



Rechallenge of afatinib for *EGFR*-mutated non-small cell lung cancer previously treated with osimertinib: a multicenter phase II trial protocol (REAL study)

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of advanced non-small cell lung cancer (NSCLC) and contributed to the development of precision medicine. Osimertinib is a standard first-line (1L) treatment for *EGFR*-mutated NSCLC and has demonstrated superior survival benefits over previous-generation TKIs. However, resistance to osimertinib is nearly inevitable, and subsequent treatment strategies remain unmet medical needs in this setting. Afatinib, a second-generation EGFR-TKI, exhibits activity against certain uncommon *EGFR* mutation types in the 1L setting. There are a few case reports on the efficacy of afatinib against *EGFR*-dependent resistance after osimertinib treatment, although these have not been prospectively investigated.

Methods: The present phase II, single-arm multicenter trial aims to verify the efficacy and safety of afatinib rechallenge after 1L osimertinib resistance. Patients (aged ≥ 20 years) with advanced or recurrent non-squamous NSCLC harboring drug-sensitive *EGFR* mutations (deletion of exon 19 or L858R) who were previously treated with 1L osimertinib and second-line chemotherapy other than TKIs are considered eligible. Undergoing next-generation sequence-based comprehensive genomic profiling is one of the key inclusion criteria. The primary endpoint is the objective response rate; the secondary endpoints are progression-free survival, overall survival, and tolerability. Thirty patients will be recruited in December 2023.

Discussion: The results of this study may promote incorporating afatinib rechallenge into the treatment sequence after 1L osimertinib resistance, a setting in which concrete evidence has not been yet established.

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Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI); afatinib; osimertinib; rechallenge

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Introduction

The first driver oncogene identified in lung cancer was an epidermal growth factor receptor (*EGFR*) mutation, the discovery of which has led to a paradigm shift in the pharmacotherapy of advanced non-small cell lung cancer (NSCLC) (1). Over the past two decades, the progress of pharmacotherapy for NSCLC has been marked by advances in precision medicine brought about by molecular-targeted therapies spearheaded by EGFR tyrosine kinase inhibitors (TKIs). Several phase III trials have demonstrated the superiority of EGFR-TKIs in NSCLC with activating *EGFR* mutations over conventional cytotoxic chemotherapy (2-4). Currently, EGFR-TKIs are the standard first-line (1L) treatment for *EGFR*-mutated advanced NSCLC.

Osimertinib is a third-generation, irreversible EGFR-TKI that selectively inhibits both drug-sensitizing and T790M resistance mutations. Initially approved as a salvage therapy for the *EGFR*-T790M mutation acquired after prior-generation EGFR-TKI therapy (5), osimertinib was later approved as a 1L therapeutic agent with a significant survival benefit compared to first-generation comparator EGFR-TKIs for previously untreated patients (6,7). Therefore, osimertinib is the mainstay for *EGFR*-mutated advanced NSCLC. Nonetheless, the reported median progression-free survival (PFS) for 1L osimertinib is 18.9 months and resistance is universal (6). Following 1L osimertinib resistance, platinum-based chemotherapy is commonly used in practice as a standard 1L treatment for advanced NSCLC without drug-sensitive oncogenic driver mutations. However, no concrete evidence is based on data from randomized controlled trials, highlighting the importance of exploring salvage therapy after 1L osimertinib resistance.

The role of EGFR-TKI rechallenge after 1L osimertinib is not elucidated. Data on subsequent therapy from the phase III FLAURA trial showed that 29% and 35% of patients in the osimertinib arm received TKI rechallenge as first- and second-subsequent chemotherapy, respectively (7). Moreover,

a Japanese subset analysis from the FLAURA trial showed that 35% of patients in the osimertinib arm received TKI rechallenge as the first-subsequent therapy (8). These data suggest the potential role of TKI administration after 1L osimertinib resistance in practice.

Afatinib, a second-generation EGFR-TKI, is an irreversible pan-ErbB family blocker anticipated to inhibit tumors by activating *EGFR* mutations more effectively than the first-generation TKIs (9). Recent preclinical data have revealed that certain types of acquired *EGFR* on-target resistance mechanisms (C797S, L718Q, and L844V), which are responsible for 1L osimertinib resistance, retain sensitivity to afatinib (10). Moreover, afatinib shows activity against acquired resistance mechanisms emerging after osimertinib treatment as reported in several case series (11,12). These findings imply the potential efficacy of afatinib rechallenge after disease progression with 1L osimertinib, which provoked the need for validating the efficacy of afatinib in this setting.

Based on these perspectives, we hypothesized that afatinib rechallenge after 1L osimertinib resistance would be effective for *EGFR*-mutated NSCLC and planned a single-arm phase II study to investigate the efficacy of afatinib in this population. This protocol article was written in accordance with the SPIRIT reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-12/rc>).

Methods

The study protocol (version 3. 22nd October 2022) and patient informed consent document (version 3. 12th October 2022) were approved by the Institutional Review Board of Shinshu University School of Medicine (approval No. 5641). All procedures for this study will be performed in accordance with the amended Declaration of Helsinki (as revised in 2013). The prescribed consent document will be used by each investigator to obtain patients' informed consent. Upon the protocol amendments, if needed, the

Table 1 Key inclusion criteria of the REAL study

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1. Age ≥ 20 years
 2. Written informed consent
 3. ECOG-PS of 0 or 1
 4. Histologically or cytologically diagnosed non-squamous non-small cell lung cancer
 5. Advanced or recurrent disease and harboring a drug-sensitive *EGFR* mutation^a at the start of first-line therapy
 6. Given osimertinib as first-line
 7. Given chemotherapy (any regimen other than EGFR-TKIs) as second-line or more therapies
 8. Undergoing NGS-based CGP testing^b after osimertinib resistance
 9. At least one measurable lesion according to RECIST v1.1
 10. Meeting the following laboratory criteria
 - AST ≤ 100 U/L
 - ALT ≤ 100 U/L
 - Creatinine ≤ 2.0 mg/dL
 - SpO₂ $\geq 92\%$
 11. Absence of the following severe complications and organ dysfunctions:
 - Active infection requiring the administration of continuous antimicrobial agents
 - Uncontrollable heart disease (non-compensated heart failure, unstable coronary artery disease, significant decline in ejection fraction^c)
 - Severe liver dysfunction (Child-Pugh class C)
 - Gastrointestinal disorders affecting digestion and absorption
 12. Absence of symptomatic CNS lesions^d
 13. Absence of uncontrollable body cavity fluid^e
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^a, exon 19 deletion and L858R; ^b, liquid biopsy is acceptable if a tissue sample is not obtained; ^c, ejection fraction ratio $<30\%$; ^d, radiotherapy within 14 d for nontarget lesions is acceptable; ^e, patients with pleural effusions, ascites, and pericardial effusions who are clinically stable with drainage are eligible. ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NGS, next-generation sequencing; CGP, comprehensive genomic profiling; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1; AST, aspartate transaminase; ALT, alanine transaminase; SpO₂, arterial oxygen saturation; CNS, central nervous system.

principal investigator (S.K.) will apply for changes to the Institutional Review Board of Shinshu University School of Medicine. The research outline of this study has been registered with the UMIN-Clinical Trials Registry (<https://www.umin.ac.jp/ctr/index-j.htm>) (UMIN000049225) and is available to the public.

Study design

This study is a prospective, multicenter, single-arm phase II trial, in which 11 Japanese institutions have participated. This study aims to evaluate the efficacy and safety of afatinib rechallenge after resistance to 1L osimertinib in

patients with advanced non-squamous (non-Sq) NSCLC harboring drug-sensitive *EGFR* mutations (exon 19 deletion mutation or exon 21 L858R point mutation). The primary endpoint is the objective response rate (ORR), and the secondary endpoints are PFS, overall survival (OS), and safety [types and frequency of adverse events (AEs)] of the afatinib rechallenge therapy.

Study setting and population

The key patient inclusion and exclusion criteria are presented in *Table 1* and *Table 2*. Written informed consent will be obtained from each participant by an assigned investigator.

Table 2 Key exclusion criteria of the REAL study

1. Having active multiple cancers
2. Current known active infection with human immunodeficiency, hepatitis B, or hepatitis C virus
3. Undergoing concurrent chemotherapy, radiotherapy, immunotherapy, and hormonal therapy as cancer treatment
4. General unsuitability to participation

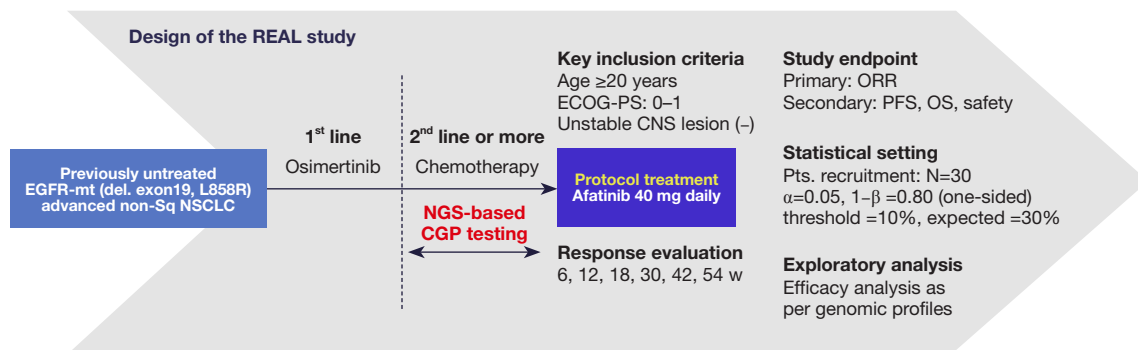


Figure 1 Design of the REAL study is presented. EGFR, epidermal growth factor receptor; Sq, squamous; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; CGP, comprehensive genome profiling; ECOG-PS, Eastern Cooperative Oncology Group performance status; CNS, central nerve system; w, weeks; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

Advanced non-Sq NSCLC patients aged 20 years with a good Eastern Cooperative Oncology Group performance status who received at least one regimen of chemotherapy other than EGFR-TKIs followed by 1L osimertinib therapy will be enrolled. Patients with symptomatic central nervous system lesions and uncontrollable body cavity fluids (i.e., pleural effusion, pericardial effusion, and ascites) will be excluded. Patients will have to undergo next-generation sequencing (NGS)-based comprehensive genomic profiling (CGP) testing during the period after 1L osimertinib resistance and study enrollment. For CGP testing, tissue biopsy is preferred, but liquid biopsy is also acceptable if sufficient tissue specimens could not be obtained. Accordingly, 30 patients will be recruited in December 2023. The estimated study completion date is March 2027. The study overview is presented in *Figure 1*.

Study assessment and intervention

The study timeline for each participant is presented in *Figure 2*. Written informed consent will be obtained before registration, and an examination to check the eligibility criteria will be conducted. Baseline target lesions will be screened using computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, chest,

and abdomen. Target lesions and treatment response will be evaluated using Response Evaluation Criteria for Solid Tumors version 1.1 (13). Afatinib monotherapy at 40 mg daily will be administered as a protocol therapy until RECIST progressive disease or up to 54 weeks. Patients will undergo response evaluation using CT or MRI every 6 weeks for the first 18 weeks and every 12 weeks thereafter until 54 weeks (*Figure 2*). The toxicity evaluation will be performed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 (14). Based on the toxicity profile, the treatment will be interrupted if required. If interrupted due to toxicity, the dose will be reduced by 10 mg/day to a minimum of 20 mg/day. In cases of grade 4 AEs and definite drug-induced pneumonitis due to afatinib, permanent treatment discontinuation will be required. The following are mandatory reporting requirements as severe AEs: (I) “death” during protocol treatment or within 28 days of the last treatment day, after 29 days of the last treatment day that is thought to be causally related to protocol treatment, (II) “life-threatening events” including grade 4 of AE occurred during protocol treatment or within 28 days of last treatment day, or during after 29 days of last treatment with a causal relationship to protocol treatment will be suspected, (III) “Hospitalization or prolonged length of

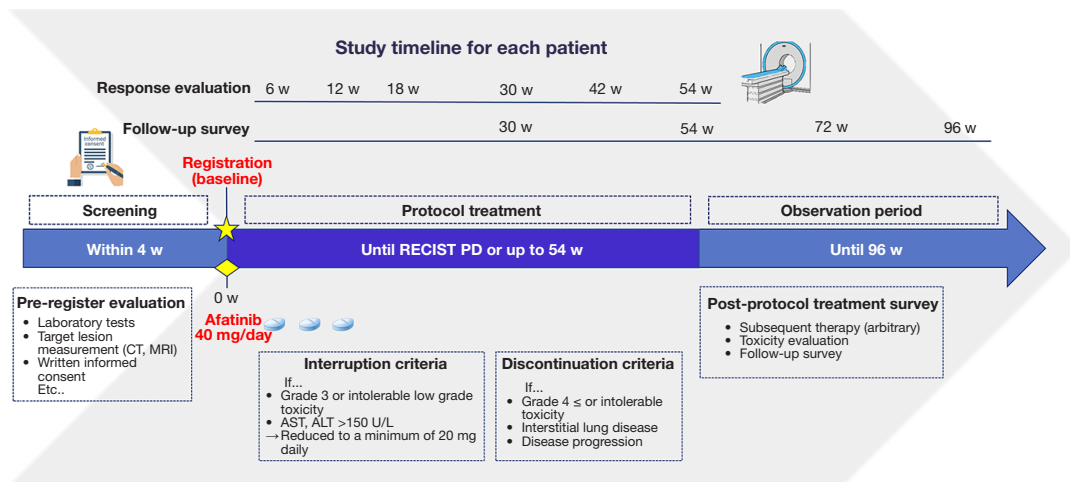


Figure 2 Study timeline for each patient is presented. CT, computed tomography; MRI, magnetic resonance imaging; AST, aspartate transaminase; ALT, alanine transaminase; w, week; RECIST, response evaluation criteria for solid tumors; PD, progressive disease.

stay” other events or reactions that are determined to be medically significant conditions are required to be reported as a severe AEs. Regardless of the duration of treatment, four times of outcome surveys (30, 54, 72, and 96 weeks) will be conducted.

Data collection and management

All patient data will be registered and managed by an electronic data capture system (Viedoc™ version 4.73.8370.15796). Once patients are enrolled, a scheduling sheet for each participant will be sent to an investigator, and protocol treatment will be carried out accordingly. Data monitoring committee (DMC) is organized by four investigators (S.K., T.A., K.T., K.S.) to monitor deviations and missing data. The DMC is organized independently of any sponsors or competing interests. Monitoring surveys will be conducted by five investigators (S.K., T.A., K.T., K.S., M.K) at least one time for each participating facility during the study period. If the estimated number of cases has been collected and the best overall response for all participants has been confirmed, the principal investigator (S.K.) will access and analyze the dataset for the primary endpoint of ORR. The secondary endpoints, OS, PFS, and safety profile, will be analyzed after the last patient outcome survey (96 weeks) is completed.

Statistical analysis

The sample size was calculated with a type I error of 0.05

(one-sided) and a power of 0.80. If the ORR is <10% (null hypothesis based on historical data), the efficacy of rechallenge afatinib will be considered not significant. The expectation is promising if the ORR is >30% (an alternative hypothesis based on retrospective data). Based on these simulations, the minimum number of patients required is 25. The number of recruited cases was set at 30, including the presumed ineligible cases. The ORR will be presented with 90% exact binomial confidence intervals. PFS and OS will be estimated using the Kaplan-Meier method.

Discussion

This prospective phase II multicenter, single-arm trial aims to evaluate the efficacy of afatinib rechallenge in *EGFR*-mutated non-Sq NSCLC previously treated with 1L osimertinib. To date, a standard treatment strategy after 1L osimertinib resistance has not been established. Novel therapeutic strategies in this setting are being explored in several clinical trials and preclinical studies (15). However, these are currently unavailable in clinical practice. Most patients are treated with conventional cytotoxic therapy following 1L osimertinib, mainly platinum doublet chemotherapy empirically as well as 1L treatment for advanced NSCLC without driver oncogene alternations. Considering that cytotoxic chemotherapy is generally less effective and more highly toxic than *EGFR*-TKI, the rationale for exploring salvage treatment with *EGFR*-TKIs in this population is highlighted.

One strength of this study is that it will be the first

prospective study to examine the efficacy of afatinib rechallenge after 1L osimertinib. Most of the previous studies on EGFR-TKI rechallenge have been conducted prior to the advent of 1L osimertinib with retrospective design. Among these studies, the ORR for rechallenge after first- or second-generation EGFR-TKIs was reported to be 7–25% (16–20). Recently, several reports on the efficacy of dacomitinib, a second-generation EGFR-TKI identical to afatinib, were published in the rechallenge setting. In a retrospective study by Tanaka *et al.* with 43 patients, 24 (55.8%) had received prior osimertinib, including 9 (20.9%) in the 1L setting, and more than half had received at least three lines of prior chemotherapy (21). The reported ORR and median PFS were 25.5% and 4.3 months, respectively. This finding supports the potential efficacy of dacomitinib after osimertinib resistance, including in the 1L setting. On the other hand, a modest efficacy of dacomitinib following 1L osimertinib was recently reported. In a prospective pilot study by Choudhury *et al.*, with 12 patients, examining the efficacy of dacomitinib immediately after 1L osimertinib resistance, the ORR was reported as 16.7% (22). However, 82% of patients in their cohort carried TP53 co-mutation before dacomitinib induction, which is known to be a poor predictive biomarker, and may have led to modest efficacy. In addition, because the study failed to recruit the estimated enrollment, statistical evaluation of the reported ORR to dacomitinib is challenging. Therefore, the efficacy of second-generation EGFR-TKI following 1L osimertinib needs to be investigated in another cohort. Since afatinib is more commonly used than dacomitinib in clinical practice, the importance of our study to prospectively validate the efficacy of afatinib is warranted.

Another strength of this study is to conduct NGS-based CGP testing after 1L osimertinib resistance. Currently, novel therapeutic strategies are being explored as the understanding of osimertinib resistance. Resistance mechanisms to osimertinib can be categorized into two major classes: *EGFR*-dependent (on-target) and -independent (off-target) mechanisms. The former includes *EGFR* pathway-dependent molecular profiles represented by C797X mutation and T790M loss (15). The latter includes several mechanisms such as amplifications (*MET* and *HER2*), oncogenic fusion genes (*ALK*, *BRAF*, *RET*, *ROS1*, etc.), downstream alternations (*KRAS*, *BRAF*, *PIK3CA*, *PTEN* loss, etc.), histological transformation, and cell cycle alternations (15). Novel therapeutic agents targeting these mechanisms are being investigated for clinical application. However, given that approximately half of the resistance

mechanisms to osimertinib are unknown, patients with undetectable resistance mechanisms might not be indicated for these agents. Although some emerging therapeutic agents, such as antibody-drug conjugates (23), bispecific antibodies (24), and next-generation EGFR inhibitors (25), have shown promising results as treatment options after osimertinib resistance irrespective of molecular profiles, these drugs are not covered by insurance in Japan. In this study, it was difficult to specify a subgroup analysis to validate the efficacy of afatinib based on each resistance mechanism due to the scale of this study. Instead, we are going to present information on afatinib efficacy and molecular profile testing in individual patients apart from the analysis of the study endpoints. Our results would provide crucial information for selecting afatinib after 1L osimertinib resistance in the future.

The present study includes several limitations. First, it is a single-arm phase II study with a limited number of patients. The study will recruit patients who have received chemotherapy after 1L osimertinib resistance as in practice. Thus, there is no specified treatment regimen between 1L osimertinib resistance and enrollment in the study, making it difficult to establish a comparator arm. Second, with regard to CGP testing, a liquid biopsy will be permitted if a tissue biopsy is unavailable. It should be noted that genome profiling information in the study population might not reflect true resistance status, considering the lower sensitivity of liquid biopsy depending on the metastatic status or tumor burden of the patient. Despite the above limitations, this is the first prospective study to investigate afatinib rechallenge after 1L osimertinib resistance. The results of this study may provide a new treatment option for *EGFR*-mutated advanced NSCLC.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-23-12/rc>

Peer Review File: Available at <https://tldr.amegroups.com/>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-12/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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. The study protocol (version 3. 22th October 2022) and patient informed consent document (version 3. 12th October 2022) were approved by the Institutional Review Board of Shinshu University School of Medicine (approval No. 5641). All procedures for this study will be performed in accordance with the amended Declaration of Helsinki (as revised in 2013). The prescribed consent document will be used by each investigator to obtain patients' informed consent. The principal investigator (S.K.) will request protocol amendments from the Institutional Review Board of Shinshu University School of Medicine if necessary. The results of this research will be published in research papers and conference presentations.

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References

- Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129-39.
- Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-8.
- Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735-42.
- Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327-34.
- Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N Engl J Med* 2017;376:629-40.
- Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;378:113-25.
- Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *N Engl J Med* 2020;382:41-50.
- Ohe Y, Imamura F, Nogami N, et al. Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset. *Jpn J Clin Oncol* 2019;49:29-36.
- Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008;27:4702-11.
- Ercan D, Choi HG, Yun CH, et al. EGFR Mutations and Resistance to Irreversible Pyrimidine-Based EGFR Inhibitors. *Clin Cancer Res* 2015;21:3913-23.
- Wei Y, Jiang B, Liu S, et al. Afatinib as a Potential Therapeutic Option for Patients With NSCLC With EGFR G724S. *JTO Clin Res Rep* 2021;2:100193.
- Aredo JV, Wakelee HA, Neal JW, et al. Afatinib After Progression on Osimertinib in EGFR-Mutated Non-Small Cell Lung Cancer. *Cancer Treat Res Commun* 2021. [Epub ahead of print]. doi: 10.1016/j.ctarc.2021.100497.
- Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-Update and clarification: From the RECIST committee. *Eur J Cancer* 2016;62:132-7.
- Common Terminology Criteria for Adverse Events (CTCAE) version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.
- Fu K, Xie F, Wang F, et al. Therapeutic strategies for EGFR-mutated non-small cell lung cancer patients with osimertinib resistance. *J Hematol Oncol* 2022;15:173.
- Miller VA, Hirsh V, Cadranet J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012;13:528-38. Erratum in: *Lancet Oncol* 2012;13:e186.

17. Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol* 2013;31:3335-41.
18. Yamaguchi O, Kaira K, Mouri A, et al. Re-challenge of afatinib after 1st generation EGFR-TKI failure in patients with previously treated non-small cell lung cancer harboring EGFR mutation. *Cancer Chemother Pharmacol* 2019;83:817-25. Erratum in: *Cancer Chemother Pharmacol* 2020;85:237-9.
19. Lee VH, Leung DK, Choy TS, et al. Efficacy and safety of afatinib in Chinese patients with EGFR-mutated metastatic non-small-cell lung cancer (NSCLC) previously responsive to first-generation tyrosine-kinase inhibitors (TKI) and chemotherapy: comparison with historical cohort using erlotinib. *BMC Cancer* 2016;16:147.
20. Tanaka H, Taima K, Itoga M, et al. Real-world study of afatinib in first-line or re-challenge settings for patients with EGFR mutant non-small cell lung cancer. *Med Oncol* 2019;36:57.
21. Tanaka H, Sakamoto H, Akita T, et al. Clinical efficacy of dacomitinib in rechallenge setting for patients with epidermal growth factor receptor mutant non-small cell lung cancer: A multicenter retrospective analysis (TOPGAN2020-02). *Thorac Cancer* 2022;13:1471-8.
22. Choudhury NJ, Makhnin A, Tobi YY, et al. Pilot Study of Dacomitinib for Patients With Metastatic EGFR-Mutant Lung Cancers With Disease Progression After Initial Treatment With Osimertinib. *JCO Precis Oncol* 2021;5:PO.21.00005.
23. Jänne PA, Baik C, Su WC, et al. Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, EGFR-Mutated Non-Small Cell Lung Cancer. *Cancer Discov* 2022;12:74-89. Erratum in: *Cancer Discov* 2022;12:1598.
24. Neijssen J, Cardoso RME, Chevalier KM, et al. Discovery of amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR and MET. *J Biol Chem* 2021;296:100641.
25. To C, Beyett TS, Jang J, et al. An allosteric inhibitor against the therapy-resistant mutant forms of EGFR in non-small cell lung cancer. *Nat Cancer* 2022;3:402-17.

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