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# Overall survival benefits of first-line EGFR tyrosine kinase inhibitors in EGFR-mutated non-small-cell lung cancers: a systematic review and meta-analysis

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**Background:** Accumulating data shows that exon 19 deletions and L858R, both activating epidermal growth factor receptor mutations in non-small-cell lung cancers (NSCLCs), are just two different entities in terms of prognosis and treatment response to tyrosine kinase inhibitors (TKIs).

**Methods:** A systematic review and meta-analysis of randomized controlled trials comparing TKIs with conventional chemotherapy was performed. Eight trials of 1498 patients and five trials of 1279 patients with either exon 19 deletions or L858R were included in the meta-analysis.

**Results:** TKI treatment demonstrated progression-free survival benefit in patients with exon 19 deletions (hazard ratio (HR): 0.27, 95% confidence interval (CI): 0.21–0.35) and L858R (HR: 0.45, 95% CI: 0.35–0.58). Patients with exon 19 deletions had significant overall survival (OS) benefit under TKI treatment (HR: 0.72, 95% CI: 0.60–0.88). Subgroup analyses showed that irreversible TKIs, but not reversible TKIs, had statistically significant OS benefit in these patients (irreversible TKIs, HR: 0.59, 95% CI: 0.47–0.73; reversible TKIs, HR: 0.84, 95% CI: 0.69–1.02). Patients with L858R demonstrated no OS benefit under first-line TKI use (HR: 1.15, 95% CI: 0.95–1.39).

**Conclusions:** In patients with advanced NSCLC harbouring exon 19 deletions, TKIs are associated with better OS compared with conventional chemotherapy. Future clinical trials should take exon 19 deletions and L858R as distinct disease entities and evaluate the treatment efficacy separately.

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Personalised medicine has an important role in the treatment of lung cancer, which accounts for 18% of all cancer-related death worldwide (GLOBOCAN, 2008). Activation of the epidermal growth factor receptor (EGFR) pathway is associated with the promotion of tumor growth, invasion, and metastasis, and the inhibition of apoptosis (Lynch *et al*, 2004; Paez *et al*, 2004; Hirsch and Bunn, 2009). In non-small-cell lung cancers (NSCLCs), EGFR-activating mutations include deletions in exon 19 (~45%), substitution of leucine-858 with arginine (L858R) in exon 21 (~45%) and other rare mutations (Sharma *et al*, 2007). Tyrosine kinase inhibitors (TKIs) like gefitinib (Mok *et al*, 2009; Maemondo *et al*, 2010; Mitsudomi *et al*, 2010; Fukuoka *et al*, 2011; Zhou *et al*, 2011; Han *et al*, 2012; Inoue *et al*, 2013), erlotinib (Rosell *et al*, 2012, Zhou *et al*, 2012; Wu *et al*, 2013), and afatinib (Sequist *et al*, 2013; Wu *et al*, 2014) target such mutations and confer remarkable response rate (RR) and PFS when compared with conventional chemotherapy in several randomized controlled trials (RCTs). However, no single RCT (Mok *et al*, 2009; Maemondo *et al*, 2010; Mitsudomi *et al*, 2010; Fukuoka *et al*, 2011; Zhou *et al*, 2011; Mitsudomi *et al*, 2012; Zhou *et al*, 2012; Han *et al*, 2012; Rosell *et al*, 2012; Inoue *et al*, 2013; Sequist *et al*, 2013; Wu *et al*, 2013, 2014) or meta-analysis (Lee *et al*, 2013; Haaland *et al*, 2014; Liang *et al*, 2014; Paz-Ares *et al*, 2014) shows overall survival (OS) benefits from TKIs.

In some retrospective studies (Lu *et al*, 2014; Skrickova *et al*, 2014) and meta-analyses (Wang *et al*, 2014; Zhang *et al*, 2014), patients with L858R seem to have poorer PFS (Rosell *et al*, 2012; Kato *et al*, 2014; Ichihara *et al*, 2015) and OS (Sequist *et al*, 2013; Wu *et al*, 2014) than those with exon 19 deletions. In several pre-clinical studies, lung cancer cell lines with exon 19 deletions or L858R have different sensitivities to reversible TKIs (gefitinib and erlotinib) and irreversible TKI (afatinib; Li *et al*, 2008; Furuyama *et al*, 2013; Cross *et al*, 2014). It may be posited that NSCLC harbouring exon 19 deletions and L858R may represent two distinct entities of lung adenocarcinoma. To validate this issue, a meta-analysis of current RCTs was performed by separating patients who received three different TKIs (gefitinib, erlotinib, and afatinib) into exon 19 deletions and L858R EGFR mutations.

## MATERIALS AND METHODS

**Data source and search strategy.** A comprehensive search to identify all published RCTs that compared the outcomes of TKI vs chemotherapy for NSCLC was done. MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant trials from inception to 31 January 2015. The search strategy was a combination of the terms 'EGFR', 'epidermal growth factor receptor', 'tyrosine kinase inhibitors', 'TKI', 'exon', 'mutation', 'non-small-cell lung cancer', and 'NSCLC' without restrictions on language and gender. Additional searches through Google Scholar and the United States National Institutes of Health trials register (<http://clinicaltrials.gov>), and a manual search through reference lists of pertinent reviews and studies were performed. Two authors conducted the search independently with no language or date restrictions set. Lastly, a pharmaceutical company (F. Hoffmann-La Roche Ltd) was contacted for information on unpublished trials.

**Inclusion and exclusion criteria.** Eligible studies should meet the following criteria:

- (1) Clinical trials that investigated local advanced or metastatic (IIIB or IV) stage NSCLC with first-line monotherapy of EGFR-TKIs.
- (2) Clinical trials with a subset of NSCLC patients with specific EGFR mutation (exon 19 deletions or L858R).

- (3) EGFR mutation analysis was performed on available tumor tissue samples instead of circulating free DNA in serum.
- (4) Prior neo-adjuvant or adjuvant chemotherapy in patients with recurrence after surgery if there was at least 6 months from the last administration to the relapse.
- (5) HRs of EGFR-TKIs compared with conventional chemotherapy for PFS and OS, and HRs of exon 19 deletions compared with L858R for PFS in terms of EGFR-TKIs were available.

Studies that did not meet these criteria were excluded.

**Selection of studies.** Duplicate records of the search results were removed. The two review authors, who were not blinded to the names of original researchers, journals, or institutions, independently checked the titles, abstracts, and keywords from the searches to identify potentially eligible studies. Upon obtaining the full texts of potentially eligible trials, the same two review authors performed an independent study selection and disagreements were resolved by consensus and, if necessary, by consult with a third reviewer.

**Data extraction and quality assessment.** Two authors independently extracted data using a standardized collection process that included first author, year of publication, intervention type, study population per group, study design (patient selection and concealment), clinical settings (doses and routes of TKI and chemotherapy), and outcomes (progression-free survival (PFS) and OS).

The Cochrane Collaboration tool was used to assess risk of bias for each trial (Higgins and Green, 2008). Seven domains associated with biased estimates of treatment effect (i.e., random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases) were evaluated. A third author resolved the differences in opinions.

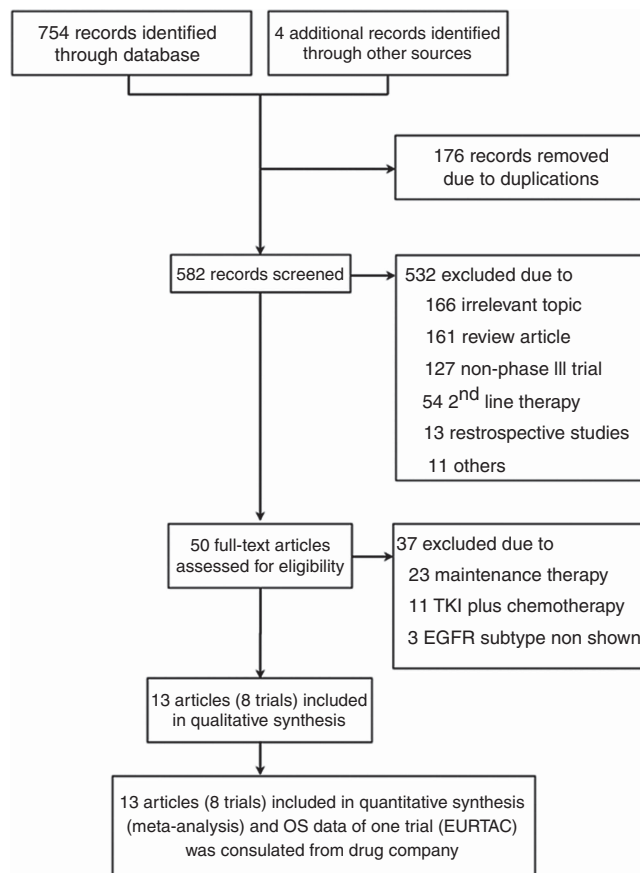


Figure 1. The trial selection process.

**Table 1. Characteristics of included trials for meta-analysis for PFS**

| Lead author (year)                  | Trial name (phase) | TKI                      | Chemotherapy   | EGFR mutation   | Sample size (TKI/ chemotherapy) | HR for PFS (TKI vs chemotherapy) mean (95% CI) |
|-------------------------------------|--------------------|--------------------------|--|-----------------|---------------------------------|--|
| Mok <i>et al</i> (2009)             | IPASS (III)        | Gefitinib 250 mg per day | Carboplatin (AUC = 5 or 6)<br>Paclitaxel (200 mg m <sup>-2</sup> ) every 3 weeks for ≤ 6 cycles <sup>a</sup>   | Del 19<br>L858R | Not available<br>Not available  | 0.38 (0.26–0.56)<br>0.55 (0.35–0.87)           |
| Maemondo <i>et al</i> (2010)        | NEJ002 (III)       | Gefitinib 250 mg per day | Carboplatin (AUC = 6)<br>Paclitaxel (200 mg m <sup>-2</sup> ) every 3 weeks for ≥ 3 cycles   | Del 19<br>L858R | 58/59<br>49/48                  | 0.35 (0.23–0.52)<br>0.32 (0.20–0.50)           |
| Mitsudomi <i>et al</i> (2010, 2012) | WJTOG3405 (III)    | Gefitinib 250 mg per day | Cisplatin (80 mg m <sup>-2</sup> )<br>Docetaxel (60 mg m <sup>-2</sup> ) every 3 weeks for 3 to 6 cycles   | Del 19<br>L858R | 50/37<br>36/49                  | 0.45 (0.27–0.77)<br>0.51 (0.29–0.90)           |
| Zhou <i>et al</i> (2011, 2012)      | OPTIMAL (III)      | Erlotinib 150 mg per day | Carboplatin (AUC = 5) on day 1<br>Gemcitabine (1000 mg m <sup>-2</sup> ) on day 1 and 8, every 3 weeks for 4 cycles  | Del 19<br>L858R | 43/39<br>39/33                  | 0.13 (0.07–0.25)<br>0.26 (0.14–0.49)           |
| Rosell <i>et al</i> (2012)          | EURTAC (III)       | Erlotinib 150 mg per day | Cisplatin (75 mg m <sup>-2</sup> ) on day 1<br>Docetaxel (75 mg m <sup>-2</sup> ) on day 1 or gemcitabine (1250 mg m <sup>-2</sup> ) on day 1 and 8, every 3 weeks for 4 cycles <sup>b</sup> | Del 19<br>L858R | 57/58<br>29/29                  | 0.30 (0.18–0.50)<br>0.55 (0.29–1.02)           |
| Wu <i>et al</i> (2013)              | EUSURE (III)       | Erlotinib 150 mg per day | Cisplatin (75 mg m <sup>-2</sup> ) on day 1<br>Gemcitabine (1250 mg m <sup>-2</sup> ) on day 1 and 8, every 3 weeks for 4 cycles   | Del 19<br>L858R | Not available<br>Not available  | 0.20 (0.12–0.33)<br>0.54 (0.32–0.90)           |
| Sequist <i>et al</i> (2013)         | LUX-Lung 3 (III)   | Afatinib 40 mg per day   | Cisplatin (75 mg m <sup>-2</sup> )<br>Pemetrexed (500 mg m <sup>-2</sup> ) every 3 weeks for ≤ 6 cycles  | Del 19<br>L858R | 112/57<br>91/47                 | 0.28 (0.18–0.44)<br>0.73 (0.46–1.17)           |
| Wu <i>et al</i> (2014)              | LUX-Lung 6 (III)   | Afatinib 40 mg per day   | Cisplatin (75 mg m <sup>-2</sup> ) on day 1<br>Docetaxel (75 mg m <sup>-2</sup> ) on day 1 or gemcitabine (1000 mg m <sup>-2</sup> ) on day 1 and 8, every 3 weeks for ≤ 6 cycles            | Del 19<br>L858R | 124/62<br>92/46                 | 0.20 (0.13–0.33)<br>0.32 (0.19–0.52)           |

Abbreviations: AUC = area under curve; CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

<sup>a</sup>AUC is the dose equivalent to an area under the concentration-time curve.

<sup>b</sup>Patients who were ineligible for cisplatin treatment received intravenous carboplatin chemotherapy instead (3-week cycles of AUC 6 on day 1 with 75 mg m<sup>-2</sup> docetaxel on day 1, or AUC 5 on day 1 with 1000 mg m<sup>-2</sup> gemcitabine on days 1 and 8).

**Statistical analysis.** The Review Manager 5.3 (Review Manager, 2014) was used for meta-analysis. Pooled HRs for PFS and OS with 95% confidence intervals (CIs) were calculated. A random-effects (RE) model was used to calculate pooled HRs or relative risks, 95% CIs, and values. A generic inverse variance meta-analysis was performed by using log hazard ratio and its standard error. If the hazard ratio is quoted in a report together with a CI or *P*-value, estimates of standard error can be obtained as described in Cochrane Handbook (Higgins and Green, 2008). Statistical significance was set at a two-sided *P* < 0.05.

For heterogeneity tests,  $\chi^2$  tests and  $I^2$  inconsistency statistics (Higgins and Thompson, 2002; Higgins *et al*, 2003) were used. A *P*-value of < 0.10 was considered significant heterogeneity.  $I^2$  values of 0–24.9%, 25–49.9%, 50–74%, and 75–100% were considered as none, low, moderate, and high heterogeneity, respectively (Higgins and Thompson, 2002; Higgins *et al*, 2003). The RE model was used for all outcomes because clinical heterogeneity could not be excluded (DerSimonian and Laird, 1986). A funnel plot method and the Egger test for asymmetry was also used to assess the potential of publication bias (Egger *et al*, 1997). A forest plot was applied for display of results.

## RESULTS

**Eligible studies.** From 758 records identified according to the search strategy, 13 studies reported advanced NSCLC patients with either exon 19 deletions or L858R mutation who received first-line monotherapy of EGFR-TKIs. There were 8 phase III RCTs (IPASS (Mok *et al*, 2009; Fukuoka *et al*, 2011), NEJ002 (Maemondo *et al*, 2010; Inoue *et al*, 2013), WJTOG3405

(Mitsudomi *et al*, 2010, 2012), OPTIMAL (Zhou *et al*, 2011, 2012), (EURTAC, 2013) (Rosell *et al*, 2012), ENSURE (Wu *et al*, 2013), LUX-Lung 3 (Sequist *et al*, 2013; Yang *et al*, 2014, 2015), and LUX-Lung 6 (Wu *et al*, 2014; Yang *et al*, 2014, 2015) with 1498 advanced NSCLC chemo-naïve patients that investigated the efficacy of EGFR-TKIs (gefitinib, erlotinib, or afatinib) and conventional chemotherapy. The PFS, OS, and subgroup analyses of different sensitive EGFR mutations were reported. Thus, these studies were included in the meta-analysis.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram is shown in Figure 1, whereas Tables 1 and 2 summarize the characteristics of the included studies.

**Risk of bias.** All the included trials had a low risk of bias when appraised using the Cochrane Collaboration's tool (Egger *et al*, 1997; Figure 2).

**PFS analysis.** There were eight trials of 1498 patients with either exon 19 deletions or L858R in this analysis. The TKI treatment demonstrated consistent PFS benefits both in patients with exon 19 deletions (HR: 0.27, 95% CI: 0.21–0.35) and L858R (HR: 0.45, 95% CI: 0.35–0.58; Figures 3A and 4A, respectively).

Subgroup analyses of reversible (gefitinib and erlotinib) and irreversible (afatinib) TKIs revealed statistically significant PFS in patients with exon 19 deletions (reversible TKIs, HR: 0.28, 95% CI: 0.20–0.40; irreversible TKI, HR: 0.24, 95% CI: 0.17–0.33; Figure 3A). Moreover, reversible TKIs also had significant PFS in patients with L858R (HR: 0.44, 95% CI: 0.34–0.57; Figure 4A). However, L858R patients treated with irreversible TKI had only marginal PFS benefit (HR: 0.48, 95% CI: 0.22–1.09; Figure 4A).

**Table 2. Characteristics of included trials for meta-analysis for OS**

| Lead author (y)             | Trial name (phase) | TKI                     | Chemotherapy  | EGFR mutation | Sample size (TKI/ chemotherapy) | HR for OS (TKI vs chemotherapy) mean (95% CI) |
|-----------------------------|--------------------|-------------------------|---|---------------|---------------------------------|---|
| Fukuoka <i>et al</i> (2011) | IPASS (III)        | Gefitinib 250mg per day | Carboplatin (AUC = 5 or 6) Paclitaxel (200 mg m <sup>-2</sup> ) every 3 weeks for ≤6 cycles <sup>a</sup>  | Del 19 L858R  | Not available<br>Not available  | 0.79 (0.54–1.15)<br>1.44 (0.90–2.30)          |
| Inoue <i>et al</i> (2013)   | NEJ002 (III)       | Gefitinib 250mg per day | Carboplatin (AUC = 6) Paclitaxel (200 mg m <sup>-2</sup> ) every 3 weeks for ≥3 cycles  | Del 19 L858R  | 58/59<br>49/48                  | 0.83 (0.52–1.34)<br>0.82 (0.49–1.38)          |
| EURTAC (2013) <sup>c</sup>  | EURTAC (III)       | Erlotinib 150mg per day | Cisplatin (75 mg m <sup>-2</sup> ) on day 1 Docetaxel (75 mg m <sup>-2</sup> ) on day 1 or gemcitabine (1250 mg m <sup>-2</sup> ) on day 1 and 8, every 3 weeks for 4 cycles <sup>b</sup> | Del 19 L858R  | 57/58<br>29/29                  | 0.94 (0.57–1.54)<br>0.99 (0.56–1.76)          |
| Yang <i>et al</i> (2015)    | LUX-Lung 3 (III)   | Afatinib 40mg per day   | Cisplatin (75 mg m <sup>-2</sup> ) Pemetrexed (500 mg m <sup>-2</sup> ) every 3 weeks for ≤6 cycles   | Del 19 L858R  | 112/57<br>91/47                 | 0.54 (0.36–0.79)<br>1.30 (0.80–2.11)          |
| Yang <i>et al</i> (2015)    | LUX-Lung 6 (III)   | Afatinib 40mg per day   | Cisplatin (75 mg m <sup>-2</sup> ) on day 1 Docetaxel (75 mg m <sup>-2</sup> ) on day 1 or gemcitabine (1000 mg m <sup>-2</sup> ) on day 1 and 8, every 3 weeks for ≤6 cycles             | Del 19 L858R  | 124/62<br>92/46                 | 0.64 (0.44–0.94)<br>1.22 (0.81–1.83)          |

Abbreviations: AUC = area under curve; CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; OS = overall survival; TKI = tyrosine kinase inhibitor.  
<sup>a</sup>AUC is the dose equivalent to an area under the concentration-time curve.  
<sup>b</sup>Patients who were ineligible for cisplatin treatment received intravenous carboplatin chemotherapy instead (3-week cycles of AUC 6 on day 1 with 75 mg m<sup>-2</sup> docetaxel on day 1, or AUC 5 on day 1 with 1000 mg m<sup>-2</sup> gemcitabine on days 1 and 8).  
<sup>c</sup>TARCEVA (erlotinib) prescribing information 2013 from drug company.

When stratified by chemotherapy (including cisplatin- or carboplatin-based regimen), both reversible and irreversible TKIs were associated with significant PFS in patients with exon 19 deletions (HR: 0.27, 95% CI: 0.20–0.36) and L858R (HR: 0.44, 95% CI: 0.33–0.58; Figures 3B and 4B, respectively).

**OS analysis.** There were five trials of 1279 patients with either exon 19 deletions or L858R in this analysis. Patients with exon 19 deletions had significant OS benefits from TKI treatment (HR: 0.72, 95% CI: 0.60–0.88; Figure 5A).

Subgroup analyses revealed that irreversible TKIs, but not reversible TKI, had statistically significant OS benefit in patients with exon 19 deletions (irreversible TKI, HR: 0.59, 95% CI: 0.47–0.73; reversible TKIs, HR: 0.84, 95% CI: 0.69–1.02; Figure 5A). But patients with L858R demonstrated no OS benefit regardless of the TKI used (HR: 1.15, 95% CI: 0.95–1.39; Figure 6A).

When stratified between cisplatin- or carboplatin-based chemotherapy, TKI treatment was associated with significant OS benefits in patients with exon 19 deletions compared with those with cisplatin-based chemotherapy (cisplatin, HR: 0.59, 95% CI: 0.47–0.73; carboplatin, HR: 0.81, 95% CI: 0.64–1.02; Figure 5B). In patients with L858R, TKI treatment showed no OS benefit over cisplatin- or carboplatin-based chemotherapy (HR: 1.18, 95% CI: 0.94–1.48; Figure 6B). The HRs for all of the different comparisons are summarised in Table 3.

**DISCUSSION**

Previous RCTs (Mok *et al*, 2009; Maemondo *et al*, 2010; Mitsudomi *et al*, 2010; Fukuoka *et al*, 2011; Zhou *et al*, 2011; Mitsudomi *et al*, 2012; Zhou *et al*, 2012; Han *et al*, 2012; Rosell *et al*, 2012; Inoue *et al*, 2013; Sequist *et al*, 2013; Wu *et al*, 2013, 2014) did not show any OS benefits for TKIs in patients harbouring EGFR mutations as compared with those undergoing chemotherapy. Other meta-analyses of treatment with TKIs demonstrate only RR and PFS benefits, but no OS benefit, in a

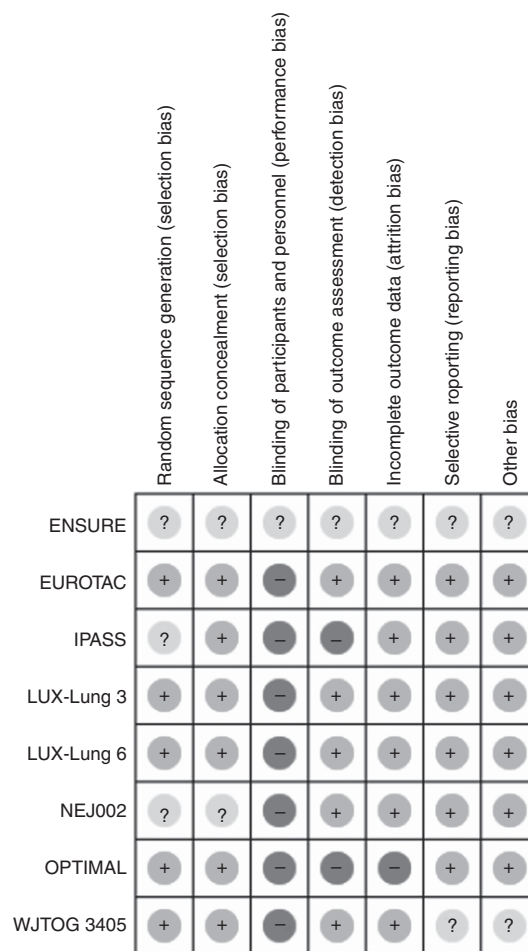


Figure 2. The risk of bias summary or review of judgments on each risk of bias item for each included study.

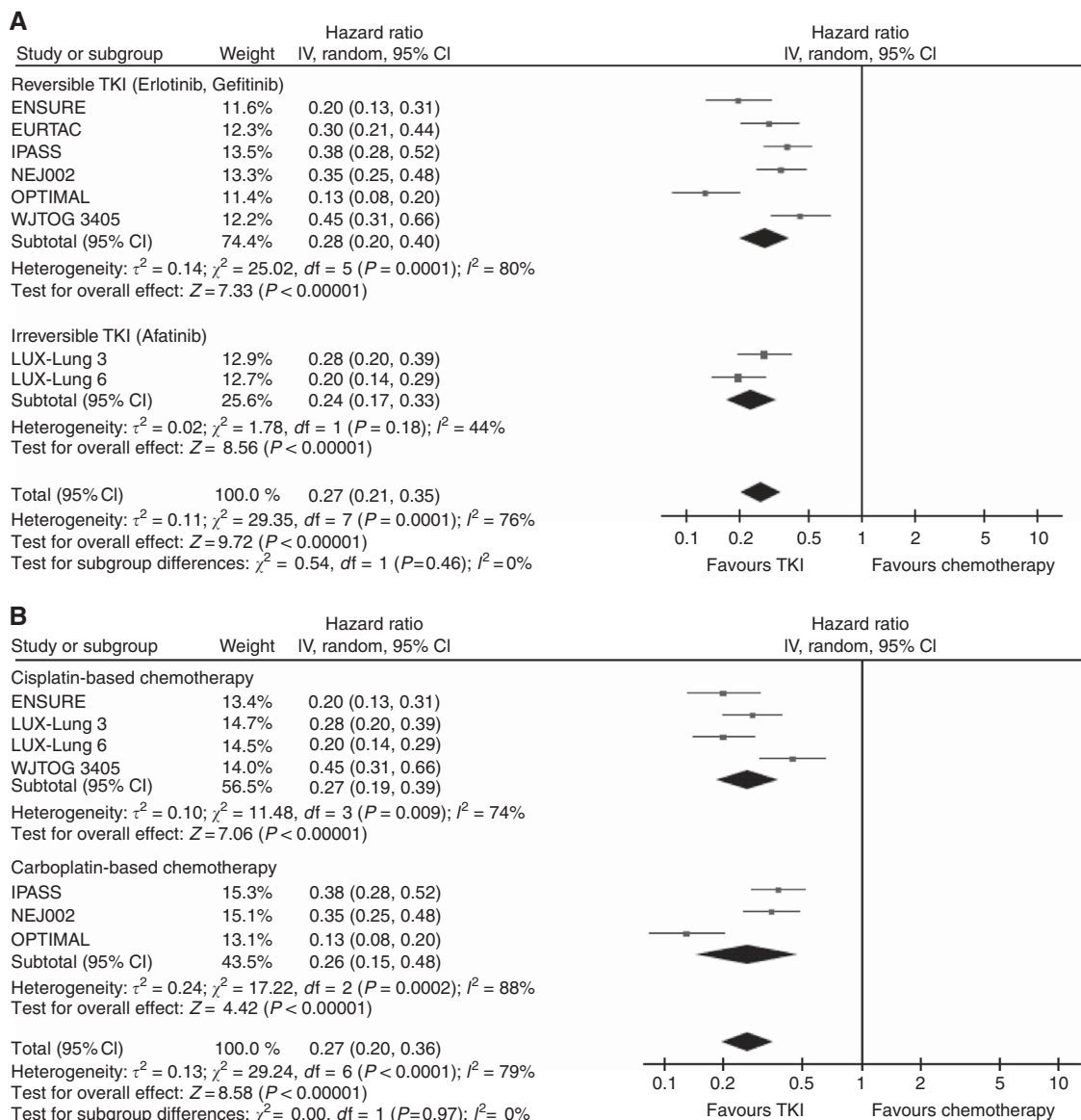


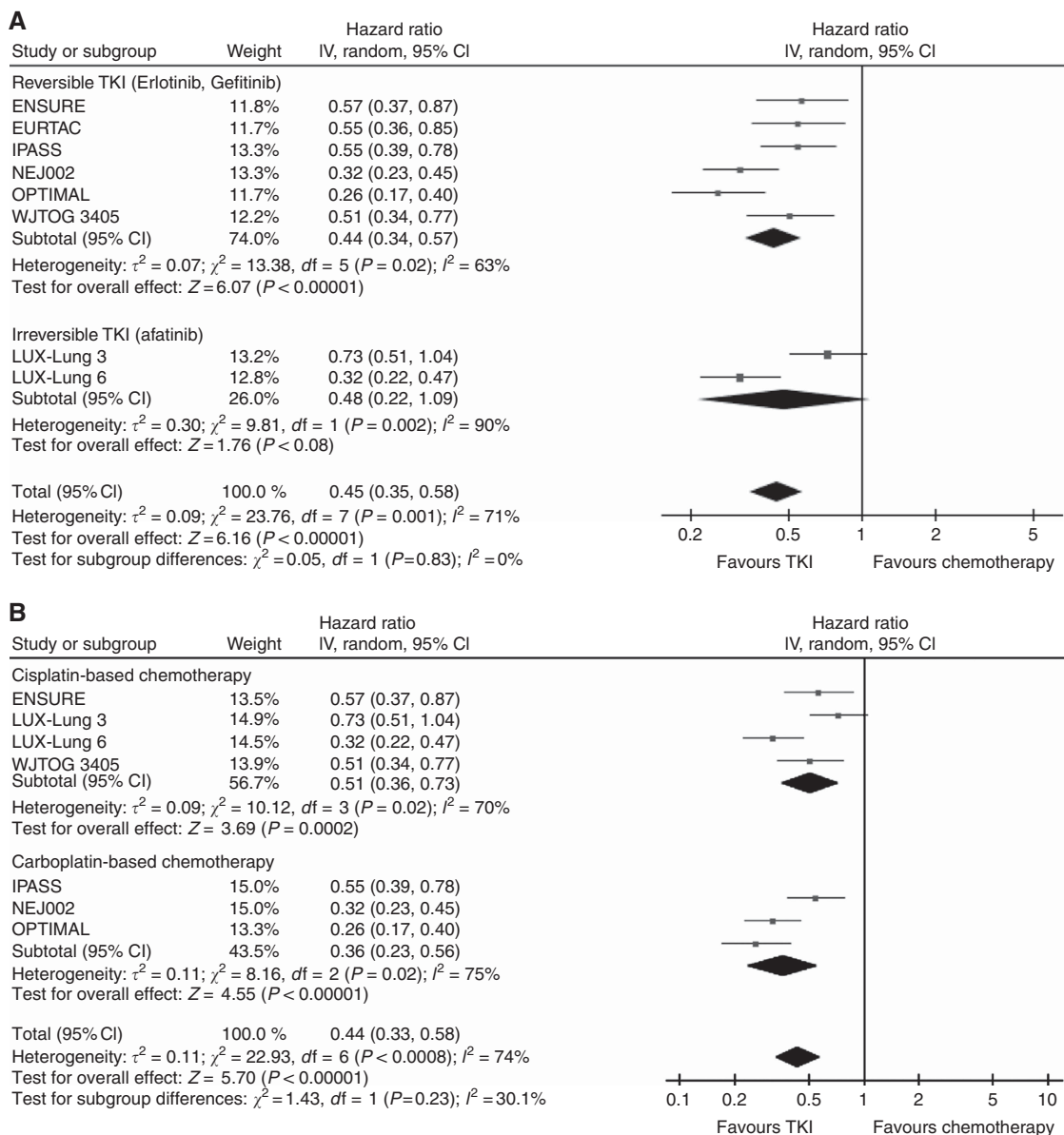
Figure 3. Progression-free survival analysis in exon 19 deletion tumours. (A) PFS analysis in exon 19 deletion tumours receiving reversible and irreversible TKIs. Pooled analysis showed significant PFS benefits in both reversible and irreversible TKIs. (B) PFS analysis in exon 19 deletion tumours receiving cisplatin- and carboplatin-based chemotherapy. Pooled analysis showed significant PFS benefit towards TKI treatment in both cisplatin- and carboplatin-based chemotherapy. Squares indicate study-specific HRs (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CI; diamond indicates the summary HR estimate with its 95% CI.

population of mixed EGFR-activating mutations (Lee *et al*, 2013; Haaland *et al*, 2014; Liang *et al*, 2014). Recently, (Yang *et al*, 2014, 2015) reported on the OS benefits of afatinib, an irreversible TKI in patients with pooled data from LUX-lung 3 (Sequist *et al*, 2013) and 6 (Wu *et al*, 2014). Although afatinib is theoretically more effective in inhibiting EGFR signalling than reversible TKIs by forming permanent covalent bonds and irreversibly inhibiting ATP binding at the tyrosine kinase domain (Kosaka *et al*, 2011), no RCT and meta-analysis has shown that afatinib is superior to gefitinib or erlotinib in OS benefit. The present meta-analysis incorporates not only RCTs of afatinib but also other currently updated RCTs, including reversible TKIs like gefitinib and erlotinib. Our study reveals significant OS benefits of TKI treatment in patients with exon 19 deletions (HR: 0.72, 95% CI: 0.60–0.88) but not in those with L858R (HR: 1.15, 95% CI: 0.95–1.39).

Patients with exon 19 deletions and L858R are separated in this analysis in view of their differing nature, based on previous literature (Sekine *et al*, 2012; Kato *et al*, 2014; Lu *et al*, 2014;

Skrickova *et al*, 2014; Wang *et al*, 2014; Ichihara *et al*, 2015). This study makes it possible to indirectly compare the efficacy of reversible and irreversible TKIs despite head-to-head RCTs are lacking in such patients. In this study, reversible TKIs demonstrate marginal OS benefits over conventional chemotherapy (HR: 0.84, 95% CI: 0.69–1.02), which is the first to be seen in such a large-scale meta-analysis. In addition, subgroup analysis of comparator chemotherapy discloses consistent OS benefit of TKI treatment irrespective of cisplatin- or carboplatin-based chemotherapy (HR: 0.68, 95% CI: 0.57–0.83). On the basis of indirect comparison, the findings imply that both irreversible and reversible TKI treatments are associated with OS benefits in patients with exon 19 deletions. In order to compare the efficacy of irreversible and reversible TKIs, further head-to-head study, such as LUX-lung 7 (ClinicalTrials.gov Identifier NCT01466660) and ARCHER 1050 (ClinicalTrials.gov Identifier NCT01774721) are currently ongoing.

On the other hand, both irreversible and reversible TKIs are not associated with OS benefits in patients with L858R (HR: 1.15, 95%



**Figure 4. Progression-free survival analysis in L858R tumours. (A)** PFS analysis in L858R tumours receiving reversible and irreversible TKIs. Pooled analysis showed significant PFS benefit only with reversible TKIs. **(B)** PFS analysis in L858R tumours receiving cisplatin- and carboplatin-based chemotherapy. Pooled analysis showed significant PFS benefit towards TKI treatment in both cisplatin- and carboplatin-based chemotherapy. Squares indicate study-specific HRs (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CI; diamond indicates the summary HR estimate with its 95% CI.

CI: 0.95–1.39), even with evident PFS benefits (HR: 0.45, 95% CI: 0.35–0.58). This study adds updated WJTOG3405 and ENSURE trials, and consistent PFS benefit parallels previous literature in patients with L858R (Wang *et al*, 2014). Furthermore, subgroup analysis of comparator chemotherapy even suggests a trend in favor of chemotherapy (HR: 1.18, 95% CI: 0.94–1.48), suggesting that first-line TKI may reduce sensitivity of chemotherapy in these patients, as proposed recently in a non-selection population (Zeng *et al*, 2014). Interestingly, in the subgroup analysis of PFS in patients with L858R, irreversible TKI demonstrates only marginal PFS benefit (HR: 0.48, 95% CI: 0.22–1.09). The major impact may be because of the superior comparator chemotherapy of cisplatin/pemetrexed in lung adenocarcinoma (Scagliotti *et al*, 2008).

In view of PFS in patients with exon 19 deletions, both reversible and irreversible TKIs are associated with significant benefits over cisplatin- or carboplatin-based chemotherapy (HR: 0.27, 95% CI: 0.21–0.35). This also parallels the results of recent

meta-analysis (Zhang *et al*, 2014). Updated WJTOG3405 and ENSURE trials are incorporated and subgroup analysis towards comparator chemotherapy shows no difference in various platinum-backbone combinations. Response towards TKI and platinum-based chemotherapy suggests that exon 19 deletions and L858R, though both are EGFR-activating mutations, have different disease nature towards treatment. This may be partly explained by a recent *in vitro* study (Furuyama *et al*, 2013), which reveals that EGFR-activating mutations have different sensitivities to gefitinib, erlotinib, and afatinib. A pre-clinical study also shows different acquired-resistance patterns of TKIs (Cross *et al*, 2014), even though a prospective re-biopsy protocol among patients with different EGFR-mutation who acquired resistance yields a similar presence of T790M mutation (Oxnard *et al*, 2011).

The L858R may form a complex with other uncommon mutations, such as G719S, which may affect hypersensitivity to TKIs (Chou *et al*, 2005; Mitsudomi and Yatabe, 2007; Wu *et al*,

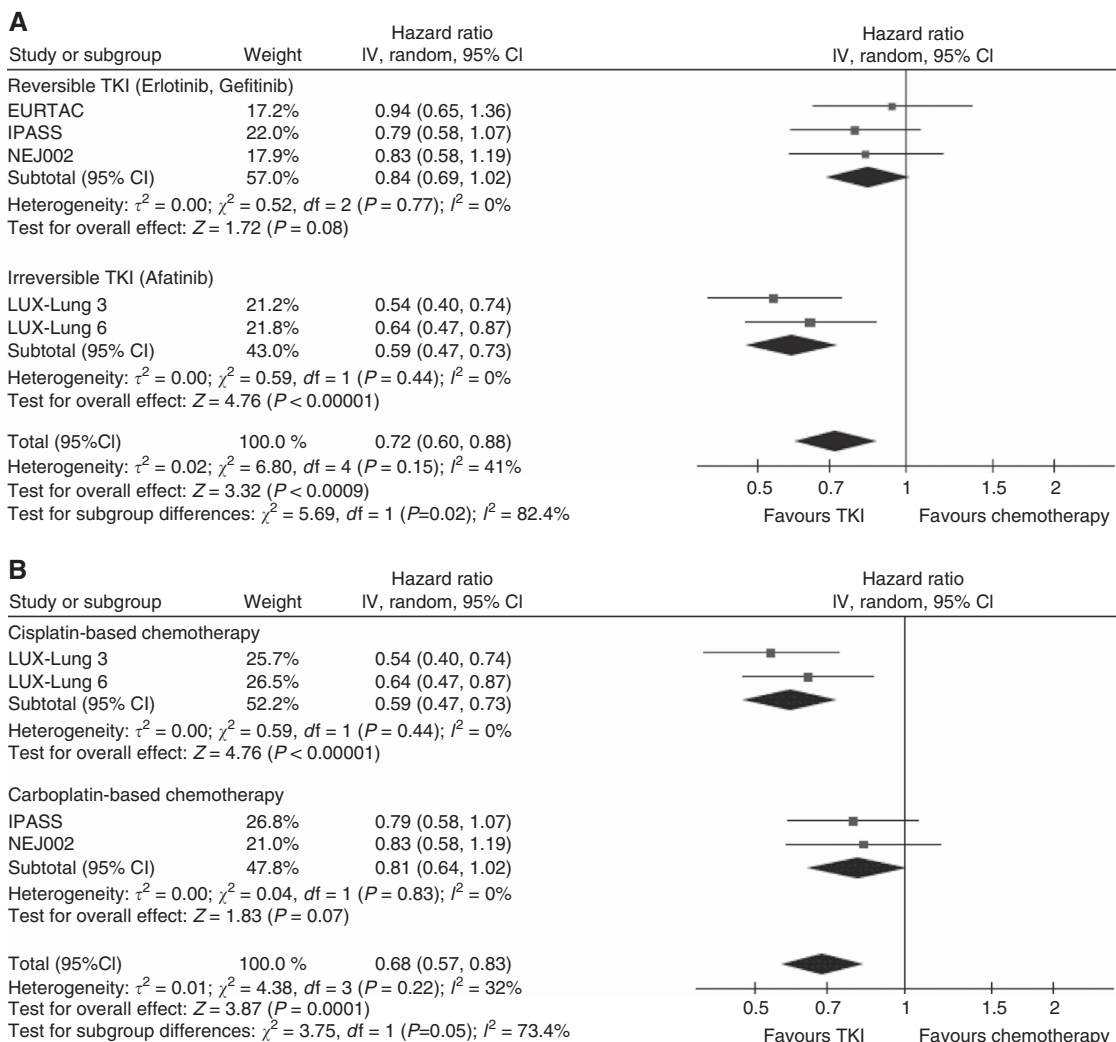


Figure 5. Overall survival analysis in exon 19 deletion tumours. (A) OS analysis in exon 19 deletion tumours receiving reversible and irreversible TKIs. Pooled analysis showed significant OS benefits only with irreversible TKIs. (B) OS analysis in exon 19 deletion tumours receiving cisplatin- and carboplatin-based chemotherapy. Pooled analysis showed significant OS benefit towards TKI treatment in cisplatin-based chemotherapy only. Squares indicate study-specific HRs (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CI; diamond indicates the summary HR estimate with its 95% CI.

2008; Hata *et al*, 2010). Although the mechanism of more favourable efficacy of exon 19 deletions compared with L858R is still not well understood, they should be regarded as different diseases and clinical trials should report corresponding outcomes to individual EGFR mutations. Current guidelines put them into one category and suggest TKI treatment in both diseases, which is far from the aim of precision medicine in cancer treatment.

Nonetheless, this study had some limitations. First, the available clinical parameters, such as the HRs of PFS and OS in the subgroup of patients of several RCTs, were pooled together. This may compromise the evidence level owing to some differences in trial design, comparator choice, inclusion criteria, and reporting standards (Sebastian *et al*, 2014). Second, the OS would be confounded by the high proportion of patients crossing over into the alternative treatment and our trial was underpowered for assessment of such effect. From 39% to 95%, the patients allocated to chemotherapy were crossover-to-reversible TKIs (Mok *et al*, 2009; Maemondo *et al*, 2010; Inoue *et al*, 2013) and only LUX-lung 3 and 6 discretely reported 75% and 53% vs 74% and 61% of crossover-to-reversible TKIs but not afatinib (0–11%; Yang *et al*, 2014). The crossover in RCTs powered for OS could not be assessed in view of exon 19 deletions and L858R. This is because

the proportion of crossover is not reported separately for these activating mutations in trials regarding reversible TKIs. Third, this study attempted to address the OS difference in terms of comparator chemotherapy, but only four trials are eligible. The cisplatin-based chemotherapy is exactly paired with irreversible TKI, whereas carboplatin-based regimen is paired with reversible TKIs, which makes the interpretation of the OS difficult. Last, gefitinib and erlotinib are pooled in one category as reversible TKIs to overcome the problem of small number size of each drug. Previous literature indicates similar efficacy between these drugs (Gao *et al*, 2012; Yoshida *et al*, 2013; Katakami *et al*, 2014), but there is no first-line RCT for head-to-head comparison.

**CONCLUSIONS**

Accumulating evidence suggests that exon 19 deletions and L858R are two different disease entities. Therapeutic strategies should differ when treating lung adenocarcinoma harbouring exon 19 deletions or L858R mutations. This study reveals that in patients with advanced NSCLC harbouring exon 19 deletions, both reversible and irreversible TKIs are associated with better OS

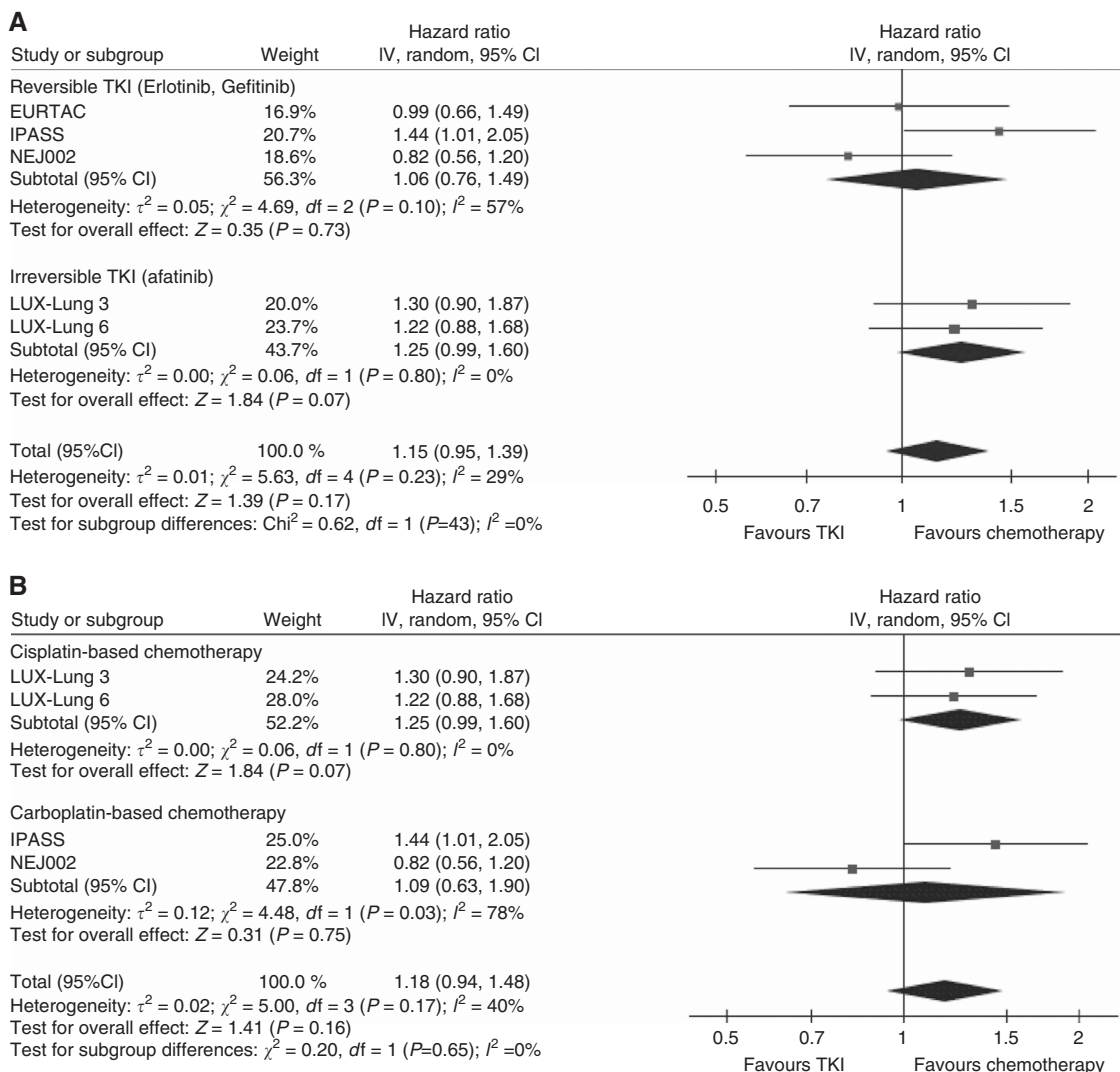


Figure 6. Overall survival analysis in L858R tumours. (A) OS analysis in L858R tumours receiving reversible and irreversible TKIs. Pooled analysis showed no OS benefits with TKIs. (B) OS analysis in L858R tumours receiving cisplatin- and carboplatin-based chemotherapy. Pooled analysis showed no OS benefits towards TKI treatment in both cisplatin- and carboplatin-based chemotherapy. Squares indicate study-specific HRs (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CI; diamond indicates the summary HR estimate with its 95% CI.

| Table 3. Summary of finding |                                       |                                       |                                   |                                   |                                   |
|-----------------------------|---------------------------------------|---------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Outcome                     | EGFR mutation                         | Subgroup                              | Studies                           | Statistical method                | Effect estimate                   |
| PFS                         | Deletion 19                           | Overall                               | 8                                 | Hazard ratio (IV, random, 95% CI) | 0.27 (0.21–0.35)                  |
|                             |                                       | Reversible TKI (erlotinib, gefitinib) | 6                                 | Hazard ratio (IV, random, 95% CI) | 0.28 (0.20–0.40)                  |
|                             |                                       | Irreversible TKI (afatinib)           | 2                                 | Hazard ratio (IV, random, 95% CI) | 0.24 (0.17–0.33)                  |
|                             |                                       | TKI vs cisplatin-based chemotherapy   | 4                                 | Hazard ratio (IV, random, 95% CI) | 0.27 (0.19–0.39)                  |
|                             |                                       | TKI vs carboplatin-based chemotherapy | 3                                 | Hazard ratio (IV, random, 95% CI) | 0.26 (0.15–0.48)                  |
|                             |                                       | L858R                                 | Overall                           | 8                                 | Hazard ratio (IV, random, 95% CI) |
|                             | Reversible TKI (erlotinib, gefitinib) | 6                                     | Hazard ratio (IV, random, 95% CI) | 0.44 (0.34–0.57)                  |                                   |
|                             | Irreversible TKI (afatinib)           | 2                                     | Hazard ratio (IV, random, 95% CI) | 0.48 (0.22–1.09)                  |                                   |
|                             | TKI vs cisplatin-based chemotherapy   | 4                                     | Hazard ratio (IV, random, 95% CI) | 0.51 (0.36–0.73)                  |                                   |
|                             | TKI vs carboplatin-based chemotherapy | 3                                     | Hazard ratio (IV, random, 95% CI) | 0.36 (0.23–0.56)                  |                                   |
| OS                          | Deletion 19                           | Overall                               | 5                                 | Hazard ratio (IV, random, 95% CI) | 0.72 (0.60–0.88)                  |
|                             |                                       | Reversible TKI (erlotinib, gefitinib) | 3                                 | Hazard ratio (IV, random, 95% CI) | 0.84 (0.69–1.02)                  |
|                             |                                       | Irreversible TKI (afatinib)           | 2                                 | Hazard ratio (IV, random, 95% CI) | 0.59 (0.47–0.73)                  |
|                             |                                       | TKI vs cisplatin-based chemotherapy   | 2                                 | Hazard ratio (IV, random, 95% CI) | 0.59 (0.47–0.73)                  |
|                             |                                       | TKI vs carboplatin-based chemotherapy | 2                                 | Hazard ratio (IV, random, 95% CI) | 0.81 (0.64–1.02)                  |
|                             |                                       | L858R                                 | Overall                           | 5                                 | Hazard ratio (IV, random, 95% CI) |
|                             | Reversible TKI (erlotinib, gefitinib) | 3                                     | Hazard ratio (IV, random, 95% CI) | 1.06 (0.76–1.49)                  |                                   |
|                             | Irreversible TKI (afatinib)           | 2                                     | Hazard ratio (IV, random, 95% CI) | 1.25 (0.99–1.60)                  |                                   |
|                             | TKI vs cisplatin-based chemotherapy   | 2                                     | Hazard ratio (IV, random, 95% CI) | 1.25 (0.99–1.60)                  |                                   |
|                             | TKI vs carboplatin-based chemotherapy | 2                                     | Hazard ratio (IV, random, 95% CI) | 1.09 (0.69–1.90)                  |                                   |

Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; IV = inverse variance; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.



compared with conventional chemotherapy. Future clinical trials should take exon 19 deletions and L858R as distinct disease entities and evaluate treatment efficacy separately.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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