Title:

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 IIIB/IV or postoperative recurrent *EGFR* mutation-positive non-small cell lung cancer.

Running head: Final overall survival results of gefitinib in WJTOG3405

Authors:

H Yoshioka[1], M Shimokawa[2,16], T Seto[3], S Morita[4], Y Yatabe[5], I Okamoto[6], J Tsurutani[7], M Satouchi[8], T Hirashima[9], S Atagi[10], K Shibata[11], H Saito[12], S Toyooka[13], N Yamamoto[14], K Nakagawa[15], T Mitsudomi[17]*

[1]Department of Thoracic Oncology, Kansai Medical University Hospital, Hirakata, Japan

[2]Department of Cancer Information Research, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

[3]Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

[4]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan

[5]Department of Pathology and Molecular Genetics, Aichi Cancer Center Hospital, Nagoya, Japan

[6]Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyusyu University, Fukuoka, Japan

[7]Advanced Cancer Translational research institute, Showa University, Tokyo, Japan

[8]Department of Thoracic Oncology, Hyogo Cancer Center, Akashi, Japan

[9]Department of Thoracic Oncology, Osaka Habikino Medical Center, Habikino, Japan

[10]Department of Thoracic Oncology, National Hospital Organization Kinki-chuo Chest Medical Center, Sakai, Japan

[11]Department of Medical Oncology, Kouseiren Takaoka Hospital, Takaoka, Japan

[12]Department of Respiratory Medicine, Aichi Cancer Center Aichi Hospital, Okazaki, Japan

[13]Department of Thoracic, Breast and Endocrinological Surgery, Okayama University Hospital, Okayama, Japan

[14]Internal Medicine III, Wakayama Medical University Hospital, Wakayama, Japan

[15]Department of Medical Oncology, Kindai University Hospital, Osaka-Sayama, Japan

[16]Department of Biostatics, Yamaguchi University Graduate School of Medicine, Ube, Japan

[17]Division of Thoracic Surgery, Department of Surgery, Kindai University Hospital, Osaka-Sayama, Japan

***Full address for correspondence**:
Dr. Tetsuya Mitsudomi,
Division of Thoracic Surgery, Department of Surgery, Kindai University Hospital, 377-2 Ohno-Higashi, Osaka-Sayama, 589-8511, Japan.
Tel: +81-72-366-0221.
Fax: +81-72-368-3382.
E-mail: mitsudom@med.kindai.ac.jp

Abstract

Background:

Primary analysis of the phase III study WJTOG 3405 demonstrated superiority of progression-free survival (PFS) for gefitinib (G)in patients treated with the epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) gefitinib compared with cisplatin plus docetaxel (CD) as first-line treatment of stage IIIB/IV or postoperative recurrent *EGFR* mutation-positive non-small cell lung cancer (NSCLC). This report presents final overall survival (OS) data.

Patients and methods;

Patients were randomized between G (250mg/day orally) and cisplatin (80mg/m^2 intravenously) plus docetaxel (60mg/m^2 intravenously), administered every 21 days for three to six cycles. After the exclusion of 5 patients, 172 patients (86 in each group, modified intention-to-treat population) were included in the survival analysis. OS was re-evaluated using updated data (data cutoff, 30 Sep. 2013; median follow-up time 59.1 months). The Kaplan-Meier method and the log-rank test were used for analysis, and hazard ratios (HRs) for death were calculated using the Cox proportional hazards model.

Results;

OS events in the G group and CD group were 68 (79.1%) out of 86, and 59 (68.6%) out of 86, respectively. Median survival time for G and CD were 34.9 and 37.3 months, respectively, with a HR of 1.252 (95% confidence interval (CI): 0.883-1.775, P = 0.2070). Multivariate analysis identified postoperative recurrence and stage IIIB/IV disease as independent prognostic factors, with a HR of 0.459 (95% CI: 0.312-0.673, $P < 0.001$). Median survival time (postoperative recurrence versus stage IIIB/IV disease) were 44.5 and 27.5 months in G group and 45.5 and 32.8 months in CD group, respectively.

Conclusion;

G did not show OS benefits over CD as first-line treatment. OS of patients with postoperative recurrence was better than that of stage IIIB/IV disease, even though both groups had metastatic disease.

This study was registered with UMIN (University Hospital Medical Information Network in Japan), number 000000539.

Key words: Overall survival, gefitinib, platinum doublet chemotherapy, *EGFR* mutation, non-small-cell lung cancer

Key message

Final overall survival (OS) analyses in five-year follow-up of this study did not show the OS benefit of gefitinib over cisplatin plus docetaxel as first-line treatment for EGFR-mutation positive NSCLC patients, possibly due to the high cross-over rate. OS of patients with postoperative recurrence was better than that of stage IIIB/IV disease, even though both groups had metastatic disease.

Introduction

In a phase II trial for gefitinib (G), dramatic response was observed in patients with Asian ethnicity, female gender and adenocarcinoma histology [1]. However, until the identification of the activating mutation of the epidermal growth factor receptor (*EGFR*) gene, the biological rationale was unknown [2,3]. First-generation EGFR-TKIs (G and erlotinib) and a second-generation EGFR-TKI (afatinib) have been repeatedly shown to be superior to platinum-doublet chemotherapy for *EGFR*-mutated patients [4-10]. All these studies showed statistically longer progression-free survival (PFS) of EGFR-TKI compared with platinum doublet chemotherapy. However, no single study has clearly demonstrated statistical difference in overall survival (OS) between EGFR-TKI and chemotherapy [8, 9, 12-15].

WJTOG 3405 was a multicenter, randomized, open-label, phase III study to compare the efficacy and safety of the EGFR-TKI G versus cisplatin plus docetaxel (CD) as first-line treatment in patients with stage IIIB/IV or postoperative recurrent *EGFR* mutation-positive NSCLC [4]. The primary analysis showed that this study met its primary PFS endpoint: 9.2 months for G versus 6.3 months for CD; hazard ratio (HR) of 0.489 (95% confidence interval (CI): 0.336-0.710). Here, final overall survival analyses in five-year follow-up were conducted, with prognostic factors being examined.

Patients and methods

Study design and treatment

The design and primary results of WJTOG 3405 study were published in 2010 [4]. In brief, patients were eligible if they were 75 years or younger, had NSCLC with activating *EGFR* mutation (either exon 19 deletion (Del19) or L858R in exon 21), had postoperative recurrence or stage IIIB/IV disease, WHO performance status of 0-1, adequate organ function, and chemotherapy-naïve with the exception of adjuvant chemotherapy other than CD for postoperative recurrence. Patients were randomly assigned in a 1:1 ratio to receive G (250mg/day, administered orally) or cisplatin (80mg/m^2 day1, intravenously) plus docetaxel (60mg/m^2 day1, intravenously) administered every 21 days for three to six cycles. Treatment continued until disease progression defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, development of unacceptable toxic effects, patient's refusal to continue treatment, serious non-compliance with the protocol, or completion of scheduled chemotherapy cycles. Post-protocol therapy was at the physician's discretion. The primary endpoint was PFS. Secondary endpoints were OS and objective response rate (ORR). Tertiary endpoints included disease control rate, safety, and survival by mutation type which was determined by PCR assay. All patients provided written informed consent before study registration, and the study protocol was approved by the institutional ethical committee of each of the participating institutions. The study was undertaken in accordance with the Declaration of Helsinki.

Updated evaluation and statistical analysis

Initially, 177 patients were enrolled and randomized to G (N = 88) or CD (N = 89) between March 31, 2006, and June 22, 2009. After the exclusion of 5 patients, 172 patients (86 in each group; modified intention-to-treat population) were included in the survival analysis.

In this post-hoc 5-year follow-up analysis, OS was evaluated using updated data (data cutoff, 30 Sep. 2013; median follow-up time was 59.1 months) for modified intention-to-treat population. Definition of OS was the interval from the date of randomization until the date of death from any cause or the final date of follow-up. Data on survivors and on patients who were lost to follow-up

were censored at the final date of follow-up. The survival curves were estimated using the Kaplan–Meier method and the log-rank test, and HRs for death were calculated using the Cox proportional hazards model. Multivariate analysis for overall survival was performed to identify potential prognostic factors using the Cox proportional hazards model including study arm, gender, age (< 65 vs. >= 65), smoking history (never vs. ever), stage (postoperative recurrence vs. stage IIIB/IV disease), and *EGFR* mutation type (Del19 or L858R) as covariates. Difference was considered significant at a two-sided *P* value of 0.05 or less. All statistical analyses were performed using SAS version 9.4 (SAS institute, Cary, NC). This study was registered with UMIN (University Hospital Medical Information Network in Japan), number 000000539.

Results

Final overall survival

Median follow-up time of all 172 patients was 59.1 months (95% CI: 56.7 to 64.0 months). Within this period, 127 (73.8%) patients died. Median survival time (MST) of all patients was 35.5 months (95% CI: 31.2-39.5). Deaths in the G and CD groups were 68 (79.1%) out of 86, and 59 (68.6%) out of 86, respectively. MST of G group and CD group were 34.9 months (95% CI: 26.1-39.5) and 37.3 months (95% CI: 31.2-45.5), respectively, with a HR of 1.252 (95% CI: 0.883-1.775, $P = 0.2070$) (Figure 1). No statistically significant difference in OS was observed between the two groups and in all subgroups (Figure S1).

Prognostic factors

When study arm, gender, age, smoking history, postoperative recurrence or stage IIIB/IV disease, and type of *EGFR* mutation (Del19 or L858R), were evaluated as potential prognostic factors using the Cox proportional hazards model, postoperative recurrence or stage IIIB/IV disease was the only independent prognostic factor, with a HR of 0.459 (95% CI: 0.312-0.673, $P < 0.001$) (Table S1). MST (postoperative recurrence and stage IIIB/IV disease) were 44.5 and 27.5 months in the G group with a HR of 2.317 (95%CI: 1.363-3.937, $P = 0.0014$) and 45.5 and 32.8 months in the CD group with a HR of 1.882 (95%CI: 1.086-3.262, $P = 0.0219$), respectively (Figure 2).

OS according to *EGFR* mutation type

Eighty-seven (51%) and 85 (49%) of 172 patients had Del19 and L858R. MST of patients with Del19 and L858R were 37.3 and 34.4 months, respectively, with a HR of 0.920 (95% CI: 0.649-1.303, $P = 0.6386$). MST of the G group and the CD group were 35.5 and 41.6 months (HR 1.411; 95% CI: 0.850-2.342, $P = 0.1804$) in Del19, and 32.2 and 34.4 months (HR 1.086; 95% CI: 0.656-1.798, $P = 0.7482$) in L858R, respectively. In the G group, MST of patients with Del19 (N =

50) and L858R (N = 36) were 35.5 and 32.2 months (HR 1.004; 95% CI: 0.618-1.630: *P* = 0.9880), respectively (Figure S2). In the CD arm, MST of patients with 19Del and L858R were 41.6 and 34.4 months (HR 0.773; 95% CI: 0.460-1.302, *P* = 0.3316), respectively.

Effect of post protocol treatment on OS

Fifty-five (64%) and eight (9.3%) out of 86 patients in the G group received platinum doublet chemotherapy and single-agent chemotherapy as post protocol treatment, respectively. Twenty-three (26.7%) patients were treated with EGFR-TKI alone. Only four out of 23 patients treated with EGFR-TKI alone received subsequent EGFR-TKI therapy (two received gefitinib re-challenge as 2nd-line therapy, one received erlotinib as 2nd-line therapy, and one received erlotinib as 2nd-line therapy followed by gefitinib re-challenge as 3rd-line therapy). On the other hand, 78 (90.7%) out of 86 patients in the CD group received EGFR-TKI as post protocol treatment, and only eight (9.3%) did not receive treatment with EGFR-TKI. Swimmer's plot on PFS and OS according to treatment sequence showed that the post progression survival seemed to be better in patients treated with CD followed by EGFR-TKI than in patients treated with G followed by chemotherapy (Figure S3 and S4). In total, 141 patients from both treatment groups were treated with both EGFR-TKI and chemotherapy (133 received platinum doublet and 8 received monotherapy). The survival curves showed a trend for the patients treated with both EGFR-TKI and chemotherapy to live longer compared with those treated with EGFR-TKI alone or especially with those with chemotherapy alone, with no statistical significance (Figure 3A). The trend was more prominent in patients with stage IIIB/IV disease (Figure 3B). In addition, a small number of patients treated with chemotherapy alone had the worst outcome (Figures 3A and 3B)

Impact of treatment sequence on OS

Post hoc comparison was performed between 55 patients in the G group who were treated with G followed by platinum doublet chemotherapy (up-front EGFR-TKI population) and 78 patients in the

CD group who were treated with CD followed by EGFR-TKI (the up-front chemotherapy population) to assess the impact of treatment sequence. MST in the up-front EGFR-TKI population and the up-front chemotherapy population were 33.1 and 37.9 months, respectively (HR 1.431 (95%CI: 0.966-2.119), P = 0.0723). (Figure 4) A trend toward prolonged survival was seen when patients were treated CD initially followed by EGFR-TKI. Moreover, in patients who had Del19, the MST of up-front EGFR-TKI population was 31.8 months, which was shorter than that of 41.6 months in the up-front chemotherapy population (HR 1.752 (95%CI: 1.001-3.065), P = 0.047), while no significant difference was observed in patients with L858R (HR 1.118 (95%CI: 0.630-1.985), P = 0.703) (Figure S5).

Discussion

There have been at least eight phase III studies comparing EGFR-TKI with platinum doublet chemotherapy in the first-line setting for patients with *EGFR* mutation-positive NSCLC [4-11]. No study has demonstrated statistically significant difference in OS between first-line EGFR-TKI and platinum doublet chemotherapy [8, 9, 12-15], which is also the case with present study. The lack of difference in OS outcomes is assumed to be due to a high rate of treatment cross-over upon disease progression. In this study, 55 (64.0%) out of 86 patients in the G group and 78 (90.7%) out of 86 patients in the CD group were sequenced to the other treatment.

According to multivariate analyses of prognostic factors, postoperative recurrence was statistically better than stage IIIB/IV disease, with a HR of 0.459 (95% CI; 0.312-0.673), and this difference was clearly reproduced in both the G group and the CD group. To the best of our knowledge, WJTOG3405 is the first phase III study that showed prolonged OS in patients with postoperative recurrence in NSCLC patients, although there are some retrospective studies indicating that OS of recurrent metastatic disease after treatment with curative intent might be better than that of de novo metastatic disease [16-18]. Therefore, in future clinical trials, postoperative recurrence or stage IIIB/IV disease should be stratified as a possible prognostic factor. One of the possible explanations for this difference in prognosis is higher tumor burden in stage IIIB/IV disease, because postoperative recurrence is usually diagnosed by a routine follow-up at intervals of several months following pulmonary resection. The mean numbers of organs with metastases at study entry (postoperative recurrence versus stage IIIB/IV disease) were 1.71 and 3.43 in the G group ($P < 0.0001$, Wilcoxon rank sum test) and 1.75 and 3.0 in the CD group ($P < 0.0001$, Wilcoxon rank sum test), respectively, if we counted the primary lesion as one affected organ, and counted the regional lymph node metastases as one affected organ irrespective of number and sites of involved lymph nodes. This data may indirectly reflect the lower tumor burden in postoperative recurrence.

Exploratory analyses of the phase III OPTIMAL study comparing erlotinib with cisplatin plus gemcitabine in chemotherapy-naïve patients with advanced *EGFR*-mutated NSCLC showed that patients who received sequential combination of EGFR-TKI and chemotherapy had significantly

improved OS compared with those who received EGFR-TKI or chemotherapy only (29.7 versus 20.7 versus 11.2 months, respectively; P < 0.0001) [12]. As for post study treatment in the current study, 141 patients from both treatment groups were treated with both EGFR-TKI and chemotherapy including protocol treatment, and 31 patients (23 received G and 8 received CD as protocol treatment) did not receive any other types of post protocol treatment. The survival curves showed the tendency for the patients treated with both EGFR-TKI and chemotherapy to live longer compared with patients treated with G alone or CD alone (Figure 3A), which was more evident in patients with stage IIIB/IV disease (Figure 3B). These results are consistent with exploratory analyses of the OPTIMAL study and also indicate that we should treat *EGFR*-mutated NSCLC patients with both EGFR-TKI and chemotherapy throughout the course of their treatment, irrespective of which one is administered first. However, it should be noted that patients who could receive both EGFR-TKI and chemotherapy, compared with those treated with only one regimen, were more likely be fitter at the time of disease progression, which would have a significant effect on patient survival thereafter. The ASPIRATION study showed that the difference between PD by RECIST and PD by physician's discretion (e.g., emergence of new lesions, symptoms, etc.) is about 3 months [19]. Therefore, when patients have disease progression by RECIST during EGFR-TKI therapy, we should switch the treatment to chemotherapy within 3 months. Otherwise, the patient may lose opportunities for chemotherapy.

Post hoc comparison to assess the impact of treatment sequence showed that patients treated with chemotherapy followed by EGFR-TKI tended to live longer than those treated in the opposite sequence (HR 1.431 (95%CI: 0.966-2.119), *P* = 0.0723) (Figure 4). The trend was remarkable in patients with Del19 of *EGFR* (HR 1.752 (95%CI: 1.001-3.065), *P* = 0.047). The same tendency was shown in a real-world retrospective study of 1660 Japanese patients with advanced NSCLC harboring *EGFR* mutations who had received at least one line of treatment. This demonstrated that patients treated with chemotherapy as first-line treatment lived longer than those treated with EGFR-TKIs in the first line in multiple logistic regression analysis (Odds ratio 1.854 (95%CI: 1.190-2.888), *P* = 0.006, multivariate analysis) [20]. These observations support the

treatment strategy that first-line treatment for patients with *EGFR* mutation should be chemotherapy. However, the fact that outcomes of patients who could only receive chemotherapy was very poor (Figures 3A and 3B) supports the first-line use of EGFR-TKI. In addition, combined analysis of LUX-Lung 3 and 6 studies that compared afatinib with chemotherapy showed prolonged OS in patients in the afatinib arm, especially in patients with Del19 of *EGFR* [13]. Recently, PFS2, which was defined as the time from randomization to progressive disease after the start of second-line treatment or death, is becoming more important in evaluating the effect of treatment sequence on OS in randomized trials. The assessment of PFS2 may clarify the issue of treatment sequence.

According to recent studies, even for patients with *EGFR* mutation, survival time is shorter for patients with additional alterations in genes such as TP53, Her2, and CDK4/6 [21, 22]. To manage these tumors, it is apparent that EGFR-TKI is not sufficient. Although we do not currently have a better strategy, we should re-evaluate the role of chemotherapy based on the recent success of the NEJ009 study, which demonstrated survival benefit of concurrent use of EGFR-TKI and chemotherapy [23].

Conclusion

G did not show OS benefits over CD as first-line treatment for patients with *EGFR*-mutation positive NSCLC, probably due to a high cross-over rate. OS of patients with postoperative recurrence was better than that of stage IIIB/IV disease, even though both groups had metastatic disease.

Acknowledgement

We appreciate patients, their families, all investigators and the staff of west Japan oncology group data center engaged in WJTOG 3405 study.

Funding

This work was supported by West Japan Oncology Group (WJOG): a non-profit organization

supported by unrestricted donation from members of WJOG, citizens, and pharmaceutical companies. There is no applicable grant number.

Disclosure

HY received honoraria from AstraZeneca, Boehringer-Ingelheim, and Chugai pharmaceutical. TS, IO, MS, SA, and TM received honoraria and grants from AstraZeneca, Boehringer-Ingelheim, and Chugai pharmaceutical. NY and KN received honoraria from AstraZeneca, Boehringer-Ingelheim and Chugai pharmaceutical and received grants from Chugai Pharmaceutical and Boehringer Ingelheim. SM received honoraria from AstraZeneca, Boehringer-Ingelheim and Chugai pharmaceutical and received grants from Boehringer-Ingelheim. HS received honoraria from AstraZeneca and Boehringer-Ingelheim and received grants from Chugai pharmaceutical. ST received honoraria from AstraZeneca and Chugai pharmaceutical. JT received honoraria from Chugai pharmaceutical and received grants from Boehringer-Ingelheim. KS received honoraria from Chugai pharmaceutical. All remaining authors have declared no conflicts of interest.

References

1. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). J Clin Oncol 2003; 21: 2237-2246.
2. Paez JG, Jänne PA, Lee JC, et al. *EGFR* mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304: 1497-1500.
3. 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: 2129-2139.
4. Mitsudomi T, Morita S, Yatabe Y, et al. 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 2010; 11:121-128.

5. 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; 362:2380-2388.
6. 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: 735-742.
7. Rosell R, Carcereny E, Gervais R, 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: 239-246.
8. Wu YL, Zhou C, Liam CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced *EGFR* mutation-positive non-small-cell lung cancer: analysis from the phase III, randomized, open-label, ENSURE study. Ann Oncol 2015; 26: 1883-1889.
9. Shi YK, Wang L, Han BH, et al. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced *EGFR* mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. Ann Oncol 2017; 28: 2443-2450.
10. 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: 3327-3334.
11. Wu YL, Zhou C, Hu CP, 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: 213-222.
12. Zhou C, Wu YL, Chen G, et al. Final overall survival results from randomized, phase III study

of erlotinib versus chemotherapy as first-line treatment of *EGFR* mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol 2015; 26: 1877-1883.

13. Yang JC, Wu YL, Schuler M, et al. 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 3 trials. Lancet Oncol 2015; 16: 141-51.
14. Karachaliou N, de Las Casas CM, Queralt C, et al. Association of EGFR L858R Mutation in Circulating Free DNA With Survival in the EURTAC Trial. JAMA Oncol 2015; 1: 149-157.
15. Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol 2013; 24: 54-59
16. Moore S, Leung B, Wu J, et al. Survival Implications of De Novo Versus Recurrent Metastatic Non-Small Cell Lung Cancer. Am J Clin Oncol 2019; 42: 292-297.
17. Sekine I, Nokihara H, Yamamoto N, et al. Comparative chemotherapeutic efficacy in non-small cell lung cancer patients with postoperative recurrence and stage IV disease, J Thorac Oncol 2009; 4: 518-521.
18. Yu HA, Sima CS, Hellmann MD, et al. Differences in the survival of patients with recurrent versus de novo metastatic KRAS-mutant and EGFR-mutant lung adenocarcinoma. Cancer 2015; 121: 2078-2082.
19. Park K, Yu CJ, Kim SW, 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: 305-312.
20. Okamoto I, Morita S, Tashiro N, 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: 14-19.
21. Blakely CM, Watkins TBK, Wu W, et al. Evolution and clinical impact of co-occurring

genetic alterations in advanced-stage *EGFR*-mutant lung cancers. Nature Genetics 2017; 49: 1693-1704.

22. Yu HA, Suzawa K, Jordan E, et al. Concurrent Alterations in EGFR-Mutant Lung Cancers Associated with Resistance to EGFR Kinase Inhibitors and Characterization of MTOR as a Mediator of Resistance. Clin Cancer Res 2018; 24: 3108-18.
23. Nakamura A, Inoue A, Morita S, et al. Phase III study comparing gefitinib monotherapy to combination therapy with gefitinib, carboplatin, and pemetrexed for untreated patients with advanced non-small cell lung cancer with *EGFR* mutations (NEJ009). J Clin Oncol 2018; 36; suppl; abstr 9005.

Figure legends

Figure 1. Kaplan-Meier plots of overall survival in modified intention-to-treat population. MST: median survival time; CD: cisplatin and docetaxel; HR: hazard ratio; CI; confidence interval.

Figure 2. Kaplan-Meier plots of overall survival according to postoperative recurrence or stage IIIB/IV disease in gefitinib arm (above) and CD arm (below). MST: median survival time; CD: cisplatin and docetaxel; HR: hazard ratio; CI: confidence interval.

Figure 3. Kaplan-Meier plots of overall survival according to treatment (both EGFR-TKI and chemotherapy, EGFR-TKI alone, or chemotherapy alone) in modified intention-to-treat population (3A) and stage IIIB/IV disease (3B). MST: median survival time.

Figure 4. Kaplan-Meier plots of overall survival according to treatment sequence. MST: median survival time; CD: cisplatin and docetaxel; HR: hazard ratio; CI: confidence interval.

Figure S1. Hazard ratios for overall survival using subgroup analysis in modified intention-to-treat population. HR: hazard ratio.

Figure S2. Kaplan-Meier plots of overall survival according to *EGFR* mutation. MST: median survival time; HR: hazard ratio; CI: confidence interval.

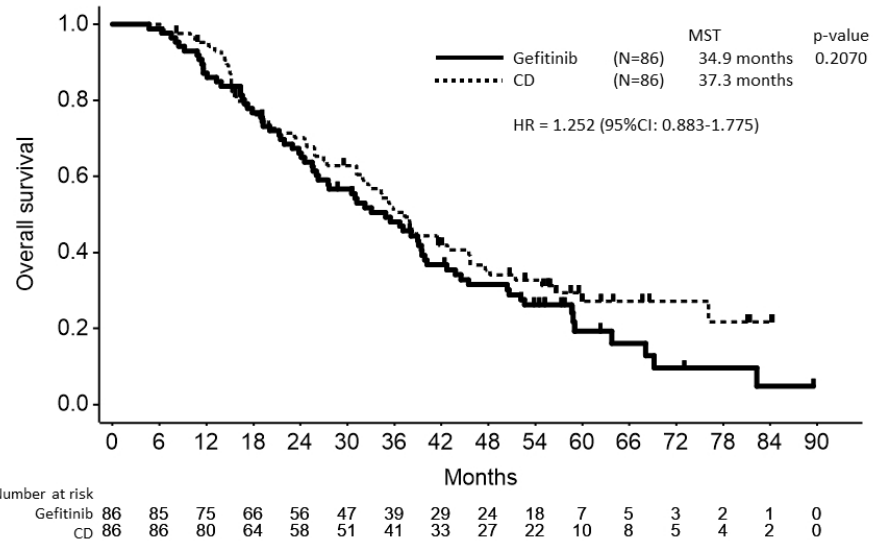
Figure S3. Swimmer's plot on progression free survival and overall survival in one glance according

to treatment sequence.

Figure S4. Post progression survival curves of the two groups received sequence treatment. Post progression survival was defined as survival after disease progression of study treatment. CD: cisplatin and docetaxel; HR: hazard ratio; CI: confidence interval.

Figure S5. Kaplan-Meier plots of overall survival according to treatment sequence in patients with exon 19 del (above) and L858R (below). MST: median survival time; CD: cisplatin and docetaxel; HR: hazard ratio; CI: confidence interval; del: deletion.

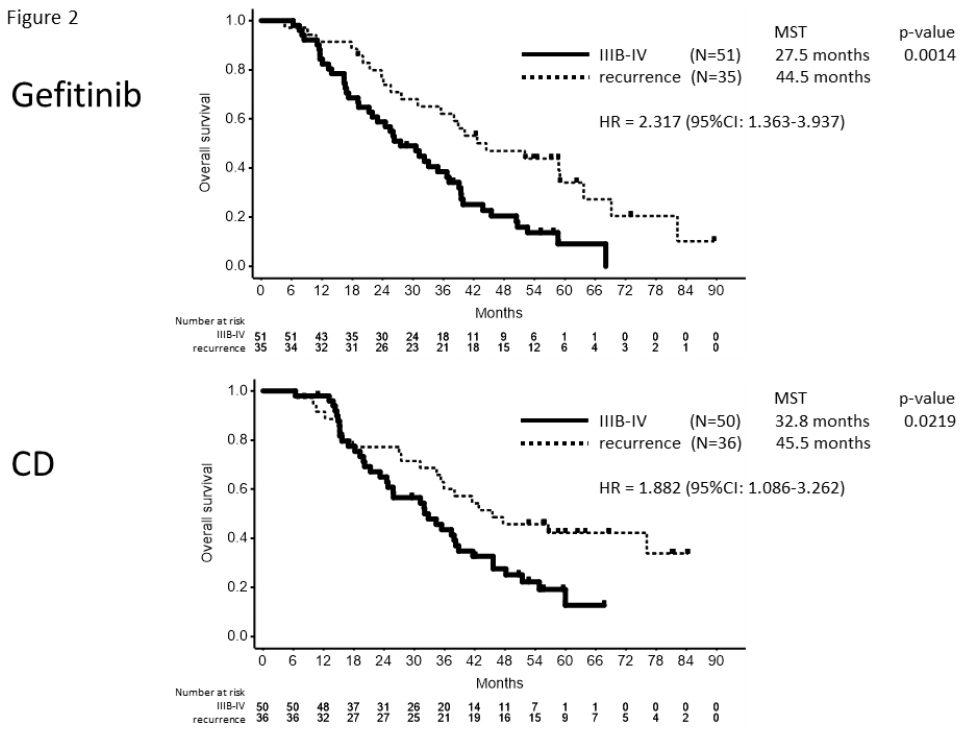
Figure 1



Kaplan-Meier plots of overall survival in modified intention-to-treat population. MST: median survival time; CD: cisplatin and docetaxel; HR: hazard ratio; CI; confidence interval.

254x190mm (96 x 96 DPI)

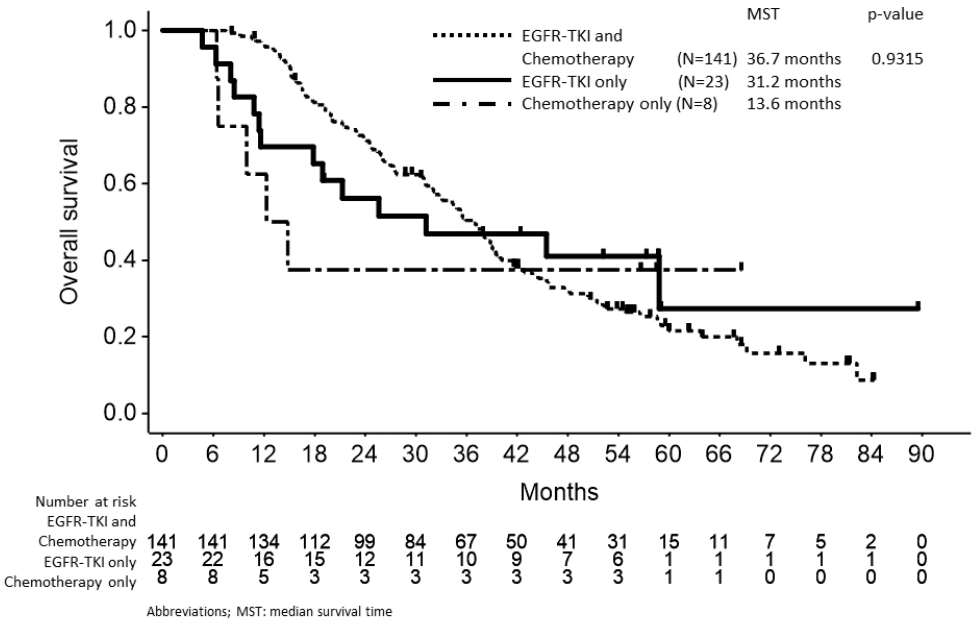
Figure 2



Kaplan-Meier plots of overall survival according to postoperative recurrence or stage IIIB/IV disease in gefitinib arm (above) and CD arm (below). MST: median survival time; CD: cisplatin and docetaxel; HR: hazard ratio; CI: confidence interval.

254x190mm (96 x 96 DPI)

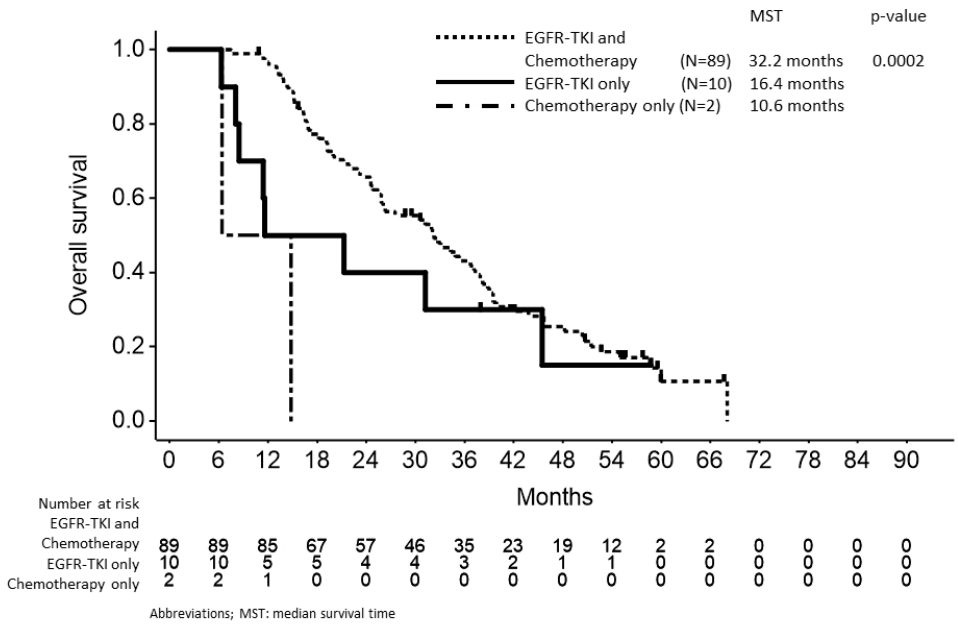
Figure 3A



Kaplan-Meier plots of overall survival according to treatment (both EGFR-TKI and chemotherapy, EGFR-TKI alone, or chemotherapy alone) in modified intention-to-treat population (3A) and stage IIIB/IV disease (3B). MST: median survival time.

254x190mm (96 x 96 DPI)

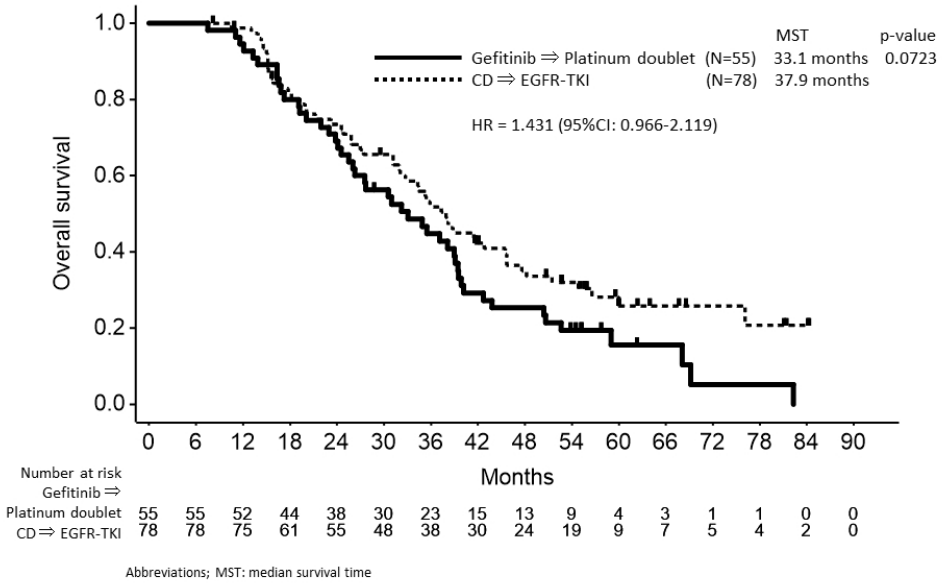
Figure 3B



Kaplan-Meier plots of overall survival according to treatment (both EGFR-TKI and chemotherapy, EGFR-TKI alone, or chemotherapy alone) in modified intention-to-treat population (3A) and stage IIIB/IV disease (3B). MST: median survival time.

254x190mm (96 x 96 DPI)

Figure 4



Kaplan-Meier plots of overall survival according to treatment sequence. MST: median survival time; CD: cisplatin and docetaxel; HR: hazard ratio; CI: confidence interval.

254x190mm (96 x 96 DPI)