Meta-Analysis of First-Line Therapies in Advanced Non–Small-Cell Lung Cancer Harboring EGFR-Activating Mutations

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Introduction: Tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib have been compared with chemotherapy as first-line therapies for patients with advanced non–small–cell lung cancer harboring epidermal growth factor receptor–activating mutations. This meta-analysis compares gefitinib, erlotinib, afatinib, and chemotherapy.

Methods: Literature search was performed using relevant keywords. Direct and indirect meta-estimates were generated using log-linear mixed-effects models, with random effects for study. Study-to-study heterogeneity was summarized using I² statistics and predictive intervals (PIs).

Results: Literature search yielded eight randomized phase 3 clinical trials comparing gefitinib, erlotinib, or afatinib with chemotherapy as first-line therapy in patients with advanced non–small–cell lung cancer during the last 5 years. Hazard ratio meta-estimates for progression-free survival were for gefitinib versus chemotherapy 0.44 (95% confidence interval [CI] 0.31–0.63; 95% PI, 0.22–0.88), erlotinib versus chemotherapy 0.25 (95% CI, 0.15–0.42; 95% PI, 0.11–0.55), afatinib versus chemotheray 0.44 (95% CI, 0.26–0.75; 95% PI, 0.20–0.98), erlotinib versus gefitinib 0.57 (95% CI, 0.30–1.08; 95% PI, 0.24–1.36), afatinib versus gefitinib 1.01 (95% CI, 0.53–1.92; 95% PI, 0.41–2.42), and erlotinib versus afatinib 0.56 (95% CI, 0.27–1.18; 95% PI, 0.22–1.46). Results for overall response rate and disease control rate were similar. There was no evidence that gefitinib, erlotinib, or afatinib improved overall survival compared with chemotherapy.

Conclusion: Gefitinib, erlotinib, and afatinib out-performed chemotherapy in terms of progression–free survival, overall response rate, and disease control rate. Differences among gefitinib, erlotinib, and afatinib were not statistically significant.

Key Words: Non–small–cell lung cancer, Epidermal growth factor receptor–activating mutations, Tyrosine kinase inhibitors, Meta-analysis.

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erlotinib, and afatinib with platinum-based chemotherapy doublets, or comparing one EGFR-TKI with another. Hence, this study aims to provide meta-estimates comparing gefitinib, erlotinib, afatinib, and chemotherapy as first-line therapies for patients with advanced NSCLC harboring EGFR-activating mutations in terms of progression-free survival, overall response rate, disease control rate, and overall survival.

**MATERIALS AND METHODS**

**Search Strategy**

We included publications on randomized phase 3 clinical trials comparing gefitinib, erlotinib, or afatinib with chemotherapy or one EGFR-TKI with another as first-line therapy in patients with advanced NSCLC whose tumors present with an EGFR-activating mutation. Studies were included if they contained only patients with EGFR-activating mutations or they reported relative efficacy within the EGFR-positive subgroup. End points of interest were progression-free survival, overall response rate, disease control rate, and overall survival. Publications were included if they provided the most up-to-date analysis of at least one of the above-mentioned end points of interest. Literature search of Medline was performed using PubMed to identify published studies using the search (“gefitinib” OR “erlotinib” OR “afatinib”) AND (“non–small-cell lung cancer” OR “adenocarcinoma”) AND (“phase 3” OR “phase III”). The search results were further limited to clinical trials published within the last 5 years. The Medline search was augmented by search of the American Society of Clinical Oncology Meeting Library, European Cancer Congress 2013, Chinese Clinical Trial Registry, clinicaltrials.gov, EU Clinical Trials Register, and UMIN Clinical Trials Registry using relevant keywords. Abstracts were screened and nonrelevant studies were excluded.

**Statistical Analysis**

Direct and indirect meta-estimates were generated in the context of log-linear mixed-effects models, similar to the model proposed by DerSimonian and Laird, with fixed effects for each relative comparison and random effects for each study. Efficacy analyses focus only on patients with EGFR-activating mutations. Heterogeneity across studies was tested and partially summarized using chi-squared tests and I² statistics as proposed by Higgins and Thompson. However, tests of heterogeneity and I² can be misleading, especially when treatments differ markedly and one treatment can be expected to outperform the other across settings despite non-negligible heterogeneity. Predictive intervals (PIs), which provide an interval within which any particular study’s relative effectiveness may be expected to fall, were calculated using the study-to-study variance estimates from each mixed-effects model. Adverse event rates (95% confidence interval [CI]; 95% PI) were summarized separately for each first-line therapy in the context of logistic mixed-effects models with a random effect for study. For adverse event summaries, the analyses were based on each study’s full safety population, potentially a mix of patients with and without EGFR-activating mutations. Details of the statistical analysis are given in Supplemental Digital Content 1 (http://links.lww.com/JTO/A562).

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**FIGURE 1.** Selection diagram for studies comparing gefitinib, erlotinib, and afatinib with chemotherapy as first-line therapies for patients with advanced NSCLC harboring EGFR-activating mutations.

ASCO, American Society of Clinical Oncology; NSCLC, non–small-cell lung cancer; EGFR, epidermal growth factor receptor.
RESULTS

Search Results

Literature search yielded 11 publications on eight randomized phase 3 clinical trials comparing gefitinib, erlotinib, or afatinib with chemotherapy or one EGFR-TKI with another as first-line therapy in patients with NSCLC harboring EGFR-activating mutations, during the last 5 years. Details of the searches are given in Figure 1.

Identified studies were IPASS,11,12 West Japan,13 North-East Japan,14,15 and First-SIGNAL,16 comparing gefitinib with carboplatin and paclitaxel, cisplatin and docetaxel, carboplatin and paclitaxel, or gemcitabine and cisplatin, respectively. OPTIMAL17,18 and EURTAC,19 respectively, compared erlotinib with gemcitabine and carboplatin, cisplatin and docetaxel, carboplatin with paclitaxel, cisplatin and docetaxel, or gemcitabine and cisplatin and cisplatin, respectively. LUX-Lung 6,20 respectively, compared afatinib with pemetrexed and cisplatin, gemcitabine and cisplatin, and cisplatin and cisplatin, respectively. LUX-Lung 3,21 compared erlotinib with gemcitabine and carboplatin, and platinum-based doublet chemotherapy. LUX-Lung 3,20 and LUX-Lung 6,22 respectively, compared afatinib with pemetrexed and cisplatin, and gemcitabine and cisplatin. The most up-to-date analyses of overall survival for IPASS, North-East Japan, and OPTIMAL were respectively reported in the studies by Fukuoka et al.,12 Inoue et al.,15 and Zhou et al.18 The IPASS and First-SIGNAL studies both recruited patients from a clinically selected population associated with EGFR-activating mutations.11,12,16 Summaries of included patient populations, sample sizes, treatment arms, and relative effectiveness, in terms of progression-free survival, overall response rate, disease control rate, and overall survival, are given in Table 1.

Progression-Free Survival

The test of heterogeneity indicated moderately high study-to-study variability with Q = 16.1 on 5 degrees of freedom (p = 0.007) and I² of 69%. The pooled hazard ratio meta-estimate for gefitinib versus chemotherapy was 0.44 (95% CI, 0.31–0.63; 95% PI, 0.22–0.88), erlotinib versus chemotherapy was 0.25 (95% CI, 0.15–0.42; 95% PI, 0.11–0.55), afatinib versus chemotherapy was 0.44 (95% CI, 0.26–0.75; 95% PI, 0.20–0.98), erlotinib versus gefitinib was 0.57 (95% CI, 0.30–1.08; 95% PI, 0.24–1.36), afatinib versus gefitinib was 1.01 (95% CI, 0.53–1.92; 95% PI, 0.42–2.42), and erlotinib versus afatinib was 0.56 (95% CI, 0.27–1.18; 95% PI, 0.22–1.46). These results are summarized in Table 2 and depicted in Figure 2.

| Study | Patient Population | Treatment Arms | Progression-Free Survival | Response | Disease Control | Overall Survival |
|-------|--------------------|----------------|----------------------------|----------|----------------|----------------|
| IPASS | East Asian nonsmoking or formerly light-smoking patients with advanced pulmonary adenocarcinoma* | Gefitinib (n = 132) Carboplatin + paclitaxel (n = 129) | 0.48 (0.36–0.64) | 2.8 (1.7–4.6) | 1.6 (0.7–3.5) | 1.00 (0.76–1.33) |
| West Japan | Japanese patients with advanced or recurrent NSCLC with EGFR-activating mutations | Gefitinib (n = 86) Cisplatin + docetaxel (n = 86) | 0.49 (0.34–0.71) | 3.4 (1.6–7.4) | 3.8 (1.2–12.5) | 1.64 (0.75–3.58) |
| North-East Japan | Japanese patients with metastatic NSCLC with EGFR-activating mutations | Gefitinib (n = 114) Carboplatin + paclitaxel (n = 114) | 0.32 (0.24–0.44) | 6.3 (3.6–11.2) | 2.1 (1.0–4.6) | 0.89 (0.63–1.24) |
| First-SIGNAL | Korean never-smoking patients with advanced or metastatic lung adenocarcinoma* | Gefitinib (n = 26) Gemcitabine + cisplatin (n = 16) | 0.54 (0.27–1.10) | 9.2 (2.1–39.8) | 0.0 (0.0–16.6) | 1.04 (0.50–2.18) |
| OPTIMAL | Chinese patients with advanced NSCLC with EGFR-activating mutations | Erlotinib (n = 82) Gemcitabine + carboplatin (n = 72) | 0.16 (0.10–0.26) | 8.6 (4.1–18.2) | 5.8 (1.6–21.3) | 1.07 (0.79–1.44) |
| EURTAC | Caucasian patients with advanced NSCLC with EGFR-activating mutations | Erlotinib (n = 86) Platinum-based doublet chemotherapy (n = 87) | 0.37 (0.25–0.54) | 7.9 (3.8–16.4) | 2.0 (1.0–3.9) | 1.04 (0.65–1.68) |
| LUX-Lung 3 | Patients with advanced lung adenocarcinoma with EGFR-activating mutations | Afatinib (n = 230) Pemetrexed + cisplatin (n = 115) | 0.58 (0.43–0.78) | 4.4 (2.6–7.3) | 2.1 (1.1–4.0) | 1.12 (0.73–1.73) |
| LUX-Lung 6 | Asian patients with advanced lung adenocarcinoma with EGFR-activating mutations | Afatinib (n = 242) Gemcitabine + cisplatin (n = 122) | 0.28 (p < 0.0001)* | 6.8 (4.1–11.2) | 3.9 (2.1–7.3) | 0.95 (0.68–1.32) |

*Only the subgroup with EGFR-activating mutations considered.

*p = 0.0001 used to construct conservative standard error.
Overall Response Rate

The test of heterogeneity indicated moderate study-to-study variability with $Q = 7.32$ on 5 degrees of freedom ($p = 0.198$) and $I^2$ of 32%. The pooled odds ratio meta-estimate for gefitinib versus chemotherapy was 4.1 (95% CI, 2.7–6.3; 95% PI, 2.3–7.6), erlotinib versus chemotherapy was 8.2 (95% CI, 4.5–15.1; 95% PI, 3.9–17.5), afatinib versus chemotherapy was 5.5 (95% CI, 3.4–8.8; 95% PI, 2.9–10.5), erlotinib versus gefitinib was 2.0 (95% CI, 0.9–4.1; 95% PI, 0.8–4.7), afatinib versus gefitinib was 1.3 (95% CI, 0.7–2.5; 95% PI, 0.6–2.8), and erlotinib versus afatinib was 1.5 (95% CI, 0.7–3.3; 95% PI, 0.6–3.7). These results are summarized in Table 2 and depicted in Figure 3.
Disease Control Rate
The test of heterogeneity indicated moderate study-to-study variability with $Q = 5.26$ on 4 degrees of freedom ($p = 0.262$) and $I^2$ of 24%. The pooled odds ratio meta-estimate for gefitinib versus chemotherapy were 2.1 (95% CI, 1.3–3.5; 95% PI, 1.2–3.7), erlotinib versus chemotherapy was 2.5 (95% CI, 1.4–4.7; 95% PI, 1.3–4.9), afatinib versus chemotherapy was 2.9 (95% CI, 1.8–4.6; 95% PI, 1.7–4.8), erlotinib versus gefitinib were 1.2 (95% CI, 0.5–2.7; 95% PI, 0.5–2.8), afatinib versus gefitinib were 1.4 (95% CI, 0.7–2.7; 95% PI, 0.7–2.8), and erlotinib versus afatinib were 0.9 (95% CI, 0.4–1.9; 95% PI, 0.4–2.0). These results are summarized in Table 2 and depicted in Figure 4.

Overall Survival
The test of heterogeneity indicated low study-to-study variability with $Q = 2.39$ on 5 degrees of freedom ($p = 0.793$) and $I^2$ of 0%. The pooled hazard ratio meta-estimate for gefitinib versus chemotherapy was 0.99 (95% CI, 0.81–1.21; 95% PI, 0.81–1.21), erlotinib versus chemotherapy was 1.06 (95% CI, 0.82–1.37; 95% PI, 0.82–1.37), afatinib versus chemotherapy was 1.01 (95% CI, 0.78–1.31; 95% PI, 0.78–1.31), erlotinib versus gefitinib was 1.07 (95% CI, 0.77–1.47; 95% PI, 0.77–1.47), afatinib versus gefitinib was 1.02 (95% CI, 0.73–1.41; 95% PI, 0.73–1.41), and erlotinib versus afatinib was 1.05 (95% CI, 0.73–1.51; 95% PI, 0.73–1.51). These results are summarized in Table 2.

Adverse Events
The more common adverse events with TKIs were diarrhea, rash or acne, dry skin, and pruritis, whereas anorexia, anemia, fatigue, nausea, vomiting, alopecia, and neutropenia were more common with chemotherapy. Liver enzyme elevations were more common with gefitinib and erlotinib than with chemotherapy, but not reported for afatinib. Grade 3 and 4 adverse events were more common with chemotherapy than with TKIs. Broadly, adverse event profiles were similar among TKIs although there was some indication that gefitinib was associated with more anemia and afatinib was associated with more stomatitis or mucositis. Adverse event profiles by first-line therapy are summarized in Supplemental Digital Content 2 (http://links.lww.com/JTO/A563).

DISCUSSION
In this meta-analysis, gefitinib, erlotinib, and afatinib out-performed chemotherapy in terms of progression-free survival.
survival, overall response rate, and disease control rate. There was no evidence that gefitinib, erlotinib, or afatinib improved overall survival when compared with chemotherapy. Differences among gefitinib, erlotinib, and afatinib were not statistically significant.

One of the proposed mechanisms of resistance to gefitinib and erlotinib is the T790M mutation on exon 20. This mutation sterically prevents reversible binding of gefitinib or erlotinib, but it can potentially be overcome by TKIs such as afatinib, which binds irreversibly to the receptor. However, our meta-analysis did not show superiority of afatinib over gefitinib or erlotinib in terms of progression-free survival, overall response rate, disease control rate, and overall survival. As the theoretical advantage of afatinib versus the first-generation EGFR-TKI did not translate into progression-free survival gains, maybe the clinical relevance of possible inhibition of T790M is minimal, at least in the first-line setting, when T790M-positive clones are rarely detected.

A limitation of our study is the indirect comparison of gefitinib, erlotinib, and afatinib with one another, which relies on the quality of variance component estimates. Indirect comparisons are increasingly used to make preliminary comparisons when direct head-to-head phase 3 trials are not available. A strength of our study is the inclusion of predictive estimates that provide an estimate of treatment effect in individual settings.

This is the first meta-analysis to provide evidence comparing gefitinib, erlotinib, and afatinib with standard chemotherapy and indirect comparisons of gefitinib, erlotinib, and afatinib with each other. Currently, the LUX-Lung 7 phase IIb trial is comparing afatinib versus gefitinib for first-line advanced NSCLC and is expected to complete late 2014 (NCT01466660). Till then, our study hopes to provide evidence to guide clinical decision making for oncologists when considering first-line therapies for patients with advanced NSCLC having EGFR-activating mutations.

In conclusion, gefitinib, erlotinib, and afatinib out-performed chemotherapy in terms of progression-free survival, overall response rate, and disease control rate. However, differences among gefitinib, erlotinib, and afatinib were not statistically significant.

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![FIGURE 4](Image)
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