Predictive biomarkers for EGFR tyrosine kinase inhibitors in treatment of advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomised controlled trials

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KEY MESSAGES

1. Of the four potential predictive biomarkers studied, epidermal growth factor receptor (*EGFR*) gene mutations are the most powerful predictor of the efficacy of EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer. They should be tested prior to treatment to select patients who are more likely to benefit from EGFR tyrosine kinase inhibitors.
2. Chemotherapy is a better choice than EGFR tyrosine kinase inhibitors in patients with wild-type *EGFR*.

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Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related mortality in Hong Kong. Approximately 85% of patients with lung cancer have a histological diagnosis of non–small-cell lung cancer (NSCLC). Two thirds of patients with NSCLC are at an advanced stage when diagnosed, and their average survival is 8 to 10 months.

Two specific epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, have been approved for second- or higher-line treatment for advanced NSCLC following failure of prior chemotherapy.[1] Erlotinib has been used as maintenance therapy after four cycles of platinum-based first-line chemotherapy.[2] Both gefitinib and erlotinib are effective as first-line treatment, and gefitinib is effective as maintenance therapy.[3] Nonetheless, among unselected patients with advanced NSCLC, the overall benefit of EGFR-TKIs is limited, possibly because only a subset of recipients responds to the treatment (objective response rate: about 10%). This, together with the risk of adverse events and ensuing costs, prompts us to identify predictors for treatment benefit to help clinical oncologists select patients who are most likely to benefit from EGFR TKIs.

As EGFR TKIs act on the EGFR pathway, molecular alterations along this pathway, such as *EGFR* mutations, high *EGFR* gene copy number, high EGFR protein expression, and *KRAS* mutations, have been indicated as potential predictive biomarkers for treatment by many single-arm studies of patients treated with EGFR TKIs. However, the association between biomarker status and outcome in patients treated with EGFR TKIs may be just a 'prognostic' effect rather than a 'predictive' one. To determine whether a biomarker is predictive of benefits from EGFR TKIs, the efficacy of EGFR TKIs is assessed with stratified (or subgroup) analysis according to biomarker status (eg mutant versus wild-type *EGFR*), which allows testing for the treatment-by-biomarker status interaction.

Previous randomised controlled trials were often statistically underpowered to detect the treatment-by-biomarker status interaction owing to the voluntary nature of tumour tissue donation, insufficient tumour tissues for biomarker testing, or undeterminable testing results. We performed this systematic review and meta-analysis to comprehensively summarise the current best evidence on the predictive values of four biomarkers for EGFR TKIs treatment in patients with advanced NSCLC.

Methods

The MEDLINE, EMBASE, CENTRAL, Chinese Biomedical Database, and Wan Fang Digital Journals databases were searched using the following keywords: 'non-small cell lung cancer', 'tyrosine-kinase inhibitor', 'gefitinib', 'erlotinib', 'biomarker', 'EGFR', and 'KRAS'. The search was limited to human studies, without restriction on the language of publication. Eligible studies were retrieved, and their bibliographies were checked for further relevant publications. If the same patient population was used in several studies, only the largest one or the one

with complete data was used to avoid overlapping. The others were used as supplementary information to obtain relevant data.

Inclusion criteria were: (1) population: patients with locally advanced or metastatic NSCLC; (2) intervention arm: EGFR-TKIs as a monotherapy or in combination with other agents; (3) control arm: chemotherapy, placebo, or no treatment; (4) outcome: progression-free survival, overall survival, and/or objective response; (5) study design: randomised controlled trial; and (6) stratified (or subgroup) analysis by biomarkers: *EGFR* mutations, *EGFR* gene copy number, EGFR protein expression, and/or *KRAS* mutations as detected by analysis of tumour samples.

Data extraction was performed independently by two researchers. Disagreements were resolved by discussion. Unsettled disagreements were settled by a third knowledgeable arbiter whose opinions were final. The data collected included: first author's name, year of publication, study design, number of patients included, number of patients stratified by relevant biomarker status, baseline characteristics of patients in different groups, methods for detection of biomarkers status, previous treatment protocols, study treatment protocols, response criteria, progression-free survival, overall survival, and objective response rate. Clinical outcome variables were extracted according to biomarker and EGFR TKIs treatment status. The quality of included studies was assessed using the Jadad score, a 5-point study quality assessment instrument.[4] The assessment was performed independently by two researchers, with differences resolved by consensus.

The primary outcome was progression-free survival, defined as the period from the start of treatment to disease progression or death from any cause before disease progression. The secondary outcomes included overall survival, defined as the period from the start of treatment to death from any cause; and objective response, defined as the sum of complete and partial responses.

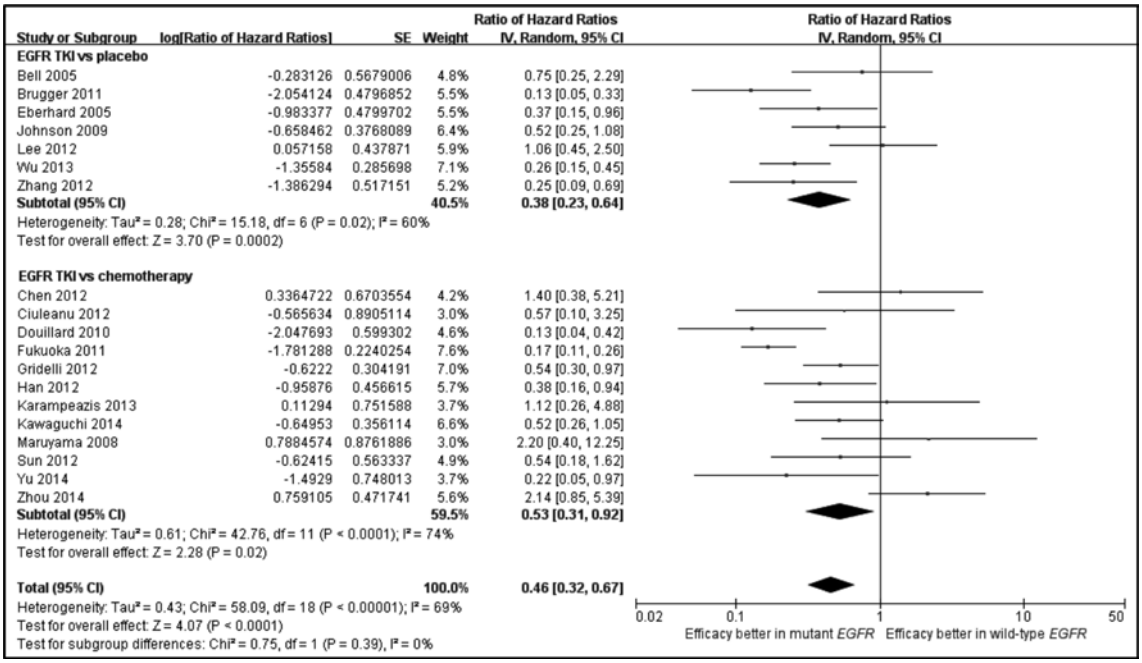
Treatment effects on progression-free survival or overall survival were measured by hazard ratios (HRs) and 95% confidence intervals (CIs). Treatment effects on objective response were expressed as risk ratios (RRs) and 95% CIs. To determine whether a biomarker was predictive of the treatment benefit of EGFR TKIs on an outcome, we calculated the ratio of HRs or RRs and 95% CIs, which indicate the treatment-by-biomarker status interaction, based on the HRs (95% CIs) or RRs (95% CIs) in the biomarker-positive and biomarker-negative subgroups.[5] A ratio of HRs or RRs equal to 1 suggests that the treatment effects of EGFR TKIs are the same in both subgroups. A ratio of HRs <1 means that biomarker-positive patients benefit more from EGFR TKIs than do biomarker-negative patients in terms of progression-free survival or overall survival. Conversely, a ratio of RRs <1 means that biomarker-positive patients benefit less from EGFR TKIs than do biomarker-negative patients in terms of objective response. If appropriate, the ratios of HRs or RRs from different studies were combined for each outcome using a random-effect model. Heterogeneity among studies was assessed by Cochran's *Q*-test and the I^2 statistic. A P value of ≤0.10 for the *Q*-test or an I^2 of >50% is suggestive of substantial between-study heterogeneity. Subgroup analyses according to comparator in trials (placebo or chemotherapy) were conducted to explore sources of heterogeneity. Sensitivity analyses were performed to determine whether study quality affected the final results. Egger's funnel plots were used to assess the possibility of publication bias, as appropriate. All meta-analyses were performed with Review Manager, Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

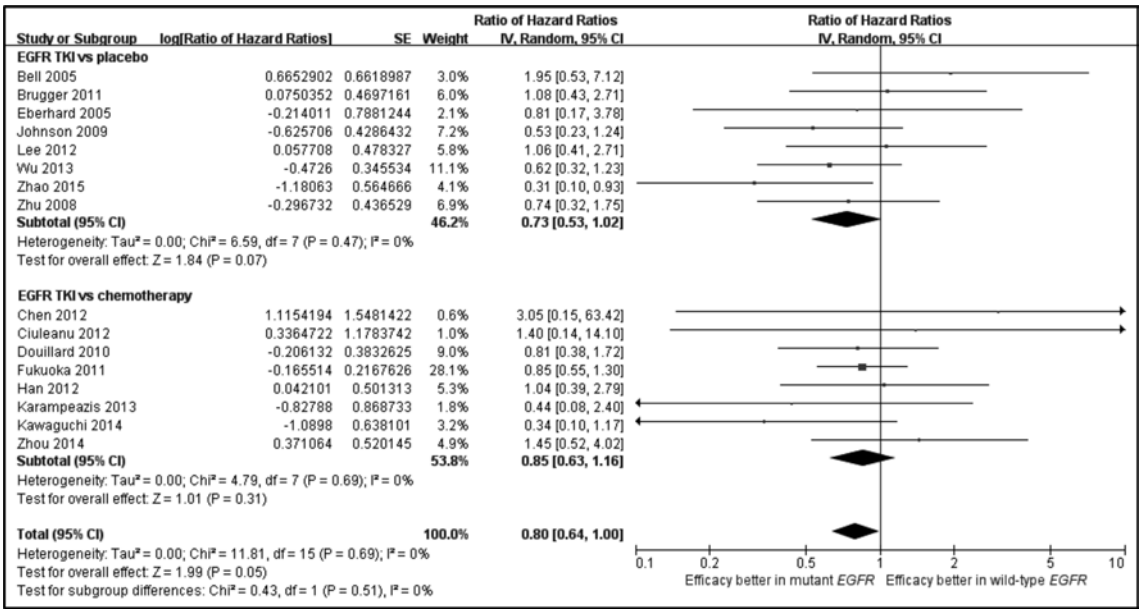
Of the 28 studies included, 21 were on *EGFR* mutations, 12 were on *EGFR* gene copy number, 9 were on EGFR protein expression, and 7 were on *KRAS* mutations. Of the studies, 16 were of high quality, with Jadad scores of 3 to 5, and the rest were of low quality, with Jadad scores of 0 to 2. The number of patients included in analyses of different biomarkers varied from 1872 to 4343. Compared with placebo, EGFR TKIs are effective at increasing progression-free and overall survival, although the effect size is smaller for overall survival than for progression-free survival. EGFR TKIs are comparable to chemotherapy in prolonging both progression-free and overall survival, except among the *EGFR* mutation group, in which EGFR TKIs seem to be much more effective than chemotherapy at prolonging progression-free survival.

For progression-free survival, the summary HRs were 0.46 (95% CI=0.32-0.67, P<0.01, Fig a) for *EGFR* mutations (versus wild-type), 0.72 (95% CI=0.52-0.99, P=0.04) for *EGFR* gene copy number gain (versus no gain), 0.99 (95% CI=0.79-1.24, P=0.92) for EGFR protein expression (versus negative), and 1.40 (95% CI=1.07-1.84, P=0.02) for *KRAS* mutations (versus wild-type). For overall survival, the summary HRs for the four biomarkers were 0.80 (95% CI=0.64-1.00, P=0.05, Fig b), 0.92 (95% CI=0.69-1.23, P=0.57), 0.86 (95% CI=0.70-1.05, P=0.14), and 1.59 (95% CI=1.00-2.54, P=0.05), respectively. For objective response, the summary RRs for the four biomarkers were 3.76 (95% CI=1.91-7.41, P<0.01, Fig c), 0.76 (95% CI=0.32-1.82, P=0.54), 0.40 (95% CI=0.11-1.48, P=0.17), and 0.03 (95% CI=0.00-5.43, P=0.19), respectively. These results indicated that an interaction may exist between EGFR TKIs treatment and *EGFR* mutations (all three

(a)



(b)



(c)

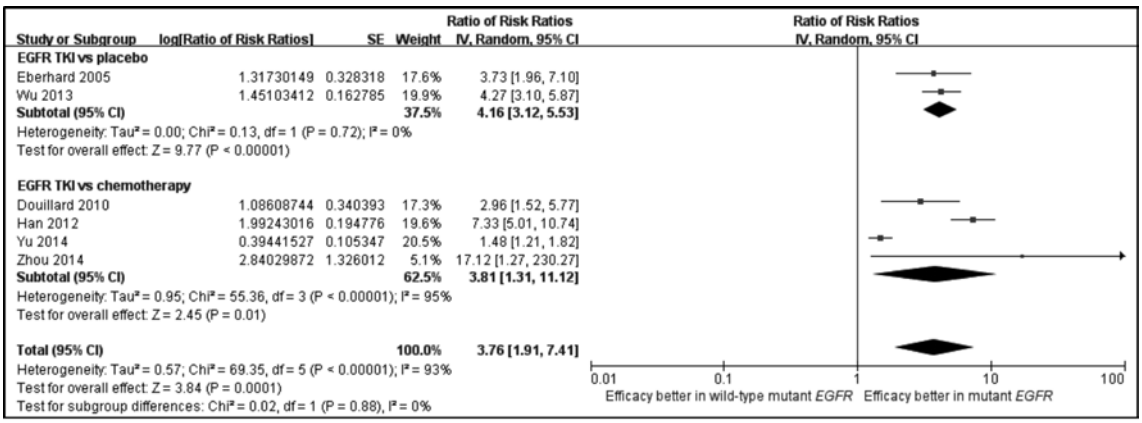


FIG. Interaction between epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) treatment and *EGFR* mutations in terms of (a) progression-free survival, (b) overall survival, and (c) objective response.

outcomes), *EGFR* gene copy number (progression-free survival), and *KRAS* mutations (progression-free survival and overall survival).

Sensitivity analyses conducted by removing studies of low quality did not change the results of the meta-analyses reported above, although the 95% CIs of some interactions tended to be wider owing to the decreased number of studies. Publication bias did not seem to be present.

Discussion

EGFR mutations, *EGFR* gene copy number gain, and *KRAS* mutations are predictive of the treatment effects of EGFR TKIs in advanced NSCLC, with EGFR mutations being the most powerful predictor. However, it is unclear whether the interactions between treatment and *EGFR* gene copy number gain, or between treatment and *KRAS* mutations are independent or mediated by association with *EGFR* mutations. There is no convincing evidence to support the predictive value of EGFR protein expression.

This study has two implications for the decision to use EGFR TKIs to treat advanced NSCLC. First, *EGFR* mutations and possibly *EGFR* gene copy number gain and *KRAS* mutations can help to determine which patients are likely to benefit from EGFR TKIs treatment. Second, chemotherapy is cheaper and causes fewer side effects and thus is generally a better choice, except in patients with *EGFR* mutations in whom EGFR TKIs are a better option. Our findings provide the most comprehensive evidence available for recommendations about current practice guidelines on testing for EGFR mutations.

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