other Pacific Islander; 3 Black/African American.
[b] Del19 or L858R mutations only (i.e., no uncommon mutations).
[c] Uncommon *EGFR* mutations with/without common mutations.
[d] Patients can appear in more than one mutation category.

3.2. Efficacy

3.2.1. TTSP (overall and by subgroup)

The overall median TTSP was 14.9 months (95 % CI: 13.8–17.6; Fig. 2A). Median TTSP was numerically longer in patients with no baseline brain metastases (15.8 months) compared with those with brain metastases at baseline (13.7 months; Fig. 2B). Median TTSP was also numerically longer in patients with an ECOG PS of 0 or 1 (15.8 months) compared with an ECOG PS of 2 (8.9 months; Fig. 2B); in patients receiving afatinib as first-line (15.6 months) or second-line therapy (14.7 months) compared with those receiving ≥ third-line afatinib (8.1 months; Fig. 2B); and in those whose tumors harbored common *EGFR* mutations Del19 only (19.3 months) and L858R only (14.5 months), compared with those whose tumors contained uncommon mutations (7.4 months; Fig. 2B). TTSP was similar regardless of age.

3.2.2. PFS (overall and by subgroup)

The overall median PFS was 13.4 months (95 % CI: 11.8–14.5; Fig. 3A). Median PFS was numerically longer in patients who had no baseline brain metastases (13.9 months), in comparison with those with brain metastases at baseline (10.1 months; Fig. 3B). Median PFS was also longer in patients with an ECOG PS of 0/1 (13.8 months) compared with those with an ECOG PS of 2 (6.2 months; Fig. 3B); in patients receiving afatinib as first-line (13.8 months) and second-line therapy (13.2

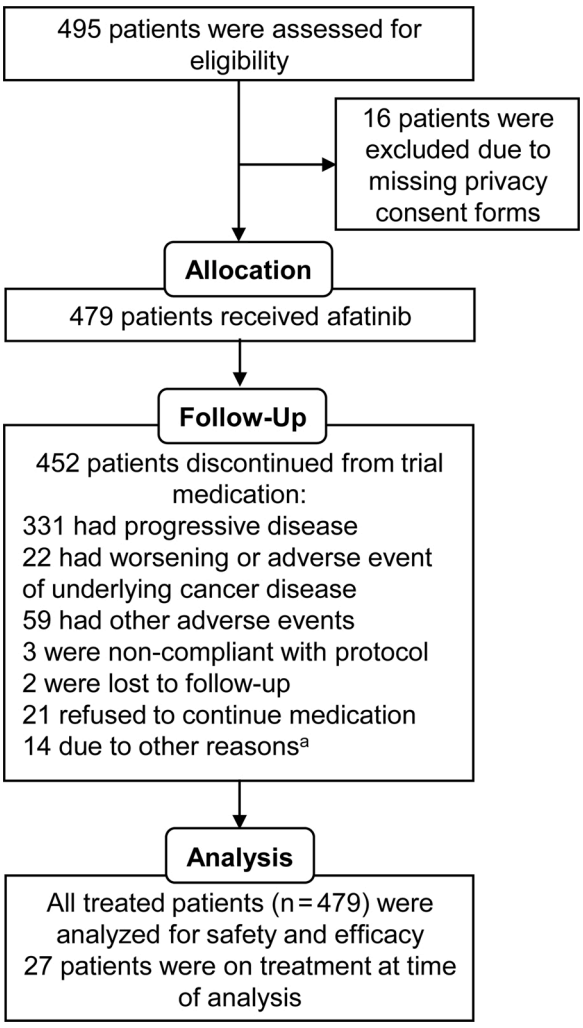

Fig. 1. Patient flow diagram. [a]4 switched to commercial drug; 3 due to investigator's decision; 3 withdrew consent; 3 had a protocol violation,1 required prohibited concomitant treatment.

months) compared to those receiving afatinib as ≥ third-line therapy (6.6 months; Fig. 3B); and in those patients whose tumors harbored the common *EGFR* mutations, Del 19 (15.9 months) and L858R (13.1 months) compared with those whose tumors contained uncommon mutations (6.0 months; Fig. 3B). PFS was similar regardless of age.

3.2.3. ORR and DCR (overall and by subgroup)

Overall, 218 of 479 patients (45.5 %) demonstrated an objective tumor response to afatinib (complete response: 25 [5.2 %]; partial response: 193 [40.3 %]; stable disease: 193 [40.3 %]; progressive disease: 34 [7.1 %]; not evaluable: 23 [4.8 %]; missing: 11 [2.3 %]). Median duration of response was 14.1 months (95 % CI: 12.2–16.4).

ORR was highest in patients receiving afatinib as an earlier line of therapy either as first-line (49.2 %) or second-line (37.0 %) compared with ≥ third-line afatinib therapy (16.7 %; Table 2); however, the median duration of response was lower in these patients: 13.8 months and 15.7 months as first- or second-line therapy compared with 20.2 months as ≥ third-line therapy (Table 2). ORR was higher and median duration of response was longer in patients whose tumors harbored common *EGFR* mutations only, Del19 (52.6 % and 16.9 months) and L858R (43.8 % and 13.2 months), compared with those whose tumors harbored uncommon *EGFR* mutations (28.6 % and 9.3 months; Table 2).

In the overall population, the DCR was 85.8 % (411/479 patients) and median duration of disease control was 14.7 months (95 % CI: 13.6–16.1).

DCR was higher in patients receiving afatinib as first-line therapy (86.6 %), than in those receiving afatinib as a third-line therapy (79.2 %; Table 2); additionally, median duration of disease control was longer in the patients receiving afatinib as first line therapy (15.0 and 8.1 months; Table 2). However, there were no marked differences in DCR and median duration of disease control between patients receiving afatinib as a first- or second-line therapy (Table 2).

DCRs were higher and median duration of disease control was longer in patients with tumors harboring common mutations, Del19 (90.1 % and 17.7 months) L858R (85.2 % and 14.4 months) in comparison with those whose tumors harbored uncommon mutations (75.0 % and 8.1 months; Table 2).

DCR and ORR were similar between patients with and without brain metastases (Table 2).

3.3. Safety and tolerability

Most patients (478/479) experienced an AE and grade ≥ 3 AEs were reported in 315 patients (66 %).

Any grade TRAEs and grade ≥ 3 TRAEs were recorded in 462 (97 %) and 210 (44 %) patients, respectively (Table 3). The most frequently reported (≥ 10 %) any grade TRAEs were diarrhea (87 %), rash (51 %), paronychia (30 %), mucosal inflammation (18 %), dry skin (17 %), stomatitis (14 %), skin fissures (11 %), nausea (10 %), dermatitis acneiform (10 %), and conjunctivitis (10 %). Overall, 8 patients had a grade 4 TRAE (dehydration 1; diarrhea 5; fatigue 1; electrolyte imbalance 1). There were two afatinib-related deaths, (grade 5 TRAE) one pneumonitis and one intestinal infarction; the intestinal infarction may have been caused by either mesenteric embolism or gastrointestinal perforation.

Serious AEs (SAEs) were reported in 202 (42 %) patients; the most common were diarrhea and pleural effusion in 16 patients each (3 %), whilst 39 (8 %) patients had a treatment-related SAE, the most common being diarrhea in 15 (3 %) patients.

AEs leading to dose reduction of afatinib were reported in 258 (54 %) of patients. Dose reductions to 30 mg occurred in 258 (54 %) patients, and further dose reductions to 20 mg occurred in 87 (18 %) patients. The most frequent AEs leading to dose reduction included diarrhea in 119 (25 %) patients, and rash in 53 (11 %) patients. AEs leading to discontinuation of afatinib were reported in 105 (22 %) patients, of whom 37 (8 %) patients experienced TRAEs leading to drug discontinuation; the most frequent was diarrhea in 16 patients (3 %). Sixty-nine (14 %) patients had a SAE that resulted in death; the most common cause was malignant neoplasm (6 %).

4. Discussion

This was an interim analysis of a Phase 3b, open-label, exploratory trial of afatinib in EGFR TKI-naïve patients with locally advanced or metastatic *EGFR*m + NSCLC. The incidence and severity of AEs reported were consistent with the known profile of afatinib in *EGFR*m + NSCLC, as observed in the LUX-Lung trials [19,20].

Treatment with afatinib resulted in TTSP and PFS times of over 1 year, with a particularly notable benefit observed among certain patient subgroups. The high proportion of patients with tumors harboring *EGFR* exon 20 insertions (60 % of patients with tumors harboring uncommon mutations) may at least partly account for the lower PFS and TTSP observed in the uncommon mutation subgroup, compared with the common mutation groups. As with all EGFR TKIs [25], exon 20 insertions are generally insensitive to afatinib. In a pooled analysis of the LUX-Lung 2, 3 and 6 trials, the response rate in patients with exon 20 insertions (n = 23) was 9% [26]. However, the response rates in patients with the major uncommon mutations, G719X (n = 18; 78 %), L861Q (n = 16; 56 %) and S768I (n = 8; 100 %) were comparable to those typically observed in patients with common *EGFR* mutations.

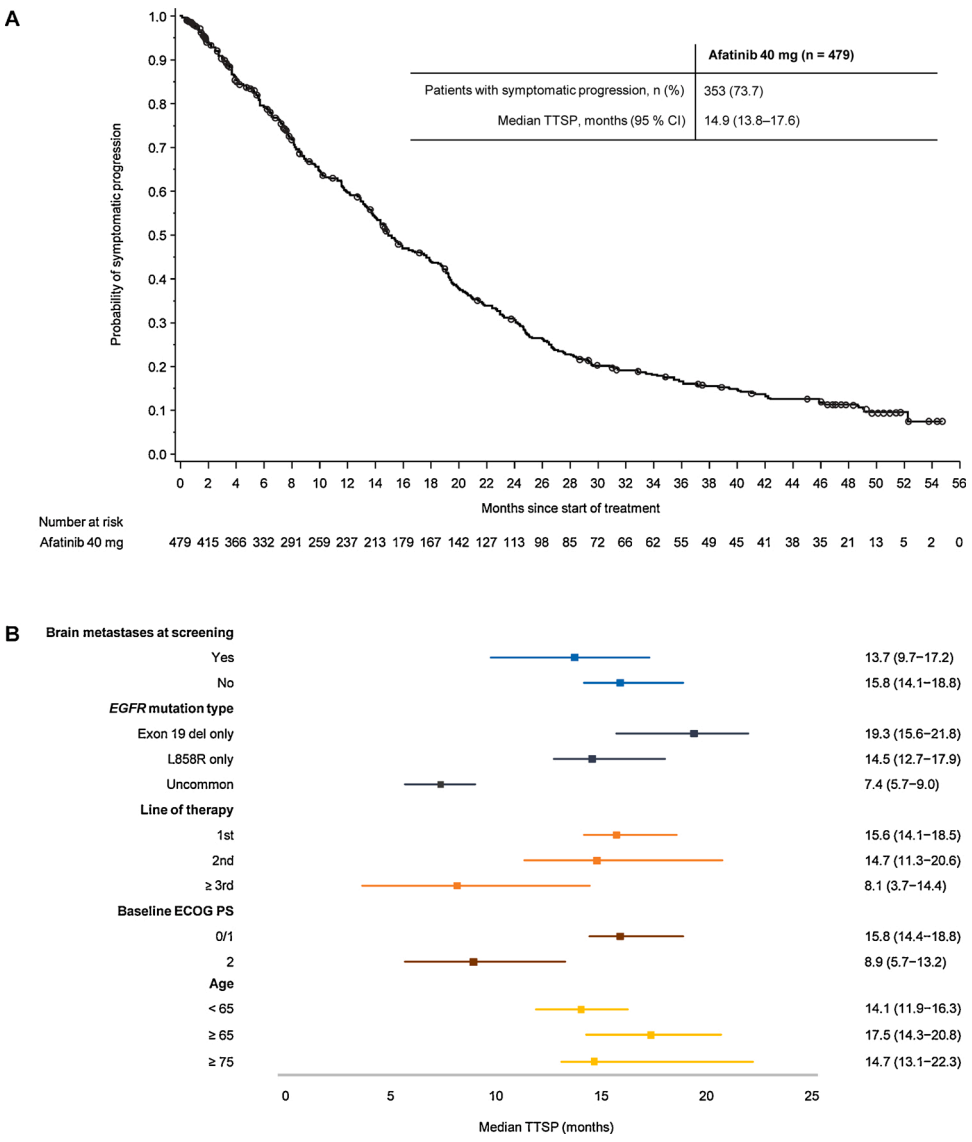

Fig. 2. TTSP **A)** in all patients (Kaplan–Meier analysis) and **B)** according to patient subgroups (forest plot). Abbreviations: CI, confidence interval; TTSP, time to symptomatic progression. Median, 95 % CI, 25th and 75th percentiles are calculated from unadjusted Kaplan–Meier estimates.

ORR and DCR results, overall and across certain subgroups, were similarly encouraging, and consistent with findings from previous trials. ORR was higher in patients with NSCLC harboring common *EGFR* mutations, lower ECOG PS and those receiving afatinib as an earlier line of therapy.

Few TRAEs led to discontinuation of afatinib, indicating these events were generally tolerable and manageable. While 54 % of patients had AEs leading to dose reduction, 22 % of patients discontinued treatment due to AEs, and only 8% specifically due to TRAEs. The proportion of patients who discontinued due to TRAEs was similar to that observed in LUX-Lung 3, 6 and 7 trials (8 %, 6 % and 6 %, respectively). These data support the previous findings from LUX-Lung 3, 6 and 7 that afatinib TRAEs are largely manageable through tolerability-guided dose reduction, permitting patients to remain on treatment for as long as possible. It has previously been reported that dose reduction does not reduce efficacy, as shown by sub-analyses of the LUX-Lung 3, 6 and 7 studies [27,28]. In addition, these results are generally supported by data from real-world studies conducted to date including the observational RealGiDo study, assessing afatinib dose adjustment [29]. The key strength of the current study is that many patients had characteristics that are often seen in routine clinical practice, but that may preclude enrolment in randomized controlled trials (including older age, comorbidities, baseline ECOG PS 2, brain metastases, tumors harboring uncommon *EGFR* mutations). Such studies are becoming more common [26], and gaining increasing recognition as a means of expanding clinical experience in broad populations that are more reflective of patients encountered in everyday clinical practice. Key real-world studies of afatinib treatment for *EGFR*m + NSCLC are summarized in a recent review by Park and Yang [26] and include: the observational RealGiDo study [29] which reported that dose adjustment of afatinib did not affect efficacy and the GioTag study [30,31] which reported that sequential afatinib and osimertinib treatment facilitates prolonged, chemotherapy-free treatment.

In this study, afatinib had a predictable and manageable safety profile in a patient population that is typically encountered in routine clinical practice. Interim efficacy findings were also encouraging, with a median PFS and TTSP of > 1 year. However, some limitations should be noted; this trial was a single arm study, without a control arm, and patient numbers in some subgroups were small.

Overall, the safety and efficacy results from this large Phase 3b study independently support findings from previous randomized controlled trials of afatinib in *EGFR*m + NSCLC, including the LUX-Lung 3/6/7 trials and other real-world studies. Further, ongoing studies of afatinib

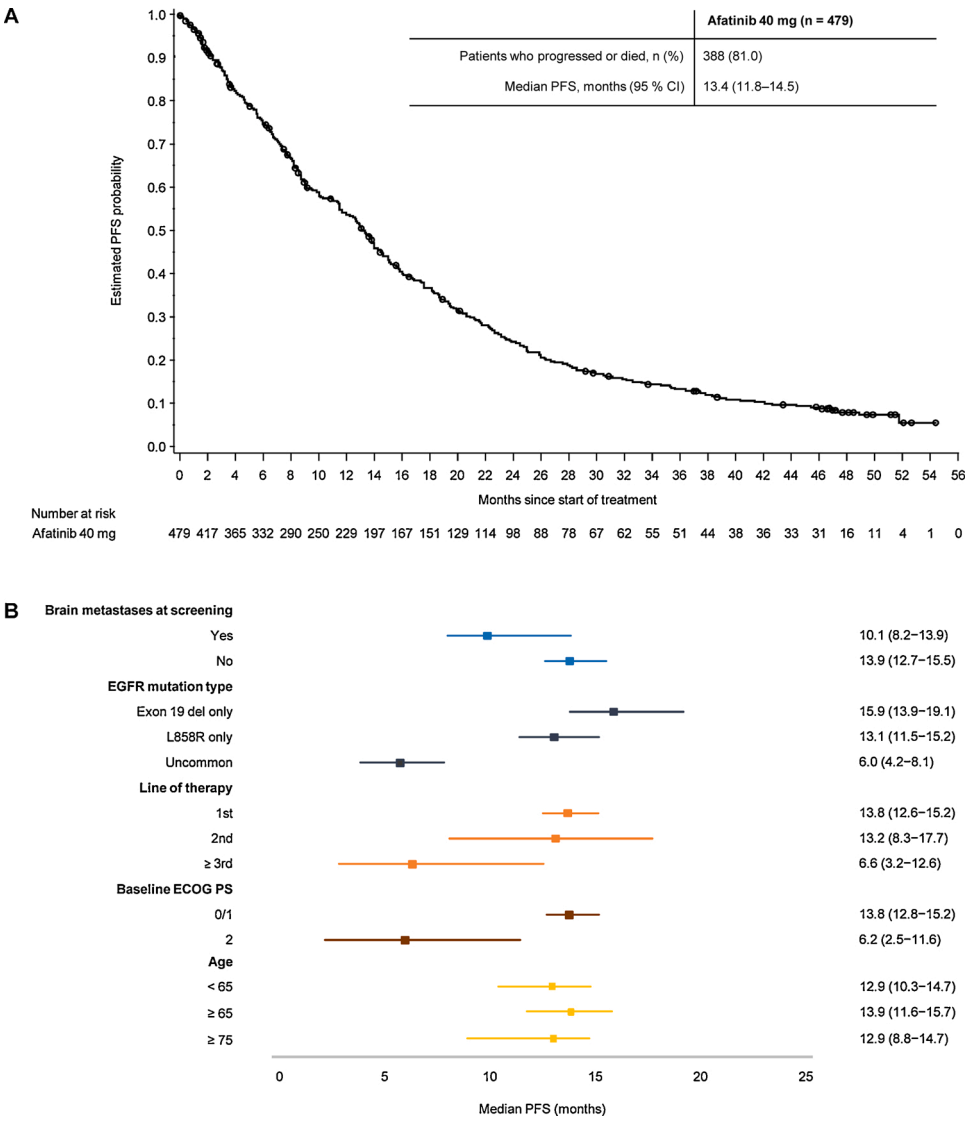

Fig. 3. PFS **A)** in all patients (Kaplan–Meier analysis), and **B)** according to patient subgroups (forest plot). Abbreviations: CI, confidence interval; PFS, progression-free survival. Median, 95 % CI, 25th and 75th percentiles are calculated from unadjusted Kaplan–Meier estimates.

in routine clinical practice populations, such as the ongoing Phase 3b study among EGFR TKI-naïve Asian patients (NCT01953913) and the Phase 4 study among chemotherapy pre-treated patients (NCT02208843) will help inform clinicians further.

Funding

This work was supported by Boehringer Ingelheim Inc. The study sponsor participated in the design of the studies, the collection, analysis, and interpretation of the data, writing this article, and the decision to submit the article for publication.

Data sharing statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical Study Reports and Related Clinical Documents can be requested via this link: https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html. All such requests will be governed by a Document Sharing Agreement. Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be

Table 2
Tumor response in patient subgroups.

	ORR n (%)	Median duration of objective response, months (95 % CI)	DCR n (%)	Median duration of disease control, months (95 % CI)
Line of therapy				
First	184 (49.2)	13.8 (11.7–16.1)	324 (86.6)	15.0 (13.7–16.8)
Second	30 (37.0)	15.7 (10.4–21.0)	68 (84.0)	15.1 (11.6–20.7)
≥ Third	4 (16.7)	20.2 (5.0–29.7)	19 (79.2)	8.1 (5.7–15.2)
EGFR mutation category				
Del19 only	122 (52.6)	16.9 (13.0–20.1)	209 (90.1)	17.7 (14.7–20.4)
L858R only	71 (43.8)	13.2 (11.1–16.4)	138 (85.2)	14.4 (12.9–17.3)
Uncommon	24 (28.6)	9.3 (5.6–12.5)	63 (75.0)	8.1 (6.0–9.0)
Brain metastases at screening				
Yes	40 (48.2)	11.1 (7.4–16.8)	71 (85.5)	11.6 (8.8–15.1)
No	178 (45.1)	15.0 (12.9–17.1)	339 (85.8)	15.2 (13.9–17.7)
Baseline ECOG PS,				
0/1	205 (46.4)	15.0 (12.3–16.9)	385 (87.1)	15.2 (13.9–17.5)
2	13 (36.1)	8.3 (5.0–14.1)	25 (69.4)	9.1 (5.7–13.9)
Age,				
<75	189 (48.8)	14.1 (11.7–16.2)	340 (87.9)	15.1 (13.6–16.8)
≥75	29 (31.5)	16.5 (10.6–21.2)	71 (77.2)	14.1 (11.6–21.4)

Abbreviations: CI, confidence interval; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ORR, objective response rate.
Data are n (%).

extended upon request. Researchers should use https://trials.boehringer-ingelheim.com to request access to study data.

Transparency document

The Transparency document associated with this article can be found in the online version.

CRediT authorship contribution statement

Filippo de Marinis: Conceptualization, Supervision, Writing - review & editing. **Konstantin K. Laktionov:** Formal analysis, Investigation, Resources, Writing - review & editing. **Artem Poltoratskiy:** Formal analysis, Investigation, Resources, Writing - review & editing. **Inna Egorova:** Formal analysis, Investigation, Resources, Writing - review & editing. **Maximilian Hochmair:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Data curation, Visualization, Supervision, Project administration, Writing - original draft, Writing - review & editing. **Antonio Passaro:** Supervision, Writing - review & editing. **Maria Rita Migliorino:** Visualization, Writing - review & editing. **Giulio Metro:** Investigation, Resources, Writing - review & editing. **Maya Gottfried:** Writing - review & editing. **Daphne Tsoi:** Investigation, Resources, Writing - review & editing. **Gyula Ostoros:** Conceptualization, Writing - review & editing. **Simona Rizzato:** Investigation, Writing - review & editing. **Guzel Z. Mukhametshina:** Conceptualization, Investigation, Writing - review & editing. **Michael Schumacher:** Resources, Writing - review & editing. **Silvia Novello:** Writing - review & editing. **Rafal Dziadziuszko:** Data curation, Writing - review & editing. **Wenbo Tang:** Methodology, Software, Validation, Formal analysis, Data curation, Writing - review & editing. **Laura Clementi:** Project administration, Writing - review & editing. **Agnieszka Cseh:** Conceptualization, Methodology, Supervision, Project administration, Writing - original draft, Writing - review & editing. **Dariusz Kowalski:** Investigation, Resources, Writing - review & editing.

Table 3
Frequency of treatment-related AEs, all grades and grade ≥ 3 occurring in ≥ 5 % of patients of the treated population (n = 479).

AE, n (%)	All grades	Grade ≥ 3
Any TRAE	462 (96.5)	210 (43.8)
Diarrhea	416 (86.8)	77 (16.1)
Rash	246 (51.4)	51 (10.6)
Paronychia	142 (29.6)	17 (3.5)
Mucosal inflammation	85 (18.2)	12 (2.5)
Dry skin	79 (16.5)	1 (0.2)
Stomatitis	67 (14.0)	8 (1.7)
Skin fissures	51 (10.6)	3 (0.6)
Nausea	50 (10.4)	5 (1.0)
Conjunctivitis	50 (10.4)	3 (0.6)
Dermatitis acneiform	49 (10.2)	8 (1.7)
Pruritus	46 (9.6)	1 (0.2)
Asthenia	43 (9.0)	14 (2.9)
Decreased appetite	39 (8.1)	3 (0.6)
Vomiting	38 (7.9)	5 (1.0)
Fatigue	37 (7.7)	8 (1.7)
Rash papular	34 (7.1)	3 (0.6)
Skin toxicity	31 (6.5)	7 (1.5)
Nail disorder	29 (6.1)	4 (0.8)
Alopecia	26 (5.4)	0

Abbreviations: AE, adverse event; TRAE, treatment-related adverse events.
Percentages are calculated using total number of patients (n = 479) as the denominator.

Declaration of Competing Interest

Konstantin K. Laktionov: membership on an advisory council and/or committee for Boehringer Ingelheim, Bristol Myers Squibb, MSD, Merck, Amgen, Roche, Takeda, and Pfizer; and receipt of grants and/or funds from Boehringer Ingelheim, Bristol Myers Squibb, MSD, Merck, Amgen, Roche, Takeda, and Pfizer. **Maximillian Hochmair:** membership on an advisory council or committee for Boehringer Ingelheim, Takeda, AstraZeneca, and Roche. **Antonio Passaro:** receipt of consulting fees from AstraZeneca, Bristol Myers Squibb, MSD, Roche, Eli Lilly, and Pfizer. **Maria Rita Migliorino:** member of the board of directors for Boehringer Ingelheim, Roche, and MSD; and honoraria from Pfizer, AstraZeneca, and Roche. **Michael Schumacher:** membership on an advisory board and consultancy for Boehringer Ingelheim, Roche, BMS, MSD, Merck, Amgen, Pfizer, AstraZeneca, Takeda. **Silvia Novello:** honoraria from AstraZeneca, Boehringer Ingelheim, MSD, Takeda, Pfizer, Bristol Myers Squibb, Roche, and Eli Lilly. **Rafal Dziadziuszko:** honoraria from Roche, AstraZeneca, Pfizer, MSD, SeattleGenetics, Takeda, and Novartis; receipt of consultant fees from PDC*line Pharma; and other financial relationships with Roche and AstraZeneca. **Wenbo Tang:** employment from Boehringer Ingelheim. **Laura Clementi:** employment from Boehringer Ingelheim Italia SpA. **Agnieszka Cseh:** employment from Boehringer Ingelheim International GmbH. **Dariusz Kowalski:** membership on an advisory board and consultancy for AstraZeneca, Boehringer Ingelheim, Roche, Amgen, Bristol Myers Squibb, Takeda, MSD, and Pfizer. The remaining authors declare no COIs.

Acknowledgements

This study was funded by Boehringer Ingelheim, Inc. Robert Lorence of Boehringer Ingelheim assisted in the study concept and design, and data analysis for this manuscript. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Hannah Simmons of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this manuscript.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, Am. Cancer Soc. 68 (6) (2018) 394–424, https://doi.org/10.3322/caac.21492.

[2] V. Hirsh, Next-generation covalent irreversible kinase inhibitors in NSCLC: focus on afatinib, BioDrugs. 29 (3) (2015) 167–183, https://doi.org/10.1007/s40259-015-0130-9.

[3] K. Hotta, Y. Fujiwara, K. Matsuo, T. Suzuki, K. Kiura, M. Tabata, N. Takigawa, H. Ueoka, M. Tanimoto, Recent improvement in the survival of patients with advanced nonsmall cell lung cancer enrolled in phase III trials of first-line, systemic chemotherapy, Cancer 109 (5) (2007) 939–948, https://doi.org/10.1002/cncr.22478.

[4] D.S. Ettinger, D.L. Aisner, D.E. Wood, W. Akerley, J. Bauman, J.Y. Chang, L. R. Chirieac, T.A. D'Amico, T.J. Dilling, M. Dobelbower, R. Govindan, M.A. Gubens, M. Hennon, L. Horn, R.P. Lackner, M. Lanuti, T.A. Leal, R. Lilenbaum, J. Lin, B. W. Loo, R. Martins, G.A. Otterson, S.P. Patel, K. Reckamp, G.J. Riely, S.E. Schild, T. A. Shapiro, J. Stevenson, S.J. Swanson, K. Tauer, S.C. Yang, K. Gregory, M. Hughes, NCCN guidelines insights: non-small cell lung cancer, Version 5.2018, J. Natl. Compr. Canc. Netw. 16 (7) (2018) 807–821, https://doi.org/10.6004/jnccn.2018.0062.

[5] Y. Shi, J.S. Au, S. Thongprasert, S. Srinivasan, C.M. Tsai, M.T. Khoa, K. Heeroma, Y. Itoh, G. Cornelio, P.C. Yang, A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER), J. Thorac. Oncol. 9 (2) (2014) 154–162, https://doi.org/10.1097/jto.0000000000000033.

[6] S.P. D'Angelo, M.C. Pietanza, M.L. Johnson, G.J. Riely, V.A. Miller, C.S. Sima, M. F. Zakowski, V.W. Rusch, M. Ladanyi, M.G. Kris, Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas, J. Clin. Oncol. 29 (15) (2011) 2066–2070, https://doi.org/10.1200/jco.2010.32.6181.

[7] T. Zhang, B. Wan, Y. Zhao, C. Li, H. Liu, T. Lv, P. Zhan, Y. Song, Treatment of uncommon EGFR mutations in non-small cell lung cancer: new evidence and treatment, Transl. Lung Cancer Res. 8 (3) (2019) 302–316, https://doi.org/10.21037/tlcr.2019.04.12.

[8] H. Shigematsu, L. Lin, T. Takahashi, M. Nomura, M. Suzuki, I.I. Wistuba, K. M. Fong, H. Lee, S. Toyooka, N. Shimizu, T. Fujisawa, Z. Feng, J.A. Roth, J. Herz, J. D. Minna, A.F. Gazdar, Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers, J. Natl. Cancer Inst. 97 (5) (2005) 339–346, https://doi.org/10.1093/jnci/dji055.

[9] P.C. Hsu, D.M. Jablons, C.T. Yang, L. You, Epidermal growth factor receptor (EGFR) pathway, yes-associated protein (YAP) and the regulation of programmed death-ligand 1 (PD-L1) in non-small cell lung cancer (NSCLC), Int. J. Mol. Sci. 20 (15) (2019) 3821, https://doi.org/10.3390/ijms20153821.

[10] Boehringer Ingelheim, GILOTRIF® (afatinib) Tablets, for Oral Use. Prescribing Information, 2019. Available at: https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Gilotrif/Gilotrif.pdf.

[11] FDA, TAGRISSO® (Osimertinib) Tablets, for Oral Use. Prescribing Information, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208065s008lbl.pdf.

[12] FDA, VIZIMPRO® (Dacomitinib) Tablets, for Oral Use. Prescribing Information, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211288s000lbl.pdf.

[13] FDA, IRESSA (Gefitinib) Tablets for Oral Use. Prescribing Information, 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206995s003lbl.pdf.

[14] FDA, TARCEVA (Erlotinib) Tablets, for Oral Use. Prescribing Information, 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf.

[15] D.A. Cross, S.E. Ashton, S. Ghiorghiu, C. Eberlein, C.A. Nebhan, P.J. Spitzler, J. P. Orme, M.R. Finlay, R.A. Ward, M.J. Mellor, G. Hughes, A. Rahi, V.N. Jacobs, M. Red Brewer, E. Ichihara, J. Sun, H. Jin, P. Ballard, K. Al-Kadhimi, R. Rowlinson, T. Klinowska, G.H. Richmond, M. Cantarini, D.W. Kim, M.R. Ranson, W. Pao, AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer, Cancer Discov. 4 (9) (2014) 1046–1061, https://doi.org/10.1158/2159-8290.Cd-14-0337.

[16] R. Shah, J.F. Lester, Tyrosine kinase inhibitors for the treatment of EGFR mutation-positive non-small-cell lung cancer: a clash of the generations, Clin. Lung Cancer 21 (3) (2020) e216–e228, https://doi.org/10.1016/j.cllc.2019.12.003.

[17] Y.L. Wu, Y. Cheng, X. Zhou, K.H. Lee, K. Nakagawa, S. Niho, F. Tsuji, R. Linke, R. Rosell, J. Corral, M.R. Migliorino, A. Pluzanski, E.I. Sbar, T. Wang, J.L. White, S. Nadanaciva, R. Sandin, T.S. Mok, Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial, Lancet Oncol. 18 (11) (2017) 1454–1466, https://doi.org/10.1016/s1470-2045(17)30608-3.

[18] J.C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K. H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.C. Su, J.E. Gray, S.M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, S.S. Ramalingam, Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer, N. Engl. J. Med. 378 (2) (2018) 113–125, https://doi.org/10.1056/NEJMoa1713137.

[19] K. Park, E.H. Tan, K. O'Byrne, L. Zhang, M. Boyer, T. Mok, V. Hirsh, J.C. Yang, K. H. Lee, S. Lu, Y. Shi, S.W. Kim, J. Laskin, D.W. Kim, C.D. Arvis, K. Kölbeck, S. A. Laurie, C.M. Tsai, M. Shahidi, M. Kim, D. Massey, V. Zazulina, L. Paz-Ares, Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial, Lancet Oncol. 17 (5) (2016) 577–589, https://doi.org/10.1016/s1470-2045(16)30033-x.

[20] J.C. Yang, Y.L. Wu, M. Schuler, M. Sebastian, S. Popat, N. Yamamoto, C. Zhou, C. P. Hu, K. O'Byrne, J. Feng, S. Lu, Y. Huang, S.L. Geater, K.Y. Lee, C.M. Tsai, V. Gorbunova, V. Hirsh, J. Bennouna, S. Orlov, T. Mok, M. Boyer, W.C. Su, K. H. Lee, T. Kato, D. Massey, M. Shahidi, V. Zazulina, L.V. Sequist, Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials, Lancet Oncol. 16 (2) (2015) 141–151, https://doi.org/10.1016/s1470-2045(14)71173-8.

[21] J.C. Yang, L.V. Sequist, S.L. Geater, C.M. Tsai, T.S. Mok, M. Schuler, N. Yamamoto, C.J. Yu, S.H. Ou, C. Zhou, D. Massey, V. Zazulina, Y.L. Wu, Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6, Lancet Oncol. 16 (7) (2015) 830–838, https://doi.org/10.1016/s1470-2045(15)00026-1.

[22] N. Sharma, S. Graziano, Overview of the LUX-Lung clinical trial program of afatinib for non-small cell lung cancer, Cancer Treat. Rev. 69 (2018) 143–151, https://doi.org/10.1016/j.ctrv.2018.06.018.

[23] L. Paz-Ares, E.H. Tan, K. O'Byrne, L. Zhang, V. Hirsh, M. Boyer, J.C. Yang, T. Mok, K.H. Lee, S. Lu, Y. Shi, D.H. Lee, J. Laskin, D.W. Kim, S.A. Laurie, K. Kölbeck, J. Fan, N. Dodd, A. Märten, K. Park, Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial, Ann. Oncol. 28 (2) (2017) 270–277, https://doi.org/10.1093/annonc/mdw611.

[24] M.J. Hochmair, A. Buder, S. Schwab, O.C. Burghuber, H. Prosch, W. Hilbe, A. Cseh, R. Fritz, M. Filipits, Liquid-biopsy-based identification of EGFR T790M mutation-mediated resistance to afatinib treatment in patients with advanced EGFR mutation-positive NSCLC, and subsequent response to osimertinib, Target. Oncol. 14 (1) (2019) 75–83, https://doi.org/10.1007/s11523-018-0612-z.

[25] Y. Kobayashi, T. Mitsudomi, Not all epidermal growth factor receptor mutations in lung cancer are created equal: perspectives for individualized treatment strategy, Cancer Sci. 107 (9) (2016) 1179–1186, https://doi.org/10.1111/cas.12996.

[26] K. Park, D. Wan-Teck Lim, I. Okamoto, J.C. Yang, First-line afatinib for the treatment of EGFR mutation-positive non-small-cell lung cancer in the' real-world' clinical setting, Ther. Adv. Med. Oncol. 11 (2019), https://doi.org/10.1177/1758835919836374.

[27] M. Schuler, E.H. Tan, K. O'Byrne, L. Zhang, M. Boyer, T. Mok, V. Hirsh, J.C. Yang, K.H. Lee, S. Lu, Y. Shi, S.W. Kim, J. Laskin, D.W. Kim, C.D. Arvis, K. Kölbeck, D. Massey, A. Märten, L. Paz-Ares, K. Park, First-line afatinib vs gefitinib for patients with EGFR mutation-positive NSCLC (LUX-Lung 7): impact of afatinib dose adjustment and analysis of mode of initial progression for patients who continued treatment beyond progression, J. Cancer Res. Clin. Oncol. 145 (6) (2019) 1569–1579, https://doi.org/10.1007/s00432-019-02862-x.

[28] J.C. Yang, L.V. Sequist, C. Zhou, M. Schuler, S.L. Geater, T. Mok, C.P. Hu, N. Yamamoto, J. Feng, K. O'Byrne, S. Lu, V. Hirsh, Y. Huang, M. Sebastian, I. Okamoto, N. Dickgreber, R. Shah, A. Märten, D. Massey, S. Wind, Y.L. Wu, Effect of dose adjustment on the safety and efficacy of afatinib for EGFR mutation-positive lung adenocarcinoma: post hoc analyses of the randomized LUX-Lung 3 and 6 trials, Ann. Oncol. 27 (11) (2016) 2103–2110, https://doi.org/10.1093/annonc/mdw322.

[29] B. Halmos, E.-H. Tan, M.K. Lee, P. Foucher, T.-C. Hsia, M.J. Hochmair, F. Griesinger, T. Hida, E.S. Kim, B.L. Melosky, A. Maerten, E.C. Costa, Real-world dose adjustment study of first-line afatinib in pts with EGFR mutation-positive (EGFRm +) advanced NSCLC, J. Clin. Oncol. 36 (Suppl15) (2018), https://doi.org/10.1200/JCO.2018.36.15_suppl.e21060 e21060–e21060.

[30] M.J. Hochmair, A. Morabito, D. Hao, C.T. Yang, R.A. Soo, J.C. Yang, R. Gucalp, B. Halmos, L. Wang, A. Märten, T. Cufer, Sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: updated analysis of the observational GioTag study, Future Oncol. 15 (25) (2019) 2905–2914, https://doi.org/10.2217/fon-2019-0346.

[31] M.J. Hochmair, A. Morabito, D. Hao, C.-T. Yang, R.A. Soo, J.C.-H. Yang, R. Gucalp, B. Halmos, A. Märten, T. Cufer, Sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: final analysis of the GioTag study, Future Oncol. 16 (34) (2020) 2799–2808, https://doi.org/10.2217/fon-2020-0740.