ORIGINAL ARTICLE

Second-line therapy with first- or second-generation tyrosine kinase inhibitors in EGFR-mutated non-small cell lung cancer patients with T790M-negative or unidentified mutation

Tadashi Nishimura1 | Tomohito Okano2 | Masahiro Naito1 | Soichi Iwanaka1 | Ayaka Ohiwa1 | Yasumasa Sakakura1 | Taro Yasuma3 | Hajime Fujimoto2 | Corina N. D’Alessandro-Gabazza3 | Yasuhiro Oomoto1 | Tetsu Kobayashi2 | Esteban C. Gabazza3 | Hidenori Ibata1

1Department of Pulmonary Medicine, Mie Chuo Medical Center, Tsu, Japan
2Department of Pulmonary and Critical Care Medicine, Mie University Graduate School of Medicine, Tsu, Japan
3Department of Immunology, Mie University Graduate School of Medicine, Tsu, Japan

Correspondence
Esteban C. Gabazza, Department of Immunology, Mie University School of Medicine, Edobashi 2-174, Tsu-city, Mie 514-8507, Japan.
Email: gabazza@doc.med.mie-u.ac.jp

[Correction added on 16 March 2021, after first online publication: the 4th author’s name has been corrected from ‘Souichi Iwanaka’ to ‘Soichi Iwanaka’.

Abstract

Background: T790M mutation causes resistance to tyrosine kinase inhibitors (TKIs) in approximately 49% of patients with epidermal growth receptor-mutant non-small cell lung cancer (NSCLC). The cause of resistance in the remaining half of the cases is a minor mutation or unknown. Here, we conducted a retrospective study of epidermal growth receptor-mutant NSCLC patients with T790M-negative or an unidentified mutation to appraise the therapeutic response to first- or second-generation tyrosine kinase inhibitors as a second-line treatment.

Methods: The study included 39 patients treated in our institution from April 2012 through March 2020 with second-line tyrosine kinase inhibitors or chemotherapy after completing a first-line therapy with tyrosine kinase inhibitors.

Results: The patients were allocated to two groups: chemotherapy (n = 28) and a tyrosine kinase inhibitor (n = 11) groups. The median progression-free survival (PFS) was 5.4 months in the chemotherapy group and 3.4 months in the tyrosine kinase inhibitor group (p-value = 0.36), while the median overall survival (OS) was 16.1 months in the chemotherapy group and 12.8 months in the tyrosine kinase inhibitor group (p-value = 0.20). This study showed no significant difference in PFS and OS between the chemotherapy and tyrosine kinase inhibitor groups.

Conclusions: These observations suggest that first- and second-generation tyrosine kinase inhibitors are not recommended for second-line treatment in epidermal growth factor receptor-mutated NSCLC patients with T790M-negative mutation who have received tyrosine kinase inhibitors as first-line treatment.

KEYWORDS
chemotherapy, EGFR mutation, EGFR tyrosine kinase inhibitors, non-small cell lung cancer, T790M negative

INTRODUCTION

Among all lung adenocarcinoma cases, epidermal growth factor receptor (EGFR) mutations account for 47.9% in the Asian population and 45% in the Japanese population.1–3 Based on clinical trials showing improvement of progression-free survival (PFS) following treatment with first- and second-generation EGFR tyrosine kinase inhibitors (TKIs), EGFR TKIs have become the first-line treatment for EGFR mutation-positive adenocarcinomas.3–6
AURA3 study showed that osimertinib, a third-generation EGFR TKI, is effective as a second-line treatment for T790M mutation-positive lung adenocarcinomas. The FLAURA study showed that, as first-line therapy, osimertinib is superior to gefitinib or erlotinib to prolong PFS and overall survival (OS). Therefore, osimertinib is currently the first therapeutic choice for EGFR mutation-positive lung adenocarcinoma. However, there is no effective second-line treatment for patients with T790M mutation-negative or unidentified mutations who have received a first- or second-generation EGFR TKI as first-line therapy. In the FLAURA study, patients from the control (27%) and osimertinib (29%) groups received first- or second-generation EGFR TKI as second-line treatment. As patients treated with first- or second-generation TKIs were long-living, we hypothesized that the therapeutic efficacy as a second-line treatment of first- or second-generation EGFR TKIs and chemotherapy would be different. To demonstrate this hypothesis, in the present study, we compared the therapeutic efficacy between chemotherapy and first- or second-generation EGFR TKIs as the second-line treatment in EGFR-mutated non-small cell lung cancer (NSCLC) patients with T790M-negative or unknown mutation.

METHODS

Patients

We retrospectively conducted this study using data retrieved from electronic medical records in our institution from April 2012 through March 2020. The study included 39 patients treated with second-line tyrosine kinase inhibitors or chemotherapy after completing a first-line therapy with TKIs (Figure 1). The total number of patients treated with EGFR-TKI during the study period was 189. We excluded patients with first-line therapy had been discontinued because of adverse events (n = 10), patients treated with chemotherapy as first-line therapy (n = 30), with EGFR wild-type (n = 52), with osimertinib as second-line therapy (n = 5), or patients under ongoing EGFR TKI therapy (n = 53) (Figure 1). The patients were allocated into two groups: chemotherapy (n = 28) and tyrosine kinase inhibitor (n = 11) groups. The reasons for treating patients with tyrosine kinase inhibitors were as follows: five patients refused treatment with chemotherapy, four had poor performance status, one had a metastatic tumor in the brain, and one was an elderly patient.

Statistical analysis

Continuous variables were assessed using the Mann–Whitney U test and categorical variables using Fisher’s test. The Kaplan–Meier method and the log-rank test were used for comparing survival. Multivariate analysis was performed using the Cox proportional hazards regression analysis. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to determine efficacy. OS was defined as the time from the initial day of the second-line treatment to death. p < 0.05 was considered statistically significant. We performed all statistical analyses using the EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria); this is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

RESULTS

Response rate and survival

In the study, we included 39 out of 189 patients with a history of treatment with TKIs (Figure 1). Tables 1 and 2 show the patient characteristics. The chemotherapy group included 28

FIGURE 1 Study flow chart. A total of 39 patients out of 189 patients with a history of tyrosine kinase treatment were included in the study. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor
patients (71.8%), whereas the TKI (28.2%) group included 11 patients. The Eastern Cooperative Oncology Group performance status (ECOG PS) at the start of first-line treatment was significantly better in the chemotherapy group \((p = 0.04)\) than in the TKI group. However, there was no bias in other patient backgrounds. The overall response rate was 46.4\% (95% confidence interval [CI]: 27.5\%–66.1\%) in the chemotherapy group and 36.4\% (95% CI: 10.9\%–69.2\%) in the TKI group \((p = 0.725)\). The disease control rate was 71.4\% (95% CI: 51.3\%–86.8\%) in the chemotherapy group and 54.5\% (95% CI: 23.4\%–83.3\%) in the TKI group \((p = 0.45)\). The median PFS was 5.4 months (95% CI: 3.2–11.0 months) in the chemotherapy group and 3.4 months (95% CI: 2.0–9.4 months) in the TKI group (Figure 2). The median survival time was 16.1 months (95% CI: 10.5–32.9 months) in the chemotherapy group and 12.8 months (95% CI: 3.0–24.6 months) in the TKI group (Figure 2).

## Table 1 Patient characteristics during first-line therapy

| Number of patients | Group | Chemotherapy group (%) | TKI group (%) | \(p\)-values |
|--------------------|-------|------------------------|---------------|-------------|
| Median age         |       | 69.0                   | 68.0          | 0.754       |
| Gender             |       | Male                   | 8 (28.6)      | 5 (45.5)    | 0.453 |
|                    |       | Female                 | 20 (71.4)     | 6 (54.5)    |       |
| EGFR mutation      |       | Ex19del                | 17 (60.7)     | 5 (45.5)    | 0.62  |
|                    |       | Ex21.L858R             | 10 (35.7)     | 6 (54.5)    |       |
|                    |       | Ex18                   | 1 (3.6)       | 0 (0.0)     |       |
| PD-L1 status       |       | <1%                    | 4 (14.3)      | 0 (0.0)     | 0.35  |
|                    |       | 1%–49%                 | 3 (10.7)      | 1 (9.1)     |       |
|                    |       | >50%                   | 0 (0.0)       | 1 (9.1)     |       |
| ECOG PS at first-line |   | 0                      | 20 (71.4)     | 5 (45.5)    | 0.042 |
|                    |       | 1                      | 6 (21.4)      | 2 (18.2)    |       |
|                    |       | 2                      | 1 (3.6)       | 4 (36.4)    |       |
|                    |       | 3                      | 1 (3.6)       | 0 (0.0)     |       |
| Disease stage      |       | I                      | 0 (0.0)       | 1 (9.1)     | 0.127 |
|                    |       | III                    | 1 (3.6)       | 2 (18.2)    |       |
|                    |       | IV                     | 19 (67.9)     | 5 (45.5)    |       |
|                    |       | Recurrence             | 8 (28.6)      | 3 (27.3)    |       |
| T790M since the third-line | | Positive            | 4 (14.3)      | 2 (18.2)    | 1      |
|                    |       | Negative               | 9 (32.1)      | 3 (27.3)    |       |
|                    |       | Not evaluated          | 15 (53.6)     | 6 (54.5)    |       |
| Smoking status     |       | Non-smoker             | 6 (54.5)      | 19 (67.9)   |       |
|                    |       | Smoker/ever smoker     | 5 (45.5)      | 9 (32.1)    |       |
| First-line treatment |    | Gefitinib              | 16 (57.1)     | 9 (81.8)    | 0.648 |
|                    |       | Erlotinib              | 5 (17.9)      | 1 (9.1)     |       |
|                    |       | Afatinib               | 4 (14.3)      | 1 (9.1)     |       |
|                    |       | Osimertinib            | 3 (10.7)      | 0 (0.0)     |       |
| Liver metastasis   |       | Positive               | 2 (7.1)       | 1 (9.1)     | 1      |
|                    |       | Negative               | 26 (92.9)     | 10 (90.9)   |       |
| Carcinomatous pleurisy |   | Positive            | 14 (50.0)     | 3 (27.3)    | 0.288 |
|                    |       | Negative               | 14 (50.0)     | 8 (72.7)    |       |
| Bone metastasis    |       | Positive               | 9 (32.1)      | 3 (27.3)    | 1      |
|                    |       | Negative               | 19 (67.9)     | 8 (72.7)    |       |
| Brain metastasis   |       | Positive               | 3 (10.7)      | 4 (36.4)    | 0.083 |
|                    |       | Negative               | 25 (89.3)     | 7 (63.6)    |       |

Abbreviations: Chemo, chemotherapy; ECOG, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Univariate and multivariate analysis

Univariate analysis showed that ECOG-PS and metastasis in bones, liver, and brain significantly affected the PFS and OS.
as assessed by the log-rank test ($p < 0.1$). Age also affected the PFS and OS. Therefore, we included seven factors in the multivariate analysis. Age ($\geq 75$ years and $<75$ years), ECOG PS ($\geq 3$ and $<3$) during first- and second-line therapy, and the presence or absence of metastasis in the brain, liver, and bones (Table 3). The dependent factors that predicted the PFS (hazard ratio [HR] = 5.24; 95% CI: 1.91–14.41, $p = 0.0013$) were ECOG PS during second-line treatment and brain metastasis (HR = 5.05 [95% CI: 1.75–14.53], $p = 0.0027$). On the other hand, the dependent factors that predicted the OS were ECOG PS during second-line treatment (HR = 3.19 [95% CI: 1.25–8.18] $p = 0.015$) and age (HR = 2.81 [95% CI: 1.00–7.84] $p = 0.049$) (Table 3).

### DISCUSSION

This study showed no significant difference in PFS and OS between the chemotherapy and TKI groups.

T790M mutation has been reported to cause therapeutic resistance to first- or second-generation TKIs in approximately 49% of EGFR mutant-associated lung adenocarcinomas.$^{11}$ Osimertinib has been reported to be the most effective treatment approach for T790M-positive lung adenocarcinomas.$^{7}$ However, there is no definite therapeutic choice for T790M-negative adenocarcinomas. The continuous use of the same TKI despite progressive disease in resistant cases has previously been reported to have shown no clinical benefit.$^{12–14}$ The indication for different TKIs or cytotoxic drugs may be considered as therapeutic options. Indeed, several studies have reported the effectiveness of chemotherapy after the administration of TKIs.$^{15–20}$ For example, a favorable clinical response has been previously observed with the combination of platinum-doublet and pemetrexed, or with the combination of docetaxel and ramucirumab.$^{19, 20}$

The mechanism of tyrosine kinase inhibition by gefitinib, erlotinib, and afatinib is different. Therefore, an indication of an EGFR TKI different from that initially used may be another alternative option for the treatment of resistant tumors.$^{21}$ In cases resistant to gefitinib, erlotinib used as second-line treatment has been shown to be moderately effective, although less effective than chemotherapy.$^{19, 22, 23}$

In previous studies, the response rate to afatinib was 8.2%, and the impact of afatinib on overall survival was reported to be significantly different from placebo in patients with progressive tumors after treatment with first-generation TKIs.$^{24, 25}$ However, patients with poor ECOG PS were not included in these previous clinical trials, and thus the results may be incomparable to those observed in the real-world clinical setting.$^{13–25}$ Here, we report the results observed in the real-world clinical setting. From our findings, ECOG PS was an independent factor for PFS in the multivariate

### TABLE 2  Patient characteristics during second-line therapy

| Factor                  | Chemotherapy group (%) | TKI group (%) | $p$-value |
|-------------------------|------------------------|--------------|-----------|
| Median age              | 70.0                   | 68.0         | 0.65      |
| Second-line treatment   |                        |              |           |
| Afatinib                | 0 (0.0)                | 5 (45.5)     | <0.001    |
| Erlotinib               | 0 (0.0)                | 6 (54.5)     |           |
| Platinum-based chemotherapy | 17 (60.7)            | 0 (0.0)      |           |
| Nonplatinum based chemotherapy | 11 (39.3)          | 0 (0.0)      |           |
| Osimertinib approved    |                        |              |           |
| Before                  | 15 (53.6)              | 4 (36.4)     | 0.48      |
| After                   | 13 (46.4)              | 7 (63.6)     |           |
| ECOG PS                 |                        |              |           |
| 0                       | 13 (46.4)              | 2 (18.2)     | 0.288     |
| 1                       | 5 (17.9)               | 3 (27.3)     |           |
| 2                       | 8 (28.6)               | 4 (36.4)     |           |
| 3                       | 1 (3.6)                | 2 (18.2)     |           |
| 4                       | 1 (3.6)                | 0 (0.0)      |           |
| Liver metastasis        |                        |              |           |
| Positive                | 6 (21.4)               | 1 (9.1)      | 0.649     |
| Negative                | 22 (78.6)              | 10 (90.9)    |           |
| Carcinomatous pleurisy  |                        |              |           |
| Positive                | 13 (46.4)              | 4 (36.4)     | 0.725     |
| Negative                | 15 (53.6)              | 7 (63.6)     |           |
| Bone metastasis         |                        |              |           |
| Positive                | 13 (46.4)              | 3 (27.3)     | 0.471     |
| Negative                | 15 (53.6)              | 8 (72.7)     |           |
| Brain metastasis        |                        |              |           |
| Positive                | 4 (14.3)               | 5 (45.5)     | 0.085     |
| Negative                | 24 (85.7)              | 6 (54.5)     |           |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor.
FIGURE 2 Progression-free survival (PFS) and overall survival (OS) in each group of patients. The median PFS was 5.4 months in the chemotherapy group and 3.4 months in the tyrosine kinase inhibitor (TKI) group. The median survival time was 16.1 months in the chemotherapy group and 12.8 months in the TKI group. CI, confidence interval; MST, median survival time; PFS, progression-free survival; OS, overall survival

|                         | Progression-free survival | Overall survival |
|-------------------------|---------------------------|-----------------|
|                         | n | HR (95% CI)     | p-value | n | HR (95% CI)     | p-value |
| Age                     |   |                |         |   |                |         |
| <75                     | 31 | Ref           | 0.81     | Ref | 2.81 (1.00–7.84) | 0.049 |
| ≥75                     | 8  | 1.13 (0.41–3.10) | 2.81 (1.00–7.84) |
| ECOG PS at first-line   |   |                |         |   |                |         |
| 0–1                     | 33 | Ref           | 0.58     | Ref | 0.92 (0.28–3.03) | 0.89 |
| 2–4                     | 6  | 0.72 (0.22–2.35) | 0.92 (0.28–3.03) |
| ECOG PS at second-line  |   |                |         |   |                |         |
| 0–1                     | 23 | Ref           | 0.0027   | Ref | 3.19 (1.25–8.18) | 0.015 |
| 2–4                     | 16 | 5.05 (1.75–14.53) | 3.19 (1.25–8.18) |
| Second-line treatment   |   |                |         |   |                |         |
| TKIs                    | 11 | Ref           | 0.90     | Ref | 0.74 (0.26–2.12) | 0.57 |
| Chemotherapy            | 28 | 1.06 (0.42–2.65) | 0.74 (0.26–2.12) |
| Liver metastasis        |   |                |         |   |                |         |
| Negative                | 36 | Ref           | 0.13     | Ref | 0.44 (0.08–2.35) | 0.33 |
| Positive                | 3  | 3.45 (0.70–16.87) | 0.44 (0.08–2.35) |
| Bone metastasis         |   |                |         |   |                |         |
| Negative                | 27 | Ref           | 0.47     | Ref | 3.06 (1.00–9.36) | 0.050 |
| Positive                | 12 | 5.45 (1.83–16.28) | 3.06 (1.00–9.36) |
| Brain metastasis        |   |                |         |   |                |         |
| Negative                | 32 | Ref           | 0.0024   | Ref | 1.89 (0.60–6.00) | 0.28 |
| Positive                | 7  | 5.36 (1.81–15.81) | 1.89 (0.60–6.00) |

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; TKIs, tyrosine kinase inhibitors.
analysis. A poor ECOG PS may influence the selection of EGFR TKI for a second-line treatment because the frequency of adverse effects is less using TKIs. However, conducting a similar prospective study is challenging because it would be against the interests of, and possibly detrimental to, patients with poor ECOG PS. A study conducted using real-world data before the launch of osimertinib revealed that there was no difference in OS between second-line treatments and that ECOG PS was a prognostic factor. ECOG PS improved in T790M-positive lung cancer patients after treatment with osimertinib. However, real-world data showed that the median OS (9 months) of patients with ECOG PS ≥2 patients treated with osimertinib as second-line therapy was shorter than patients with ECOG PS 0 or 1.

Clinical trials are currently underway to assess the efficacy of novel molecular-targeted drugs or immune checkpoint inhibitors in EGFR-mutated lung adenocarcinoma patients with T790M-negative or with an unknown mutation. These studies may provide new strategies for treating patients with EGFR mutation-associated NSCLC with T790M-negative or unidentified mutations.

The inclusion of patients from a single-institution, the retrospective nature of our study, and the small number of cases are limitations of our current study. Another limitation of our study is the inclusion of cases in which the T790M test was not performed (53.8%) because the patients died before osimertinib was available in Japan. Future studies should validate the results reported here in a larger population and in patients from multiple institutions.

In conclusion, the present results showed no significant difference in PFS and OS between the chemotherapy and TKI groups for second-line treatment in EGFR-mutated NSCLC patients with T790M-negative mutation or unidentified mutations that received EGFR tyrosine kinase inhibitors as first-line treatment.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

ORCID
Tadashi Nishimura https://orcid.org/0000-0002-1688-1602
Esteban C. Gabazza https://orcid.org/0000-0003-2536-898X

REFERENCES
1. Dearden S, Stevens J, Wu YL, Blowers D. Mutation incidence and coincidence in non-small cell lung cancer: Meta-analyses by ethnicity and histology (mutMap). Ann Oncol. 2013;24:2371–6.
2. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: A systematic review and global map by ethnicity (mutMapII). Am J Cancer Res. 2015;5:2892–911.
3. Lee CK, Davies L, Wu YL, Mitsudomi T, Inoue A, Rosell R, et al. Gefitinib or Erlotinib vs chemotherapy for EGFR mutation-positive lung cancer: Individual patient data meta-analysis of overall survival. J Natl Cancer Inst. 2017;109.
4. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saigo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947–57.
5. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239–46.
6. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small cell lung cancer harbouring EGFR mutations (LUX-lung 6): An open-label, randomised phase 3 trial. Lancet Oncol. 2014;15:213–22.
7. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376:629–40.
8. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378:113–25.
9. Ramalingam SS, Vansteenkiste J, Planchar D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020;382:41–50.
10. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
11. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. 2011;3:75ra26.
12. Mok TSK, Kim SW, Wu YL, Nakagawa K, Yang JJ, Ahn MJ, et al. Gefitinib plus chemotherapy versus chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer resistant to first-line gefitinib (IMPRESS): Overall survival and biomarker analyses. J Clin Oncol. 2017;35:4027–34.
13. Park K, Yoo CJ, Kim SW, Lin MC, Suriyapong V, Tsai CM, et al. First-line Erlotinib therapy until and beyond response evaluation criteria in solid tumors progression in Asian patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer: The ASPIRATION study. JAMA Oncol. 2016;2:305–12.
14. Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): A phase 3 randomised trial. Lancet Oncol. 2015;16:990–8.
15. Furuya N, Ito K, Sakaguchi T, Hida N, Kakinuma K, Morikawa K, et al. The impact of EGFR mutation status and brain metastasis for non-small cell lung cancer treated with Ramucirumab plus docetaxel. Oncology. 2020;98:661–8.
16. Hattori Y, Satouchi M, Shimada T, Urata Y, Yoneda T, Mori M, et al. A phase 2 study of bevacizumab in combination with carboplatin and paclitaxel in patients with non-squamous non-small-cell lung cancer harboring mutations of epidermal growth factor receptor (EGFR) after failing first-line EGFR-tyrosine kinase inhibitors (HANSHIN oncology group 0109). Lung Cancer. 2015;87:136–40.
17. Masuda T, Imai H, Kuwako T, Miura Y, Yoshino R, Kaira K, et al. Efficacy of platinum combination chemotherapy after first-line gefitinib treatment in non-small cell lung cancer patients harboring sensitive EGFR mutations. Clin Transl Oncol. 2015;17:702–9.
18. Miyachi E, Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, et al. Efficacy of chemotherapy after first-line gefitinib therapy in EGFR mutation-positive advanced non-small cell lung cancer data from a randomized phase III study comparing gefitinib with carboplatin plus paclitaxel (NEJ002). Jpn J Clin Oncol. 2015;45:670–6.
19. Yang CJ, Tsai MJ, Hung JY, Liu TC, Chou SH, Lee JY, et al. Pemetrexed had significantly better clinical efficacy in patients with stage IV lung adenocarcinoma with susceptible EGFR mutations receiving platinum-based chemotherapy after developing resistance to the first-line gefitinib treatment. Onco Targets Ther. 2016;9:1579–87.
20. Yoshioka H, Shimokawa M, Seto T, Morita S, Yatabe Y, Okamoto I, et al. Final overall survival results of WJTOG3405, a randomized
phase III trial comparing gefitinib versus cisplatin with docetaxel as the first-line treatment for patients with stage IIIIB/IV or postoperative recurrent EGFR mutation-positive non-small-cell lung cancer. Ann Oncol. 2019;30:1978–84.

21. Kohsaka S, Nagano M, Ueno T, Suehara Y, Hayashi T, Shimada N, et al. A method of high-throughput functional evaluation of EGFR gene variants of unknown significance in cancer. Sci Transl Med. 2017;9:eaan6566.

22. Cho BC, Im CK, Park MS, Kim SK, Chang J, Park JP, et al. Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. J Clin Oncol. 2007;25:2528–33.

23. Horiike A, Yamamoto N, Tanaka H, Yanagitani N, Kudo K, Ohyanagi F, et al. Phase II study of erlotinib for acquired resistance to gefitinib in patients with advanced non-small cell lung cancer. Anticancer Res. 2014;34:1975–81.

24. Katakami N, Atagi S, Goto K, Hida T, Horai T, Inoue A, 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.

25. Miller VA, Hirsh V, Cadranel J, Chen YM, Park K, Kim SW, 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.

26. Okamoto I, Morita S, Tashiro N, Imamura F, Inoue A, Seto T, et al. Real world treatment and outcomes in EGFR mutation-positive non-small cell lung cancer: Long-term follow-up of a large patient cohort. Lung Cancer. 2018;117:14–9.

27. Nakashima K, Kimura M, Akamatsu H, Daga H, Imai H, Taira T, et al. Osimertinib for patients with EGFR T790M mutation-positive non-small-cell lung cancer and a poor performance status. Jpn J Clin Oncol. 2019;49:671–5.

28. Hochmair MJ, Morabito A, Hao D, Yang CT, Soo RA, Yang JCH, et al. Sequential afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: Updated analysis of the observational GioTag study. Future Oncol. 2019;15:2905–14.

29. Liao BC, Griesing S, Yang JC. Second-line treatment of EGFR T790M-negative non-small cell lung cancer patients. Ther Adv Med Oncol. 2019;11:1758835919890286.

How to cite this article: Nishimura T, Okano T, Naito M, et al. Second-line therapy with first- or second-generation tyrosine kinase inhibitors in EGFR-mutated non-small cell lung cancer patients with T790M-negative or unidentified mutation. Thorac Cancer. 2021;12:1067–1073. https://doi.org/10.1111/1759-7714.13870