

Clinical efficacy and safety of afatinib in the treatment of non-small-cell lung cancer in Chinese patients

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Abstract: Compared with various malignant tumors, lung cancer has high incidence and the highest mortality worldwide. Non-small-cell lung cancer (NSCLC), the most common kind of lung cancer, is still a great threat to the world, including China. Surgery, platinum-based chemotherapy, and radiotherapy are still the primary treatments for NSCLC patients in the clinic, whereas immunotherapy and targeted therapy are gradually playing more important roles. A next-generation tyrosine kinase inhibitor (TKI), afatinib, was developed as a targeted reagent for epidermal growth factor receptor (EGFR). This targeted drug was effective in a series of trials. The US Food and Drug Administration then approved afatinib as a new first-line treatment for EGFR L858R and exon 19 deletion mutant patients in 2013. This review focused on current clinical studies of afatinib. Although this TKI was not widely available in China until recently, we aim to provide a reference for its future use in China.

Keywords: afatinib, NSCLC, Chinese patients, drug resistance, side effect, companion diagnosis

Introduction

Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer (>80%),¹ which is still a leading cause of death among various cancers worldwide.² Malignant lung epithelial cells seem to be responsible for the two leading pathologies of NSCLC, namely adenocarcinoma and squamous cell carcinoma.³ In China, over 7,333,000 new lung cancer patients were diagnosed, and nearly 6,102,000 patients die of lung cancer each year.⁴ A suitable treatment is important to benefit a large number of Chinese NSCLC patients and relieve their suffering.

Surgery to remove the solid tumor and the nearby lymph nodes in early-stage NSCLC patients is an optimal choice.⁵ However, one challenge is that most NSCLC patients are diagnosed at an advanced stage where surgery is not suitable. It is well known that many patients benefited from chemotherapy.⁶ Recently, the immunotherapy and targeted therapy also showed unexpected potency in NSCLC patients with some special characteristics.^{7,8} For example, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) was proven to be much more effective in patients with mutant EGFR than traditional chemotherapy.^{9,10} In addition, trials for a second-generation TKI, afatinib, which was recently approved in China, show inspiring results. This review focuses on current studies of afatinib and discusses its efficacy and safety in Chinese NSCLC patients to facilitate its further use in China.



TKI and EGFR/HER2 in NSCLC

EGFR and human epidermal growth factor receptor 2 (HER2) are the most two important members of the ERBB receptor tyrosine kinase family (ERBB1–4).^{11,12} EGFR tyrosine kinase can be activated and can cause a series of effects when it is combined with its special ligands such as epidermal growth factor (EGF), epigen (EPG), and transforming growth factor- α (TGF- α).¹³ It has been reported that EGFR is overexpressed in some human carcinoma cell lines such as MDA and A431.¹⁴ Subsequent experiments showed that a high level of EGFR and HER2 expression may be a sign for cancers including NSCLC.^{15–17} HER2 is a half-functional receptor without the ability to bind other ligands; however, HER2 maintains the tyrosine kinase activity when heterodimerized with other receptors such as EGFR.¹¹ Some studies have indicated that patients with *HER2* mutations demonstrated phenotypes similar to those with *EGFR* mutations.^{18,19} There is evidence that both EGFR and HER2 can facilitate cancer cell survival during anticancer therapy.^{20–22} Many signal pathways such as the mitogen-activated protein kinase (MAPK) pathway have been involved in this intricate process.^{23,24} The MAPK pathway was found to play a critical role in cell growth²⁵ and was demonstrated to be an important downstream pathway of EGFR.²⁶ Another

significant pathway regulated by EGFR/HER2, which helps in the progression of cancer, is the phosphatidylinositol 3 kinase–serine/threonine kinase (PI3K–AKT) pathway,²⁷ a well-known pathway that has an important relationship with the occurrence of various cancers.²⁸ In recent years, research has shown that autophagy may be affected when the expression level of EGFR is abnormal.²⁹ Some evidence indicates that the EGFR may interfere in cancer processes through the regulation of expression levels of cancer-related proteins.³⁰ These evidences indicate that EGFR and HER2 play an important role in NSCLC through various pathways. The pathways associated with EGFR and HER2 are summarized in Figure 1.

To selectively target mutant EGFR in cancer patients, the first-generation TKI therapies, gefitinib and erlotinib, were developed.^{31,32} It was reported that first-generation TKI therapies showed a notable curative effect in patients with deletion mutations in exon 19 or L858R mutations in exon 21.⁹ However, secondary mutations such as T790M can severely hamper the efficacy of gefitinib and erlotinib in the TKI therapy process.³³ Researchers also wondered if the efficacy of the first-generation TKI could be improved by changing its reversible targeted characteristics.³⁴ These concerns prompted pharmacologists to develop a

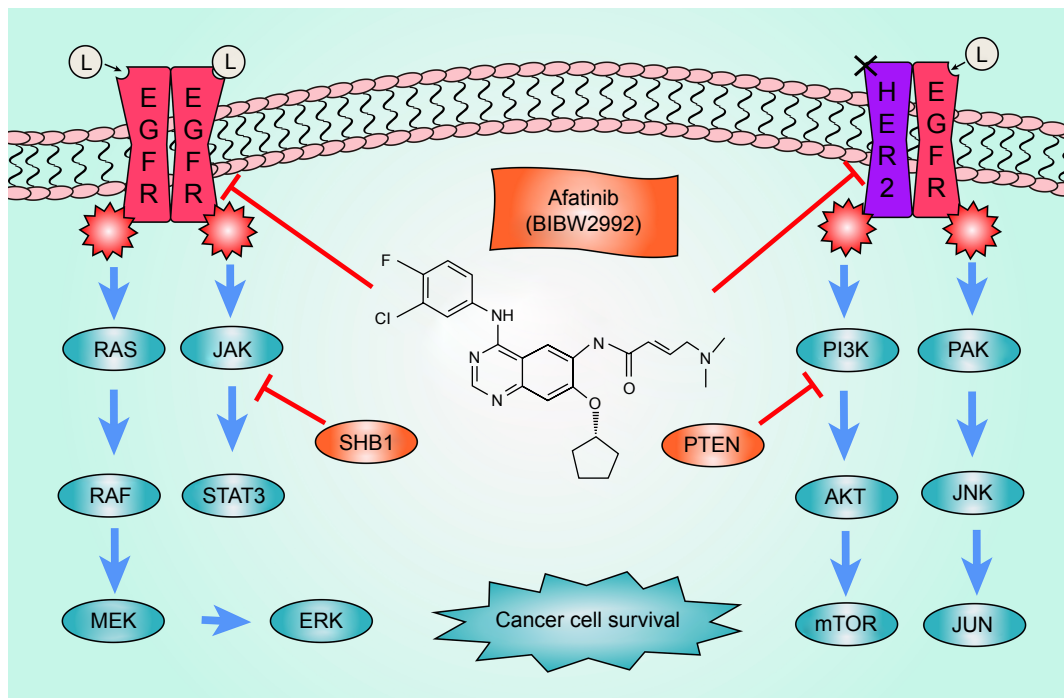


Figure 1 Signaling pathways of EGFR and HER2.

Notes: Pathways downstream of EGFR and HER2 are presented in this figure. Afatinib can inhibit these pathways which facilitate cancer cell survival through inhibiting EGFR and HER2 directly. L indicates the ligands that have the ability to activate the EGFR such as EGF and TGF- α .

Abbreviations: AKT, serine/threonine kinase; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PI3K, phosphatidylinositol 3 kinase; TGF- α , transforming growth factor- α .

new-generation TKI, which may be more effective than the first generation.

Afinib (BIBW2992) is an irreversible next-generation EGFR inhibitor that targets both EGFR and HER2³⁵ and is effective in NSCLC patients with first-generation TKI resistance.³⁶ The irreversible antagonism facilitates its anticancer activity compared with the first-generation TKI, although some studies revealed that T790M mutation can reduce the efficacy of irreversible TKI.³⁷ It is noted that the third-generation TKI therapies, osimertinib (AZD9291), rociletinib (CO1686), and olmutinib (HM61713), have been reported to be powerful for T790M-mutant EGFR patients.^{38–40} Once these new-generation TKIs are approved by China Food and Drug Administration (CFDA), they will be a good alternative to afinib in Chinese patients with T790M-mutant EGFR.⁴¹ Afinib can inhibit EGFR and HER2 through modifying the ATB-binding site cys797 (EGFR), cys805 (HER2), and cys803 (ERBB4) in covalent binding.³⁵ In vitro experiments showed that afinib is effective in reducing the phosphorylation levels of EGFR and suppressing the survival of cancer cell lines such as H1666 and HCC827.⁴² Xenograft models and clinical trials showed that afinib has a strong antitumor effect against NSCLC with a high expression of EGFR levels and was efficacious in EGFR L858R/T790M-mutant patients.^{43,44} These evidences

highlight the advantage of afinib compared with that of first-generation TKI drugs and demonstrate the effectiveness of afinib as a therapy for mutant EGFR NSCLC patients.

EGFR/HER2 mutation in Chinese NSCLC patients

As clinical trials have previously indicated, afinib is effective in EGFR-mutated patients and suggests that the frequency of mutant *EGFR* in NSCLC patients is a key factor in the utilization of afinib. It was reported that activation can be found only in tumor tissues and not in normal tissues of the same patient,⁴⁵ and these mutations were more familiar in non-smoking women.^{46,47} The frequency of EGFR mutations among different regions also varies, particularly between those from Asia and non-Asian regions.⁴⁸ It was reported that EGFR deletion in exon 19 or L858R in exon 21 accounted for over 85% of all EGFR mutant individuals,⁴⁹ indicating that afinib can benefit this large segment of NSCLC patients. The frequency of mutant *EGFR* in Chinese patients was over 30%,⁵⁰ whereas the frequency of mutant *EGFR* in White and Caucasian patients was ~10%.⁵¹ This difference indicates that afinib can benefit about one-third of the Chinese NSCLC patients with mutant EGFR. The mutation frequency of *EGFR* in NSCLC patients from different regions is listed in Table 1.

Table 1 EGFR mutation status in cancer patients all over the world

Region/country/ race	Sample size	EGFR state		Sensitive ratio ^a	M/F ^b	Year
		Mutant	Wild type			
Asia						
China						
Shi et al ⁵²	1,074	556 (51.8%)	518 (48.2%)	89.9%	NA ^c	2014
Hong et al ⁵³	1,160	392 (33.8%)	768 (66.2%)	100%	706/454	2014
Xie et al ⁵⁴	494	176 (35.6%)	318 (64.4%)	100%	334/160	2015
Malaysia						
Liam et al ⁵⁵	151	55 (36.4%)	96 (63.6%)	100%	87/64	2014
Japan						
Tomita et al ⁵⁶	184	91 (49.5%)	93 (50.5%)	100%	90/94	2014
America						
Latin America						
Arrieta et al ⁵⁷	1,150	382 (33.2%)	768 (66.8%)	100%	478/670	2011
North America						
Shiau et al ⁵⁸	2,169	446 (20.6%)	1,723 (79.4%)	100%	NA	2014
Europe						
Serbia						
Zaric et al ⁵⁹	360	42 (11.7%)	318 (88.3%)	100%	244/166	2014
Finland						
Maki-Nevala et al ⁶⁰	510	58 (11.4%)	452 (88.6%)	84.5%	269/241	2014
Caucasian						
Ramlau et al ⁶¹	1,785	247 (13.8%)	1,538 (86.2%)	89.1%	1,083/702	2015

Notes: ^aRatio of sensitizing EGFR mutations in all mutant individuals including mutation in exon 18, 19, or 21. ^bRatio of gender (male/female). ^cNA indicates that relative information was not mentioned in the original research paper.

Abbreviations: EGFR, epidermal growth factor receptor; F, female; M, male; NA, not applicable.

It is worth noting that HER2 is also reported to be a therapeutic target of afatinib.^{62,63} There are three kinds of abnormal HER2s, including overexpression of HER2 protein, amplification of the *HER2* gene, and mutation in the *HER2* gene.⁶⁴ *HER2* mutation was reported to be the driving mutation of NSCLC,⁶⁵ and afatinib is a good choice for patients with *HER2* mutations according to the National Comprehensive Cancer Network (NCCN) guideline.⁶⁶ However, unlike the EGFR mutation status, the mutation rate of HER2 in NSCLC is much lower (2%) and is similar between Chinese and non-Chinese patients.^{67–69} The rate of *HER2* amplification or overexpression in NSCLC is higher than the mutation rate,⁶⁴ but there are no clinical trials on the use of afatinib in HER2 amplification or overexpression in NSCLC patients to guide the use of afatinib for this segment of the population.

Efficacy and safety of afatinib in Chinese NSCLC patients

To investigate the efficacy and safety of afatinib in NSCLC patients, a series of clinical trials were carried out comparing its effectiveness with traditional chemotherapy and first-generation TKI therapy. Information about some important trials studying NSCLC and afatinib are listed in Table 2.^{70–77} In this review, trials for primarily Chinese populations are discussed in detail.

Efficacy

There have been many clinical trials of afatinib to evaluate its efficacy compared with that of traditional chemotherapy. The largest scale clinical trial of afatinib in a Chinese population (327 Chinese patients) was NCT01121393.⁷⁴ The 364 NSCLC patients were enrolled from 36 centers in China, Thailand, and South Korea. Control group was treated with gemcitabine and cisplatin (122 patients), whereas others (242 patients) were treated with afatinib. In this trial, the progression-free survival

(PFS) period and Response Evaluation Criteria in Solid Tumors (RECIST) assessment results were collected as the criteria to evaluate the efficacy of afatinib versus traditional chemotherapy. The clinical characteristics of these two groups were similar except for their Eastern Cooperative Oncology Group (ECOG) performance status ($p=0.004$, χ^2 test), which was worse in the afatinib group. All patients had mutant EGFR (Leu858Arg, exon 19 deletions, or others) in their tumor tissues.⁷⁴ The outcome of the therapeutic efficacy evaluation indicated that afatinib is more desirable for EGFR mutant patients, especially for patients mutated with Leu858Arg or exon 19 deletions. The median PFS period of the afatinib group was 13.7 months (95% confidence interval [CI], 11.5–13.9), while it was 5.6 months (95% CI, 0.19–0.36) in the gemcitabine and cisplatin group according to the investigators. Similar results were obtained for the RECIST assessment: 66.9% complete response (CR) + partial response (PR) patients in afatinib group and 23.0% in chemotherapy group according to the investigators.⁷⁴ Compared with clinical trials of afatinib and traditional chemotherapy all over the world, similar conclusions were drawn regarding the efficacy of afatinib not only as a first-line therapy but also as a second-line regimen.^{71,73} The median PFS periods of the afatinib group were 11.1 (first-line therapy) and 5.6 (second-line therapy) months, which were significantly higher than those of the chemotherapy group (6.8 months for first-line therapy and 2.9 months for second-line therapy). The RECIST assessment in the two global trials (NCT00949650 and NCT01085136) also demonstrated the superior performance of afatinib (Table 2). These results suggest that afatinib is more effective than platinum-based chemotherapies for EGFR-mutated patients including Chinese patients as both a first-line and second-line cancer therapy.

To compare the efficacy of afatinib with the first-generation TKI, more trials were selected for discussion in this review. NCT02625168 is a clinical trial under a compassionate use

Table 2 Clinical trials about afatinib

Trial information	Phase	Type ^a	Afatinib	Gefitinib	Erlotinib	Chemotherapy	Efficacy ^b	Safety ^c	References
NCT00525148	II	F	129	NA ^d	NA	NA	N	N	70
NCT00949650	III	F	230	NA	NA	115	+++	–	71
NCT00711594	II	S	62	NA	NA	NA	N	N	72
NCT01085136	III	S	134	NA	NA	68	+++	—	73
NCT01121393	III	F	242	NA	NA	122	+++	0	74
NCT01466660	IIb	F	160	159	NA	NA	+	–	75
NCT01523587	III	F	398	NA	397	NA	++	0	76
NCT02625168	II	S	25	NA	28	NA	+++	0	77

Notes: “F” means first-line therapy, while “S” means second-line therapy. “b+” means ratio of sensitivity rates >100%, “+++” means ratio of sensitivity rates >150%, “++++” means ratio of sensitivity rates >200%, and “N” means non-comparable (afatinib vs others). “0” means ratio of the most significant adverse rates <100%, “–” means ratio of the most significant adverse rates >100%, “—” means ratio of the most significant adverse rates >150%, and “N” means non-comparable (afatinib vs others, grade ≥3). “NA” refers the group with no patients or the incalculable ratio.

program that compares the efficacy between afatinib and erlotinib groups in Chinese NSCLC patients who failed in pre-therapy with first-generation TKI and chemotherapy.⁷⁷ Twenty-five patients were treated with afatinib, whereas 28 patients were treated with erlotinib. All patients had documented EGFR mutations including exon 18 and exon 19 mutations. More patients in the afatinib group were evaluated as having worse ECOG2 stages, whereas the other clinical characteristics were similar between the two groups. RECIST assessment and survival time were recorded in this trial to evaluate the efficacy of afatinib compared with that of erlotinib in Chinese NSCLC patients who received a less than ideal first-line TKI therapy. Although the objective response rate (ORR; CR + PR, 20% in afatinib group vs 7.1% in erlotinib group, $p=0.17$), the median PFS period (4.1 months in afatinib group vs 3.3 months in erlotinib group, $p=0.97$), and the median overall survival (OS; 10.3 months in afatinib group vs 10.8 months in erlotinib group, $p=0.51$) duration were similar between two groups, the disease control rate of the afatinib-treated group (CR + PR + stable disease = 68.0%) was significantly superior to that of the erlotinib group (39.3%) in all patients. In addition, the PFS period of the afatinib-treated group was significantly superior to that of the erlotinib group in patients aged 70 years or younger or for whom the time to progression for the first-generation TKI therapy was ≥ 18 months. The author also compared the efficacy of afatinib in this study with that in the LUX-Lung 1 clinical trial;⁷⁸ a similar outcome was obtained, indicating that the results were solid even though the sample size was limited in this trial. Two additional global trials (NCT01466660 and NCT01523587) also indicated that afatinib was more ideal for EGFR mutant patients in first-line and second-line antitumor therapies (Table 2). However, similar to the results of NCT02625168, the median PFS period of the afatinib-treated group was similar to the group treated with gefitinib in NCT01466660 (11.0 months in the afatinib group vs 10.9 months in the gefitinib group).⁷⁵ As a second-line regimen, the median PFS period of the afatinib-treated group was 2.4 months, whereas the median PFS period of the erlotinib-treated group was 1.9 months.⁷⁶

In addition to clinical trials conducted worldwide, a retrospective study conducted in Linkou Chang-Gung Memorial Hospital, Taiwan, indicated that compared with the first-generation TKI, afatinib is better for Chinese NSCLC patients as well. In this study, 448 patients who had EGFR-activating mutations were treated with three different kinds of TKI (gefitinib, 304 patients; erlotinib, 63 patients; and afatinib, 81 patients) as a first-line therapy in one hospital enrolled from February 16, 2011 to October 30, 2015.⁷⁹ The aim of

this study was to compare the efficacy among these three different TKI therapies. Similar to the NCT01466660 trial, this study showed that Chinese EGFR-mutated NSCLC patients can also benefit more from afatinib than gefitinib ($p<0.001$) when TKI was chosen as the first-line therapy regimen.⁷⁵ Consistent results were obtained in multivariable analysis (hazard ratio [HR], 0.51; 95% CI, 0.34–0.78). Although many limitations existed in this study, such as side effects that were not reported, it was obvious from this study that compared with gefitinib, afatinib is an effective first-line treatment for Chinese NSCLC patients with EGFR mutations. Another research study indicated that afatinib showed strong efficacy for adenocarcinoma patients with both EGFR and HER2 mutations in kinase domains; this is a potential advantage of afatinib over the first-generation TKI therapies.⁸⁰ We compared the efficacy between Chinese and non-Chinese patients; this result is shown in Figure 2A. A non-significant difference was observed.

Safety

Although the efficacy of afatinib is much better than that of traditional chemotherapy in EGFR mutant patients, the safety of afatinib is undoubtedly as important as its efficacy. Significantly higher frequencies of some adverse events including dyspnea, diarrhea, rashes, and acne were observed in afatinib group. On the other hand, afatinib may be safer due to its lower incidence of other adverse events. In NCT01121393, patients in the gemcitabine and cisplatin group showed a higher frequency of some adverse events, including vomiting, nausea, neutropenia, and leucopenia than patients in the afatinib group (Table 2). In addition, there were 21 patients (11.5%) who discontinued their afatinib therapy, whereas 45 (39.8%) patients discontinued their chemotherapy for intolerable adverse events in this study.⁷⁴ Furthermore, 23 afatinib patients (10.0%) and 17 chemotherapy patients (15.3%) discontinued their therapy for intolerable adverse events in NCT00949650.⁷¹ In NCT01085136, afatinib and paclitaxel were provided as a combined regimen. As a result, a larger proportion of patients (18.9%) discontinued their therapy for intolerable adverse events, whereas in the control group 6.8% of patients discontinued their chemotherapy.⁷³ Although these adverse reactions may be a shortcoming of afatinib, it is obvious that these trials successfully demonstrated the safety of afatinib compared with that of traditional platinum-based chemotherapy in Chinese NSCLC patients.

The efficacy of afatinib is superior to erlotinib (Table 2), but compared with erlotinib, afatinib resulted in more diarrhea events but less acneiform rash. Similar treatment interruption

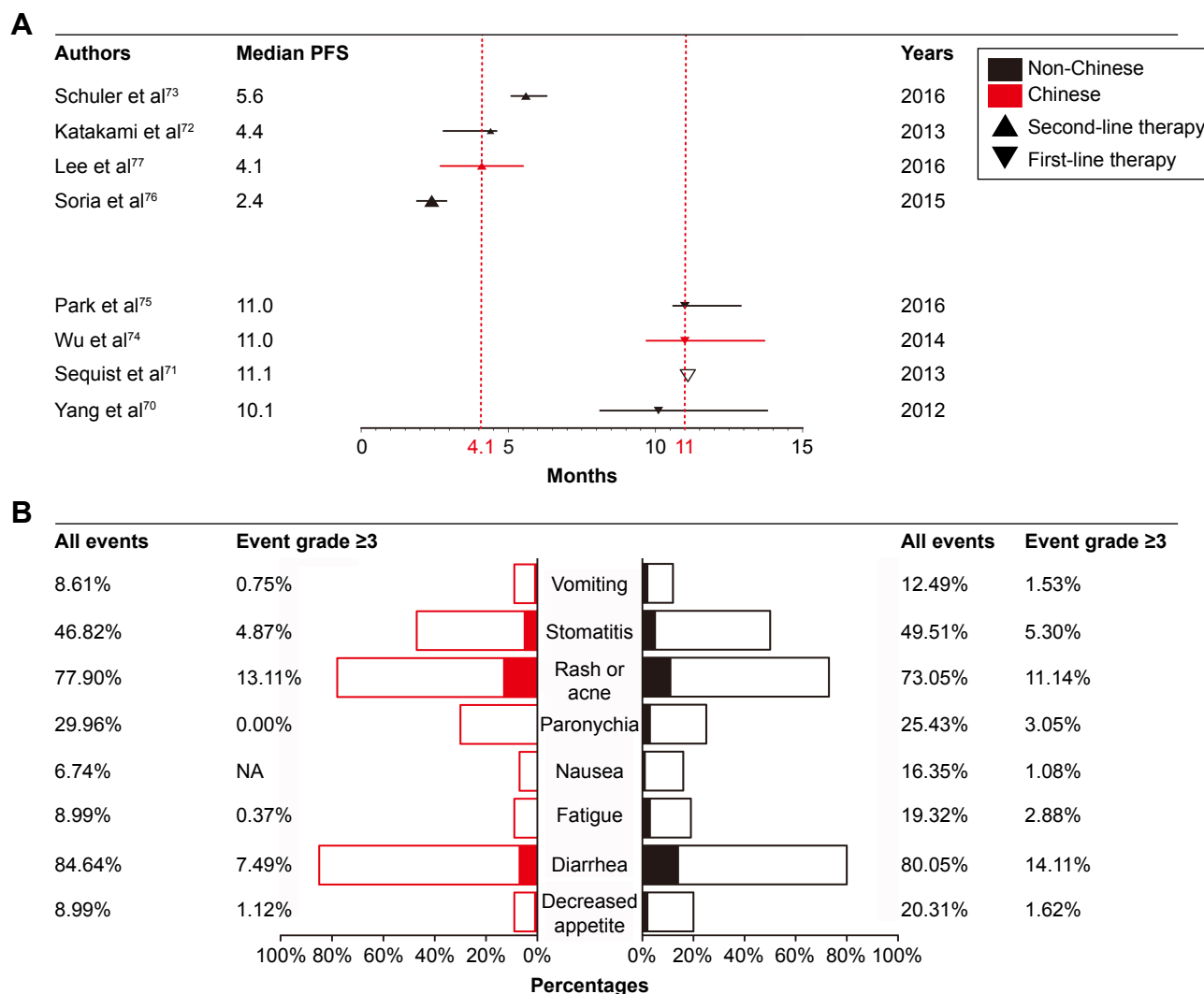


Figure 2 The difference of efficacy and safety between Chinese and non-Chinese patients.

Notes: Red refers to Chinese patients, whereas black refers to non-Chinese patients. **(A)** The PFS period of Chinese and non-Chinese NSCLC patients are presented. The hollow triangle indicates data without 95% CI value. **(B)** The adverse events rate in Chinese and non-Chinese NSCLC patients are presented.

Abbreviations: CI, confidence interval; NA, not applicable; NSCLC, non-small-cell lung cancer; PFS, progression-free survival.

rates (28% in the afatinib group vs 28.6% in the erlotinib group, $p=0.96$) and the rate of patients with dose reductions (24.0% in the afatinib group vs 17.9% in the erlotinib group, $p=0.58$) were obtained in the two groups. All patients in both groups continued the therapy despite treatment-related toxicity.⁷⁷ In NCT01466660 and NCT01523587, similar treatment interruption rates were found: 11.2% in the afatinib group versus 10.6% in the gefitinib group in NCT01466660 and 17.3% in the afatinib group versus 13.1% in the erlotinib group in NCT01523587. In consideration of the limited sample size, we compared the safety between Chinese and non-Chinese patients; these results are presented in Figure 2B. We found that there was no significant difference between Chinese NSCLC patients and non-Chinese NSCLC patients, indicating the experience of dealing with adverse

side effects of afatinib can be learned from other countries also. Overall, these trials indicate that afatinib is a powerful therapy regimen for NSCLC patients with mutant EGFR.

Companion diagnosis

It is obvious that Chinese patients carry a higher *EGFR*-mutated frequency than European and American patients (Table 1). A suitable *EGFR* mutant detection procedure would benefit this part of patients who could potentially receive afatinib therapy. It is reported that mutant *EGFR* can be potentially detected in biopsy and blood.^{81–84} Biopsy has been widely used for *EGFR* mutant detection for years.^{85,86} There are many DNA extraction kits designed for fresh or formalin-fixed paraffin-embedded biopsy samples to conveniently ensure high-quality tumor DNA.⁸⁷ However,

transthoracic biopsies are invasive, and the heterogeneity of tumors may lead to inaccurate results.^{88,89} In this case, cell-free tumor DNA (Cft-DNA) has arisen as a new possibility for tumor somatic mutation detection in recent years, and it is reported that *EGFR* mutations could be successfully detected in Cft-DNA from serum.⁹⁰ This approach indicates that blood sample may replace biopsy samples for Chinese NSCLC patients to detect *EGFR* mutations with qualified techniques. Many techniques such as high-resolution melting analysis, immunohistochemistry, polymerase chain reaction-restriction fragment length polymorphism, amplification refractory mutation system (ARMS), and direct sequencing have been reported as effective in detecting mutated *EGFR* in biopsy and Cft-DNA.^{86,91–93} Meanwhile, increasingly emerged technology such as the new generation of sequencing may benefit patients too.^{94,95} For most patients who need to detect mutant *EGFR* results quickly for their therapy in clinic, ARMS is preferred for its economical and reliable characteristics.^{96,97} For drug resistance population, direct sequencing could obtain more information in genomic scale so that more potential therapeutic choices would be provided.^{98,99} Thus, the development of companion diagnosis-related technology will benefit more NSCLC patients.

Conclusion and challenge

As discussed, it is obvious that the efficacy and safety of afatinib in Chinese *EGFR* mutant NSCLC patients are similar to those in patients with the same mutation worldwide (Figure 2). This clue indicates that afatinib can be utilized in Chinese populations as indicated in the NCCN guideline.⁶⁶ In addition, the mutation frequency of *EGFR* in Chinese NSCLC patients is higher than that in European and American patients, indicating that a higher proportion of Chinese NSCLC patients could benefit from afatinib. Moreover, as variation detection technology has recently rapidly developed in China, more NSCLC patients can be conveniently detected if their *EGFR* mutation is suitable for afatinib therapy. We have reached the conclusion that afatinib could be utilized as a powerful antitumor drug in the near future in Chinese NSCLC patients.

However, there are still some challenges we must face in afatinib therapy in Chinese patients. First, over 30% of *EGFR*-mutated patients are not susceptible to afatinib for unknown reasons. This drug resistance phenomenon attenuated the efficacy of afatinib. Some evidence indicates that some afatinib-resistant patients may carry other mutated genes such as L792F and C797S in *EGFR*.¹⁰⁰ Some abnormal

pathways were also reported to be the reason for this resistance to afatinib.^{101,102} In these cases, genomic scale sequencing is suitable to reveal the underlying mechanism in drug-resistant patients from information in their mutation profile. Second, it is important to develop a suitable technique for patients to fully and accurately obtain their genomic codes for personalized therapy. Although next-generation sequencing (NGS) is popular due to its high-throughput characteristics, the error occurred in PCR process, and the short length of reads limited its ability. The third-generation sequencing is superior in these aspects compared with NGS, but it is still immature, so revolutions are required in the future. Finally, the number and sample size of afatinib clinical trials in Chinese NSCLC patients are limited. More trials should be conducted in the future to draw more solid conclusions about the efficacy and safety of afatinib in the treatment of NSCLC in Chinese patients.

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Disclosure

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