Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors vs Conventional Chemotherapy in Non–Small Cell Lung Cancer Harboring Wild-Type Epidermal Growth Factor Receptor
A Meta-analysis

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IMPORTANCE Current guidelines recommend both epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and cytotoxic chemotherapy drugs as standard treatment options for patients with wild-type (WT) EGFR who were previously treated for non–small cell lung cancer (NSCLC). However, it is not clear that EGFR TKIs are as efficacious as chemotherapy in patients with WT EGFR.

OBJECTIVE To determine the association between first-generation EGFR TKI vs chemotherapy and survival in advanced NSCLC patients with WT EGFR.

DATA SOURCES PubMed, EMBASE, Cochrane database, and meeting abstracts of the American Society of Clinical Oncology and European Society of Medical Oncology through December 2013.

STUDY SELECTION Eligible studies were randomized controlled trials comparing EGFR TKI with conventional chemotherapy in patients with advanced NSCLC. Out of 1947 retrieved articles, 11 trials incorporating 1605 patients with WT EGFR were included.

DATA EXTRACTION AND SYNTHESIS Two reviewers extracted trial characteristics and outcomes. The risk of bias was evaluated using the Cochrane tool. All measures were pooled using random-effects models and 95% CIs were calculated.

MAIN OUTCOMES AND MEASURES The primary outcome was progression-free survival (PFS), measured as hazard ratios (HRs). The secondary outcomes were objective response rate and overall survival, expressed as relative risks and HRs, respectively.

RESULTS Among patients with WT EGFR tumors, chemotherapy was associated with improvement of PFS, compared with TKI (HR for TKI, 1.41; 95% CI, 1.10-1.81). No statistically significant subgroup difference was identified in terms of line of treatment (first-line vs second- or later-line), experimental drug, dominant ethnicity, or EGFR mutation analysis method. Trials using more sensitive platforms than direct sequencing were associated with a significant PFS benefit with chemotherapy (HR for TKI, 1.84; 95% CI, 1.35-2.52). The association of chemotherapy with improvement in PFS was also significant in second- or later-line trials (HR, 1.34; 95% CI, 1.09-1.65). The objective response rate was higher with chemotherapy (92/549, 16.8%, vs 39/540, 7.2%, for TKI; relative risk for TKI, 1.11; 95% CI, 1.02-1.21); however, no statistically significant difference was observed with respect to overall survival (HR for TKI, 1.08; 95% CI, 0.96-1.22).

CONCLUSIONS AND RELEVANCE Among patients with advanced NSCLC harboring WT EGFR, conventional chemotherapy, compared with first-generation EGFR TKI, was associated with improvement in PFS but not overall survival.
Epiddermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the standard treatment option for advanced non–small cell lung cancer (NSCLC) patients harboring EGFR-activating mutations. These drug-sensitive mutations are found in about 10% of Western patients and almost 50% of Asian patients with NSCLC. Large randomized controlled trials enriching for the patients harboring EGFR-activating mutations showed the superiority of TKI treatment over conventional cytotoxic drugs in terms of progression-free survival (PFS) and objective response rate. However, a majority of patients with advanced NSCLC worldwide do not have tumors harboring EGFR-activating mutations. Although the EGFR TKI treatment has been widely used in patients with wild-type (WT) tumors, its benefit is less pronounced. Originally EGFR TKI was approved as a second- or third-line standard treatment based on the BR.21 trial, which demonstrated prolongation of overall survival compared with the best supportive care in an EGFR-unselected, pretreated NSCLC population. However, while TKI showed superior efficacy over best supportive care, there has been no evidence indicating better efficacy of TKI when compared with conventional chemotherapy, although the toxicity profile was better with TKI.

Recent clinical trials among patients with WT EGFR NSCLC showed the superior efficacy of chemotherapy over TKIs. In addition, subgroup analyses of previous trials comparing TKI with chemotherapy in patients with or without EGFR-mutated tumors suggested that the efficacy of TKI might differ depending on the patients’ EGFR mutation status but were inconclusive largely because of the small number of patients examined for their EGFR mutation status (NCBI Entrez Gene 1956). Therefore, a pooled analysis of currently available studies restricted to patients with WT EGFR tumors may provide important and clinically useful information with respect to TKI treatment in patients with WT EGFR tumors. We performed a systematic review and meta-analysis of randomized controlled trials comparing first-generation EGFR TKI (erlotinib or gefitinib) treatment with conventional chemotherapy in patients with advanced NSCLC harboring WT EGFR.

Methods
Two authors (J.K.L. and K.J.S.) independently abstracted data with a predefined information sheet, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. The following items were abstracted from the published articles: acronym of the trial, journal, study period, institution, country, study phase, line of treatment (first vs second or later), main inclusion and exclusion criteria, schedule of tumor assessment, randomization method, stratification, EGFR mutation analysis tool, definition of EGFR mutation, interventional and control treatments, number of patients randomized, demographic and clinical information on the study patients (age, sex, ethnicity, histology), outcome results in patients with WT EGFR tumors, and duration of follow-up. Two other reviewers (D.W.K. and S.H.) discussed and resolved all discrepancies in the extracted data. When we needed additional information that was not reported in the published articles, we contacted the corresponding authors via email to request the information.

Two reviewers (J.K.L. and S.H.) independently conducted the risk of bias assessment of the included studies using the Cochrane Collaboration’s tool.

Statistical Analysis
The primary analysis investigated the association between first-generation EGFR TKI vs conventional chemotherapy and PFS in patients with WT EGFR tumors. The PFS outcome was measured in terms of the hazard ratio (HR) of using EGFR TKI compared with conventional chemotherapy. For each trial, the HR with its 95% confidence interval was directly extracted from the research article or calculated using other available statistical methods.
tical information by 2 independent reviewers (J.K.L. and S.H.). The secondary outcomes were objective response rate, which was defined as the proportion of complete response and partial responses among all evaluable patients, and overall survival.

A random-effects model was used to calculate pooled HRs or relative risks (RRs), 95% confidence intervals, and \( P \) values. Two-sided \( P \) values less than .05 were considered statistically significant. A \( \chi^2 \) statistic was used to test for statistical heterogeneity. The \( F \) statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials.\(^{18}\) To investigate the sources of heterogeneity, predefined subgroup analyses were performed: line of treatment (first vs second or later), experimental drug (erlotinib vs gefitinib), ethnicity (Asian-dominant vs white-dominant trials), and \( EGFR \) mutation analysis method (direct sequencing only vs more sensitive platforms; eg, fragment length analysis,\(^{19}\) amplification-refractory mutation system,\(^{20-22}\) and mass spectrometric genotyping\(^{29}\)). The statistical significance of the difference in treatment effects between subgroups was evaluated using meta-regression models.

In addition to the prespecified subgroup analyses, we conducted further analysis to explore the remaining heterogeneity; a meta-regression analysis was conducted to investigate the association between the percentage of adenocarcinoma and PFS outcome. In addition, we examined the PFS outcome of patients who were positive for \( KRAS \) mutations from the trials with available \( KRAS \) mutation data, because several studies have reported \( KRAS \) mutation (NCBI Entrez Gene 3845) as a negative predictive factor for \( EGFR \) TKI treatment.\(^{24-26}\) We also applied a funnel plot method together with the Egger test for asymmetry to assess the possibility of publication bias among the trials. We used Stata version 12.0 (StataCorp) for all of the analyses.

Results

A total of 1947 articles were identified by the initial search strategy. After eligibility screening of the study titles and abstracts, 1864 articles were removed. After we reviewed the full texts of the 83 potentially eligible articles, 11 trials meeting the inclusion criteria were selected for the final analysis (Figure 1).\(^{5,12-15,27-34}\) These trials enrolled a total of 5471 patients with advanced NSCLC. After excluding patients who did not have a known \( EGFR \) mutational status, 1605 patients with WT \( EGFR \) (811 in the TKI group; 794 in the chemotherapy group) were included in the analysis. All trials except one\(^{29}\) provided PFS outcomes by \( EGFR \) mutation status; this trial reported the time to progression instead. The objective response rate and overall survival outcomes were available in 7 and 9 trials, respectively.

The baseline characteristics of the 11 trials are summarized in the Table and eTable 1 in the Supplement. Four trials\(^{5,14,25,26}\) were performed in first-line settings, \(^{4,23,15,31,34}\) in second-line, and \(^{27,32,33}\) in second- or later-line settings. All of the trials used TKIs in their standard dosing and schedule (erlotinib, 150 mg daily; gefitinib, 250 mg daily). All trials except one\(^{29}\) used commonly recommended chemotherapy drugs as the control group (doublet chemotherapy including cisplatin or carboplatin for the first-line treatment; docetaxel or pemetrexed for second- or later-line treatment; category 2A in the National Comprehensive Cancer Network guideline\(^{1}\); ML20322 used oral vinorelbine as a control drug\(^{29}\)) following the standard dosing schedule. Seven trials\(^{13,27,29-32,34}\) used only direct sequencing for detecting \( EGFR \) mutations; 4 trials\(^{5,14,15,33}\) used other platforms (amplification-refractory mutation system, fragment length polymorphism analysis, or mass spectrometry) to enhance the sensitivity of the analysis. All trials recruited patients with histologically or cytologically confirmed NSCLC with a performance status of 0 through 2 in the Eastern Cooperative Oncology Group or World Health Organization classification, apart from 1 trial,\(^{29}\) which also included patients with performance status 3. Six trials\(^{5,29-31,33,34}\) included mostly Asian patients; the other 5 trials\(^{13,15,27,32,34}\) had a majority of white patients.

The result of risk of bias assessment is provided in eTable 2 in the Supplement. All 11 trials were open-labeled. Random sequence generation and allocation concealment were performed adequately in most of the trials. We judged the adequacy of blinding by whether the treatment outcomes were evaluated by a third assessor who did not know the treatment group of the patient, because it is an important aspect in the assessment of outcomes such as PFS. In 4 studies,\(^{29-32}\) the patients’ treatment responses were assessed by a third person who was not aware of the treatment, whereas in 2...
largely attributable to the 2 trials29,31 that showed a different
to progression instead of PFS. (Progression-free survival in
TKI, 1.11; 95% CI, 1.02-1.21) (Figure 2). A significant statisti-
cal heterogeneity was noted in this analysis (I² = 79.1%),
largely attributable to the 2 trials that showed a different
direction of effect from the other 8 trials (HRs from
1.24-2.85).5,13,15-27,30-33,34 The CT/06.05 trial32 reported time
to progression (TTP) instead of PFS (HRs from
1.35; 95% CI, 1.06-1.72). The objective response rate was also
better in the TKI group compared with the chemotherapy group,
no statistically significant difference was observed between
the chemotherapies tested (Figure 3). The funnel plot asymmetry
can also be explained by 2 outlying small trials that caused hetero-
geneity, rather than by a publication bias (eFigure 1 in the
Supplement).

Table. Characteristics of the Included Randomized Controlled Trials Comparing EGFR TKI With Chemotherapy

| Source | Line of Treatment | Experimental Drugs | Dominant Ethnicity, No. (%) | Age, Median (Range), y | Adeno-
carcinoma, No. (%) | EGFR Mutation Analysis | TTKI Group | Control Group | Follow-up Duration, Median (Range), mo |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>INTEREST,22,27 2008 and 2010</td>
<td>Second or later</td>
<td>Gefitinib vs Docetaxel</td>
<td>White 1090 (74.4)</td>
<td>61 (20-84)</td>
<td>830 (56.6)</td>
<td>Direct sequencing</td>
<td>106</td>
<td>733</td>
<td>123</td>
</tr>
<tr>
<td>IPASS,5,28 2009 and 2011</td>
<td>First</td>
<td>Gefitinib vs Paclitaxel + Carboplatin</td>
<td>Asian 1214 (99.8)</td>
<td>57 (24-84)</td>
<td>1214 (99.8)</td>
<td>ARMS</td>
<td>91</td>
<td>609</td>
<td>85</td>
</tr>
<tr>
<td>ML20322,29 2012</td>
<td>First</td>
<td>Erlotinib vs Vinorelbine (oral)</td>
<td>Asian (100)</td>
<td>77 (70-90)</td>
<td>73 (64.6)</td>
<td>Direct sequencing</td>
<td>21</td>
<td>57</td>
<td>15</td>
</tr>
<tr>
<td>TITAN,13 2012</td>
<td>Second</td>
<td>Erlotinib vs Docetaxel or Pemetrexed</td>
<td>White 362 (85.4)</td>
<td>59 (22-80)</td>
<td>210 (49.5)</td>
<td>Direct sequencing</td>
<td>75</td>
<td>203</td>
<td>74</td>
</tr>
<tr>
<td>First-SIGNAL,30 2012</td>
<td>First</td>
<td>Gefitinib vs Gemcitabine + Cisplatin</td>
<td>Asian (100)</td>
<td>57 (19-74)</td>
<td>313 (100)</td>
<td>Direct sequencing</td>
<td>27</td>
<td>159</td>
<td>27</td>
</tr>
<tr>
<td>TORCH,14 2012</td>
<td>First</td>
<td>Erlotinib vs Gemcitabine + Cisplatin</td>
<td>Non-Asian 736 (96.8)</td>
<td>62 (27-81)</td>
<td>422 (55.5)</td>
<td>Direct sequencing + fragment analysis + MS</td>
<td>119</td>
<td>380</td>
<td>117</td>
</tr>
<tr>
<td>KCSG-LU08-01,31 2012</td>
<td>Second</td>
<td>Gefitinib vs Pemetrexed</td>
<td>Asian (NR)</td>
<td>NR (30-78)</td>
<td>141 (100)</td>
<td>Direct sequencing</td>
<td>18</td>
<td>71</td>
<td>20</td>
</tr>
<tr>
<td>CT/06.05,32 2013</td>
<td>Second or third</td>
<td>Erlotinib vs Pemetrexed</td>
<td>White (NR)</td>
<td>66 (37-86)</td>
<td>257* (77.4)</td>
<td>Direct sequencing</td>
<td>55*</td>
<td>179</td>
<td>57*</td>
</tr>
<tr>
<td>TAILOR,15 2013</td>
<td>Second</td>
<td>Erlotinib vs Docetaxel</td>
<td>White 217 (99.1)</td>
<td>67 (35-83)</td>
<td>155 (70.8)</td>
<td>Direct sequencing + fragment analysis</td>
<td>109</td>
<td>112</td>
<td>110</td>
</tr>
<tr>
<td>DELTA,33 2013</td>
<td>Second or third</td>
<td>Erlotinib vs Docetaxel</td>
<td>Asian (NR)</td>
<td>67 (31-85)</td>
<td>207 (68.8)</td>
<td>Highly sensitive PCR-based method†</td>
<td>109</td>
<td>150</td>
<td>90</td>
</tr>
<tr>
<td>CTONG-0806,34 2013</td>
<td>Second</td>
<td>Gefitinib vs Pemetrexed</td>
<td>Asian (NR)</td>
<td>57 (24-78)</td>
<td>151 (96.2)</td>
<td>Direct sequencing</td>
<td>81</td>
<td>81</td>
<td>76</td>
</tr>
</tbody>
</table>

Abbreviations: ARMS, amplification/refractory mutation system; EGFR, epidermal growth factor receptor; MS, mass spectrometry; NR, not reported; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitors; WT, wild type.

* Numbers used in the analyses of progression-free survival.
† Numbers used in the analyses of time to progression.
‡ Numbers of randomized patients.
§ TKI group vs chemotherapy group.
© Numbers of nonsquamous histology (number of adenocarcinoma was not available).

Association of First-Generation EGFR TKI With PFS in Patients With WT EGFR

The pooled model showed a significantly longer PFS with chemotherapy than with TKI in the patients with WT EGFR (HR, 1.41; 95% CI, 1.10-1.81) (Figure 2). A significant statistical heterogeneity was noted in this analysis (I² = 79.1%), largely attributable to the 2 trials that showed a different direction of effect from the other 8 trials (HRs from 1.24-2.85). The CT/06.05 trial reported time to progression instead of PFS. (Progression-free survival in patients with WT EGFR tumors was not analyzed.) Under the assumption that the PFS outcome might not differ from the time to progression, we pooled these data with the PFS outcomes of the other 10 trials; the result differed little (HR, 1.35; 95% CI, 1.06-1.72). The objective response rate was also significantly higher with chemotherapy (92/549, 16.8%) compared with TKI (39/540, 7.2%; RR of nonresponse for TKI, 1.11; 95% CI, 1.02-1.21) (Figure 3). For overall survival, no statistically significant difference was observed between the TKI groups (HR for TKI, 1.08; 95% CI, 0.96-1.22) (Figure 3). The funnel plot asymmetry can also be explained by the 2 outlying small trials that caused heterogeneity, rather than by a publication bias (eFigure 1 in the Supplement).

Subgroup Analyses

Subgroup analyses were carried out to explore the heterogeneity in the analysis of PFS (Figure 4). In the 4 predefined subgroup analyses, the treatment effects were similar between the subgroups by line of treatment, experimental drug, and dominant ethnicity. The differences in treatment effects in these subgroups were not statistically significant (P values for subgroup difference: line of treatment, .58; experimental drug, .67; and dominant ethnicity, .78). However, the subgroup result by EGFR mutation analysis methods appeared to be discordant: trials using only direct sequencing showed no significant improvement in PFS with chemotherapy (HR, 1.12; 95% CI, 0.79-1.58). On the other hand, in trials using more sensitive platforms, conventional chemotherapy demonstrated a longer PFS (HR, 1.84; 95% CI, 1.35-2.52) compared with TKI. The EGFR mutation analysis method can partly explain the heterogeneity between the trials, but the subgroup difference did not yet reach the level of statistical significance (P = .11). In a meta-

studies, the researchers did not perform an independent radiologic review. One trial had an imbalanced baseline characteristic with greater age in the control group, and 2 trials were terminated prematurely.
regression analysis regarding histology, the percentages of adenocarcinoma in each trial were not associated with their PFS HRs (P = .93). In 133 patients with KRAS mutation from 3 trials, chemotherapy was not significantly related to a longer PFS (HR, 1.29; 95% CI, 0.88-1.90) (eFigure 2 in the Supplement).

Discussion

To the best of our knowledge, this study is the first meta-analysis with a focus on investigating the association between first-generation EGFR TKI vs chemotherapy and sur-

**Figure 2. Progression-Free Survival From the 10 Randomized Controlled Trials Comparing EGFR TKI With Chemotherapy**

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients With WT EGFR</th>
<th>Progression-Free Survival, HR (95% CI)</th>
<th>Favors</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTEREST,12,27 2008 and 2010</td>
<td>106 123</td>
<td>1.24 (0.94-1.64)</td>
<td>←</td>
<td>11.57</td>
</tr>
<tr>
<td>IPASS,5,28 2009 and 2011</td>
<td>91 85</td>
<td>2.85 (2.05-3.98)</td>
<td>←</td>
<td>10.90</td>
</tr>
<tr>
<td>ML20322,29 2012</td>
<td>21 15</td>
<td>0.50 (0.25-0.97)</td>
<td>←</td>
<td>6.81</td>
</tr>
<tr>
<td>TITAN,31 2012</td>
<td>75 74</td>
<td>1.25 (0.88-1.78)</td>
<td>←</td>
<td>10.64</td>
</tr>
<tr>
<td>First-SIGNAL,30 2012</td>
<td>27 27</td>
<td>1.42 (0.82-2.47)</td>
<td>←</td>
<td>8.12</td>
</tr>
<tr>
<td>TORCH,14,15 2012</td>
<td>119 117</td>
<td>2.07 (1.58-2.71)</td>
<td>←</td>
<td>11.67</td>
</tr>
<tr>
<td>KCS6-LU08-01,31 2012</td>
<td>18 20</td>
<td>0.56 (0.28-1.13)</td>
<td>←</td>
<td>6.56</td>
</tr>
<tr>
<td>TAILOR,15 2013</td>
<td>109 110</td>
<td>1.39 (1.06-1.82)</td>
<td>←</td>
<td>11.66</td>
</tr>
<tr>
<td>DELTA,33 2013</td>
<td>109 90</td>
<td>1.49 (1.09-1.94)</td>
<td>←</td>
<td>11.45</td>
</tr>
<tr>
<td>CTONG-0806,34 2013</td>
<td>81 76</td>
<td>1.96 (1.37-2.78)</td>
<td>←</td>
<td>10.62</td>
</tr>
<tr>
<td>Overall: $I^2 = 79.1%$; $P &lt; .001$</td>
<td>756 737</td>
<td>1.41 (1.10-1.81)</td>
<td>←</td>
<td>100</td>
</tr>
</tbody>
</table>

The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis. The treatment effects were calculated with a random-effects model. (Numbers of events when reported are shown in eTable 1 in the Supplement.) EGFR indicates epidermal growth factor receptor; HR, hazard ratio; TKI, tyrosine kinase inhibitor.

**Figure 3. Relative Risks for Objective Response Rate and Hazard Ratios for Overall Survival From the Trials With Available Data**

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients With WT EGFR</th>
<th>RR* (95% CI)</th>
<th>Favors</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTEREST,12,27 2008 and 2010</td>
<td>106 111</td>
<td>1.03 (0.96-1.12)</td>
<td>←</td>
<td>18.46</td>
</tr>
<tr>
<td>IPASS,5,28 2009 and 2011</td>
<td>90 65</td>
<td>1.29 (1.15-1.46)</td>
<td>←</td>
<td>15.08</td>
</tr>
<tr>
<td>First-SIGNAL,30 2012</td>
<td>27 23</td>
<td>1.54 (0.98-2.41)</td>
<td>←</td>
<td>2.96</td>
</tr>
<tr>
<td>CT/06.05,32 2013</td>
<td>53 57</td>
<td>1.00 (0.90-1.11)</td>
<td>←</td>
<td>16.44</td>
</tr>
<tr>
<td>TAILOR,15 2013</td>
<td>97 82</td>
<td>1.15 (1.05-1.26)</td>
<td>←</td>
<td>17.31</td>
</tr>
<tr>
<td>DELTA,33 2013</td>
<td>106 68</td>
<td>1.18 (1.05-1.32)</td>
<td>←</td>
<td>15.38</td>
</tr>
<tr>
<td>CTONG-0806,34 2013</td>
<td>75 75</td>
<td>0.98 (0.87-1.12)</td>
<td>←</td>
<td>14.36</td>
</tr>
<tr>
<td>Overall: $I^2 = 71.7%$; $P = .002$</td>
<td>560 549</td>
<td>1.11 (1.02-1.21)</td>
<td>←</td>
<td>100</td>
</tr>
</tbody>
</table>

**Overall survival**

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients With WT EGFR</th>
<th>HR (95% CI)</th>
<th>Favors</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTEREST,12,27 2008 and 2010</td>
<td>119 134</td>
<td>1.02 (0.78-1.33)</td>
<td>←</td>
<td>20.28</td>
</tr>
<tr>
<td>IPASS,5,28 2009 and 2011</td>
<td>91 85</td>
<td>1.18 (0.86-1.63)</td>
<td>←</td>
<td>14.12</td>
</tr>
<tr>
<td>ML20322,29 2012</td>
<td>21 15</td>
<td>0.62 (0.30-1.24)</td>
<td>←</td>
<td>2.87</td>
</tr>
<tr>
<td>TITAN,31 2012</td>
<td>75 74</td>
<td>0.85 (0.59-1.22)</td>
<td>←</td>
<td>10.94</td>
</tr>
<tr>
<td>First-SIGNAL,30 2012</td>
<td>27 27</td>
<td>1.00 (0.52-1.91)</td>
<td>←</td>
<td>3.44</td>
</tr>
<tr>
<td>TORCH,14,15 2012</td>
<td>119 117</td>
<td>1.29 (0.97-1.71)</td>
<td>←</td>
<td>17.96</td>
</tr>
<tr>
<td>CT/06.05,32 2013</td>
<td>55 57</td>
<td>1.19 (0.77-1.84)</td>
<td>←</td>
<td>7.61</td>
</tr>
<tr>
<td>TAILOR,15 2013</td>
<td>109 110</td>
<td>1.28 (0.95-1.96)</td>
<td>←</td>
<td>11.01</td>
</tr>
<tr>
<td>DELTA,33 2013</td>
<td>109 90</td>
<td>0.98 (0.69-1.39)</td>
<td>←</td>
<td>11.77</td>
</tr>
<tr>
<td>Overall: $I^2 = 0%$; $P = .496$</td>
<td>709 725</td>
<td>1.08 (0.96-1.22)</td>
<td>←</td>
<td>100</td>
</tr>
</tbody>
</table>

* The RR was calculated from the nonresponse events of the 2 treatment groups.
vival outcomes in advanced NSCLC patients with WT EGFR tumors. This study included 11 randomized controlled trials incorporating 1605 patients with WT EGFR tumors. The pooled analysis demonstrated that chemotherapy was associated with longer PFS compared with EGFR TKI in patients with WT tumors. For a median PFS of 6.4 months in patients treated with standard chemotherapy,\(^2\) the corresponding reduction of PFS with EGFR TKI would be 1.9 months. The higher objective response rate of chemotherapy also supported the longer PFS in patients with WT EGFR tumors. However, the overall survival did not differ between the chemotherapy and TKI groups. The apparent discrepancy between the PFS/objective response rate and the overall survival can be explained by the large crossover rates of the included trials (eTable 1 in the Supplement), as acknowledged by the authors.\(^2\) Therefore, this study suggests that, in patients with WT EGFR tumors, conventional chemotherapy could be a preferable treatment option over EGFR TKI, although this recommendation cannot be conclusive because the overall comparisons were not based on randomization. Furthermore, the toxicity outcome was not assessed.

For first-line settings, current guidelines already do not support the use of EGFR TKI as a first-line agent for patients with WT EGFR tumors.\(^1\) On the other hand, second-line trials have generated more controversy. Two large trials (INTEREST\(^2\) and TITAN\(^3\)) comparing TKI with US Food and Drug Administration-approved second-line chemotherapy agents (docetaxel or pemetrexed) failed to show greater efficacy of chemotherapy in patients with WT EGFR tumors. However, the recently reported TAILOR,\(^4\) DELTA,\(^5\) and CTONG-0806\(^6\) trials demonstrated a significant improvement in PFS with second-line chemotherapy compared with TKI, in patients with WT EGFR tumors. The INTEREST and TITAN trials both used direct sequencing for EGFR mutation analysis, while the TAILOR and DELTA trials used more sensitive platforms. In the pooled analysis of all these trials, a significantly longer PFS with chemotherapy was noted in patients with WT EGFR tumors for the second- or later-line treatment. Therefore, these findings suggest that current guidelines recommending EGFR TKI as a standard treatment in this setting without consideration of the EGFR mutation status may need to be reevaluated, in consideration of the shorter PFS of TKI compared with conventional chemotherapy agents for patients with WT EGFR tumors.

The trials using sensitive EGFR mutation analysis were associated with longer PFS with chemotherapy in patients with WT EGFR tumors. Direct sequencing of exon 18 to exon 21 by Sanger method has been the most commonly used approach for detecting EGFR mutation.\(^2\) However, the suboptimal sensitivity of this method has been criticized.\(^7\) In general, a mutant allele needs to comprise more than 25% of the total DNA to be optimally detected by direct sequencing. However, many clinical specimens obtained by cytology, needle aspiration, or surgical resection may include a significant proportion of non-neoplastic cells; false-negative results are not uncommon by direct sequencing only. A recent study reported that EGFR mutations were detected by massively parallel RNA sequencing in 22 of 87 patients who had negative results by direct sequencing of both EGFR and KRAS.\(^8\) Therefore, recent trials\(^9\) have applied advanced platforms to detect EGFR mutation with higher sensitivity.\(^10\) The lack of a significant difference in PFS between TKI and chemotherapy groups in trials using only direct sequencing can be partly explained by possible misclassification of EGFR mutation as WT. If the false-negative pa-
patients were correctly diagnosed as harboring EGFR mutations, the treatment effect in terms of PFS in patients with WT EGFR tumors might have been found to have deviated toward favoring chemotherapy. Thus, implementation of a more sensitive method for detecting EGFR mutation is relevant for discrimination of the favorable TKI responders from patients with true WT EGFR tumors, especially in areas with a high prevalence of EGFR mutation.

There was significant statistical heterogeneity in the PFS meta-analysis. The primary source of the heterogeneity was from 2 outlying small Asian studies,29,31 which showed a different direction of treatment effect from the others and also used a less sensitive method for detecting EGFR mutations. The ML20322 trial29 exclusively accrued elderly patients (aged ≥70 years), used a less potent control drug (oral vinorelbine), and had imbalances of EGFR mutation frequency between the 2 treatment groups despite the randomization process (No. with EGFR mutation/No. analyzed; TKI group, 9/30; chemotherapy group, 15/30). KCSG-LU08-0131 had more young patients in the TKI group and classified a small number of EGFR-activating mutations into the EGFR-negative group in the PFS analysis: 1 case of EGFR L861Q mutation in the TKI group and 2 G719A mutations in the chemotherapy group, which could have biased the PFS outcome. The other 8 trials,5,13–15,27,30,33,34 which included a total of 1443 patients (96.7%) with WT EGFR tumors, had a treatment effect in the same direction, but some heterogeneity remained (I² = 69.6%) due to the different magnitudes of effect sizes (HRs from 1.24–2.85).

We encountered several limitations during this study. First, a large number of trials had available data on the EGFR mutation status in only a small portion of the enrolled patients. This is largely because these trials were performed in the early days of TKI usage, before the establishment of the role of the EGFR mutation as a predictive marker for TKI treatment. Although most of these trials carried out the randomization process adequately, an imbalance of patient characteristics between the 2 treatment groups of the WT EGFR subgroup could exist. Therefore, these data should be interpreted cautiously, because the extracted data used for this analysis could not be considered randomized. Second, the published articles provided the crossover rate only for the entire group of enrolled patients without WT/mutation subgroup data. Therefore, we could not examine the effect of treatment crossover on the outcomes. Third, the toxicity profile is another important factor for choosing treatment options. However, it was not possible to perform an analysis to deal with such a concern because reports of adverse events from each subgroup were not available. The better toxicity profile of EGFR TKI compared with chemotherapy has been demonstrated in the clinical trials included in this study; this should be considered when selecting a treatment option for patients with a poor performance status. Fourth, we identified 3 large randomized controlled trials comparing TKI treatment with placebo.11,41,42 These 3 trials did not report the PFS outcome by EGFR mutation status. Although the overall survival prolongation by erlotinib was demonstrated in the BR.21 trial, the PFS gain was 0.4 months.11 In addition, the response rate was significantly higher in the patients with EGFR mutations.20 Data for PFS from these studies by the patients’ EGFR mutation status could have provided a better understanding of predictive biomarkers for refractory disease. If the PFS prolongation were limited only to patients harboring EGFR mutations, the use of TKI in refractory patients might also be worth reconsidering.

The treatment of advanced NSCLC patients with EGFR TKI has progressed since the discovery of a robust biomarker, the presence of activating EGFR mutations. Many trials have demonstrated that the benefit of EGFR TKI was closely related to the EGFR mutation status.

Conclusions

In patients with advanced NSCLC harboring WT EGFR tumors, conventional chemotherapy was associated with improvement in PFS and a higher objective response rate, compared with first-generation EGFR TKI. However, there was no statistically significant difference in terms of overall survival between the 2 treatment groups.

REFERENCES

EGFR Tyrosine Kinase Inhibitors vs Conventional Chemotherapy

Original Investigation Research


