# Comparison of Gefitinib *Versus* Chemotherapy in Patients with Non-small Cell Lung Cancer with Exon 19 Deletion

SATOSHI WATANABE[1], AKIRA INOUE[2], TOSHIHIRO NUKIWA[3] and KUNIHIKO KOBAYASHI[4]

[1]*Department of Respiratory Medicine and Infectious Disease, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori, Niigata, Japan;*
[2]*Department of Respiratory Medicine, Tohoku University, Aobaku, Sendai, Japan;*
[3]*Japan Anti-Tuberculosis Association, Chiyoda-ku, Tokyo, Japan;*
[4]*Respiratory Medicine, Saitama International Medical Center, Hidaka City, Saitama, Japan*

**Abstract**. *Background: Second-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) afatinib as first-line treatment has been demonstrated to improve overall survival (OS) in patients with non-small cell lung cancer (NSCLC) harboring an exon 19 deletion (del19) of EGFR compared to platinum-doublet chemotherapy. However, it is unclear whether first-generation EGFR-TKIs improve OS in patients with del19 in the first-line treatment. Patients and Methods: We performed a post-hoc analysis of patients with del19 or L858R mutation of EGFR who received gefitinib in the NEJ002 study, which compared gefitinib to carboplatin-paclitaxel. Results: A total of 58 patients and 57 patients with del19 EGFR received gefitinib and carboplatin-paclitaxel, respectively. No OS differences were observed between patients receiving gefitinib and carboplatin-paclitaxel irrespective of del19 (29.3 months vs. 29.7 months, p=0.53) or L858R (28.4 months vs. 25.1 months, p=0.45). Conclusion: In contrast to afatinib, it is suggested that first-line gefitinib does not improve OS in patients with del19 of EGFR compared with platinum-doublet chemotherapy.*

The clinical efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) has been demonstrated in patients with non-small cell lung cancer (NSCLC) harboring activating *EGFR* mutations (1, 2). Previous randomized phase III studies have proven that the first-generation reversible EGFR-TKIs, such as gefitinib and erlotinib, significantly improve progression-free survival (PFS) compared to platinum-doublet chemotherapy in patients with NSCLC with *EGFR* mutations (3-6). By contrast, gefitinib and erlotinib failed to produce an improvement in overall survival (OS) compared to platinum-doublet chemotherapy in these same studies. Recently, the results of the combined analysis of LUX-Lung 3 and LUX-Lung 6 studies were reported by Yang and colleagues (7). Both studies were open-label, multicenter, randomized phase III studies that compared the second-generation irreversible TKI, afatinib, with platinum-based chemotherapy (pemetrexed-cisplatin in LUX-Lung 3, and gemcitabine-cisplatin in LUX-Lung 6) in previously untreated patients with EGFR mutation-positive lung adenocarcinoma (8, 9). The primary end-point of these studies was PFS, which was significantly longer in the afatinib-treated group compared to the chemotherapy-treated group. Importantly, this combined analysis of LUX-Lung 3 and LUX-Lung 6 demonstrated that compared to first-line chemotherapy, first-line afatinib significantly improved OS in patients with an exon 19 deletion (del19) of *EGFR* but not in patients with the L858R mutation. In previous phase III studies comparing gefitinib and erlotinib with chemotherapy, the OS differences by treatment group for patients with del19 or L858R have not been evaluated. To compare first-generation reversible TKI gefitinib with platinum-doublet chemotherapy in patients with del19 or the L858R mutation of *EGFR*, we reanalyzed the OS data from the NEJ002 study, which examined first-line gefitinib in patients with NSCLC with activating *EGFR* mutations (3).

*Correspondence to:* Satoshi Watanabe, Department of Respiratory Medicine and Infectious Disease, Niigata University Medical and Dental Hospital, 1-754, Asahimachi-dori, Niigata, 951-8510, Japan. Tel: +81 253689324, Fax: +81 253689326, e-mail: satoshi7@med.niigata-u.ac.jp

*Key Words:* Gefitinib, *EGFR* mutation, non-small cell lung cancer, exon 19 deletion, L858R.

## Materials and Methods

The eligibility criteria of the NEJ002 study (UMIN-CTR number, C000000376) included the presence of untreated advanced NSCLC harboring an EGFR mutation (del19 or L858R, G719X or L861Q point mutation) without presence of the resistant T790M EGFR mutation (identified using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method), an age of 75 years or younger, an Eastern Cooperative Oncology Group performance status

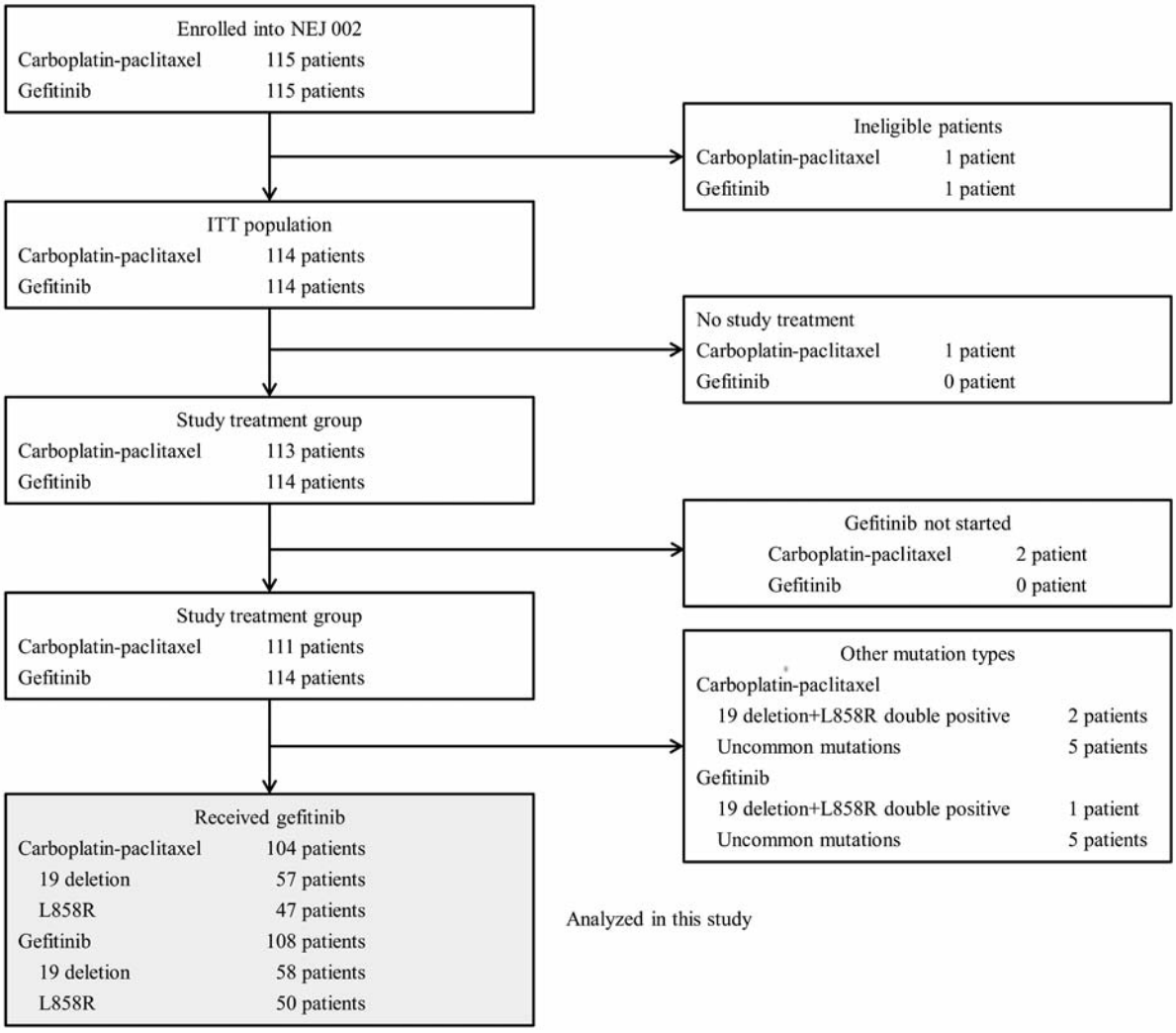



Figure 1. *Diagram showing patient registration, treatment assignments and exclusions. ITT: Intention-to-treat analysis.*

of 0-1 and adequate organ function (3). Patients were randomly assigned to gefitinib (250 mg/day) or paclitaxel (200 mg/m$^2$)/carboplatin (area under the blood concentration-time curve 6.0) on day 1 every 3 weeks (up to six cycles). The NEJ002 study recommended that the crossover regimen as second-line treatment.

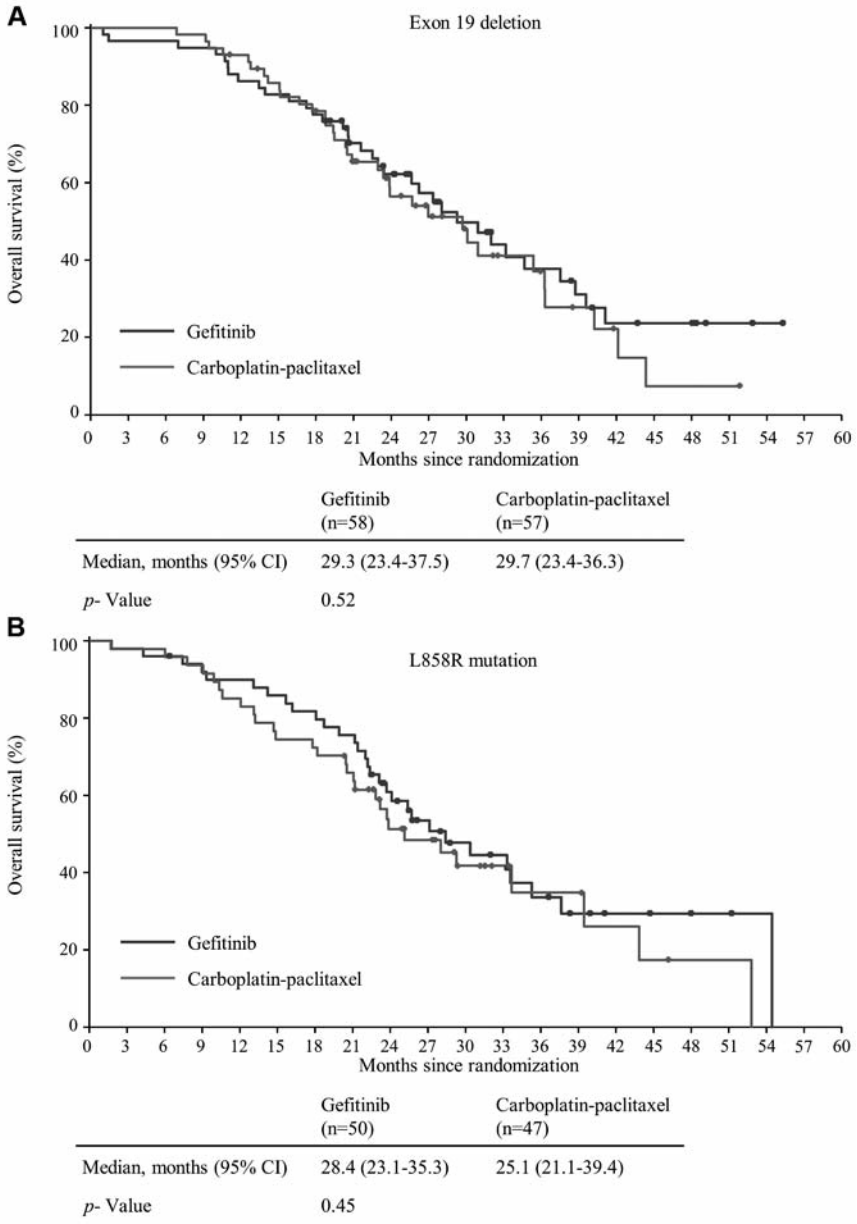
Kaplan–Meier survival curves were constructed for OS, and differences between groups were identified using the log-rank test. Differences in response rates were identified using Fisher's exact test. Each analysis was two-sided, with a 5% significance level and a 95% confidence interval. All analyses were performed using SAS for Windows software (release 9.1, SAS Institute, Cary, NC, USA).

Patients provided their written informed consent. The NEJ002 study was conducted in accordance with the Helsinki Declaration of the World Medical Association. The protocol was approved by the Institutional Review Board of each participating institution. This *post-hoc* analysis was also approved by the Research Ethics Committee of the Niigata University.

## Results

In total, 230 patients were enrolled in the NEJ002 study. In the carboplatin-paclitaxel group, 112 patients (98%) received gefitinib after disease progression (10). By contrast, in the gefitinib group, 74 patients (65%) were treated with platinum-doublet regimen as second-line or later chemotherapy. We identified 225 patients with del19 or L858R who received gefitinib at any point. Patients who had G719X, L861Q or both del19 and L858R were excluded (Figure 1). The data of a total of 212 patients were retrospectively analyzed in this *post-hoc* analysis.

In patients with *EGFR* del19, the OS did not differ significantly between the gefitinib-treated group and the carboplatin-paclitaxel-treated group (29.3 months *vs.* 29.7




| | Gefitinib (n=58) | Carboplatin-paclitaxel (n=57) |
|---|---|---|
| Median, months (95% CI) | 29.3 (23.4-37.5) | 29.7 (23.4-36.3) |
| *p*- Value | 0.52 | |

| | Gefitinib (n=50) | Carboplatin-paclitaxel (n=47) |
|---|---|---|
| Median, months (95% CI) | 28.4 (23.1-35.3) | 25.1 (21.1-39.4) |
| *p*- Value | 0.45 | |

Figure 2. *Kaplan–Meier curve for overall survival by treatment arm for patients with exon 19 deletion (A) and those with L858R mutation (B) of epidermal growth factor receptor gene.*

months, $p$=0.52; Figure 2). Similarly, the median OS was not significantly different between two treatment groups in patients with L858R (28.4 months *vs*. 25.1 months, respectively, $p$=0.45).

## Discussion

The combined analysis of LUX-Lung 3 and LUX-Lung 6 demonstrated that afatinib significantly prolonged OS compared to platinum-doublet chemotherapy in untreated patients with del19 of *EGFR* (7). In contrast to the results from the combined analysis of LUX-Lung 3 and LUX-Lung 6 studies, we observed no differences in OS between patients receiving gefitinib and patients receiving carboplatin-paclitaxel irrespective of del19 or L858R mutation of *EGFR*.

In contrast to NEJ002, in which most patients treated by first-line chemotherapy received gefitinib thereafter, only about two-thirds of the patients harboring *EGFR* del19

treated by the first-line chemotherapy received EGFR-TKI (75% and 53% of patients in LUX-LUNG 3 and LUX-LUNG 6, respectively) (7). Because an EGFR-TKI is the most important drug for patients with common EGFR mutations, the decrease in OS in patients with del19 who received first-line chemotherapy could be from the lower percentage of patients treated with EGFR-TKIs post-chemotherapy. Yang and his colleagues demonstrated that 91% of patients with del19 in countries with universal reimbursement policies for EGFR-TKIs received EGFR-TKIs post-chemotherapy in LUX-Lung 3 and LUX-Lung 6. In such countries, OS in patients with EGFR del19 receiving first-line afatinib was found to be increased compared with patients their counterparts receiving first-line chemotherapy. Because very few patients received afatinib in the chemotherapy-treated group, these findings suggested that afatinib has greater antitumor efficacy in patients with del19 compared with first-generation TKIs.

On the other hand, the combined analysis of LUX-Lung 3 and LUX-Lung 6 also demonstrated that OS did not significantly differ among patients receiving first-line afatinib compared to patients receiving first-line chemotherapy in the group with L858R mutation. Previous studies indicated that afatinib has greater antitumor efficacy compared to gefitinib in patients with uncommon mutations (11). Collectively, second-generation irreversible TKI afatinib, compared with first-generation reversible TKIs, appears to possess superior antitumor activity for patients with del19 and uncommon mutations but not those with the L858R mutation.

This *post-hoc* analysis clarifies that first-line gefitinib does not improve OS in patients with NSCLC with *EGFR* del19 compared to first-line platinum doublet chemotherapy, although first-line gefitinib contributed to maintaining quality of life (12). When using afatinib, the del19 and the L858R mutation of EGFR may need to be analyzed separately. Moreover, these findings should stimulate investigations to clarify the mechanisms underlying the different clinical responses to afatinib between patients with del19 and those with L858R mutation.

## Conflicts of Interest

Dr. Watanabe and Dr. Kobayashi have declared no conflicts of interest; Dr. Inoue reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from AstraZeneca, grants and personal fees from Chugai, outside the submitted work. Dr. Nukiwa reports personal fees from Boehringer Ingelheim outside the submitted work.

## Acknowledgements

The collection of data used in this analysis was supported by the Tokyo Cooperative Oncology Group.

## References

1 Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J and Haber DA: 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, 2004.

2 Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE and Meyerson M: EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science *304*: 1497-1500, 2004.

3 Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S and Nukiwa T: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med *362*: 2380-2388, 2010.

4 Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K and Fukuoka M: 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 III trial. Lancet Oncol *11*: 121-128, 2010.

5 Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Munoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M and Paz-Ares L: 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 III trial. Lancet Oncol *13*: 239-246, 2012.

6 Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J and You C: 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 III study. Lancet Oncol *12*: 735-742, 2011.

7 Yang JC-H, Wu Y-L, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu C-P, O'Byrne K, Feng J, Lu S, Huang Y, Geater SL, Lee KY, Tsai C-M, Gorbunova V, Hirsh V, Bennouna J, Orlov S, Mok T, Boyer M, Su W-C, Lee KH, Kato T, Massey D, Shahidi M, Zazulina V and Sequist LV: Afatinib *versus* cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase III trials. Lancet Oncol *16*: 141-151, 2015.

8 Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M and Schuler M: Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol *31*: 3327-3334, 2013.

9 Wu Y-L, Zhou C, Hu C-P, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Xu C-R, Massey D, Kim M, Shi Y and Geater SL: 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 III trial. Lancet Oncol *15*: 213-222, 2014.

10 Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Saijo Y, Hagiwara K, Morita S and Nukiwa T: Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol *24*: 54-59, 2013.

11 Watanabe S, Minegishi Y, Yoshizawa H, Maemondo M, Inoue A, Sugawara S, Isobe H, Harada M, Ishii Y, Gemma A, Hagiwara K and Kobayashi K: Effectiveness of gefitinib against non-small-cell lung cancer with the uncommon EGFR mutations G719X and L861Q. J Thorac Oncol *9*: 189-194, 2014.

12 Oizumi S, Kobayashi K, Inoue A, Maemondo M, Sugawara S, Yoshizawa H, Isobe H, Harada M, Kinoshita I, Okinaga S, Kato T, Harada T, Gemma A, Saijo Y, Yokomizo Y, Morita S, Hagiwara K and Nukiwa T: Quality of life with gefitinib in patients with EGFR-mutated non-small cell lung cancer: quality of life analysis of North East Japan Study Group 002 Trial. Oncologist *17*: 863-870, 2012.

*Received September 21, 2015*
*Revised October 17, 2015*
*Accepted October 23, 2015*