



# What is the best drug as a front-line treatment for EGFR activating mutation?

Hidetaka Uramoto

Department of Thoracic Surgery, Kanazawa Medical University, Ishikawa, Japan

Correspondence to: Hidetaka Uramoto. Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa, 920-0293, Japan. Email: hidetaka@kanazawa-med.ac.jp.

**Abstract:** The landscape of lung cancer treatment is dramatically changing. Non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations are associated with a therapeutic response to tyrosine kinase inhibitors (TKIs). EGFR-inhibiting agents, including first-, second-, and third-generation drug are now available for patients with EGFR mutation-positive NSCLC. However, their clinical impact may differ in such individuals. Physicians now need to consider how to use these drugs to provide the best chance of a long-term survival. This mini-review discusses intratumor heterogeneity, outcomes of head-to-head trials of EGFR-TKIs, the effect of uncommon/compound EGFR mutations, and the current provisions for first-line treatment and perspectives regarding molecular target drug for patients with EGFR mutation putting into focus of second-generation EGFR-TKI.

**Keywords:** Non-small cell lung cancer (NSCLC); epidermal growth factor receptor mutation (EGFR mutation); first line; overall survival (OS)

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## Introduction

Lung cancer is the leading cause of cancer related mortality (1,2). There are two reasons for this: first, lung cancer cells easily metastasize, so when lung cancer is detected, it is frequently found at an advanced stage. Second, the recurrence rate after complete resection is relatively high (3), even in early-stage cases (4). The essential qualities of a poor prognosis are ascribed to the diversity of gene mutations (5). Among the identified gene alterations, the epidermal growth factor receptor (EGFR) mutation is the best studied, and its inhibitors are currently deemed essential for the treatment of lung cancer.

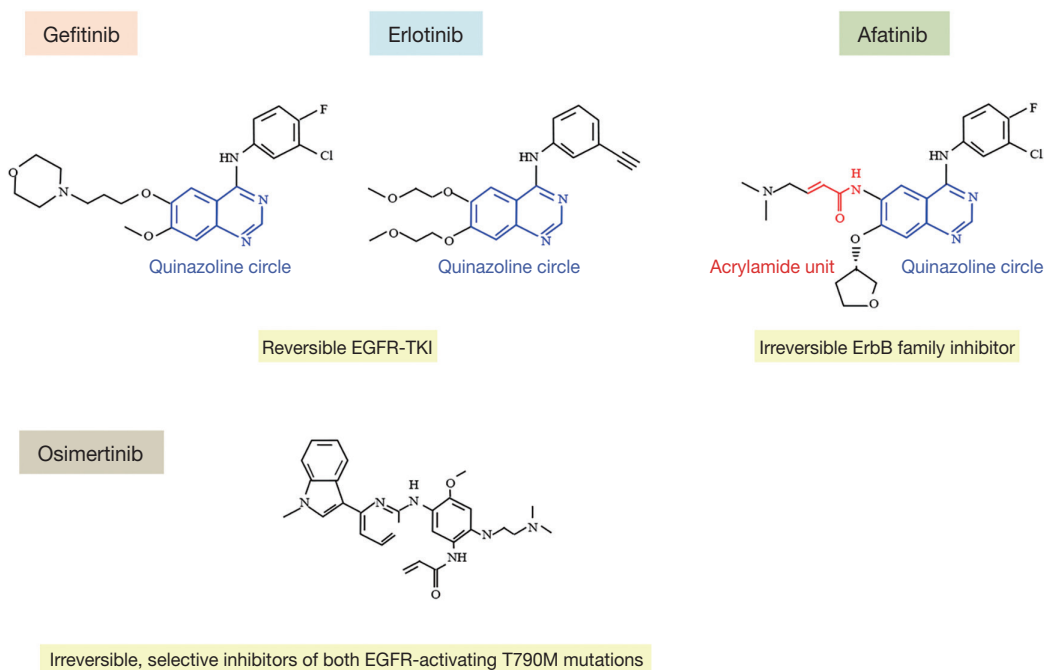
This review discusses intratumor heterogeneity, compares the effects EGFR-tyrosine kinase inhibitors (TKIs), and evaluates the outcomes of head-to-head trials of EGFR-TKIs, considers the overall survival (OS) and effect of uncommon/compound EGFR mutations, and describes the current perspectives regarding first-line treatment and molecular-targeted drugs for patients with EGFR mutations.

## Intratumor heterogeneity

In the initial stage, driver mutations trigger cancer development. Through the process of proliferation, various gene alterations are therefore known to occur (6). In the process, tumor tissue changes into various types of transforming cells. Therefore, simple EGFR mutations, such as Del19 or L858R, simultaneously occur along with the various changes in tumor tissue at specific frequencies (7).

## Comparisons of EGFR-TKIs

So-called “first-generation” EGFR-TKIs, such as gefitinib/erlotinib, are reversible competitors for adenosine triphosphate (ATP) binding sites with a quinazoline circle (*Figure 1*). As the targeting molecule is only EGFR (ErbB1) (8), the general term of reversible EGFR-TKIs has been applied (9). In contrast, “second-generation” EGFR-TKIs, such as afatinib, are irreversible competitors for ATP binding sites. These agents are aniline-quinazoline derivatives that covalently bind to specific catalytic sites of



**Figure 1** Structures of chemical entities targeting EGFR (gefitinib, erlotinib afatinib, and osimertinib). EGFR, epidermal growth factor receptor.

different members of the ErbB receptor family, including EGFR (ErbB1) as well as ErbB2 and ErbB4, and block the transphosphorylation of ErbB3 in order to inhibit all ERBB family signaling (10). Thus, agents such as afatinib have been given the generic name of irreversible ErbB family blockers (10).

Of note, afatinib reportedly improved the progression-free survival (PFS), OS and disease control rate (DCR) compared with erlotinib (11). EGFR mutations are rare (<5%) in squamous cell carcinoma (SQ) of the lung (12). However, around 5–20% of SQ cases express HER2, with substantial overexpression (13), and roughly 30% of them overexpress HER3 (14). Furthermore, genetic aberrations in HER2 and HER3 in several signaling molecules downstream of the ErbB receptors have been identified in SQ (12). These findings show that afatinib not only targets EGFR but is also an irreversible ErbB family blocker.

“Third-generation” EGFR-TKIs, such as osimertinib, have been developed, showing high potency for T790M mutation-positive tumors (15). Osimertinib exerts irreversible covalent binding to mutant EGFR (16).

### Head-to-head trials of EGFR-TKIs

Five pivotal studies have compared the outcomes with several EGFR-TKIs in head-to-head trials for patients with EGFR mutations (*Table 1*). Direct comparisons of first-generation EGFR-TKIs showed a reasonable long-term survival equivalent to the outcomes with gefitinib/erlotinib. Thus, gefitinib exerts virtually the same clinical effect as erlotinib, with no marked differences noted among first-generation EGFR-TKIs. However, the second-generation EGFR-TKI afatinib might offer improved efficacy compared with gefitinib (17–19), as afatinib has also shown greater anticancer activity than other reversible EGFR-TKIs as mentioned above. This suggests that first- and second-generation EGFR-targeted drugs might not be interchangeable (19,20). Furthermore, the length of the survival for the patients treated with the third-generation agent osimertinib was longer than that for those treated by first-generation EGFR-TKIs (21). The clinical usefulness of third-generation EGFR-TKIs is thus considerably superior to that of first-generation EGFR-TKIs. At present, there are no data available regarding the direct comparison of

**Table 1** Comparison of relevant completed studies of head to head trial of EGFR-TKI for the patients with EGFR mutation

Generation TKI	Trial	TKI	Line	PFS (months) (HR, P value)	OS (months) (HR, P value)
1st vs. 1st	WJOG 5108L	G vs. E	2nd	8.3 vs. 10.0; HR: 1.093, P=0.424	26.5 vs. 31.4; HR, 1.189, P=0.221
1st vs. 1st	CTONG 0901	G vs. E	All	10.4 vs. 13.0; HR, 0.81, P=0.108	20.1 vs. 22.9; HR, 0.84, P=0.250
2nd vs. 1st	LUX-Lung 7	A vs. G	1st	11.0 vs. 10.9; HR, 0.74; P=0.0178	27.9 vs. 24.5; HR, 0.86, P=0.2580
2nd vs. 1st	ARCHER 1050	D vs. G	1st	14.7 vs. 9.2; HR, 0.59, P<0.0001	34.1 vs. 26.8; HR, 0.76, P 0.0438
3rd vs. 1st	FLAURA	O vs. G/E	1st	18.9 vs. 10.2; HR: 0.46, P<0.001	Not reported

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; HR, hazard ratio; OS, overall survival; G, gefitinib; E, erlotinib; A, afatinib; D, dacomitinib; O, osimertinib.

second- and third-generation EGFR-TKIs.

### Consideration of the OS

Clinical trials have shown that the OS with first-generation EGFR-TKIs was 19.3–36.3 months (22–26). In contrast, the OS in Japanese patients treated with the second-generation afatinib was reportedly 41.7–46.9 months (27), suggesting that the PFS is longer in patients treated with second-generation EGFR-TKIs than in those treated with first-generation EGFR-TKIs.

### Effects of uncommon EGFR mutations

EGFR mutations are loosely grouped into common and uncommon (minor) mutations (28). The two most common EGFR mutations, EGFR exon 19 deletion (del19) and the Leu858Arg point mutation in exon 21 (L858R), account for roughly 90% of all mutation-positive, non-small cell lung cancer (NSCLC) tumors and are sensitive to drugs that target EGFR (29). The remaining 10% of EGFR mutations fall into a heterogeneous group of molecular alterations (uncommon mutations) with variable responses to EGFR-targeted drugs (30). An *in vitro* study showed that uncommon EGFR mutations are generally insensitive to gefitinib and erlotinib but are sensitive to afatinib and osimertinib (31). Indeed, gefitinib and erlotinib are not expected to imbue any further survival improvement in patients with uncommon EGFR mutations (32,33). However, afatinib induced clinical shrinkage in patients with uncommon EGFR mutations. Furthermore, the PFS and OS were quite favorable, with a high response rate (RR) (30).

Interestingly, a phase II study conducted in Japan in a population with EGFR-mutation-positive NSCLC showed the modest but noteworthy efficacy of afatinib,

with a median PFS of 4.4 months and an RR of 8.2%, in third- and fourth-line patients with NSCLC who had acquired resistance to first-generation EGFR-TKIs (34). These reasons might explain the efficacy of afatinib against uncommon and compound EGFR mutations (described below).

### Effects of compound EGFR mutation

Rare EGFR mutations are expected to be more frequently encountered with the advent of more sensitive and precise tumor genotyping systems (35). Compound EGFR mutations, defined as double or multiple mutations in the EGFR-TK domain, are being more frequently detected with advances in sequencing technology, but their clinical significance is unclear (36).

We previously reported the frequency of compound EGFR mutations to be around 20% (28). This frequency is consistent with the findings of previous studies (31,36). In an *in vitro* study, the sensitivity of first-generation EGFR-TKIs was low for tumor cells harboring compound EGFR mutations. In contrast, that of afatinib was very high (31). A patient harboring complex exon 18 G719X and exon 20 S768I mutations started to receive afatinib and has exhibited a good response without progression for one year (37). Saxon *et al.* reported that first- and third-generation TKIs exhibited a decreased capacity to prevent EGFR phosphorylation in EGFR L858M/L861Q cells compared with cells harboring the common EGFR L858R point mutation. In contrast, afatinib treatment reduced the proliferation and inhibited the EGFR phosphorylation in L858M/L861Q and L858R mutant cells at similar concentrations. Furthermore, a patient with EGFR L858M/L861Q mutations demonstrated primary resistance to erlotinib and was subsequently treated with afatinib, which

resulted in tumor regression (38). Afatinib may therefore be a beneficial therapeutic option for a subset of patients with lung cancer who harbor not only rare EGFR mutations but also compound mutations. Various multiple mutations, including uncommon and compound mutations, might therefore sometimes be detected in clinical practice. The Japan Lung Cancer Society guideline reported the RR of afatinib to be 71%, which is higher than that of gefitinib and erlotinib in actuality (39).

Interestingly, the sensitivity of osimertinib was lower than that of afatinib in cancer cells with compound EGFR mutations (31). As described above, the clinical benefit of osimertinib has been shown to be superior to that of first-generation EGFR-TKIs. However, the survival was not found to differ markedly between patients with L858R mutations treated by the second-generation EGFR-TKI afatinib and those treated by osimertinib. The prevalence of compound EGFR mutations in L858R was relatively high, reaching approximately 20% (31). As a result, T790M mutation clone might remain due to the growth inhibition of afatinib in both uncommon EGFR mutations and compound EGFR mutations. This resulted in the surprising complete and partial RRs of 22% and 88%, respectively, for osimertinib after afatinib treatment (40).

## Perspective

First and second-generation TKIs have developed T790M-positive tumors (41,42). Osimertinib has exerted clinical activity and been proven to be effective in a first-line TKI setting (21). However, subsequent treatment options for osimertinib are not clearly defined, and mature OS data are as yet unavailable (21). In the FLAURA trial, the second-generation EGFR-TKI afatinib was not included as a comparator (16). However, long-term survival of Japanese patients of Lux Lung 3 in a post hoc analysis, which reached to 46.9 months is considered to be satisfactory (43). However, these findings must be interpreted with caution, as they were obtained from a relatively small sample (n=54). Nevertheless, the OS in Japanese patients receiving first-line afatinib was extremely encouraging. Furthermore, the median PFS of patients treated by afatinib was 13.8 months, resulting in a post-PFS of 33.1 months (46.9 minus 13.8). New drugs such as ramucirumab, -immune checkpoint inhibitors, and osimertinib might be administered as a post-progression therapy after afatinib in this study since the data cut-off for the analysis at the time was November 2013, which was before these drugs became available in

Japan. The median OS of afatinib followed by osimertinib has not yet been reached (44). Thus, the sequential use of afatinib followed by osimertinib might therefore be a beneficial treatment for patients harboring EGFR mutations.

In contrast, the median PFS of patients treated by osimertinib was reported to be 19.1 months. The resistance mechanisms associated with osimertinib are various and complex. In the future, it is important to consider alternative therapy options, while carefully evaluating local therapy, and patient tolerability for the long-term treatment of such patients (16). Therefore, the optimum first-line choice of treatment remains unclear, and we are looking forward to conducting head-to-head trials of second-generation *vs.* third-generation EGFR-TKIs as first-line molecular-targeted drugs in patients with EGFR mutations.

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## Footnote

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*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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