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# Impact of Specific Epidermal Growth Factor Receptor (*EGFR*) Mutations and Clinical Characteristics on Outcomes After Treatment With EGFR Tyrosine Kinase Inhibitors Versus Chemotherapy in *EGFR*-Mutant Lung Cancer: A Meta-Analysis

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A B S T R A C T

**Purpose**
We examined the impact of different epidermal growth factor receptor (*EGFR*) mutations and clinical characteristics on progression-free survival (PFS) in patients with advanced *EGFR*-mutated non–small-cell lung cancer treated with EGFR tyrosine kinase inhibitors (TKIs) as first-line therapy.

**Patients and Methods**
This meta-analysis included randomized trials comparing EGFR TKIs with chemotherapy. We calculated hazard ratios (HRs) and 95% CIs for PFS for the trial population and prespecified subgroups and calculated pooled estimates of treatment efficacy using the fixed-effects inverse-variance-weighted method. All statistical tests were two sided.

**Results**
In seven eligible trials (1,649 patients), EGFR TKIs, compared with chemotherapy, significantly prolonged PFS overall (HR, 0.37; 95% CI, 0.32 to 0.42) and in all subgroups. For tumors with exon 19 deletions, the benefit was 50% greater (HR, 0.24; 95% CI, 0.20 to 0.29) than for tumors with exon 21 L858R substitution (HR, 0.48; 95% CI, 0.39 to 0.58; $P_{interaction} < .001$). Never-smokers had a 36% greater benefit (HR, 0.32; 95% CI, 0.27 to 0.37) than current or former smokers (HR, 0.50; 95% CI, 0.40 to 0.63; $P_{interaction} < .001$). Women had a 27% greater benefit (HR, 0.33; 95% CI, 0.28 to 0.38) than men (HR, 0.45; 95% CI, 0.36 to 0.55; treatment-sex interaction $P = .02$). Performance status, age, ethnicity, and tumor histology did not significantly predict additional benefit from EGFR TKIs.

**Conclusion**
Although EGFR TKIs significantly prolonged PFS overall and in all subgroups, compared with chemotherapy, greater benefits were observed in those with exon 19 deletions, never-smokers, and women. These findings should enhance drug development and economic analyses, as well as the design and interpretation of clinical trials.

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## INTRODUCTION

Advanced non–small-cell lung cancer (NSCLC) with activating mutations in the epidermal growth factor receptor (*EGFR*) gene is a distinct subtype of disease that is characterized by a high tumor response rate when treated with small-molecule EGFR tyrosine kinase inhibitors (TKIs). Randomized trials[1-8] and meta-analyses[9-11] have consistently demonstrated longer progression-free survival (PFS) with EGFR TKI therapy compared with chemotherapy.

Deletions in exon 19 and substitution of leucine for arginine (L858R) in exon 21 of the *EGFR* gene (so-called common mutations) constitute approximately 90% of all *EGFR* mutations that are detected in patients with advanced NSCLC who are enrolled onto randomized trials.[1,2,6,7] Common and uncommon mutation status is used as a stratification factor in many EGFR TKI trials. Although the two common mutations have been regarded as similar in predicting the benefit of EGFR TKIs, subgroup analyses of two studies[6,8] suggested that the benefit of EGFR TKIs is greater in exon 19 deletion

than in exon 21 L858R substitution tumors. However, these findings have not been consistently observed in other trials.[2-5,7]

In the landmark NCIC Clinical Trials Group study BR.21,[12] Asian origin, adenocarcinoma histology, never smoking, and erlotinib were associated with improved overall survival (OS). Subsequent molecular analysis also showed that the benefit of erlotinib was strongly associated with *EGFR* mutation in this trial, and *EGFR* mutations were also more commonly detected in women, patients of Asian origin, patients with adenocarcinoma, and never-smokers.[13,14] Among patients with *EGFR* mutations, the influence of these clinical characteristics on the additional benefit of EGFR TKIs is unknown.

Individual randomized trials have not been designed nor adequately powered to demonstrate a treatment difference between subgroups of patients with these common mutations and other clinicopathologic characteristics. Identifying such factors may be important for future clinical trial design and development of newer generations of EGFR TKIs. To address these questions, this study was designed with the primary objective of testing the hypothesis that the relative effect on PFS of first-line therapy with EGFR TKIs versus chemotherapy is affected by mutation type. Secondary objectives were to test for interactions between clinical characteristics (age, sex, ethnicity, smoking status, performance status, tumor histology) that might be associated with EGFR TKI benefit in a population with *EGFR* mutations.

Ideally, a meta-analysis of randomized trials with OS as the primary end point will address these questions. However, in all of these trials, the effect of EGFR TKIs on OS has been diminished for two reasons: first, nearly all of the patients who were randomly assigned to chemotherapy crossed over to receive EGFR TKIs after disease progression, and second, EGFR TKIs are commercially available outside of clinical trial settings. Furthermore, unlike with EGFR TKIs, the benefit of chemotherapy diminished in second-line as compared with first-line settings. For these reasons, we performed this meta-analysis of PFS outcome using randomized trial data from patients undergoing first-line treatment with first-and second-generation EGFR TKIs.

## PATIENTS AND METHODS

### Study Eligibility and Identification

Eligible studies were identified from our previous broad systematic review that assessed the effectiveness of EGFR TKIs by *EGFR* mutation status.[9] The included studies were randomized trials that compared EGFR TKIs against platinum-based combination chemotherapy in adult patients with good performance status who did not receive any systemic therapy for their histologically or cytologically confirmed, newly diagnosed advanced NSCLC with sensitizing *EGFR* mutations. In brief, we updated our bibliographic search of MEDLINE, EMBASE, CANCERLIT, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases for articles published in English between January 1, 2004, and February 28, 2014, using the following search terms: lung neoplasms, non–small-cell lung cancer, gefitinib, erlotinib, afatinib, EGFR, meta-analysis, systematic review, randomized, and clinical trials. To identify unpublished studies, we also searched abstracts from conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Lung Cancer Conference. Individual study sponsors and study investigators were contacted for conference presentation slides whenever slides were unavailable.

### Data Extraction

For each included trial, we extracted the trial name, year of publication or conference presentation, clinicopathologic characteristics, type of chemotherapy, and type of EGFR TKIs. We also retrieved treatment estimates for these subgroups: age ($< 65$ *v* $\geq 65$ years), sex (female *v* male), ethnicity (Asian *v* non-Asian), smoking status (never-smoker *v* current or former smoker), Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 *v* 2), tumor histology (adenocarcinoma *v* other), and *EGFR* mutation (exon 19 deletion *v* exon 21 L858R substitution) subtype. Data were extracted independently by two authors (P.N.D. and C.K.L.), and discrepancies were resolved by consensus that included a third author (S.J.L.). Risk of bias for PFS analysis in each trial was assessed by examining the methods used in random assignment, allocation concealment, outcome assessments, handling of patient attrition, use of intention-to-treat analysis, and handling of missing data for subgroup analyses.

### Statistical Analyses

We extracted the hazard ratios (HRs) and 95% CIs for the overall cohort and subgroups. Data from independent assessment of PFS were used in preference to investigator assessment whenever both types of review were available. We used the fixed-effects inverse-variance-weighted method to pool the results from the studies and to estimate the size of the treatment benefit. Tests for interaction were used to assess differences in treatment effect across subgroups as defined by their baseline clinicopathologic characteristics.

Subgroups with statistically significant heterogeneity in treatment effect were examined further using individual patient data from four trials: NEJ002 (North East Japan 002),[2,15] OPTIMAL,[4] EURTAC (European Tarceva Versus Chemotherapy),[5] and WJTOG (West Japan Thoracic Oncology Group) trial 3405.[3,16] We re-estimated the HRs and 95% CIs in multivariable analyses for the treatment effect for each of these subgroups after adjusting for the other baseline characteristics. We repeated the tests for interaction on the basis of the adjusted HRs to assess differences in treatment effect.

Comparisons between *EGFR* mutations with exon 19 deletions versus exon 21 L858R substitution, with respect to baseline characteristics, involved data from the four trials.[2-5,15,16] The Kaplan-Meier approach was used to examine the difference in PFS between exon 19 deletion and exon 21 L858R substitution in patients who were randomly assigned to the chemotherapy and EGFR TKIs arms separately, and univariable Cox regressions were used to estimate the HRs and 95% CIs.

We performed three sensitivity analyses in which, first, studies were excluded if they reported highly significant subgroup differences in the treatment effect, given that such studies might skew the results if there was selective reporting of chance positive findings; second, the analysis was limited to first-generation EGFR TKIs (gefitinib and erlotinib) because we recognized that there might be differences in efficacy between first- and second-generation EGFR TKIs (afatinib); and third, studies were excluded if the median PFS of the chemotherapy arm differed substantially from that of other included trials because we recognized that there might be differences in efficacy between the different types of platinum combination chemotherapies.

Publication bias was evaluated using the approach of Gleser and Olkin,[17] with an examination of a funnel plot of the effect size for each subgroup of the trial against the reciprocal of its SE.

We used the $\chi^2$ Cochran Q test to detect any heterogeneity across the different studies and between subgroups. The nominal level of significance was set at 5%. All 95% CIs were two sided.

## RESULTS

We identified seven eligible studies[2-8,15,18] for inclusion in this meta-analysis (Fig 1). Trial data were obtained from published manuscripts and conference abstracts for three trials.[6-8] Updated individual patient data from the NEJ002[2,15] and OPTIMAL[4] trials were used for subgroup results. Individual patient data with longer follow-up than previously published for EURTAC[5] and WJTOG 3405[3,16] trials were used. Data that were based on independent reviews for PFS were used

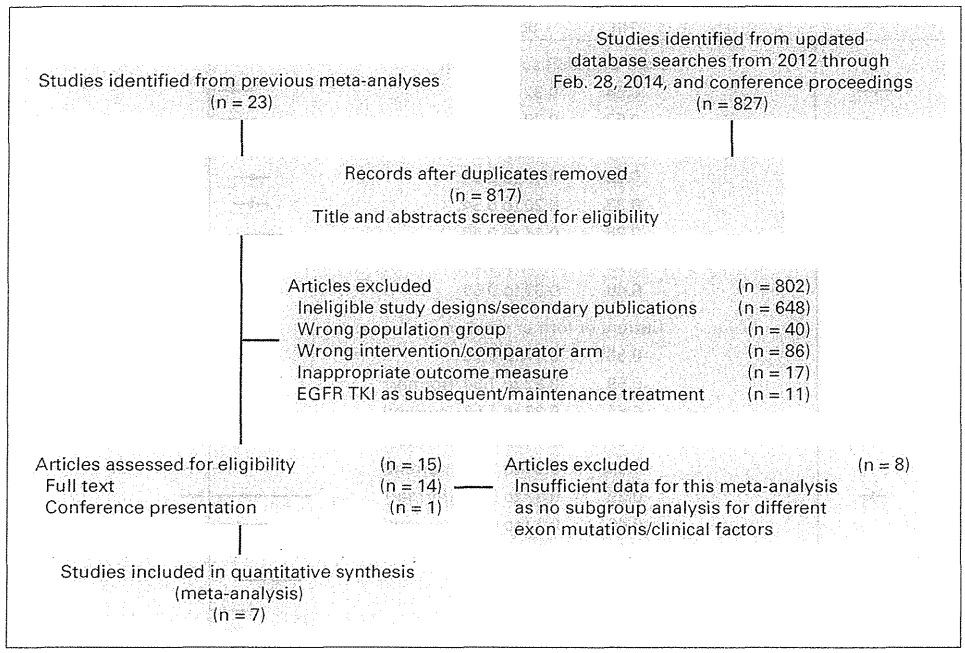


**Fig 1.** Flow diagram showing inclusion and exclusion of studies. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

for two studies.[6,7] Hoffmann-La Roche provided unpublished subgroup data for the ENSURE trial that was based on investigator assessment only.[8] All included trials were open label. Risk of bias was assessed as unclear in one unpublished trial,[8] and low for all other studies, although one trial[4] did not include independent review of disease progression.

A total of 1,649 patients participated in these trials. All trials except NEJ002,[2] LUX-Lung 3,[6] and LUX-Lung 6[7] recruited only patients with the two common *EGFR* mutations, exon 19 deletions and exon 21 L858R substitution. Other clinicopathologic characteristics of patients are summarized in Table 1.

### *Benefit of EGFR TKIs for PFS*

Of the 1,649 patients, 950 (58%) had been randomly assigned to EGFR TKIs, and 699 (42%) patients had been randomly assigned to chemotherapy. Treatment with EGFR TKIs compared with chemotherapy was statistically significantly associated with a 63% reduction in the risk of disease progression or death (HR, 0.37; 95% CI, 0.32 to 0.42; $P < .001$).

### *Subgroup Analyses*

Of the 1,558 patients with common mutations, 872 (56%) patients had exon 19 deletions and 686 (44%) had exon 21 L858R

**Table 1.** Characteristics of Patients in Constituent Trials

| Study Name, Year | Treatment Comparison | Median PFS (months) | No. of Patients | Exon 19 Deletion (%) | Exon 21 L858R Substitution (%) | Age < 65 Years (%) | ECOG PS 0 and 1 (%) | Asian (%) | Women (%) | Never-Smoker (%) | Adenocarcinoma (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NEJ002, 2010, 2013[2,15*] | Gefitinib *v* CP | 10.8 *v* 5.4 | 224† | 51 | 43 | 49 | 99 | 100 | 63 | 62 | 93 |
| WJTOG 3405, 2010, 2012[3,16] | Gefitinib *v* CisD | 9.6 *v* 6.5 | 172 | 51 | 49 | 53 | 100 | 100 | 69 | 69 | 97 |
| OPTIMAL, 2011, 2012[4,18] | Erlotinib *v* CG | 13.1 *v* 4.6 | 154 | 53 | 47 | 75 | 94 | 100 | 59 | 71 | 87 |
| EURTAC, 2012[5] | Erlotinib *v* platinum-G or platinum-D | 9.7 *v* 5.2 | 173 | 66 | 34 | 49 | 86 | 0 | 73 | 69 | 92 |
| LUX-Lung 3, 2013[6*] | Afatinib *v* CisPem | 11.1 *v* 6.9 | 345 | 49 | 40 | 61 | 100 | 72 | 65 | 68 | 100 |
| LUX-Lung 6, 2014[7*] | Afatinib *v* CisG | 11.0 *v* 5.6 | 364 | 51 | 38 | 76 | 100 | 100 | 65 | 77 | 100 |
| ENSURE, 2014[8‡] | Erlotinib *v* CisG | 11.0 *v* 5.5 | 217 | 54 | 45 | 79 | 94 | 100 | 61 | 71 | 94 |

Abbreviations: CG, carboplatin-gemcitabine; CisD, cisplatin-docetaxel; CisG, cisplatin-gemcitabine; CisPem, cisplatin-pemetrexed; CP, carboplatin-paclitaxel; ECOG, Eastern Cooperative Oncology Group; EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; PFS, progression-free survival; PS, performance status; WJTOG, West Japan Thoracic Oncology Group.

*Includes patients with uncommon mutations of the *EGFR* gene.

†NEJ002 recruited a total of 228 patients; PFS outcome was only reported for 224 patients.

‡Reported in abstract only.

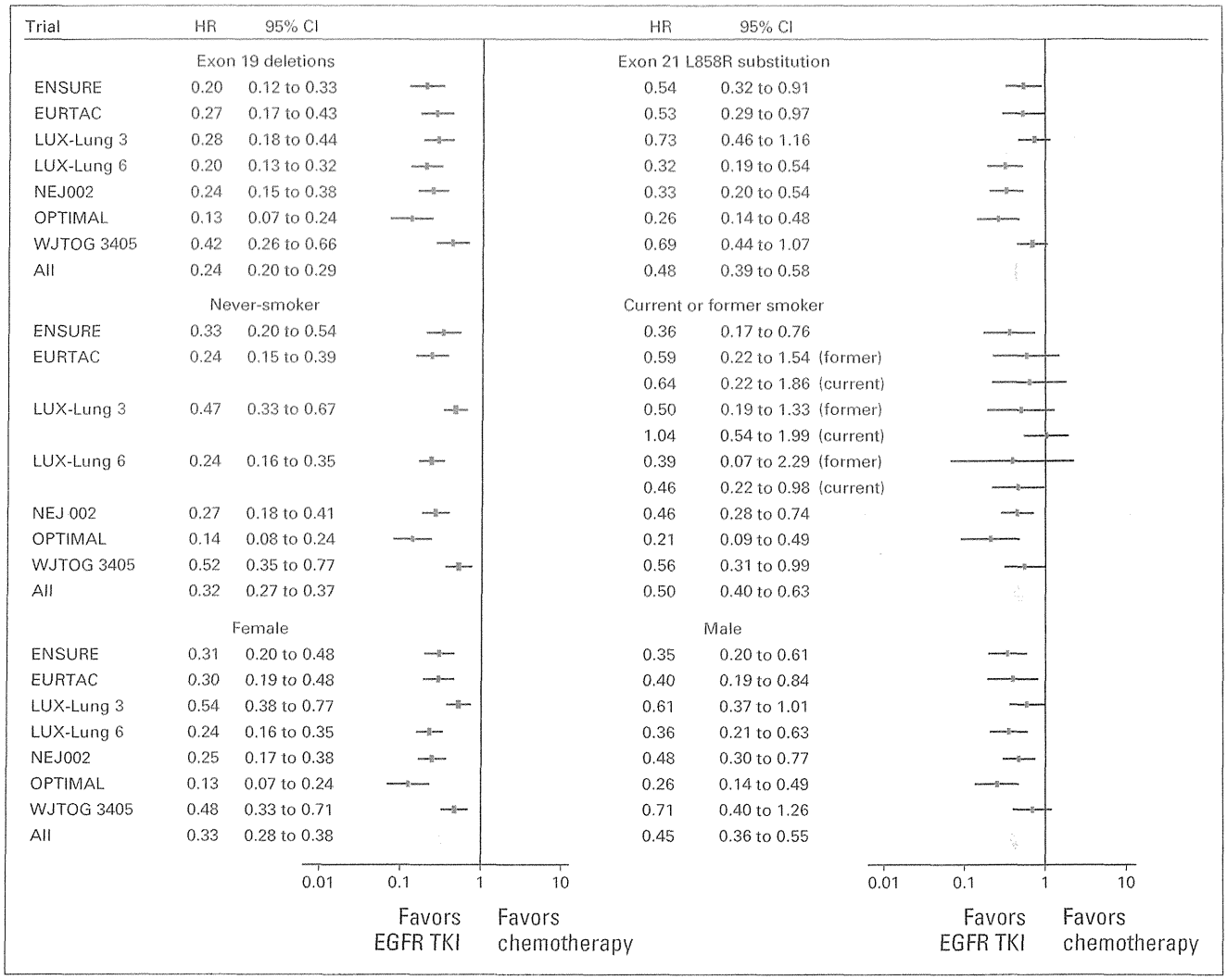


**Fig 2.** Forest plot of the effect of treatment on progression-free survival in subgroups of patients according to mutations of the epidermal growth factor receptor (*EGFR*) gene, smoking status, and sex. Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis fixed effect. All statistical tests were two sided. EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

substitution. In the subgroup with exon 19 deletions, the pooled HR for PFS was 0.24 (95% CI, 0.20 to 0.29; $P < .001$). In the exon 21 L858R substitution subgroup, the pooled HR for PFS was 0.48 (95% CI, 0.39 to 0.58; $P < .001$). Compared with chemotherapy, treatment with EGFR TKIs demonstrated 50% greater benefit in exon 19 deletions than in exon 21 L858R substitution (interaction $P < .001$; Fig 2).

Of the 1,649 patients, most were never-smokers (n = 1,155; 70%) and 494 (30%) were current or former smokers. Among the never-smokers, the pooled HR for PFS was 0.32 (95% CI, 0.27 to 0.37; $P < .001$). Among the current or former smokers, the pooled HR for PFS was 0.50 (95% CI, 0.40 to 0.63; $P < .001$). Compared with chemotherapy, treatment with EGFR TKIs demonstrated a 36% greater benefit in never-smokers than current or former smokers (interaction $P = .002$; Fig 2).

Most patients (n = 1,073; 65%) were women; 576 (35%) were men. Among the women, the pooled HR for PFS was 0.33 (95% CI, 0.28 to 0.38; $P < .001$). Among the men, the pooled HR for PFS was 0.45 (95% CI, 0.36 to 0.55; $P < .001$). Compared with chemotherapy, EGFR TKI treatment demonstrated a 27% greater benefit in women than men (interaction $P = .02$; Fig 2).

In multivariable analysis using data from the four trials,[2-5,15,16] the pooled HRs for PFS were 0.26 and 0.44, adjusted for smoking status and sex, for exon 19 deletions and exon 21 L858R substitution subgroups, respectively (interaction $P = .004$). There was negligible difference in the result between unadjusted and adjusted HRs (exon 19 deletions: unadjusted pooled HR, 0.26; exon 21 L858R substitution: unadjusted pooled HR, 0.45; interaction $P = .004$). Table 2 compares the unadjusted and adjusted HRs of treatment effect to assess any potential inter-related impact of type of *EGFR* mutation, sex, and smoking on benefit with EGFR TKIs.

The improvement in PFS with EGFR TKI treatment compared with chemotherapy did not differ by ethnicity (interaction $P = .37$), age (interaction $P = .27$), tumor histologic subtype (interaction $P = .59$), or performance status (interaction $P = .85$; Fig 3).

  

**Table 2.** Unadjusted and Adjusted Treatment Effect of EGFR TKIs Versus Chemotherapy in Four Clinical Trials

| Subgroup | Unadjusted Analysis HR | Unadjusted Analysis 95% CI | Adjusted Analysis HR | Adjusted Analysis 95% CI |
|---|---|---|---|---|
| Exon 19 deletions | | | | |
| EURTAC | 0.27 | 0.17 to 0.43 | 0.25* | 0.15 to 0.41 |
| NEJ002 | 0.24 | 0.15 to 0.38 | 0.24* | 0.15 to 0.38 |
| OPTIMAL | 0.13 | 0.07 to 0.25 | 0.12* | 0.06 to 0.22 |
| WJTOG 3405 | 0.42 | 0.26 to 0.68 | 0.46* | 0.28 to 0.76 |
| Pooled result | 0.26 | 0.20 to 0.34 | 0.26 | 0.20 to 0.33 |
| Exon 21 L858R substitution | | | | |
| EURTAC | 0.53 | 0.29 to 0.97 | 0.51* | 0.28 to 0.94 |
| NEJ002 | 0.33 | 0.20 to 0.54 | 0.33* | 0.20 to 0.55 |
| OPTIMAL | 0.26 | 0.14 to 0.49 | 0.23* | 0.12 to 0.45 |
| WJTOG 3405 | 0.69 | 0.44 to 1.07 | 0.69* | 0.44 to 1.08 |
| Pooled result | 0.45 | 0.34 to 0.58 | 0.44 | 0.34 to 0.58 |
| Treatment-*EGFR* mutation interaction | $P = .004$ | | $P = .004$ | |
| Never-smoker | | | | |
| EURTAC | 0.24 | 0.15 to 0.39 | 0.23† | 0.14 to 0.38 |
| NEJ002 | 0.27 | 0.18 to 0.41 | 0.24† | 0.16 to 0.37 |
| OPTIMAL | 0.14 | 0.08 to 0.25 | 0.14† | 0.08 to 0.25 |
| WJTOG 3405 | 0.52 | 0.35 to 0.77 | 0.52† | 0.34 to 0.79 |
| Pooled result | 0.29 | 0.24 to 0.37 | 0.28 | 0.22 to 0.35 |
| Current or former smoker | | | | |
| EURTAC (former) | 0.59 | 0.22 to 1.54 | 0.67† | 0.25 to 1.78 |
| EURTAC (current) | 0.64 | 0.22 to 1.86 | 0.56† | 0.19 to 1.71 |
| NEJ002 | 0.46 | 0.28 to 0.74 | 0.45† | 0.28 to 0.73 |
| OPTIMAL | 0.21 | 0.09 to 0.49 | 0.20† | 0.08 to 0.47 |
| WJTOG 3405 | 0.56 | 0.31 to 0.99 | 0.57† | 0.32 to 1.02 |
| Pooled result | 0.46 | 0.34 to 0.62 | 0.46† | 0.34 to 0.62 |
| Treatment-smoking interaction | $P = .02$ | | $P = .01$ | |
| Women | | | | |
| EURTAC | 0.30 | 0.19 to 0.48 | 0.29‡ | 0.18 to 0.47 |
| NEJ002 | 0.25 | 0.17 to 0.38 | 0.21‡ | 0.14 to 0.33 |
| OPTIMAL | 0.13 | 0.07 to 0.24 | 0.13‡ | 0.07 to 0.24 |
| WJTOG 3405 | 0.48 | 0.33 to 0.71 | 0.50‡ | 0.33 to 0.76 |
| Pooled result | 0.30 | 0.24 to 0.38 | 0.28 | 0.22 to 0.36 |
| Men | | | | |
| EURTAC | 0.40 | 0.19 to 0.84 | 0.37‡ | 0.17 to 0.81 |
| NEJ002 | 0.48 | 0.30 to 0.77 | 0.45‡ | 0.28 to 0.74 |
| OPTIMAL | 0.26 | 0.14 to 0.50 | 0.23‡ | 0.12 to 0.45 |
| WJTOG 3405 | 0.71 | 0.40 to 1.26 | 0.69‡ | 0.39 to 1.22 |
| Pooled result | 0.46 | 0.34 to 0.61 | 0.43 | 0.32 to 0.58 |
| Treatment-sex interaction | $P = .02$ | | $P = .03$ | |

Abbreviations: EGFR, epidermal growth factor receptor; EURTAC, European Tarceva Versus Chemotherapy; HR, hazard ratio; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.
*HR (EGFR TKI *v* chemotherapy) adjusted for smoking status and sex.
†HR (EGFR TKI *v* chemotherapy) adjusted for sex and type of *EGFR* mutation.
‡HR (EGFR TKI *v* chemotherapy) adjusted for smoking status and type of *EGFR* mutation.

### Benefit of EGFR TKIs for OS

At the point of data cutoff for this analysis, several trials had reported preliminary OS data and had patients still in active follow-up. The data for OS remained immature for many of these studies. The OS data for the ENSURE trial was unavailable.[8] With the available preliminary OS data from the remaining six trials, treatment with EGFR TKIs compared with chemotherapy was not statistically significantly associated with reduction in the risk of death (HR, 1.01; 95% CI, 0.86 to 1.19; $P = .88$).

### Association Between Mutations and Baseline Clinical Characteristics

In four trials,[2-5,15,16] there were no significant correlations between *EGFR* mutation type and age, performance status, sex, histology, or smoking status (Table 3).

### Prognostic Outcomes for Patients With Common Mutations

Of the 348 patients in the four trials[2-5,15,16] who were randomly assigned to chemotherapy, those with exon 21 L858R substitution (n = 158) had a median PFS of 6.1 months, which was statistically significantly longer than those with exon 19 deletions (n = 190), who had a median PFS of 5.1 months (HR, 0.70; 95% CI, 0.56 to 0.89; $P = .003$). In comparison, of the 362 patients who were randomly assigned to EGFR TKIs in these trials, patients with exon 21 L858R substitution (n = 154) had a median PFS of 10.0 months, which was statistically significantly shorter than that of patients with exon 19 deletions (n = 208), who had a median PFS of 11.8 months (HR, 1.39; 95% CI, 1.10 to 1.76; $P = .006$).

### Publication Bias

A funnel plot of the effect size for each subgroup category of the trial against the precision showed no asymmetry (not shown). A formal test[17] for potential publication bias yielded no potential unpublished studies.

### Sensitivity Analyses

Two trials[6,8] individually demonstrated greater PFS benefit for EGFR TKIs versus chemotherapy in tumors with exon 19 deletions compared with those with exon 21 L858R substitution; therefore, we excluded these studies and observed consistent results (HR, 0.24 *v* 0.42; interaction $P < .001$; Appendix Fig A1, online only).

Restricting our analyses to trials of first-generation reversible EGFR TKIs, erlotinib[4,5,8,18] and gefitinib[2,3,15,16] (Appendix Fig A2, online only), we also found consistent results: greater benefit with EGFR TKIs for exon 19 deletions (interaction $P < .001$), never-smokers (interaction $P = .03$), and women (interaction $P = .03$).

Two trials[3,6] individually demonstrated median PFS greater than 6 months in the chemotherapy arm. Given that this was a longer PFS than reported in other studies (Table 1), we excluded these two studies and observed consistent results: greater benefit for EGFR TKIs for exon 19 deletions (interaction $P < .001$), never-smokers (interaction $P = .003$), and women (interaction $P = .01$; Appendix Fig A3, online only).

## DISCUSSION

Treatment with EGFR TKIs compared with chemotherapy is associated with a 63% overall reduction in the risk of disease progression or death. Furthermore, the relative effect of EGFR TKIs compared with chemotherapy on PFS is 50% greater for patients with exon 19 deletions than for those with exon 21 L858R substitution. Other crucial findings include a 36% greater PFS benefit for never-smokers than

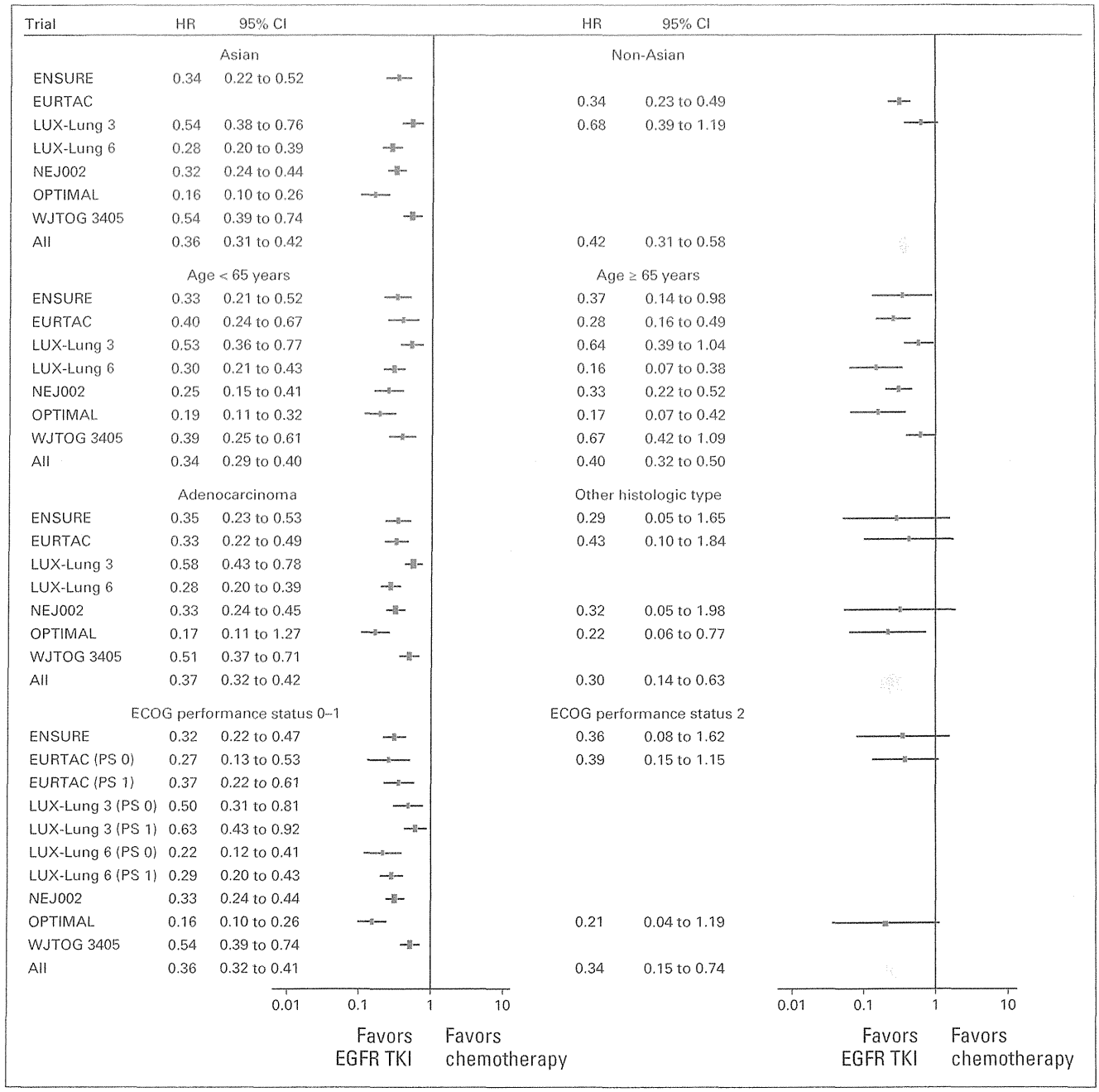


**Fig 3.** Forest plot of the effect of treatment on progression-free survival in subgroups of patients according to ethnicity, age, tumor histologic subtype, and performance status (PS). Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis fixed effect. All statistical tests were two sided. ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

current or former smokers and a 27% greater PFS benefit for women than men with EGFR TKIs compared with chemotherapy.

Consistent with previous studies, patients with exon 19 deletions have a longer OS than those with exon 21 L858R substitution after gefitinib or erlotinib therapy.[19,20] In contrast, in patients who are not treated with EGFR TKIs, exon 21 L858R substitution, rather than exon 19 deletions, has been associated with longer OS.[14] Using data from four trials,[2-5,15,16] we found that patients randomly assigned to chemotherapy who had exon 21 L858R substitution had statistically significantly longer PFS than those with exon 19 deletions (median PFS, 6.1 *v* 5.1 months; $P = .003$). This indicates that patients who harbor exon 19 deletions and are not treated with EGFR TKIs have a poorer prognosis than those with exon 21 L858R substitution. Treatment with EGFR TKIs improves the prognosis more in those with exon 19 deletions than in those with exon 21 L858R substitution (median PFS, 11.8 *v* 10.0 months; $P = .006$).

  

**Table 3.** Association Between Baseline Characteristics and Exon 19 Deletion or Exon 21 L858R Substitution: Pooled Data From Four Clinical Trials

| | Exon 19 Deletion (n = 401) | | Exon 21 L858R Substitution (n = 313) | | |
|---|---|---|---|---|---|
| Characteristic | No. | % | No. | % | *P* |
| Age, years | | | | | .20 |
| < 65 | 233 | 58 | 166 | 53 | |
| ≥ 65 | 168 | 42 | 147 | 47 | |
| ECOG PS | | | | | .32 |
| 0 | 186 | 46 | 136 | 44 | |
| 1 | 191 | 48 | 164 | 52 | |
| 2 | 24 | 6 | 13 | 4 | |
| Sex | | | | | .81 |
| Female | 268 | 67 | 206 | 66 | |
| Male | 133 | 33 | 107 | 34 | |
| Smoking | | | | | .81 |
| Never | 268 | 67 | 212 | 68 | |
| Ever | 133 | 33 | 101 | 32 | |
| Histologic subtype | | | | | .11 |
| Adenocarcinoma | 377 | 94 | 284 | 91 | |
| Other | 24 | 6 | 29 | 9 | |

Abbreviations: EGOG, Eastern Cooperative Oncology Group; PS, performance status.

The associations between different *EGFR* mutations and baseline clinicopathologic characteristics remain unclear. Several studies report that exon 21 L858R substitution is more frequently associated with female sex, never smoking, and having adenocarcinoma.[21-23] Use of the largest pooled individual patient data set of common mutations (n = 714) from four trials[2-5,15,16] failed to detect any association between the type of mutation and smoking status ($P = .81$), histology ($P = .11$), or sex ($P = .81$).

Our finding that smoking status modifies EGFR TKI benefit is also supported by existing studies. Smoking was found to be independently associated with poorer tumor response with gefitinib.[24] Smoking was also associated with significantly less drug exposure after ingestion of erlotinib.[25] A phase I study[26] of smokers reported a maximum tolerated erlotinib dose of 300 mg, which was much higher than the dose of 150 mg per day used in randomized trials.[4,5,8] Whether this metabolic difference is the true reason for the PFS difference or whether other factors are involved has yet to be determined, and further research is warranted.

Another interesting finding was that women had a 27% greater PFS benefit with EGFR TKIs than men. The benefit of EGFR TKIs in women has been previously attributed to the higher rate of *EGFR* mutations in women.[14] In this meta-analysis involving only trials conducted in populations with *EGFR* activating mutations, a difference in PFS benefit on the basis of sex was still detected. As a majority of the nonsmokers were also women in these trials, it is possible that smoking is confounding the interaction between sex and EGFR TKI efficacy. However, multivariable analysis performed using individual patient data from four trials[2-5,15,16] suggests that the predictive effect of sex is largely independent of smoking status and *EGFR* mutation type (Table 2). We acknowledge that there may be a difference between current and former smokers, but our analysis does not discriminate between these two cohorts of patients.

This meta-analysis has several strengths. We performed a comprehensive review, used the most up-to-date published data, and contacted individual investigators or trial sponsors to obtain relevant unpublished data. Another strength is that individual patient data from four trials[2-5,15,16] were available to investigate the relationships between different *EGFR* mutations and baseline clinical characteristics, for multivariable adjustment, and for prognostic analyses.

There are also limitations of this study. We have not reported the treatment effects within subgroups for OS because many of the trials have yet to report mature OS data. In a recently presented pooled analysis of two randomized trials, OS was longer with afatinib than chemotherapy, and a statistically significant prolongation of OS was reported in tumors with exon 19 deletions but not exon 21 L858R substitution.[27] It remains unknown whether there would be a similar finding in first-generation EGFR TKI trials. We restricted our study to common *EGFR* mutations, and the predictive value of uncommon mutations remains unknown. We are currently planning an individual patient data meta-analysis using all randomized trials with mature OS data to address the limitations of our current work.

Our results have several important clinical and research implications. Our findings will be useful for counseling patients. Our meta-analysis demonstrates that exon 19 deletion and exon 21 L858R substitution mutations have different prognostic and predictive roles and are hence important as a stratification factor in future clinical trials. Further drug development of EGFR TKIs to enhance antitumor activity, particularly for tumors with exon 21 L858R substitution, remains important.

Another potential use of these findings is in economic analyses. With differences in PFS benefits for various subgroups, there will be differences in the costs required to achieve these benefits. In addition, economic factors related to patient screening may also identify greater cost-benefit for different identifiable subgroups.

In conclusion, EGFR TKIs significantly prolong PFS in all patients with advanced NSCLC with *EGFR* mutations compared with chemotherapy. The relative benefits of EGFR TKIs compared with chemotherapy were greatest in patients with exon 19 deletions. Greater PFS benefit with EGFR TKIs compared with chemotherapy was also seen in never-smokers and women. These findings have important implications for clinical trial design and interpretation, economic analyses, and future drug development for *EGFR*-mutated, advanced NSCLC.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Impact of Specific Epidermal Growth Factor Receptor (*EGFR*) Mutations and Clinical Characteristics on Outcomes After Treatment With EGFR Tyrosine Kinase Inhibitors Versus Chemotherapy in *EGFR*-Mutant Lung Cancer: A Meta-Analysis**

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## Appendix

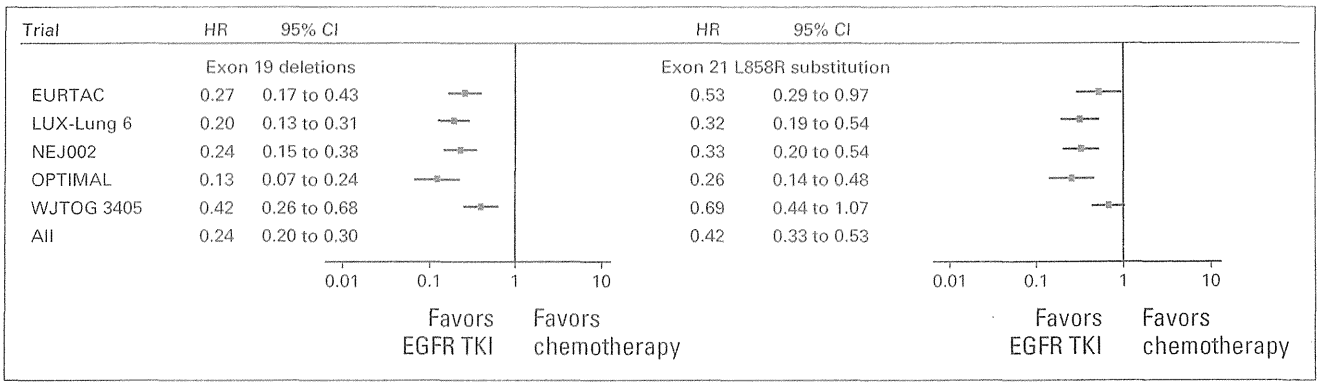


**Fig A1.** Forest plot of effect of treatment on progression-free survival in subgroups of patients according to different mutations of the epidermal growth factor receptor (*EGFR*), with exclusion of the LUX-Lung 3 and ENSURE trials. Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis fixed effect (all $P < .001$). All statistical tests were two sided. EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

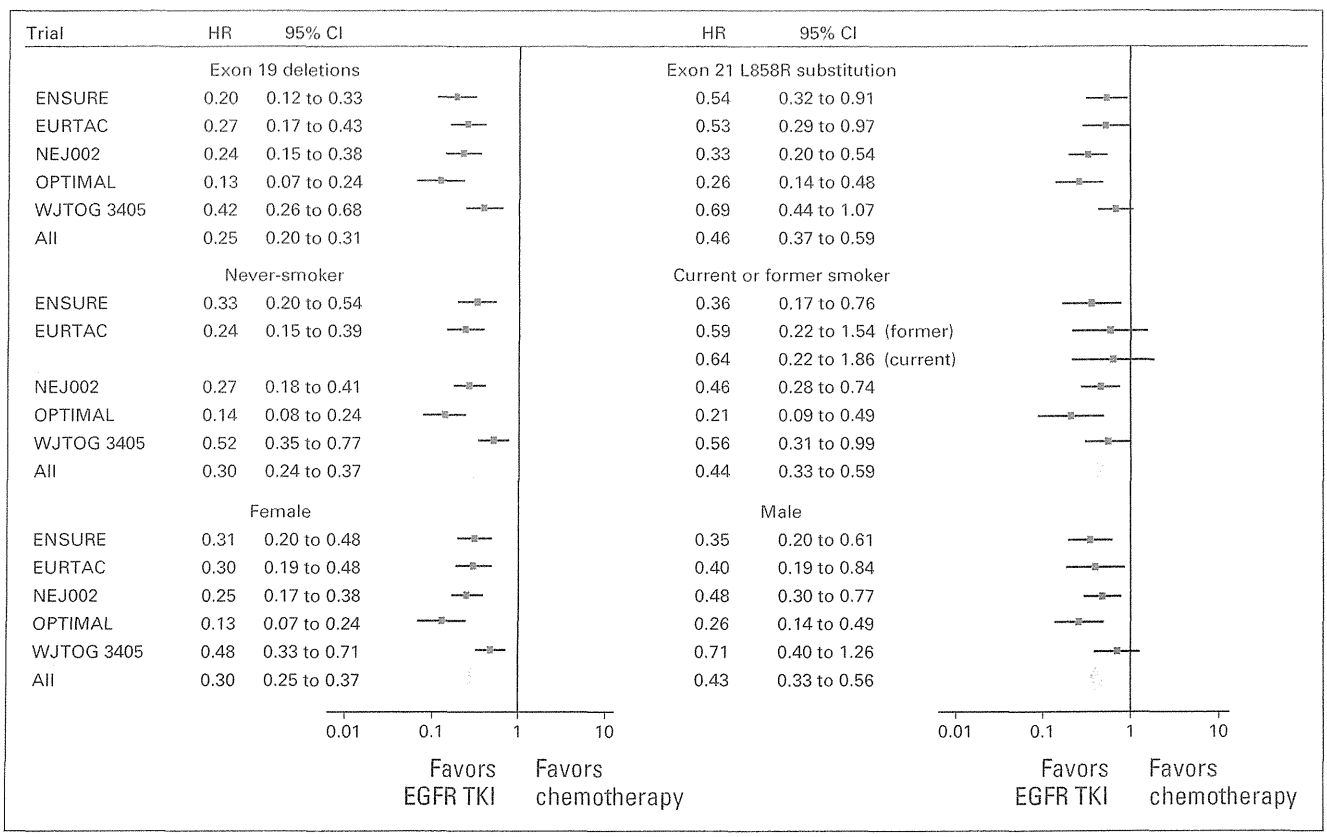


**Fig A2.** Forest plot of effect of treatment on progression-free survival in subgroups of patients according to mutations of the epidermal growth factor receptor (*EGFR*) gene, smoking status, and sex in gefitinib and erlotinib trials only. Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis of fixed effect (all $P < .001$). All statistical tests were two sided. EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

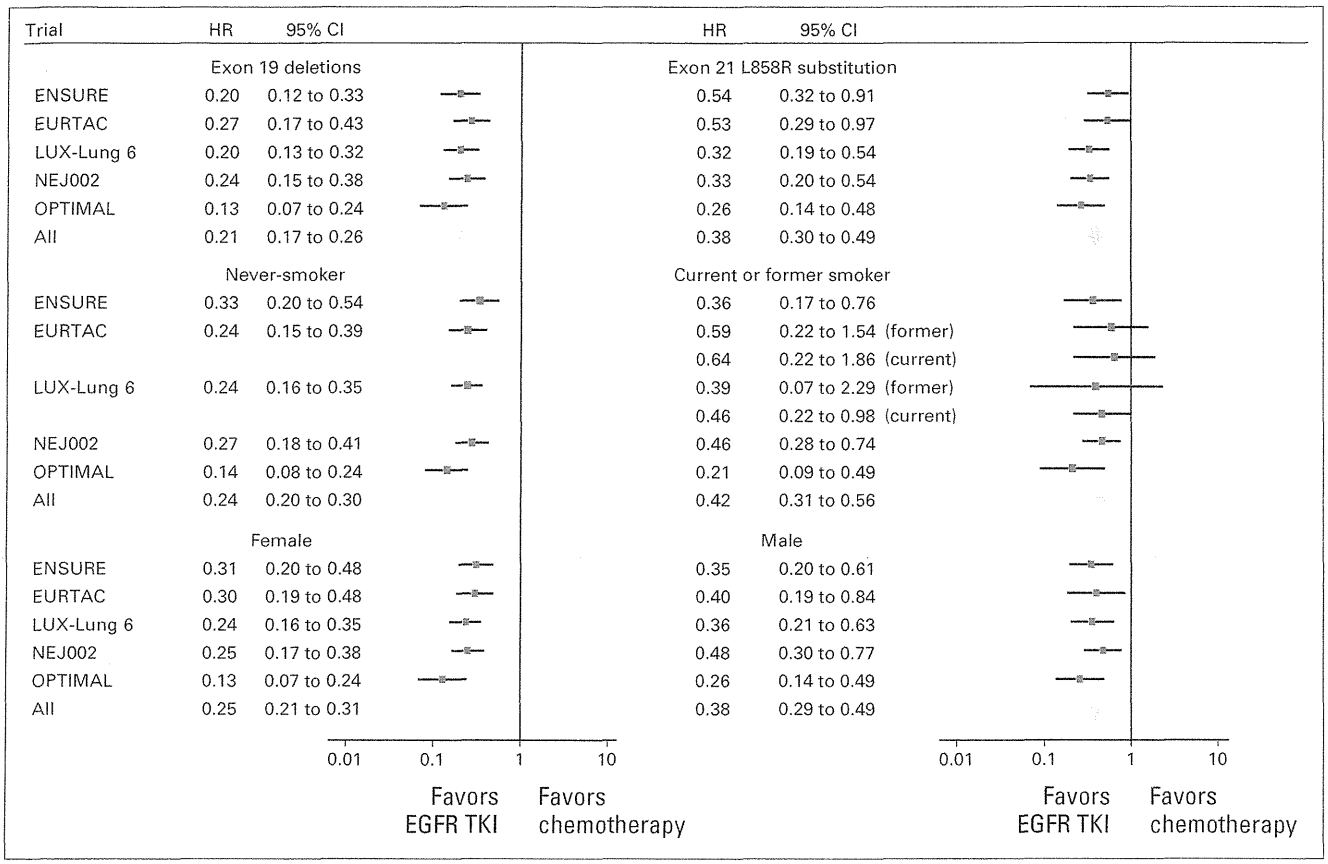


**Fig A3.** Forest plot of effect of treatment on progression-free survival in subgroups of patients according to different mutations of the epidermal growth factor receptor (*EGFR*), with exclusion of the LUX-Lung 3 and WJTOG 3405 (West Japan Thoracic Oncology Group 3405) trials. HR, hazard ratio; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor.

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# Factors associated with a poor response to gefitinib in the NEJ002 study: Smoking and the L858R mutation

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ABSTRACT

*Introduction:* Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) treatment is the standard therapy for non-small cell lung cancer (NSCLC) harbouring EGFR-activating mutations. The NEJ002 phase 3 clinical trial demonstrated the efficacy of EGFR-TKI; gefitinib was significantly superior in both progression-free survival (PFS) and objective response rate (ORR) than carboplatin plus paclitaxel. However, several cases showed no response. In this study, we performed further analysis of the characteristics of these non-responders.
*Methods:* Available data from NEJ002 on maximum changes in tumour size were obtained from 103 cases (90.4%) and 110 cases (96.5%) in the carboplatin–paclitaxel and gefitinib groups, respectively. Waterfall plots of maximum tumour size changes were created for non-responders.
*Results:* Five (4.9%) and 9 (8.2%) cases in the carboplatin–paclitaxel and gefitinib groups were non-responders, respectively. The mean pack years of the non-responders in the carboplatin–paclitaxel and gefitinib groups were 0.33 and 31.7, respectively. The ORR of total smokers (61.5%) and heavy smokers (over 40 pack years, 52.6%) in the gefitinib group were significantly lower compared to people who have never smoked (80.0%) ($P = 0.044$ and $P = 0.020$, respectively). Smoker cases also showed a tendency towards lower PFS and overall survival (OS). In addition, the EGFR common mutation types did not affect PFS and OS in gefitinib-treated cases in NEJ002. However, in this study, the ORR and waterfall plots showed that gefitinib-treated non-responders who had a deletion in exon 19 in the EGFR gene exhibited a tendency towards a higher response compared to those with a L858R mutation.
*Conclusions:* NSCLC patients with a smoking history or the EGFR L858R mutation may demonstrate a poorer response to gefitinib treatment.


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## 1. Introduction

Lung cancer is the leading cause of cancer death worldwide. Most lung cancer patients are diagnosed in the advanced stages of the disease; thus, despite a significant improvement in the treatment for this malignancy, the prognosis remains poor [1]. Recent studies have demonstrated driver gene mutations, which promote the development of lung cancer [2]. In 2004, epidermal growth factor receptor (EGFR)-activating mutations were discovered in lung cancer by two different groups [3,4]. Subsequently, EGFR-TKI treatment was established as the standard treatment for lung cancer harbouring EGFR mutations based on the results of pivotal trials [5,6].

Currently, the clinically available EGFR-TKIs are gefitinib, erlotinib, and afatinib. In Japan, the North East Japan Study Group (NEJ) demonstrated the efficacy of gefitinib treatment [6]. This study revealed significantly higher objective response rates (ORR) and longer progression-free survival (PFS) of patients with gefitinib treatment compared to patients treated with carboplatin plus paclitaxel, which is the standard cytotoxic chemotherapy (73.7%, 10.8 months vs. 30.7%, 5.4 months, respectively) [6,7]. Although there was no difference in overall survival (OS) (27.7 months for the gefitinib group vs. 26.6 months for the carboplatin plus paclitaxel group), this was assumed to be due to a high crossover rate because gefitinib was administered as a second-line therapy to most patients who received unsuccessful first-line chemotherapy [7]. Smoking history and type of EGFR common mutations (exon 19 deletion or L858R point mutation) did not affect the OS of each treatment group [7].

Gefitinib treatment for EGFR mutation-positive lung cancer demonstrated a significantly higher ORR; however, we observed several cases that showed a poor treatment response. Using data collected from the pivotal NEJ002 study, we analysed the characteristics of these poor response cases or non-responders.

## 2. Methods

### 2.1. Patient population

This was a retrospective analysis of clinical data obtained from 230 patients from the NEJ002 study. The eligibility criteria were previously described in the NEJ002 study [6]. Briefly, the criteria included the presence of advanced non-small cell lung cancer (NSCLC) harbouring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M (in which threonine at amino acid 790 was substituted by methionine), no history of chemotherapy, and an age of 75 years or younger. From March 2006 to May 2009, 230 patients were enrolled in the NEJ002 study.

### 2.2. Study design and treatment

After the exclusion of 2 patients, gefitinib was administered to 114 patients, and the other 114 patients were allocated to receive carboplatin plus paclitaxel. Prior to randomisation, patients were stratified according to sex, clinical stage of NSCLC (IIIB, IV, or postoperative relapse), and institution. Eligible patients were randomly assigned to receive gefitinib (at a dose of 250 mg per day orally) or carboplatin (at a dose equivalent to an area under the concentration–time curve of 6) plus paclitaxel (at a dose of 200 mg per square metre of body surface area). Gefitinib was administered until disease progression, development of intolerable toxic effects, or withdrawal of consent. Carboplatin plus paclitaxel were both administered on the first day of every 3-week cycle for at least three cycles. Retrospective analysis was performed using the currently available data. The available data on maximum changes in the tumour target lesion size from baseline were evaluated in 103 patients (90.4%) and 110 patients (96.5%) in the carboplatin plus paclitaxel and gefitinib groups, respectively. Seven patients in the carboplatin plus pactlitaxel group and 1 patient in the gefitinib group could not be evaluated for treatment response [6]. The remaining 4 patients in the carboplatin plus paclitaxel group and 3 patients in the gefitinib group showed that the tumour progression after each treatment made the tumour-target-lesion immeasurable. Progression of atelectasis or increased pleural effusion occurred in most of the cases.

### 2.3. Clinical assessments

An assessment of the maximum changes in tumour size was performed using data for the evaluation of ORR with computed tomography (CT) every 2 months. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria In Solid Tumours (RECIST, version 1.0). We defined a non-responder as a patient whose tumour-target-lesion size showed no change or increased despite the administration of each treatment during complete first-line treatment. Treatment response and PFS were determined by an external review of the CT scans by experts who were blinded to the treatment assignments. OS was evaluated for the period from the date of randomisation to the date of death.

### 2.4. Statistical analysis

The smoking pack years between two the groups were compared using the Wilcoxon rank sum test. The ORR was compared using Fisher's exact test. Kaplan–Meier survival curves were drawn for PFS and OS and were compared using the log-rank test. Each analysis was performed using a two-sided, 5% significance level and a 95% confidence interval using SAS for Windows software (release 9.1.3, SAS Institute, Cary, NC).

## 3. Results

### 3.1. Fourteen cases showed no response to either treatment

Waterfall plots showing maximum changes in the tumour target lesion size from baseline are indicated in Fig. 1A (lower). As previously demonstrated in the NEJ002 study, in which gefitinib treatment showed a higher response rate than carboplatin–paclitaxel treatment, the gefitinib group had more cases that showed a partial and complete response to the treatment compared to the carboplatin–paclitaxel group. However, 5 patients (4.9%) in the carboplatin–paclitaxel group and 9 patients (8.2%) in the gefitinib group showed no response and instead experienced no decrease in tumour size or an increased tumour size (Table 1). We analysed the characteristics of these non-responder cases for specific predictive factors of response to treatment.

### 3.2. Non-responders to gefitinib treatment showed a tendency towards higher smoking pack years than the carboplatin plus paclitaxel group

The number of smoking pack years of each case is indicated in Fig. 1A (upper). When only non-responders were evaluated, those in the gefitinib treatment group showed a tendency towards higher smoking pack years. The mean pack years of cigarette smoking of the non-responders in the carboplatin plus paclitaxel and gefitinib groups were 0.3 and 31.7, respectively ($P = 0.164$. Fig. 1B).

Among the 9 non-responders of the gefitinib treatment group, 4 of the subjects were never smokers (Table 1). Case GC-007 showed a long duration of stable disease, which indicated the partial efficacy of gefitinib. Case GC-054 had an exon 18 minor mutation in

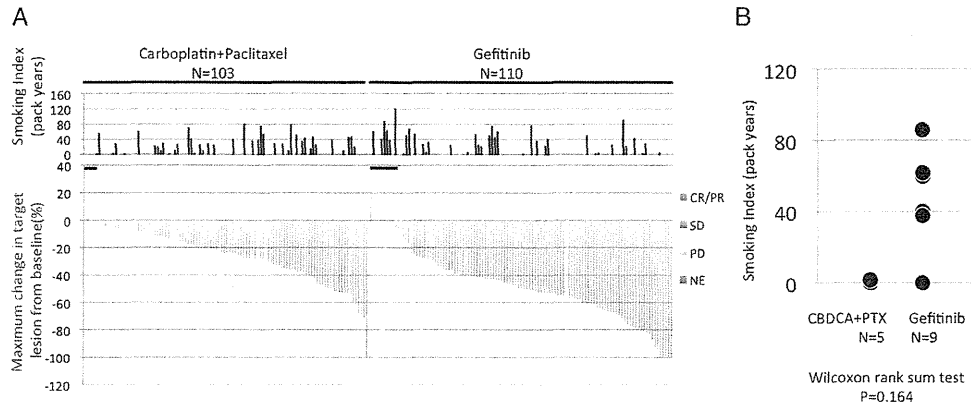


**Fig. 1.** (A) Lower: maximum changes in the target lesion size from the baseline of each case in the NEJ002 study were demonstrated using waterfall plots. The black line indicates the cases with an equivalent or increased tumour size as non-responders. Upper: smoking pack years of each case. (B) Smoking pack years of non-responder cases of each treatment group.

the EGFR gene. Our group previously published data on the poor treatment response to gefitinib in patients with minor mutations [8]. Both case GC-194 and case GC-063 discontinued gefitinib treatment due to serious adverse event, including drug-induced lung disease and liver dysfunction, respectively. In contrast, among the remaining 5 patients who had a smoking history, only 1 patient had an exon 18 minor mutation, and the other patients had no episodes of serious adverse events. In the carboplatin plus paclitaxel group, only 1 patient ceased the first-line treatment due to the onset of ileus, and the remaining non-responders did not show any specific clinical characteristics.

### 3.3. PFS and OS of the gefitinib-treated smoker group showed a tendency towards poor prognosis

The ORR of the gefitinib group was 73.7% [6]. When divided into 2 groups by smoking history, the ORR of the smoker group was significantly lower than the never smoker group (61.5% vs. 80.0%, $P=0.044$, Table 2). Moreover, the ORR of the heavy smoker group (over 40 pack years) was 52.6% and significantly lower than the non-smoker group ($P=0.020$).

Kaplan–Meier curves of the PFS and OS are shown in Fig. 2A and B. Although not statistically significant, the smoker cases showed a tendency towards lower PFS and OS compared to the non-smoker cases ($P=0.074$ and $P=0.164$, respectively).

### 3.4. NSCLC patients with the EGFR L858R mutation showed a relatively poor response to gefitinib compared to patients with an exon 19 deletion mutation

Although we previously reported the PFS and OS of the gefitinib treated exon 19 deletion mutant group did not show any difference compared to the L858R mutation group [6,7], the types of EGFR mutations may also be an important predictive factor of the treatment response, as shown in Table 1, which depicts the non-responders' EGFR mutation status. Namely, three non-responders (GC-007, 011, 194) with gefitinib treatment, who showed increases of over 20% in tumour growth from baseline, had a L858R mutation. A comparison of the patients based on EGFR common activating mutations, L858R and exon 19 deletion, revealed that ORR (Table 3) and the maximum tumour size changed from baseline (Fig. 3A and B) in gefitinib-treated patients and indicated that the L858R mutation was worse than an exon 19 deletion mutation. In contrast, patients who received carboplatin plus paclitaxel did not show any differences.

**Table 1**
Individual non-responders cases from NEJ002. Non-responder denotes patients who never had decrease in the size of measurable lesion during first-line treatment.

| Case No. | Maximum change[a] | Sex | Age | ECOG-PS | Histology | Stage | EGFR mutation | Smoking pack years | Response | Duration[b] | OS (month) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Carboplatin + paclitaxel | | | | | | | | | | | |
| GC-068 | +9.7 | Female | 72 | 1 | AD | IV | Exon 19 deletion | 0 | PD | 0.9 | 43.7 |
| GC-176 | +2.7 | Female | 69 | 1 | AD | IV | Exon 19 deletion | 0 | SD | 1.6 | 25.6 |
| GC-001 | 0 | Female | 72 | 1 | AD | IV | G719S | 0 | SD | 1.9 | 9.8 |
| GC-077 | 0 | Male | 71 | 1 | AD | IV | Exon 19 deletion | 0 | SD | 1.7 | 16.4 |
| GC-220 | 0 | Male | 75 | 1 | AD | IV | Exon 19 deletion | 1.65 | NE | 0.8 | 20.6 |
| Gefitinib | | | | | | | | | | | |
| GC-007 | +33.3 | Female | 70 | 1 | AD | IIIB | L858R | 0 | SD | 22.0 | 53.6 |
| GC-011 | +32.1 | Male | 56 | 1 | AD | Relapse | L858R | 60 | PD | 2.3 | 21.9 |
| GC-194 | +22.2 | Female | 60 | 1 | AD | IV | L858R | 0 | PD | 1.1 | 1.7 |
| GC-054 | +21.1 | Male | 68 | 1 | AD | IV | G719C | 0 | PD | 1.9 | 11.8 |
| GC-158 | +8.8 | Male | 65 | 0 | AD | IV | Exon 19 deletion | 40 | SD | 2.3 | 27.6 |
| GC-183 | +7.8 | Male | 63 | 0 | AD | IIIB | Exon 18 | 86 | PD | 2.2 | 5.7 |
| GC-195 | +7.6 | Male | 51 | 1 | AD | IV | Exon 19 deletion | 62 | PD | 2.0 | 10.9 |
| GC-031 | +2.4 | Male | 64 | 1 | AD | IV | Exon 19 deletion | 37.5 | PD | 0.3 | 10.8 |
| GC-063 | 0 | Female | 67 | 0 | AD-SQC | IIIB | Exon 19 deletion | 0 | SD | 1.2 | 37.1 |

AD: adenocarcinoma; AD-SQC: adenosquamous carcinoma; PD: progressive disease; SD: stable disease; NE: not evaluated.
[a] Maximum change from baseline during the first-line treatment (%).
[b] Duration from entry to maximum size (month).

**Table 2**
Response of cases categorised by smoking history in the gefitinib treatment group.

| Gefitinib Treatment Group | | | | |
|---|---|---|---|---|
| | Non Smoker | Smoker Total | | |
| | | | Light Smoker Under 40 pack years | Heavy Smoker Over 40 pack years |
| Total | 75 (100.0%) | 39 (100.0%) | 20 (100.0%) | 19 (100.0%) |
| CR | 5 ( 6.7%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| PR | 55 ( 73.3%) | 24 ( 61.5%) | 14 ( 70.0%) | 10 ( 52.6%) |
| SD | 9 ( 12.0%) | 9 ( 23.1%) | 5 ( 25.0%) | 4 ( 21.1%) |
| PD | 6 ( 8.0%) | 5 ( 12.8%) | 1 ( 5.0%) | 4 ( 21.1%) |
| NE | 0 ( 0.0%) | 1 ( 2.6%) | 0 ( 0.0%) | 1 ( 5.3%) |
| CR + PR | 60 ( 80.0%) | 24 ( 61.5%) | 14 ( 70.0%) | 10 ( 52.6%) |
| 95%CI | (69.2%, 88.4%) | (44.6%, 76.6%) | ( 45.7%, 88.1%) | ( 28.9%, 75.6%) |
| | P=0.044 | | | |
| | P=0.020 | | | |
| Fisher's exact test | | | | |

CR: complete response; PR: partial response; PD: progressive disease; SD: stable disease; NE: not evaluated.

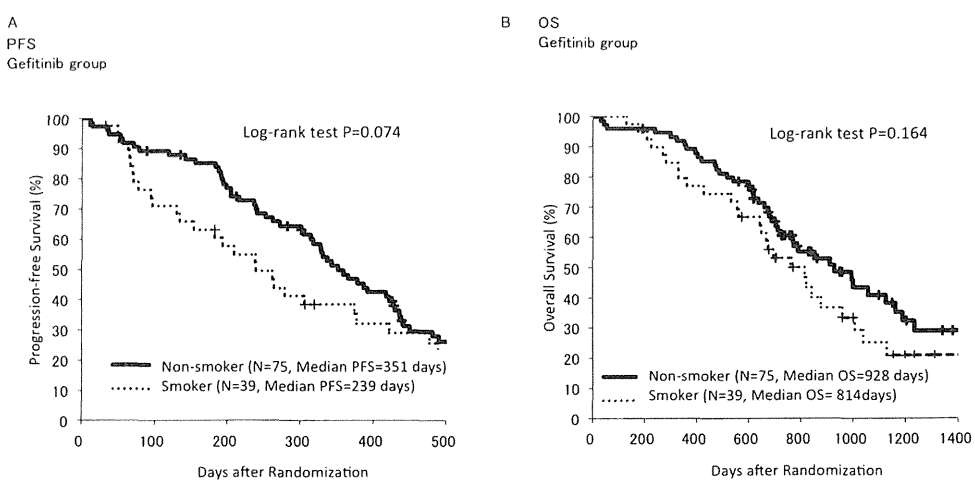


**Fig. 2.** The survival curves of non-smokers and smokers in the gefitinib treatment group of the NEJ002 study, as described by the Kaplan–Meier method and compared using the log-rank test. (A) PFS. (B) OS.

## 4. Discussion

For NSCLC cases with an EGFR mutation, gefitinib treatment increased both the ORR and PFS more than carboplatin plus paclitaxel treatment. Nevertheless, the number of non-responders to gefitinib treatment was also higher compared to patients treated with carboplatin plus paclitaxel, 9 (8.1%) vs. 5 (4.4%), respectively. Interestingly, non-responders of the gefitinib group, who had neither a serious adverse event nor minor EGFR mutations, had a smoking history. This result indicates that a smoking history may be an important predictive factor for gefitinib treatment. The type of EGFR-activating mutation may also be another predictive factor for the response to gefitinib treatment; NSCLC patients with a L858R mutation exhibited a poorer response to gefitinib compared to patients with an exon 19 deletion mutation.

Most of the EGFR-mutant patients who had a smoking history or L858R mutation showed a better response to gefitinib compared to carboplatin plus paclitaxel. However, the response rate was significantly lower, particularly in the heavy smoker group compared to the non-smoker group.

Several studies indicated that NSCLC patients harbouring EGFR mutations with many smoking pack years showed a relatively poor response to EGFR-TKI treatment [9–11]. Several mechanisms have been proposed to explain the poorer response to EGFR-TKI in patients with a smoking history. One group found that cigarette smoking induced EGFR posttranslational changes [12] and that the Src oncogene may confer resistance to treatment [13]. Another group demonstrated that activation of the nicotinic acetylcholine receptor by cigarette smoking induced EGFR-TKI resistance [14]. Furthermore, many chemicals contained in cigarette smoke have a high activity of mutagenesis [15]. Consistent with this finding, the rate of gene alteration in smoker patients with NSCLC harbouring EGFR mutations was considerably higher compared to non-smokers [16,17]. Moreover, lung cancer cells derived from lung

**Table 3**
Response of cases categorised by the types of EGFR common mutation.

| | Gefitinib | | Carboplatin+paclitaxel | |
|---|---|---|---|---|
| | L858R | exon 19 deletion | L858R | exon 19 deletion |
| Total | 49 (100.0%) | 58 (100.0%) | 48 (100.0%) | 59 (100.0%) |
| CR | 1 ( 2.0%) | 4 ( 6.9%) | 0 ( 0.0%) | 0 ( 0.0%) |
| PR | 32 ( 65.3%) | 44 ( 75.9%) | 15 ( 31.3%) | 18 ( 30.5%) |
| SD | 11 ( 22.4%) | 6 ( 10.3%) | 23 ( 47.9%) | 28 ( 47.5%) |
| PD | 4 ( 8.2%) | 4 ( 6.9%) | 8 ( 16.7%) | 8 ( 13.6%) |
| NE | 1 ( 2.0%) | 0 ( 0.0%) | 2 ( 4.2%) | 5 ( 8.5%) |
| CR + PR | 33 ( 67.3%) | 48 ( 82.8%) | 15 ( 31.3%) | 18 ( 30.5%) |
| 95%CI | (52.5%, 80.1%) | (70.6%, 91.4%) | (18.7%, 46.3%) | (19.2%, 43.9%) |
| Fisher's exact test | P=0.074 | | P=1.000 | |

CR: complete response; PR: partial response; PD: progressive disease; SD: stable disease; NE: not evaluated.

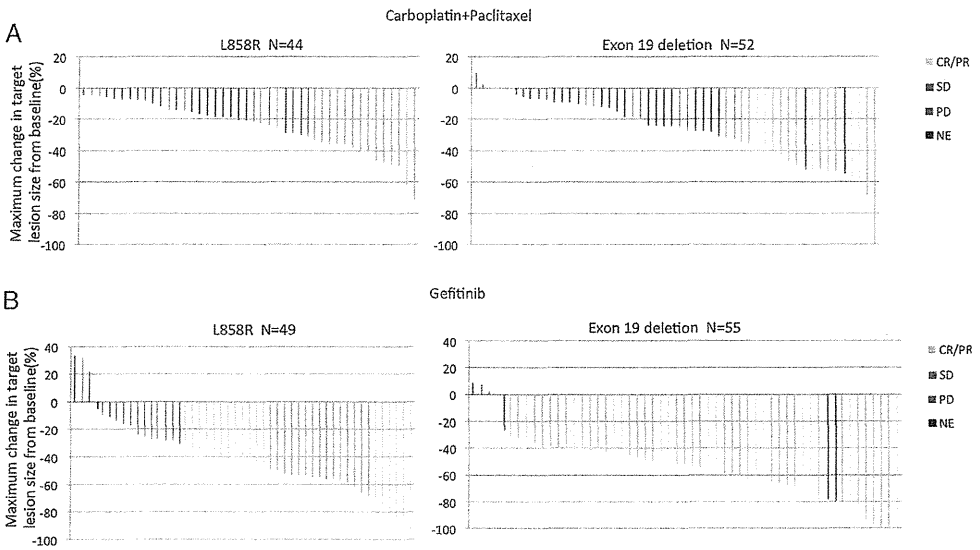


**Fig. 3.** Maximum changes in the target lesion size from the baseline of each case in the carboplatin plus paclitaxel (A) and gefitinib (B) groups. The patients were categorised into 2 groups according to the type of EGFR common mutation, L858R and exon 19 deletion.

of heavy smokers contained "driver" EGFR mutations and many other "passenger" gene mutations. These passenger genes may modify signal transduction pathways that render cell death more difficult to be induced by treatment with EGFR-TKI alone.

Recently, treatment of other clinically available EGFR-TKI, such as erlotinib and afatinib, in NSCLC patients with an exon 19 deletion showed a higher response than those with the L858R mutation [18,19]. However, for gefitinib phase 3 studies, the type of EGFR mutation did not affect PFS and OS [5–7]. In the present study, we found that gefitinib treatment also showed a tendency towards a favourable response in patients with an exon 19 deletion mutation based on an evaluation of short-term responses, such as ORR and the maximum change in tumour size from baseline. If the response of gefitinib treatment was affected by EGFR subtypes, then all three EGFR-TKIs demonstrated a higher treatment response in patients with an exon 19 deletion compared to those with the L858R mutation to varying degrees. There was no difference in the half maximal inhibitory concentration ($IC_{50}$) of gefitinib given to cancer cell lines harbouring an exon 19 deletion and those with the L858R mutation [20,21]. However, a recent study revealed that the crystal structure of the L858R mutation is more stable in maintaining the active form than the exon 19 deletion mutation [22]. The rationale underlying these differences in response to EGFR-TKI may be explained by their activating mechanism.

In this study, we found candidate predictive factors of the response to gefitinib treatment. Due to the high efficacy of gefitinib treatment, the number of non-responders was very small. To confirm the results of this study, additional data on non-responders to EGFR-TKI treatment should be collected for further analysis.

## 5. Conclusion

In this study, on the basis of the characteristics of non-responders to gefitinib in the NEJ002 study, we found two potential factors for a poor response to EGFR-TKI treatment. Patients who had a smoking history showed a significantly lower response rate to gefitinib treatment. Gefitinib treatment may be more effective in patients with an exon 19 deletion than those with the L858R mutation. To clarify these relationships, further studies using additional data on non-responders are needed.

## Conflict of interest

Dr. Maemondo, Dr. Inoue, Dr. Oizumi, Dr. Gemma, Dr. Hagiwara, and Dr. Nukiwa received a lecture fee from Astrazeneca Pharmaceutical for this work that is under consideration for publication. Dr. Maemondo participated on the advisory board. Dr. Kinoshita, Dr. Saijo, and Dr. Morita received a lecture fee from Astrazeneca Pharmaceutical for other work. All of the remaining authors have declared no conflicts of interest.

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Original article

# Phase II study of amrubicin combined with carboplatin for refractory relapsed small-cell lung cancer: North Japan Lung Cancer Group Trial 0802

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ABSTRACT

*Background:* Amrubicin (AMR), a new anthracycline agent, has shown promising results for advanced small-cell lung cancer (SCLC), although the efficacy of AMR alone against refractory relapsed SCLC is insufficient. This study was conducted to evaluate the safety and efficacy of the combination of AMR and carboplatin (CBDCA) in patients with refractory relapsed SCLC.

*Methods:* Patients with advanced SCLC who relapsed within 90 days after the completion of first-line chemotherapy received AMR (30 mg/m$^2$, days 1–3) and CBDCA (area under the curve 4.0 mg mL$^{-1}$ min$^{-1}$, day 1) every 3 weeks. The primary endpoint of this study was the overall response rate (ORR), and the secondary endpoints were progression-free survival (PFS), overall survival, and the toxicity profile. Assuming that an ORR of 45% in eligible patients would indicate potential usefulness and an ORR of 20% would be the lower limit of interest, with $\alpha$=0.10 and $\beta$=0.10, at least 24 patients were required.

*Results:* Among 29 eligible patients, the ORR was 34% (90% confidence interval, 20–48). The median PFS was 3.5 months, whereas the median survival time was 7.3 months. The most common grade 3–4 toxicity was neutropenia (79%), although only one patient (3%) suffered from febrile neutropenia. Non-hematological toxicities were of moderate severity and no treatment-related death was observed.

*Conclusions:* This is the first prospective study of AMR combined with CBDCA for refractory relapsed SCLC, which was effective and well tolerated. However, further investigation of this regimen is warranted.



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## 1. Introduction

Lung cancer is currently the leading cause of cancer death in many countries, and small-cell lung cancer (SCLC) accounts for 12–15% of all lung cancer cases [1]. SCLC is chemosensitive, and the standard first-line chemotherapy for advanced SCLC is platinum-doublet regimens such as cisplatin (CDDP) plus etoposide (ETP) or CDDP plus irinotecan (CPT) [2,3]. Despite high response rates to first-line chemotherapy, most patients experience SCLC relapse. The efficacy of second-line chemotherapy differ according to the relapse type (sensitive relapse, defined as relapse after >90 days from the completion of first-line chemotherapy or refractory relapse, defined as relapse during first-line chemotherapy or within 90 days after completion of first-line chemotherapy). There has been no standard treatment for patients with refractory relapsed SCLC, and few single agents have shown a response rate of >10% [4].

Amrubicin (AMR), a new anthracycline agent, has shown some promising results for advanced SCLC. A Japanese phase II study of the intravenous administration of single-agent first-line AMR therapy (45 mg/m$^2$) for 3 consecutive days demonstrated a high overall response rate (ORR) (75.8%) and long median survival time (MST) (11.7 months) [5]. AMR was also more effective than topotecan (TOP) for chemosensitive relapsed SCLC in our previous phase II trial (response rates, 38% and 13%, respectively), although the response rate of AMR for refractory relapsed SCLC was only 17% (that of TOP was 0%) [6], a finding compatible with the result of AMR in a similar population in a subsequent large phase II study by Ettinger [7].

Since some of the patients with refractory relapsed SCLC did not receive a sufficient dose of platinum agent during first-line chemotherapy, we thought that second-line chemotherapy consisting of AMR combined with platinum might be worth investigating. Thus, we conducted this phase II study to evaluate the safety and efficacy of the combination of AMR and CBDCA in patients with refractory relapsed SCLC.

## 2. Patients and methods

### 2.1. Patient selection

This multicenter phase II trial was conducted in accordance with the principles outlined in the Helsinki Declaration of the World Medical Association, and the protocol was approved by the institutional review board of each participating institution (Approval date: December 15, 2008; Approved No: 2008-365). Patients >20 years of age with histologically or cytologically confirmed SCLC who had progressed during first-line chemotherapy or had relapsed within 90 days after the completion of first-line chemotherapy were enrolled in this study. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status (PS) of 0–2, measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST), an estimated life expectancy ≥3 months, and adequate organ function (white blood cell count ≥4000/mm$^3$, absolute neutrophil count ≥2000/mm$^3$, platelet count ≥100,000/mm$^3$, hemoglobin ≥9.0 g/dL, serum bilirubin ≤1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, creatinine level ≤1.5 mg/dL, and arterial oxygen pressure ≥60 mmHg). Written informed consent was obtained from all enrolled patients. Patients with symptomatic brain metastasis, interstitial lung disease, massive effusion requiring drainage, or severe comorbidities such as uncontrolled diabetes or cardiac disease were excluded. This trial was registered at UMIN (ID: R000001597).

### 2.2. Treatment schedule

The AMR was diluted in 50 mL of normal saline and administered by 10-min intravenous infusion at a dose of 30 mg/m$^2$ on days 1–3 of each treatment cycle. CBDCA was diluted in 250 mL of 5% glucose solution or normal saline and administered at infusion intervals of ≥30 min at a dose of area under the curve (AUC) 4.0 mg mL$^{-1}$ min$^{-1}$ after AMR on day 1. The doses of both agents were determined according to our previous phase I study of this combination for patients with untreated SCLC [8]. The treatment was repeated every 21 days. Premedication with corticosteroids and an antiemetic 5-HT$_3$ antagonist was recommended. The dose of AMR was reduced by 5 mg/m$^2$ each in the subsequent cycle in cases of severe toxic effects such as grade 3 or more non-hematological toxicities, thrombocytopenia ≤20,000/mm$^3$, grade 4 neutropenia lasting ≥4 days, or febrile neutropenia in the previous cycle. Use of granulocyte colony-stimulating factor (G-CSF) was permitted for neutropenia but not for prophylaxis. No prophylactic antibiotic support was planned. All patients were scheduled to receive at least three cycles of treatment unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician

decided to discontinue the treatment. Subsequent chemotherapy after disease progression was not limited.

### 2.3. Patient assessment

Patient assessments, including a physical examination, a complete blood count, and biochemistry analysis, were repeated once a week after the initial evaluation. Tumor measurement was performed during the baseline assessment by computed tomography (CT) and was repeated every month until the best response to the protocol treatment was identified. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined based on RECIST version 1.0. CR and PR were confirmed by re-assessment performed at least 4 weeks after the first observation. SD was confirmed by re-assessment performed at least 6 weeks after registration. After confirmation, CT scans were acquired every 2 months until PD was observed. The CT scans of all patients were extramurally reviewed to confirm the response and progression-free survival (PFS). PFS was defined as the time from the date of registration to the date of the first observation of PD or death. Overall survival (OS) was defined as the time from the date of registration to the date of death or the latest follow-up (censored case). Toxicities were evaluated according to Common Terminology Criteria for Adverse Events version 3.0.

### 2.4. Statistical analysis

The primary endpoint of this study was the overall response rate (ORR), and secondary endpoints were PFS, OS, and the toxicity profile. Assuming that an ORR of 45% in eligible patients would indicate potential usefulness while an ORR of 20% would be the lower limit of interest, with $\alpha$=0.10 and $\beta$=0.10, at least 24 patients were required. Survival estimation was performed using the Kaplan–Meier method.

## 3. Results

### 3.1. Patient characteristics and treatment delivery

Between September 2008 and May 2011, 30 patients were enrolled from 10 institutions. One patient was excluded because of ineligible histology. Most of patients were male with a good PS (Table 1). Most patients received a CBDCA-based regimen as first-line chemotherapy, with a median of 4 cycles (range, 2–11 cycles). The median number of treatment cycles in the current study was 4 (range, 1–7), and 83% (24 of 29) of patients received three or more cycles.

### 3.2. Efficacy

All 29 patients were evaluable for response. The ORR was 34% (90% confidence interval, 20–48) and the disease-control rate was 83% (Table 2). The response rate of patients treated with CBDCA-based first-line chemotherapy was 40%, whereas that of patients treated with CDDP-based first-line chemotherapy was 22%, although the difference was not statistically significant. The response rates of patients treated with ETP and of those treated with CPT as first-line chemotherapy were 35% and 33%, respectively. At the data cut-off point in September 2013, the median PFS was 3.5 months and the median survival time was 7.3 months (Fig. 1).

**Table 1 – Patient characteristics.**

| | |
|---|---|
| Number of patients | 29 |
| Gender | |
| Male | 26 |
| Female | 3 |
| Age (years) | |
| Median | 67 |
| Range | 50–81 |
| Performance status | |
| 0 | 9 |
| 1 | 16 |
| 2 | 4 |
| Prior chemotherapy | |
| Cisplatin+etoposide | 2 |
| Carboplatin+etoposide | 15 |
| Cisplatin+irinotecan | 7 |
| Carboplatin+irinotecan | 5 |

**Table 2 – Response.**

| Response | Number of patients | % | 90% CI |
|---|---|---|---|
| Complete response | 0 | 0 | |
| Partial response | 10 | 34 | |
| Stable disease | 14 | 48 | |
| Progressive disease | 5 | 17 | |
| Overall response rate | 10 | 34 | 20–48 |
| Disease control rate | 24 | 83 | |

CI, confidence interval.

### 3.3. Safety

The toxicities (>grade 2) are summarized in Table 3. The most common adverse event in this study was neutropenia (79%), although only one patient (3%) suffered from febrile neutropenia. Thirteen patients (45%) required G-CSF support, the median duration of which was 4 days (range, 1–11). Two patients (7%) received a blood transfusion. Eight patients (28%) required AMR dose reduction due to hematological toxicity. Non-hematological toxicities were moderate. One patient died only 5 days after the initiation of protocol treatment. The attending physician reported that the cause of death was rapid progression of SCLC, and the independent data and safety monitoring committee of this study reviewed the clinical course and accepted the physician's decision. No treatment-related death was observed.

## 4. Discussion

This study met its primary endpoint. Since there have been few promising monotherapy options for refractory relapsed