

# 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



Tetsuya Mitsudomi, Satoshi Morita, Yasushi Yatabe, Shunichi Negoro, Isamu Okamoto, Junji Tsurutani, Takashi Seto, Miyako Satouchi, Hirohito Tada, Tomonori Hirashima, Kazuhiro Asami, Nobuyuki Katakami, Minoru Takada, Hiroshige Yoshioka, Kazuhiko Shibata, Shinzoh Kudoh, Eiji Shimizu, Hiroshi Saito, Shinichi Toyooka, Kazuhiko Nakagawa, Masahiro Fukuoka, for the West Japan Oncology Group

## Summary

**Background** Patients with non-small-cell lung cancer harbouring mutations in the epidermal growth factor receptor (*EGFR*) gene respond well to the *EGFR*-specific tyrosine kinase inhibitor gefitinib. However, whether gefitinib is better than standard platinum doublet chemotherapy in patients selected by *EGFR* mutation is uncertain.

**Methods** We did an open label, phase 3 study (WJTOG3405) with recruitment between March 31, 2006, and June 22, 2009, at 36 centres in Japan. 177 chemotherapy-naïve patients aged 75 years or younger and diagnosed with stage IIIB/IV non-small-cell lung cancer or postoperative recurrence harbouring *EGFR* mutations (either the exon 19 deletion or L858R point mutation) were randomly assigned, using a minimisation technique, to receive either gefitinib (250 mg/day orally; n=88) or cisplatin (80 mg/m<sup>2</sup>, intravenously) plus docetaxel (60 mg/m<sup>2</sup>, intravenously; n=89), administered every 21 days for three to six cycles. The primary endpoint was progression-free survival. Survival analysis was done with the modified intention-to-treat population. This study is registered with UMIN (University Hospital Medical Information Network in Japan), number 000000539.

**Findings** Five patients were excluded (two patients were found to have thyroid and colon cancer after randomisation, one patient had an exon 18 mutation, one patient had insufficient consent, and one patient showed acute allergic reaction to docetaxel). Thus, 172 patients (86 in each group) were included in the survival analyses. The gefitinib group had significantly longer progression-free survival compared with the cisplatin plus docetaxel group, with a median progression-free survival time of 9.2 months (95% CI 8.0–13.9) versus 6.3 months (5.8–7.8; HR 0.489, 95% CI 0.336–0.710, log-rank p<0.0001). Myelosuppression, alopecia, and fatigue were more frequent in the cisplatin plus docetaxel group, but skin toxicity, liver dysfunction, and diarrhoea were more frequent in the gefitinib group. Two patients in the gefitinib group developed interstitial lung disease (incidence 2.3%), one of whom died.

**Interpretation** Patients with lung cancer who are selected by *EGFR* mutations have longer progression-free survival if they are treated with gefitinib than if they are treated with cisplatin plus docetaxel.

**Funding** West Japan Oncology Group (WJOG): a non-profit organisation supported by unrestricted donations from several pharmaceutical companies.

## Introduction

Lung cancer is a major cause of cancer-related mortality worldwide.<sup>1</sup> However, current standard platinum doublet therapy seems to have reached a therapeutic plateau,<sup>2</sup> although it has recently been shown that patients with non-squamous histology who are treated with pemetrexed disodium have better survival than if they are treated with older drugs.<sup>3</sup>

Targeted therapies are actively being developed to improve efficacy in selected patient populations.<sup>4</sup> Small-molecule tyrosine kinase inhibitors (TKIs) that target the epidermal growth factor receptor (*EGFR*), such as gefitinib and erlotinib, are the first targeted drugs to enter clinical use for the treatment of lung cancer. Subgroups of patients of east-Asian origin, female sex, adenocarcinoma, and no history of smoking

have been shown to be significantly associated with a favourable response to *EGFR* TKIs.<sup>5,6</sup> In 2004, researchers noted that activating mutations of the *EGFR* gene present predominantly in patients with the above-mentioned clinical characteristics, and determine sensitivity to *EGFR* TKIs.<sup>7,8</sup> *EGFR* mutations are present in the first four exons of the tyrosine kinase domain of the *EGFR* gene, and about 90% of these *EGFR* mutations are either short in-frame deletions in exon 19, or point mutations that result in a substitution of arginine for leucine at aminoacid 858 (L858R).<sup>7–9</sup> Subsequent retrospective and prospective trials confirmed that the response rate to gefitinib or erlotinib in patients with *EGFR* mutations is about 70–80%.<sup>10–13</sup> Furthermore, patients with *EGFR* mutations have a significantly longer survival than those with wild-type *EGFR* when treated

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Department of Thoracic Surgery, Aichi Cancer Center Hospital, Nagoya, Japan (T Mitsudomi MD); Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan (Prof S Morita PhD); Department of Pathology and Molecular Genetics, Aichi Cancer Center Hospital (Y Yatabe MD); Department of Medical Oncology (S Negoro MD), and Department of Thoracic Oncology (M Satouchi MD), Hyogo Cancer Center, Akashi, Japan; Department of Medical Oncology, Kinki University School of Medicine, Osaka-sayama, Japan (I Okamoto MD, J Tsurutani MD, Prof K Nakagawa MD); Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan (T Seto MD); Department of General Thoracic Surgery, Osaka City General Hospital, Osaka, Japan (H Tada MD); Department of Thoracic Oncology, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Japan (T Hirashima MD); Department of Respiratory Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan (K Asami MD); Clinical Research Center, Division of Pulmonary Medicine Kobe City Medical Center General Hospital, Kobe, Japan (N Katakami MD); Department of Medical Oncology Sakai Hospital Kinki University School of Medicine, Osaka, Sakai, Japan (Prof M Takada MD,

Prof M Fukuoka MD); Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan (H Yoshioka MD); Department of Medical Oncology, Koseiren Takaoka Hospital, Takaoka, Japan (K Shibata MD); Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan (S Kudoh MD); Division of Medical Oncology and Molecular Respiriology, Faculty of Medicine, Tottori University, Tottori, Japan (Prof E Shimizu MD); Department of Respiratory Medicine, Aichi Cancer Center, Aichi Hospital, Okazaki, Japan (H Saito MD); Department of Cancer and Thoracic Surgery, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan (S Toyooka MD)

Correspondence to: Dr Tetsuya Mitsudomi, Department of Thoracic Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan [mitsudom@aichi-cc.jp](mailto:mitsudom@aichi-cc.jp)

with EGFR TKIs.<sup>14,15</sup> We proposed that the absence of any survival advantage conferred by gefitinib monotherapy in previous studies<sup>16–18</sup> is due at least in part to a lack of patient selection, and that gefitinib would confer a survival advantage compared with platinum doublet chemotherapy in a first-line setting if eligible patients were selected on the basis of *EGFR* mutation status. To address this issue, we did a phase 3 trial that compared gefitinib with cisplatin plus docetaxel in patients with an *EGFR* mutation.

Methods  
Patients

This study (WJTOG 3405) was a multicentre, randomised, open-label, phase 3, trial of first-line treatment with gefitinib versus cisplatin plus docetaxel for patients with advanced or recurrent non-small-cell lung cancer (NSCLC) harbouring an activating mutation of the *EGFR*

gene. We recruited patients between March 31, 2006, and June 22, 2009, at 36 centres in Japan. All centres were members of the West Japan Oncology Group (WJOG), which is a Japanese non-profit organisation for oncological clinical trials (formerly the West Japan Thoracic Oncology Group, or WJTOG).

Initially, only patients with postoperative recurrence were eligible, because these surgical specimens were expected to ensure good sample quality. However, because of the initial slow accrual, the protocol was amended on July 10, 2006, to include patients with stage IIIB/IV disease. Patients were eligible if they had histologically or cytologically confirmed NSCLC, harbouring activating *EGFR* mutations (either exon 19 deletion or L858R in exon 21), were aged 75 years or younger, had WHO performance status 0–1, had measurable or non-measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST), and had adequate organ function. Patients with postoperative recurrence, treated with adjuvant therapy other than cisplatin plus docetaxel, were included when the interval between the end of adjuvant chemotherapy and registration exceeded 6 months for platinum-doublet

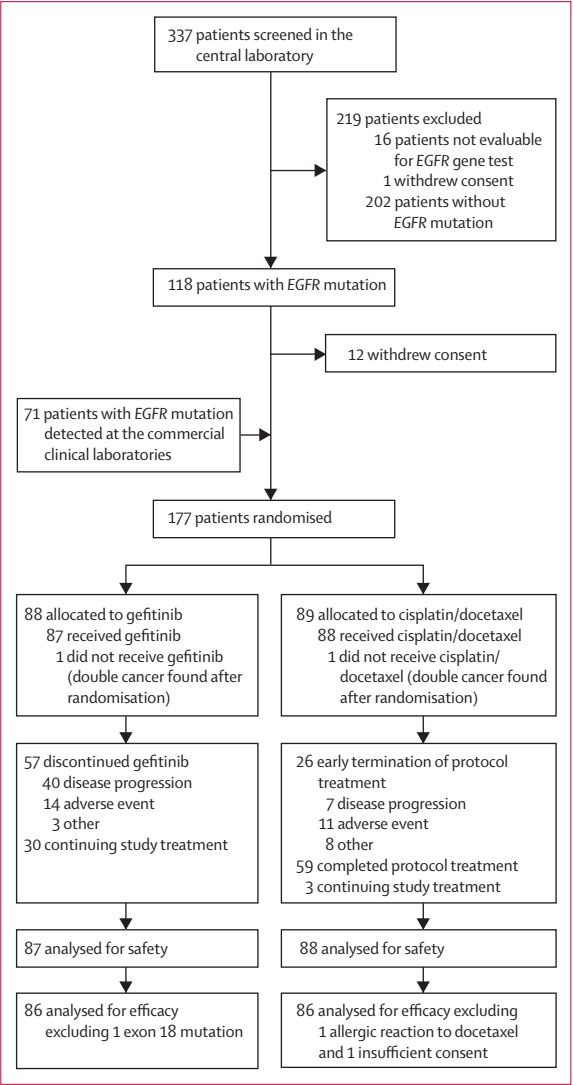


Figure 1: Trial profile

|                                                     | Gefitinib (N=86) | Cisplatin plus docetaxel (N=86) |
|-----------------------------------------------------|------------------|---------------------------------|
| Sex                                                 |                  |                                 |
| Male                                                | 27               | 26                              |
| Female                                              | 59               | 60                              |
| Age (years; median; range)                          | 64.0 (34–74)     | 64.0 (41–75)                    |
| Histological type                                   |                  |                                 |
| Adenocarcinoma                                      | 83               | 84                              |
| Adenosquamous carcinoma                             | 0                | 1                               |
| Squamous-cell carcinoma                             | 1                | 0                               |
| Non-small-cell lung cancer; not otherwise specified | 2                | 1                               |
| Smoking history                                     |                  |                                 |
| Never                                               | 61               | 57                              |
| Former/current                                      | 25               | 29                              |
| Performance status                                  |                  |                                 |
| 0                                                   | 56               | 52                              |
| 1                                                   | 30               | 34                              |
| Stage                                               |                  |                                 |
| Postoperative recurrence                            | 35               | 36                              |
| With postoperative adjuvant chemotherapy            | 19               | 23                              |
| Without postoperative adjuvant chemotherapy         | 16               | 13                              |
| IIIB                                                | 10               | 9                               |
| IV                                                  | 41               | 41                              |
| EGFR mutation                                       |                  |                                 |
| Exon 19 deletion                                    | 50               | 37                              |
| L858R                                               | 36               | 49                              |

Table 1: Demographic and baseline characteristics of the modified intention-to-treat population

therapy and more than 1 month for oral tegafur plus uracil therapy. Patients were not eligible if they had received previous drug therapy that had targeted EGFR, had a history of interstitial lung disease, severe drug allergy, active infection or other serious disease condition, symptomatic brain metastases, poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysorbate 80. Patients in pregnancy or lactation, or whose participation in the trial was judged to be inappropriate by the attending doctor, were not eligible. All patients provided written informed consent. Study approval was obtained from independent ethics committees at every institution. The study was undertaken in accordance with the Declaration of Helsinki.

### Procedures

Patients were randomly assigned in a 1:1 ratio to receive gefitinib (250 mg/day, administered orally), or docetaxel (60 mg/m<sup>2</sup>, administered intravenously over a 1 h period) followed by cisplatin (80 mg/m<sup>2</sup>, administered intravenously over a 90-min period), with adequate hydration, in cycles of once every 21 days for three to six cycles. Treatment continued until progression of the disease, development of unacceptable toxic effects, a request by the patient to discontinue treatment, serious non-compliance with the protocol, or completion of three to six chemotherapy cycles. Further therapy after progression of the disease was at the physician's discretion. The primary endpoint was progression-free survival. Secondary endpoints included overall survival and response rate. Tertiary endpoints were disease control rate, safety, and mutation-type-specific survival.

Initially, patients were screened for *EGFR* mutation in a central laboratory at the Department of Molecular Diagnostics, Aichi Cancer Centre Hospital, Nagoya, Japan. The exon 19 deletion mutation was screened by fragment analysis and the L858R point mutation was screened by the Cycleave method, as described previously,<sup>19</sup> followed by confirmation by direct sequencing. On Feb 16, 2008, the protocol was amended to allow outsourcing of *EGFR* genetic testing from each institution to commercial clinical laboratories, either at SRL in Tokyo (direct sequencing), Mitsubishi Chemical Medience in Tokyo (peptide nucleic acid-locked nucleic acid PCR clamp<sup>20</sup>), or BML in Tokyo (PCR invader<sup>21</sup>), as this amendment would further facilitate patient accrual. The sensitivity of direct sequencing was anticipated to be less than that of other methods; however, false negativity was not a problem in this trial, since patients judged to lack *EGFR* mutations were not randomly allocated to a treatment.

Progression-free survival was assessed from the date of randomisation to the earliest sign of disease progression as determined by CT or MRI imaging using RECIST criteria, or death from any cause. Overall survival was assessed from the date of randomisation until death from any cause. Tumour response was assessed every 2 months

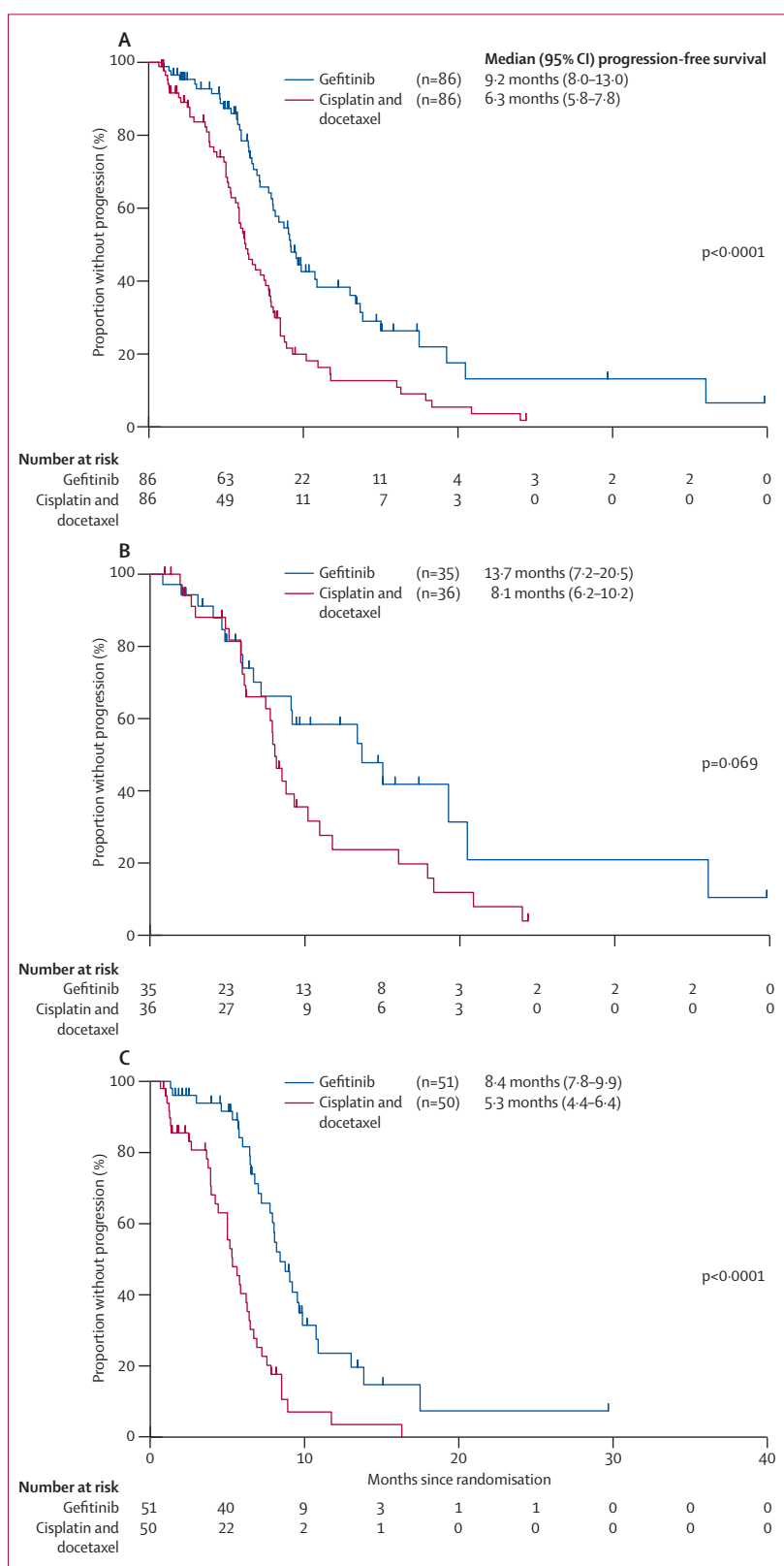


Figure 2: Progression-free survival in the overall population (A), in patients with postoperative recurrence (B), and in patients with stage IIIB/IV disease (C)

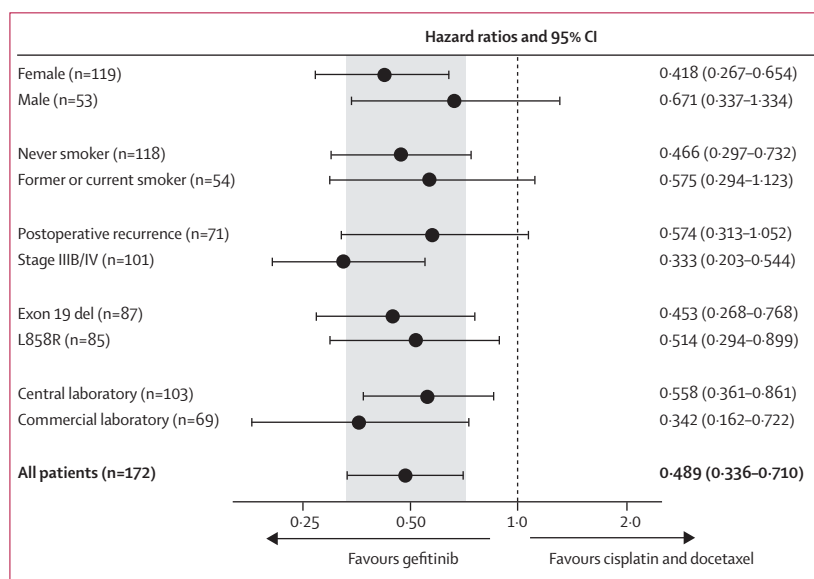


**Figure 3: Hazard ratios for progression-free survival using subgroup analysis in the overall population**  
The shaded band represents the 95% CI of the hazard ratio for the overall population of patients.

|                                            | Univariate analysis |        | Multivariate analysis |         |
|--------------------------------------------|---------------------|--------|-----------------------|---------|
|                                            | HR (95% CI)         | p      | HR (95% CI)           | p       |
| Group (gefitinib/cisplatin plus docetaxel) | 0.489 (0.336-0.710) | 0.0002 | 0.258 (0.385-0.575)   | <0.0001 |
| Sex (male/female)                          | 0.935 (0.625-1.398) | 0.742  | 0.628 (0.361-1.092)   | 0.099   |
| Age (<65 years / ≥65 years)                | 1.091 (0.757-1.572) | 0.641  | 1.183 (0.813-1.721)   | 0.380   |
| Smoking history (never/former or current)  | 0.801 (0.541-1.186) | 0.268  | 0.646 (0.378-1.105)   | 0.111   |
| Stage (recurrence/IIIB-IV)                 | 0.463 (0.220-0.976) | 0.043  | 0.433 (0.290-0.649)   | <0.0001 |
| Mutation (exon 19 del/L858R)               | 1.001 (0.694-1.444) | 0.996  | 1.135 (0.777-1.658)   | 0.514   |

**Table 2: Univariate and multivariate analysis of progression-free survival**

during the first year after randomisation, every 3 months between 12 and 18 months, and thereafter the interval of assessment was at the physician's discretion. Safety and tolerability were assessed according to National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events, version 3.0. All events were confirmed via source-document verification at site visits to each participating institution by members of the WJOG data centre and the investigators.

### Randomisation and masking

The investigator provided the necessary information to personnel at the WJOG data centre by fax. After an eligibility check, patients were allocated at the WJOG data centre to each treatment group using a desktop computer programmed for the minimisation method.<sup>22</sup> In this way, patient allocation was concealed from the investigator.

Because of the nature of treatment in each group, the study was open label. Stratification factors were: institution; postoperative adjuvant chemotherapy (presence vs absence); interval between surgery and recurrence (≥1 vs

<1 year) for patients with postoperative recurrent disease; and institution; stage (IIIB vs IV); and sex (male vs female) for patients with stage IIIB/IV disease.

### Statistical analysis

In previous studies the progression-free survival of patients harbouring EGFR mutations and treated with gefitinib was reported as 12.6 months,<sup>15</sup> compared with 6.6 months for patients harbouring EGFR mutations treated with carboplatin plus paclitaxel.<sup>23</sup> Assuming a progression-free survival for gefitinib and platinum doublet chemotherapy of 12.5 and 7 months, respectively, would yield a hazard ratio (HR) of 0.56. Taking this HR into consideration, 146 patients would be required to achieve 90% power to show superiority with  $\alpha=0.05$  (two-sided). Therefore, sample size was initially set at 200 patients. While this trial was ongoing, the results of the Iressa Pan-Asia Study (IPASS) were presented at the annual meeting of the European Society for Medical Oncology (Stockholm, Sweden, Sept 12-16, 2008), and were later published.<sup>24</sup> Subgroup analysis of patients with EGFR mutations using about a third of the patients showed that the HR of gefitinib compared with carboplatin plus paclitaxel for progression-free survival was 0.48. Similarly, the HR of gefitinib compared with carboplatin plus paclitaxel for progression-free survival in patients with EGFR mutations was 0.36 in the study done by the North East Japan (NEJ) 002 Gefitinib Study Group, which was presented at the annual meeting of the American Society of Clinical Oncology (Orlando, FL, USA, May 29-June 2, 2009).<sup>25</sup> NEJ 002 was a phase 3 trial that analysed 198 patients with EGFR mutation randomised either to gefitinib or carboplatin plus paclitaxel. 177 patients had been randomised in our trial as of June 13, 2009, and 79 events had been noted during the regular monitoring done in March, 2009. The number of events needed to detect a conservative HR of 0.48 was calculated to be 78, based on normal approximation of the logarithm of the hazard ratio under  $\alpha=0.05$  (two-sided) and 90% power. Therefore, further accrual of patients was considered to be futile and potentially unethical. Although interim analysis was originally planned to analyse progression-free survival, this analysis was not done. Instead, the steering committee held on June 13, 2009, proposed the amendment of the sample size and the final analyses be done using available data. This proposal was approved by the independent data and safety monitoring committee on Aug 28, 2009. The data were locked on June 30, 2009. Patient follow-up for safety and survival will continue until 1.5 years after the last patient entry, as originally described in the study protocol.

Progression-free and overall survival were analysed for the modified intention-to-treat population as defined previously.<sup>26</sup> They were analysed using the Kaplan-Meier method, and were compared using the log-rank test. Hazard ratios in the overall population and in patient

subsets were calculated using the Cox proportional hazards model. The  $\chi^2$  test was used to compare proportions. Differences were considered significant at a two-sided p value of 0.05 or less. All statistical analyses were done with SAS version 9.1. This study is registered with UMIN (University Hospital Medical Information Network in Japan), number 000000539.

### Role of the funding source

There was no sole study sponsor for this trial. The WJOG designed and did the trial independently of any pharmaceutical company. The report was written by the corresponding author, who had unrestricted access to the study data and is responsible for the accuracy and completeness of the reported analyses. The corresponding author had final responsibility for the decision to submit for publication.

### Results

118 patients were positive for EGFR mutation at the central laboratory, 106 of whom were randomly allocated a treatment together with 71 patients with EGFR mutations who were tested at the commercial laboratories, giving a modified intention-to-treat population of 172 patients (figure 1). Baseline characteristics were well balanced between the two treatment groups (table 1), with the exception that the gefitinib group had an excess of exon 19 deletion mutations (50 of 86; 58.1%) compared with the cisplatin plus docetaxel group (37 of 86; 43.0%). Most of the patients had adenocarcinoma. 71 of 172 (41.3%) patients had postoperative recurrent disease, and 54 of 172 (31.4%) of the patients had a history of smoking. At the data collection cut-off time, the median follow-up was 81 days (range 74–1253 days), the median exposure to gefitinib was 165 days (range 22–1100 days), and the median number of cycles of cisplatin plus docetaxel chemotherapy was four, or 64 days (range one to six cycles, or 1–106 days).

Median progression-free survival was 9.2 months (95% CI 8.0–13.9) in the gefitinib group and 6.3 months (5.8–7.8) in the cisplatin plus docetaxel group ( $p<0.0001$ ; figure 2A). Gefitinib treatment resulted in significantly longer progression-free survival than cisplatin plus docetaxel (HR 0.489; 95% CI 0.336–0.710;  $p<0.0001$ ). Progression-free survival can be affected by the schedule of clinic visits and the interpretation of evidence of disease progression. We were able to confirm that the time schedule for clinic visits was almost the same in the two treatment groups (data not shown). In our trial, 71 patients had postoperative recurrent disease, and the remaining 101 patients had stage IIIB/IV disease. In both patient subsets, progression-free survival in the gefitinib group was longer than that in the cisplatin plus docetaxel group (figure 2B, 2C), although this was not a pre-specified analysis and was non-significant for those patients with postoperative recurrence. We noted that curves for each treatment group in the postoperative recurrence

subgroup (figure 2B) overlapped during the first 6 months, while the separation was clear during this time in the stage IIIB/IV group (figure 2C).

Patients treated with gefitinib had better progression-free survival than patients treated with cisplatin plus docetaxel in all subgroup analyses (figure 3). Additionally, gefitinib was better than cisplatin plus docetaxel, irrespective of where EGFR genetic testing was done. Exploratory analyses for progression-free survival showed that, in addition to the treatment group, patients with postoperative recurrent disease had a significantly better prognosis than those with stage IIIB/IV disease (table 2). We did a pre-planned comparison of exon 19 deletion with L858R in each treatment group. As shown in figure 4, mutation type was not prognostic. Therefore,

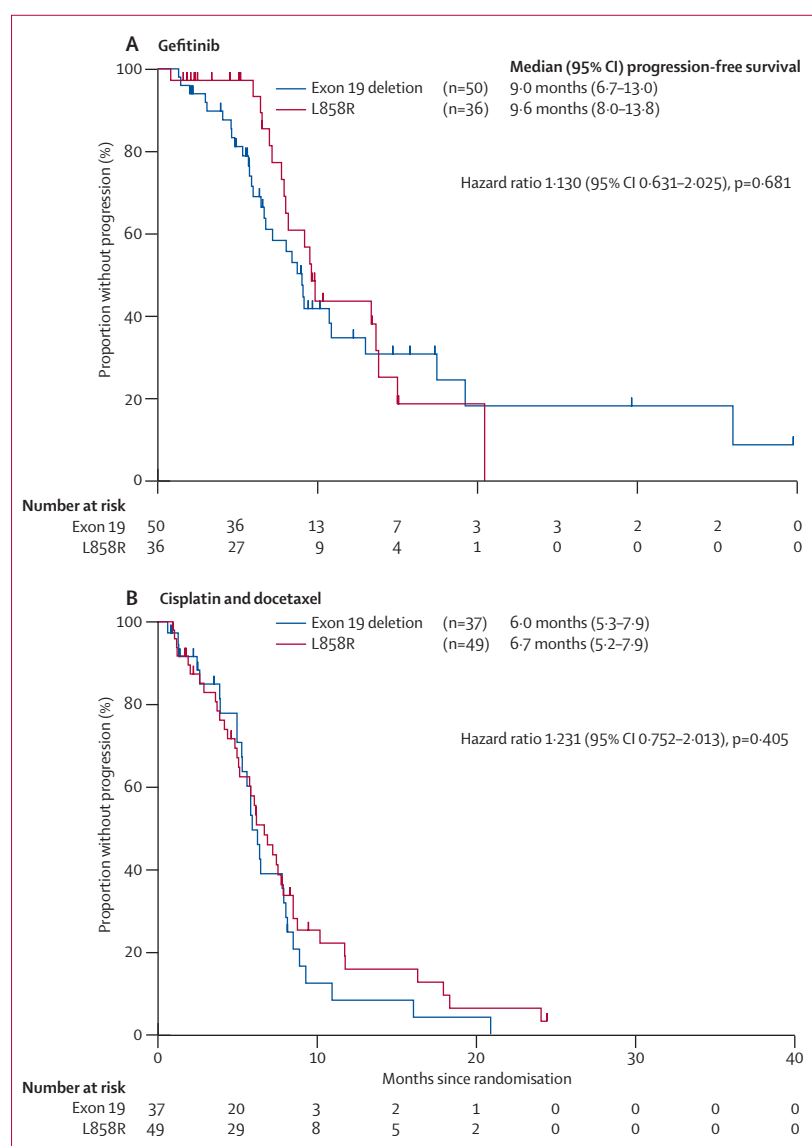


Figure 4: Progression-free survival in (A) the gefitinib group and (B) the cisplatin plus docetaxel group according to type of the EGFR mutation

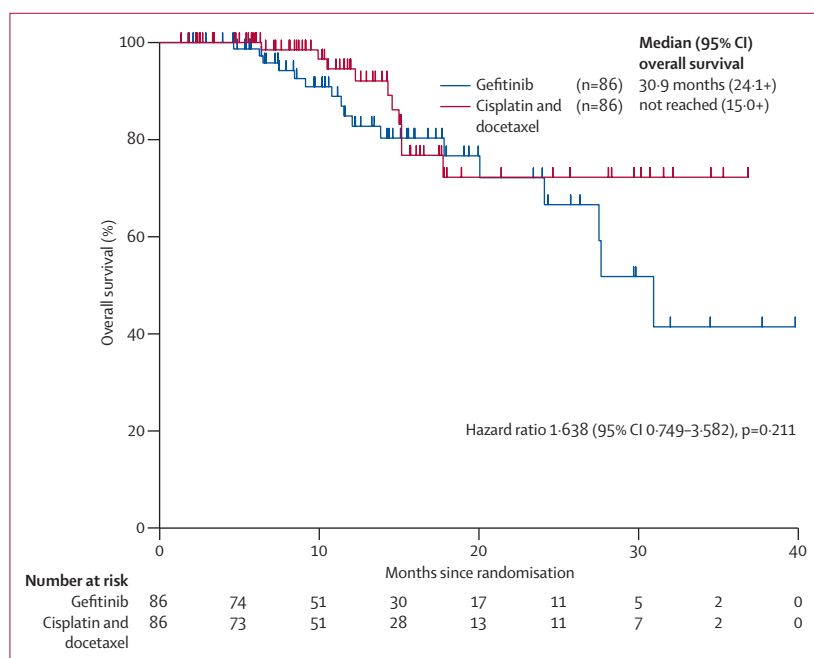


Figure 5: Overall survival in the overall population

See Online for webappendix

|                                    | Gefitinib (n=87) |              | Cisplatin plus docetaxel (n=88) |              |
|------------------------------------|------------------|--------------|---------------------------------|--------------|
|                                    | All              | CTC grade ≥3 | All                             | CTC grade ≥3 |
| <b>Non-haematological toxicity</b> |                  |              |                                 |              |
| Rash*                              | 74               | 2            | 7                               | 0            |
| AST*                               | 61               | 14           | 17                              | 1            |
| ALT*                               | 61               | 24           | 35                              | 2            |
| Dry skin*                          | 47               | 0            | 3                               | 0            |
| Diarrhoea                          | 47               | 1            | 35                              | 0            |
| Fatigue*                           | 34               | 2            | 73                              | 2            |
| Paronychia*                        | 28               | 1            | 1                               | 0            |
| Stomatitis                         | 19               | 0            | 13                              | 0            |
| Nausea*                            | 15               | 1            | 83                              | 3            |
| Constipation*                      | 14               | 0            | 39                              | 0            |
| Alopecia*                          | 8                | 0            | 67                              | 0            |
| Sensory disturbance*               | 7                | 1            | 23                              | 0            |
| <b>Haematological toxicity</b>     |                  |              |                                 |              |
| Leucocytopenia*                    | 13               | 0            | 82                              | 43           |
| Thrombocytopenia*                  | 12               | 0            | 29                              | 0            |
| Neutropenia*                       | 7                | 0            | 81                              | 74           |
| Anaemia*                           | 33               | 0            | 79                              | 15           |

ALT=alanine aminotransferase. AST=aspartate aminotransferase. CTC=National Cancer Institute Common Terminology Criteria. \*p<0.001.

**Table 3: Adverse events occurring in more than 10% of either of the treatment groups listed according to incidence in the gefitinib group**

imbalance of mutation types was not likely to affect the interpretation of the overall results.

The objective response rate in the overall population with measurable disease (n=117) was 62.1% (36 of 58 patients) in the gefitinib group and 32.2% (19 of

59 patients) in the cisplatin plus docetaxel group ( $p<0.0001$ ). The difference was significant (29.9%, 95% CI 12.6–47.1%;  $p<0.0001$ ). The disease control rate was also higher in the gefitinib group (54/58, 93.1%) than in the cisplatin plus docetaxel group (46/59, 78.0%; difference in disease control rate 15.1%, 95% CI 2.7–27.6,  $p=0.020$ ; webappendix). Because of frequent and detailed postoperative follow-up, which is standard practice in Japan, only 28 of 71 patients were found to have recurrent disease that met criteria for RECIST—ie, greater than 1 cm in the largest diameter. At the data cut-off, only 27 patients (15.7%) had died. Therefore, data for overall survival were immature, with follow-up still ongoing; 17 events (deaths) in the gefitinib group versus 10 events in the chemotherapy group—with an HR for gefitinib of 1.638 (95% CI, 0.75–3.58; figure 5). 51 patients in the chemotherapy group received an EGFR-TKI after they completed the study; 17 patients in the gefitinib group received post-protocol platinum doublet chemotherapy.

Adverse events occurring in more than 10% of either of the treatment groups are listed (table 3). The most common adverse event in the gefitinib group was skin rash followed by liver dysfunction, dry skin, and diarrhoea. However, adverse events with CTC grade 3 or more were infrequent, with the exception of liver dysfunction. By contrast, the most common adverse events in the cisplatin plus docetaxel group, which occurred in more than half of patients, were nausea, myelosuppression, fatigue, and alopecia.

Other potentially treatment-related toxicities included allergic reaction (one in gefitinib group, four in cisplatin plus docetaxel group) and oedema (one in gefitinib group, seven in the cisplatin plus docetaxel group). Two patients in the gefitinib group developed interstitial lung disease. There was one treatment-related death in the gefitinib group due to interstitial lung disease; there were no deaths in the cisplatin plus docetaxel group. There were no other serious adverse events.

## Discussion

Our results show that first-line treatment with gefitinib conferred longer progression-free survival than treatment with cisplatin plus docetaxel in a molecularly defined (ie, EGFR mutation positive) group of patients with NSCLC.

In the IPASS study for patients with lung adenocarcinoma with no or former light smoking history, the progression-free survival of patients treated with gefitinib was significantly longer.<sup>25</sup> However, the curves crossed at the 6-month timepoint (initially chemotherapy was better, while gefitinib was better later). Molecular analysis for about a third of the patients suggested that the benefit of gefitinib was limited to patients with EGFR mutations with an HR of 0.48 (95% CI 0.36–0.64) and that gefitinib treatment was detrimental for patients without mutations (HR 2.85).<sup>25</sup> This result might seem similar to ours; however, the primary objective of the IPASS study was to assess gefitinib treatment in clinically selected patients,

| Patient group                                                                                 |                                              | N   | Median progression-free survival (months) |              |                     | Median overall survival (months) |              |
|-----------------------------------------------------------------------------------------------|----------------------------------------------|-----|-------------------------------------------|--------------|---------------------|----------------------------------|--------------|
|                                                                                               |                                              |     | Gefitinib                                 | Chemotherapy | HR (95% CI)         | Gefitinib                        | Chemotherapy |
| Non-randomised pooled analysis                                                                |                                              |     |                                           |              |                     |                                  |              |
| I-CAMP <sup>11</sup>                                                                          | Japanese, EGFR mutation                      | 148 | 10.7                                      | 6.0          | 0.35 (0.23–0.52)    | 27.7                             | 25.7         |
| Subset analyses of the phase 3 trials for patients selected according to clinical backgrounds |                                              |     |                                           |              |                     |                                  |              |
| IPASS <sup>25</sup>                                                                           | East Asian, light-non-smoker, adenocarcinoma | 261 | 9.5                                       | 6.3          | 0.48 (0.36–0.64)    | ~20                              | ~20          |
| First SIGNAL <sup>33</sup>                                                                    | Korean, non-smoker, adenocarcinoma           | 42  | 8.4                                       | 6.7          | 0.61 (0.31–1.22)    | 30.6                             | 26.5         |
| Phase 3 trials of patients selected according to EGFR mutation status                         |                                              |     |                                           |              |                     |                                  |              |
| NEJ 002 <sup>26</sup>                                                                         | Japanese, EGFR mutation                      | 194 | 10.4                                      | 5.5          | 0.357(0.252–0.507)  | 28.0                             | 23.6         |
| WJTOG3405                                                                                     | Japanese, EGFR mutation                      | 172 | 9.2                                       | 6.3          | 0.489 (0.336–0.710) | ..                               | ..           |

Table 4: Recent clinical trials assessing EGFR mutations as predictors of efficacy of gefitinib compared with chemotherapy

**Table 4:** Recent clinical trials assessing EGFR mutations as predictors of efficacy of gefitinib compared with chemotherapy

and not in molecularly selected patients, as was the case in our trial. In this context, a HR of 0.36 (95% CI 0.25–0.51)<sup>26</sup> for gefitinib compared with carboplatin plus paclitaxel in patients selected by EGFR mutation is highly relevant. Furthermore, our pooled analyses based on individual patient data from seven Japanese phase 2 studies that assessed prospectively the efficacy of gefitinib for patients with EGFR mutations (I-CAMP study)<sup>11</sup> and the pooled analysis of 1006 patients enrolled in a phase 3 trial of gefitinib<sup>27</sup> also showed similar progression-free survival of about 10 months for patients harbouring an EGFR mutation who were treated with gefitinib, while the median progression-free survival of patients treated with chemotherapy was 6.0 months (table 4).<sup>11</sup> These results strongly suggest that the presence of EGFR mutations, and not the clinical background of patients, determines clinical efficacy, and this knowledge should lead to molecularly based, personalised treatment of lung cancer.

Since the median duration of each treatment was quite different (165 days for gefitinib compared with 64 days for chemotherapy), one interpretation might be that a maintenance effect of gefitinib therapy contributed to the positive progression-free survival outcome, at least in part. Indeed, the progression-free survival curves of both groups in IPASS were initially similar, and then separate at about the time that chemotherapy stops. However, this was not the case in our trial, especially in patients with stage IIIB/IV disease. Furthermore, the SATURN<sup>28</sup> and the FAST-ACT<sup>29</sup> trials that tested maintenance erlotinib after chemotherapy showed that progression-free survival (both trials) and overall survival (SATURN) was prolonged. The benefit was much greater in patients with an EGFR mutation than in those without it in the SATURN trial.<sup>28</sup>

According to analyses of five US and European clinical trials that assessed first-line TKI treatment,<sup>12</sup> patients with the exon 19 deletion have a significantly longer progression-free and overall survival than patients with L858R (30.8 vs 14.8 months;  $p < 0.0001$ ). A similar trend was shown in a recent Spanish study.<sup>13</sup> In IPASS, the HR for progression-free survival for gefitinib versus chemotherapy was 0.38 (95% CI 0.25–0.56) in the subgroup of patients with exon 19 deletions, and 0.55 (95% CI 0.35–0.87) in the L858R mutation

subgroup, although a direct comparison between exon 19 deletion and L858R in the gefitinib group was not done.<sup>30</sup> However, recent Japanese trials, including I-CAMP<sup>11</sup> and this study, did not detect any difference. The reason for this discrepancy is not clear, although it might be attributable to ethnic differences or difference of EGFR-TKI used between study populations.

Two patients in the gefitinib group (2.3%) developed interstitial lung disease, one of whom died. This incidence was low compared with previous Japanese reports of 4.0% (59/1482)<sup>31</sup> and 3.5% (70/1976).<sup>32</sup> Selecting patients according to EGFR mutation status is expected to reduce the risk of interstitial lung disease, because risk factors for interstitial lung disease include smoking, male sex, and squamous histology, all of which are negative predictors of the presence of EGFR mutations.<sup>31,32</sup>

Our study indicates that EGFR genetic testing is feasible and should be done when possible. Although patients without EGFR mutations were not included in our study, potential harm of first-line gefitinib therapy compared with chemotherapy for patients without EGFR mutation shown in the IPASS<sup>25</sup> and the First-SIGNAL<sup>33</sup> study indicate the necessity of patient selection by EGFR mutation.

Clinical background might help identify patients who have a higher chance of carrying EGFR mutations. However, it should be noted that in a previous study,<sup>9</sup> eight of 37 (22%) patients with lung adenocarcinoma with a history of heavy smoking (>50 pack-years) harboured EGFR mutations.<sup>9</sup>

In conclusion, gefitinib significantly prolonged the progression-free survival of patients with NSCLC who carry EGFR mutations compared with cisplatin plus docetaxel. It is not yet known whether the prolonged progression-free survival conferred by gefitinib will translate into prolonged overall survival; we will continue to carefully follow-up our patients to determine its long-term effects. Considering the efficacy and toxicity of gefitinib, it is a reasonable option for the first-line treatment of patients with activating EGFR mutations.

#### Contributors

TM, SM, SN, TS, MS, NK, and KN were involved in the conception and design of the study. KN and MF supervised the study. TM, IO, TS, MS, HT, TH, KA, NK, MT, HY, KS, SK, ES, HS, and ST were involved in the

provision of study material, patients, and data acquisition. TM, SM, YY, SN, IO, JT, TH, NK, MT, HY, KS, ES, HS, ST, and KN were involved in data analysis and interpretation. SM was in charge of the statistical design of the study. YY was in charge of *EGFR* gene testing at the central laboratory. All authors were involved in writing the report and approved the final version.

#### Conflicts of interest

TM has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. SN has received honoraria from AstraZeneca and Sanofi-Aventis. MS has received honoraria from AstraZeneca. HT has received honoraria from AstraZeneca and Sanofi-Aventis. ST has received honoraria from AstraZeneca and Chugai. KN has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. MF has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. All other authors declared that they have no conflicts of interest.

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# THE LANCET Oncology

## Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed.  
We post it as supplied by the authors.

Supplement to: Mitsudomi T, Morita S, Yatabe Y, et al, for the West Japan Oncology Group. 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* 2009; published online Dec 21. DOI:10.1016/S1470-2045(09)70364-X.

|                          | <b>n</b> | <b>CR</b> | <b>PR</b> | <b>SD</b> | <b>PD</b> | <b>NE</b> | <b>Response rate</b><br><b>95%CI</b> | <b>Disease control rate</b><br><b>95%CI</b> |
|--------------------------|----------|-----------|-----------|-----------|-----------|-----------|--------------------------------------|---------------------------------------------|
| Gefitinib                | 58       | 0         | 36        | 18        | 4         | 0         | 62·1%<br>(48·4- 74·5)                | 93·1%<br>(83·3-98·1)                        |
| Cisplatin /<br>docetaxel | 59       | 0         | 19        | 27        | 9         | 4         | 32·2%<br>(20·6- 44·6)                | 78·0%<br>(65·3- 87·7)                       |
| Total                    | 117      | 0         | 55        | 45        | 13        | 4         | 47·0%<br>(37·7- 56·5)                | 85·5%<br>(77·8- 91·3)                       |

Supplementary table 1. Tumour response