Treatment of Non-small Cell Lung Cancer with $EGFR$-mutations

Kazue Yoneda, Naoko Imanishi, Yoshinobu Ichiki and Fumihiro Tanaka*

Second Department of Surgery (Chest Surgery), School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan

Abstract: The discovery of activating mutations in the epidermal growth factor receptor ($EGFR$) gene and development of tyrosine kinase inhibitors (TKIs) of $EGFR$ have achieved a paradigm shift in treatment strategy of non-small cell lung cancer (NSCLC). For advanced NSCLC harboring activating $EGFR$ mutations, an $EGFR$-TKI is preferably prescribed as it provides a superior survival benefit over platinum-based chemotherapy. To further improve the therapeutic outcomes, more potent $EGFR$-TKIs through irreversible inhibition of tyrosine kinase have been developed. In a recent clinical trial, an irreversible $EGFR$-TKI (osimertinib) showed a superior survival benefit with lower toxicity profile. In addition, combination treatments such as an $EGFR$-TKI plus platinum-based chemotherapy may achieve a long-term survival. For earlier-stage resectable NSCLC with $EGFR$-mutations, several clinical trials to assess the efficacy of $EGFR$-TKIs in pre-operative induction setting and in postoperative adjuvant setting are now ongoing. Here we review and discuss the current status and future perspectives of treatment for $EGFR$-mutated NSCLC.

Keywords: epidermal growth factor receptor (EGFR), activating mutation, resistance mutation, tyrosine kinase inhibitor (TKI), lung cancer.

(Received November 13, 2018, accepted December 26, 2018)

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide [1], and is clinically classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [2]. NSCLC comprises various histologic types such as squamous cell carcinoma and adenocarcinoma, which accounts for approximately 85% of lung cancer. Surgery is the most effective treatment, but is indicated only for a small subset of patients, as the majority of NSCLC patients present at an advanced stage of disease [1, 2]. For advanced NSCLC patients, systemic treatment with cytotoxic agents is usually employed as a standard treatment of care [3, 4]. However, the current standard platinum-based chemotherapy has provided only a modest survival benefit for advanced NSCLC patients, with the overall survival (OS) of less than 2 years [5, 6]. The discovery of activating mutations in the epidermal growth factor receptor (EGFR) gene and development of tyrosine kinase inhibitors (TKIs) of EGFR have provided a tremendous impact on treatment strategy for advanced NSCLC patients (Fig. 1) [2, 7–9]. EGFR-TKIs provide superior anti-tumor activity over platinum-based chemotherapy for NSCLC harboring $EGFR$ mutations [2–4]. Accordingly, genotyping of $EGFR$ mutations is mandatory in decision-making of systemic treatment for advanced NSCLC, especially NSCLC other than squamous cell carcinoma (non-Sq), as $EGFR$ mutations are commonly seen in non-Sq NSCLC [2–4, 10]. Here we review the

*Corresponding Author: Fumihiro Tanaka, Second Department of Surgery (Chest Surgery), School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan, Tel: +81-93-691-7442, Fax: +81-93-692-4004, E-mail: ftanaka@med.uoeh-u.ac.jp
current status and discuss the treatment strategy for
EGFR-mutated NSCLC.

EGFR and discovery of activating EGFR mutations

The epidermal growth factor receptor (EGFR), a
transmembrane receptor, plays important roles in nor-
mal biological processes, including cell proliferation
and migration (Fig. 2A). When a specific ligand such
as epidermal growth factor (EGF) binds to the extra-
cellular ligand-binding domain, EGFR forms either
homo-dimer with EGFR or hetero-dimer with other
EGFR family members (HER-2, HER-3, HER-4),
leading to activation of the intracellular tyrosine kinase
(TK) domain through increasing the binding affinity
for adenosine triphosphate (ATP). Subsequently, mul-
tiple downstream signaling pathways were activated
through auto-phosphorylation of tyrosine residues,
which results in accelerated cell proliferation and mi-
gration, prolonged cell survival via evasion from apop-
tosis, and promoted angiogenesis (Fig. 2B) [9].

The EGFR gene comprises 28 exons, and exons 18–
21 encode the “cleft” for ATP-binding within the TK
domain (Fig. 2A). In 2004, somatic mutations in exons
18–21 of the EGFR gene, which caused ligand-indepen-
dent activation of tyrosine kinase of EGFR, were identi-
fied in NSCLC [7, 8]. Since the discovery, a variety
of activating EGFR mutations have been revealed pre-
dominantly in East Asian patients with lung adenocar-
cinoma [9, 11]. The most common mutations are dele-
tions in exon 19, affecting elimination of 5 amino-acid
sequences including “leucine (L) at codon 747, arginine
(R) at codon 748, glutamic acid (E) at codon 749 and
alanine (A) at codon 750” (ΔLREA), and the point mu-
tation in exon 21 affecting a “leucine (L) to arginine (R)
substitution at codon 858” (L858R) (Fig. 3). These ac-
tivating mutations are oncogenic through constitutive
tyrosine kinase activation of EGFR, and are responsible
for development and progression in approximately 50%
of lung adenocarcinoma in Japan [9, 11, 12].

Development of EGFR-TKIs (Table 1)

Inhibition of tyrosine kinase activity of EGFR may
provide a significant anti-tumor effect for EGFR-mutat-
ed tumor in which tumor progression solely depends on
tyrosine kinase activation caused by EGFR mutations
[9]. Gefitinib is the first approved agent targeting the
tyrosine kinase of EGFR, which competitively inhibits
ATP-binding to the TK domain (Fig. 4). As expected,
a large-scale clinical study (IRESSA Pan-Asia Study
[IPASS]) showed that gefitinib provided a striking anti-
tumor activity for lung adenocarcinoma with
EGFR mutations [9]. Gefitinib is the first approved agent targeting the
tyrosine kinase of EGFR, which competitively inhibits
ATP-binding to the TK domain (Fig. 4). As expected,
a large-scale clinical study (IRESSA Pan-Asia Study
[IPASS]) showed that gefitinib provided a striking anti-
tumor activity for lung adenocarcinoma with
EGFR mutations (overall response rate [ORR], 71.2%), but
not for that without EGFR-mutations (ORR, 1.1%) [13]. Erlotinib is also a competitive inhibitor of TK,
and gefitinib or erlotinib (“first-generation” EGFR-
TKI) showed a significantly longer progression-free
survival (PFS) as compared with platinum-based che-
motherapy in first-line treatment for EGFR-mutated
NSCLC patients in several phase 3 randomized con-
trolled trials [14–20] (Fig. 5).

Although a majority of EGFR-mutated NSCLC pa-
tients initially respond to gefitinib or erlotinib, patients
usually develop a progressive disease in one year after
initiation of treatment (“acquired resistance”) [9, 21]
(Fig. 6). The most frequent molecular mechanism re-
sponsible for the acquired resistance is the develop-
ment of a second mutation in exon 20 of the EGFR gene af-
flicting a “threonine (T) to methionine (M) substitution
at codon 790” (T790M), which appears in 50–60% of
EGFR-mutated non-small cell lung cancer

patients with acquired resistance after treatment with a first-generation EGFR-TKI [22]. The T790M substitution may cause both increase in binding affinity of ATP and decrease in binding affinity of a first-generation EGFR-TKI, which allows tyrosine kinase activation by ATP-binding to the TK domain even in the presence of gefitinib or erlotinib [23–25].

To overcome acquired resistance caused by T790M, second-generation EGFR-TKIs such as afatinib and dacomitinib have been developed (Table 1) [9, 26]. These agents have shown more potent inhibition of TK activity through covalent and irreversible binding to the cysteine at codon 797 (C797) in the TK domain (Fig. 4). In fact, two randomized controlled studies (LUX-Lung 7 and ARCHER1050) showed each irreversible EGFR-TKI achieved a superior PFS over gefitinib [27, 28]. More importantly, in experimental studies, second-generation EGFR-TKIs can inhibit tyrosine kinase activation of EGFR even when T790M is present, in addition to activating mutations [29], suggesting that second-generation EGFR-TKIs may be effective for patients with acquired resistance. However, in clinical studies, afatinib showed only a limited anti-tumor activity in lung cancer that progressed after treatment with first-generation EGFR-TKIs (ORR, less than 10%) [30, 31]. Second-generation EGFR-TKIs
Fig. 3. Oncogenic mutations in the epidermal growth factor receptor (EGFR) gene. Deletions in exon19 affecting elimination of amino-acid sequences of “leucine (L) at codon 747 through alanine (A) at codon 750” (Δ LREA) and a point mutation in the exon 21 affecting “leucine (L) to arginine (R) substitution” at codon 858 (L858R) are oncogenic through ligand-independent constitutive activation of the EGFR. Dimerization partner in activated form of mutated EGFR is deleted in the figure (Reprinted by permission from the Springer Nature Customer Service Center GmbH: Springer Nature Singapore, Molecular diagnosis and targeting for lung cancer by Yoneda K and Tanaka F. In: Molecular Diagnosis and Targeting for Thoracic and Gastrointestinal Malignancy. [Shimada Y and Yanaga K, ed], 2018 [9]). T: thymine, G: guanine, U: uracil, Δ LREA: Deletions in exon19 affecting elimination of amino-acid sequences of “leucine (L) at codon 747 through alanine (A) at codon 750” of the EGFR gene, L858R: point mutation in the exon 21 affecting “leucine (L) to arginine (R) substitution” at codon 858 of the EGFR gene, ATP: adenosine triphosphate, Y: tyrosine, PI3K: phosphatidylinositol-3 kinase, mTOR: mammalian target of rapamycin, Jak: Janus kinase, STAT: signal transducer and activator of transcription, MEK: mitogen-activated protein kinase/ERK kinase, ERK: extracellular-signal-regulated kinase.

Table 1. Characteristics of currently available tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) for non-small cell lung cancer

| Classification | First generation | Second generation | Third generation |
|----------------|-----------------|------------------|-----------------|
| Agent          | Gefitinib       | Erlotinib        | Afatinib        |
| Chemical structure | Quinazoline compound | Pyrimidine compound |
| Mode of inhibition | Reversible inhibition by competition with ATP | Irreversible inhibition by covalent binding to the cysteine at codon 797 in the tyrosine kinase domain |

IC50 in inhibiting in vitro cell proliferation (nmol/l) (data from [32])

| PC-9 VnR (Del19+T790M) | 4232 | 5778 | 679 | 531 | 11 |
| Calu3 (WT) | 1933 | 4101 | 071 | 65 | 650 |
| NCI-H2079 (WT) | 200 | 692 | 30 | 54 | 461 |
| PC-9 (Del19) | 23 | 28 | 0.8 | 0.4 | 8 |
| H1975 (L858R+T790M) | 6962 | 6165 | 483 | 335 | 11 |

Clinical indication (in Japan)

- Advanced NSCLC with activating EGFR mutations
- Not approved
- Advanced NSCLC with activating EGFR mutations (when no prior EGFR-TKI) or with T790M in addition to activating EGFR mutations (upon PD after EGFR-TKI)

EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor, NSCLC: non-small cell lung cancer, ATP: adenosine triphosphate, IC50: half maximal inhibitory concentration, WT: wild type, Del19: Exon 19 deletion, L858R: “leucine (L) to arginine (R) substitution” at codon 858, T790M: “threonine (T) to methionine (M) substitution” at codon 790, PD: progressive disease
**EGFR-mutated non-small cell lung cancer**

**Fig. 4. Tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR).** Activated tyrosine kinase (TK) of the epidermal growth factor receptor (EGFR) can be effectively inhibited by a reversible inhibitor by competitive inhibition or by an irreversible inhibitor by covalent binding to the cysteine (C) at codon 797 (C797) (Reprinted by permission from the Springer Nature Customer Service Center GmbH: Springer Nature Singapore, Molecular diagnosis and targeting for lung cancer by Yoneda K and Tanaka F. In: Molecular Diagnosis and Targeting for Thoracic and Gastrointestinal Malignancy. [Shimada Y and Yanaga K, ed], 2018 [9]). A LREA: Deletions in exon19 affecting elimination of amino-acid sequences of “leucine (L) at codon 747 through alanine (A) at codon 750” of the epidermal growth factor receptor (EGFR) gene, L858R: point mutation in the exon 21 affecting “leucine (L) to arginine (R) substitution” at codon 858 of the EGFR gene, ATP: adenosine triphosphate, Y: tyrosine, Q: glutamine, L: leucine, M: methionine, P: proline, F: phenylalanine, G: glycine, C: cysteine.

**Fig. 5. Phase 3 randomized controlled trials comparing tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) and platinum-based chemotherapy as first-line treatment for advanced non-small cell lung cancer (NSCLC) with activating EGFR mutations.** All phase 3 randomized controlled trials showed a significantly longer progression-free survival (PFS) treated with tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) as first-line treatment for advanced non-small cell lung cancer (NSCLC) harboring activating EGFR mutations. NEJ: North East Japan Study Group, WJTOG: West Japan Thoracic Oncology Group.
are associated with higher toxicity through inhibition of TK activity of wild-type EGFR as well as mutated EGFR, and may not be prescribed at higher doses that are enough to overcome acquired resistance (Table 1).

Osimertinib is a third-generation EGFR-TKI that selectively inhibits mutated-EGFR through irreversible and covalent binding to C797 in the TK domain (Fig. 4 and Table 1) [9, 26, 32, 33]. In a phase 3 trial comparing osimertinib with chemotherapy for patients who developed acquired resistance caused by T790M after first-line EGFR-TKI treatment (AURA3 trial), osimertinib showed a superior PFS over chemotherapy (10.1 months versus 4.4 months; hazard ratio [HR], 0.30; \( P < 0.001 \)) [34]. Based on those results, osimertinib has been approved and recommended for the treatment of acquired resistant with T790M after treatment with gefitinib, erlotinib or afatinib. More recently, in a phase 3 trial comparing osimertinib with a first-generation EGFR-TKI (gefitinib or erlotinib) in the first-line treatment of patients with activating EGFR mutations (FLAURA trial), osimertinib showed a significantly better PFS (18.9 months versus 10.2 months; HR, 0.46; \( P < 0.001 \)) [35]. Of note, as osimertinib may selectively inhibit TK activity of mutated EGFR, severe adverse events were less frequent in patients treated with osimertinib.

Treatment strategy for EGFR-mutated NSCLC

First-generation reversible EGFR-TKIs, gefitinib and erlotinib, have led to a paradigm-shift in the treatment
of advanced NSCLC, and had been predominantly prescribed in the first-line systemic treatment for NSCLC harboring activating EGFR mutations [2–4]. However, recent clinical studies have shown that irreversible EGFR-TKIs achieved superior survival benefits [27, 28, 35]. In addition, combination treatments using first-generation EGFR-TKIs such as gefitinib plus platinum-based chemotherapy and erlotinib plus bevacizumab provided superior survival benefits (Fig. 7) [36–38]. Accordingly, a single-agent reversible EGFR-TKI (gefitinib or erlotinib) may no longer be preferably prescribed as a standard care of treatment for untreated EGFR-mutated NSCLC, which shall be replaced either by a single-agent irreversible EGFR-TKI or by a combination treatment using an EGFR-TKI. Among them, a combination treatment may be associated with increased toxicity which may cause a significant reduction in quality of life of patients, and a single-agent treatment with a second-generation or third-generation EGFR-TKI may be a preferable treatment option for most patients with advanced NSCLC with activating EGFR mutations (Fig. 8).

When a third-generation EGFR-TKI, osimertinib, was employed in a first-line treatment, a longer PFS was achieved with the median PFS of 18.9 months in the FLAURA trial [35]. On disease progression, platinum-based chemotherapy is usually employed as a subsequent treatment, which may prevent disease progression during a definite time period. In the FLAURA trial, the first-line osimertinib following a second-line treatment achieved a longer PFS in total (> 26.0 months) [35]. When the second-generation EGFR-TKI, afatinib, is prescribed in the first-line treatment, the expected PFS may be shorter with the median PFS of 11.0 months in the LUX-Lung 7 trial [27]. However, when T790M is detected on tumor progression either in tumor tissue or in the plasma, osimertinib can be employed as a subsequent treatment, which may further achieve a longer PFS with the median PFS of 10.1 months in the AURA3 trial [34]. As a result, the sequential treatment with afatinib followed by osimertinib might achieve the longest OS for advanced NSCLC with activating EGFR mutations. On the other hand, when T790M is not detected on tumor progression after first-line afatinib treatment, osimertinib is not indicated and platinum-based chemotherapy is employed as a subsequent treatment. Such patients may die due to tumor progression without osimertinib treatment during the entire

Fig. 7. Randomized controlled trials evaluating irreversible tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) or combination treatments using EGFR-TKIs. Three randomized controlled trials compared irreversible tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) with reversible EGFR-TKIs, and three randomized controlled trials compared combination treatments using reversible EGFR-TKIs with single-agent reversible EGFR-TKIs. The LUX-Lung 7 and the JO25567 were randomized phase 2 trials, and the others were phase 3 trials. EGFR-TKI: tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR), Cb/PEM: chemotherapy with carboplatin plus pemetrexed, NEJ: North East Japan Study Group.
clinical course (Fig. 8). In fact, in the FLAURA trial, only a small subset (26%) of patients, who progressed after assigned first-line treatment with either gefitinib or erlotinib, actually received subsequent treatment with osimertinib [35]. Accordingly, osimertinib may be preferably prescribed as a standard treatment of care in the first-line treatment for advanced NSCLC harboring activating EGFR-mutations.

Conclusions

The discovery of activating EGFR mutations in NSCLC and development of tyrosine kinase inhibitors of EGFR have launched the era of personalized medicine in advanced NSCLC. Tumor genotyping of EGFR and other oncogenic driver mutations is essential in decision-making of treatment for advanced NSCLC. For advanced NSCLC harboring activating EGFR mutations, first-line treatment with an EGFR-TKI is recommended as a standard treatment of care, and now a third-generation EGFR-TKI (osimertinib) may be preferably prescribed due to higher survival benefit and lower toxicity. For early-stage EGFR-mutated NSCLC, a recent phase 3 trial showed a significant survival benefit with adjuvant gefitinib treatment following surgery [39]. Ongoing trials may reveal the clinical benefit of EGFR-TKIs in post-operative adjuvant setting for resectable EGFR-mutated NSCLC.

Conflicts of Interest

F Tanaka has received lecture fees and research funds from Chugai Pharmaceutical Co. Ltd., AstraZeneca Co. Ltd., Taiho Pharmaceutical Co. Ltd., and MSD Co. Ltd. K Yoneda, N Imanishi, and Y Ichiki have no conflict of interest.

Acknowledgements

This study was supported in part by the UOEH Grant for Advanced Research (for F Tanaka) and the UOEH Research Grant for Promotion of Occupational Health (for K Yoneda).

References

1. Siegel RL, Miller KD & Jemal A (2018): Cancer statistics, 2018. CA Cancer J Clin 68: 7–30
2. Herbst RS, Heymach JV & Lippman SM (2008): Lung cancer. N Engl J Med 359: 1367–1380
3. Hanna N, Johnson D, Temin S et al (2017): Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35: 3484–3515
4. Hsu WH, Yang JC, Mok TS & Loong HH (2018): Overview of current systemic management of EGFR-mutant NSCLC. Ann Oncol 29 (suppl 1): i3–i9
5. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J & Johnson DH (2002): Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346: 92–98
6. Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saigo N, Ariyoshi Y & Fukuoka M (2007): Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Co-operative Study in Japan. Ann Oncol 18: 317–323
7. Lynch TJ, Bell DW, Sordella R et al (2004): Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350: 2129–2139
8. Paez JG, Jänne PA, Lee JC et al (2004): EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304: 1497–1500
9. Yoneda K & Tanaka F (2018): Molecular diagnosis and targeting for lung cancer. In: Molecular Diagnosis and Targeting for Thoracic and Gastrointestinal Malignancy. (Shimada Y & Yanaga K, ed). Springer Nature Singapore, Singapore pp 1–32
10. Kalemkerian GP, Narula N, Kennedy EB et al (2018): Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/IACAP/International Association for the Study of Lung Cancer/Association for molecular pathology clinical practice guideline update. J Clin Oncol 36: 911–919
11. Kobayashi Y & Mitsudomi T (2016): Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. Cancer Sci 107: 1179–1186
12. Saito M, Shiraiishi K, Kunitoh H, Takenoshita S, Yokota J & Kohno T (2016): Gene aberrations for precision medicine against lung adenocarcinoma. Cancer Sci 107: 713–720
13. Mok TS, Wu YL, Thongprasert S et al (2009): Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361: 947–957
14. Maemondo M, Inoue A, Kobayashi K et al (2010): Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362: 2380–2388
15. Mitsudomi T, Morita S, Yatabe Y et al (2010): Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11: 121–128
16. Zhou C, Wu YL, Chen G et al (2011): 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 12: 735–742
17. Rosell R, Carcereny E, Gervais R et al (2012): 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 13: 239–246
18. Wu YL, Zhou C, Lianck CK et al (2015): First-line erlotinib versus carboplatin-gemcitabine in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol 26: 1883–1889
19. Sequist LV, Yang JC, Yamamoto N et al (2013): Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31: 3327–3334
20. Wu YL, Zhou C, Hu CP et al (2014): 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 15: 213–222
21. Zhou C & Yao LD (2016): Strategies to improve outcomes of patients with EGFR-mutant non-small cell lung cancer: Review of the literature. J Thorac Oncol 11: 174–186
22. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, Kris MG, Miller VA, Ladanyi M & Riely GJ (2013): Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 pa-
Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG & Halmos B (2005): EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 352: 786–792

Kwak EL, Sordella R, Bell DW et al (2005): Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. Proc Natl Acad Sci U S A 102: 7665–7670

Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, Meyerson M & Eck MJ (2008): The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci USA 105: 2070–2075

Hossam M, Lasheen DS & Abouzid KA (2016): Covalent EGFR inhibitors: Binding mechanisms, synthetic approaches, and clinical profiles. Arch Pharm (Weinheim) 349: 573–593

Park K, Tan EH, O’Byrne K et al (2016): Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 17: 577–589

Wu YL, Cheng Y, Zhou X et al (2017): Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 18: 1454–1466

Li D, Ambrogio L, Shimamura T et al (2008): BIBW 2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene 27: 4702–4711

Miller VA, Hirsh V, Cadranel J et al (2012): 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 13: 528–538

Katakami N, Atagi S, Goto K et al (2013): 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 31: 3335–3341

Cross DA, Ashton SE, Ghiorghiu S et al (2014): AZD 9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 4: 1046–1061

Erkan D, Choi HG, Yun CH, Capelletti M, Xie T, Eck MJ, Gray NS & Jänne PA (2015): EGFR mutations and resistance to irreversible pyrimidine-based EGFR inhibitors. Clin Cancer Res 21: 3913–3923

Mok TS, Wu Y-L, Ahn MJ et al (2017): Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 376: 629–640

Soria JC, Ohe Y, Vansteenkiste J et al (2018): Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 378: 113–125

Seto T, Kato T, Nishio M et al (2014): Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol 15: 1236–1244

Furuya N, Fukushima T, Saito H et al (2018): Phase III study comparing bevacizumab plus erlotinib to erlotinib in patients with untreated NSCLC harboring activating EGFR mutations: NEJ026. J Clin Oncol 36 (suppl 15): 9006

Nakamura A, Inoue A, Morita S et al (2018): Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). J Clin Oncol 36 (suppl 15): 9005

Zhong WZ, Wang Q, Mao WM et al (2018): Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomized, open-label, phase 3 study. Lancet Oncol 19: 139–148
EGFR遺伝子変異陽性非小細胞肺がん（NSCLC）の治療

米田 和恵，今西 直子，市来 嘉伸，田中 文啓
産業医科大学 医学部 第2外科学講座

要　旨：上皮成長因子受容体（EGFR）遺伝子の活性化変異の発見とEGFRチロシンキナーゼ阻害剤（TKIs）の開発は、非小細胞肺がん（NSCLC）の治療戦略に変革をもたらした。EGFR変異を有する進行非小細胞肺がんに対しては、EGFRチロシンキナーゼ阻害剤はプラチナ製剤を含む化学療法よりも優れた生存期間の延長効果を認めるため、EGFRチロシンキナーゼ阻害剤が優先的に治療に用いられる。更に治療効果を高めるため、不可逆的なEGFR阻害に由ってより効果的な阻害作用を発揮するEGFRチロシンキナーゼ阻害剤が開発された。最近の臨床試験により、不可逆的EGFRチロシンキナーゼ阻害剤であるオシメルチニブは、優れた生存期間延長効果と低い毒性をもたらすことが示された。また、EGFRチロシンキナーゼ阻害剤とプラチナ併用化学療法等との併用治療も、長期の生存をもたらす可能性が示されている。EGFR変異を有する早期の切除可能非小細胞肺がんについても、術前導入療法や術後補助療法におけるEGFRチロシンキナーゼ阻害剤の効果を検証するいくつかの臨床試験が進行中である。本稿では、EGFR変異陽性の非小細胞肺がんに対する治療の現状と将来展望につき概説および議論する。

キーワード：上皮成長因子受容体（EGFR）、活性化変異、耐性変異、チロシンキナーゼ阻害剤（TKI）、肺がん。