Erlotinib and pemetrexed as maintenance therapy for advanced non-small-cell lung cancer: a systematic review and indirect comparison
Qi WX, Tang LN, He AN, Shen Z, Lin F, Yao Y

CRD summary
The review concluded that maintenance treatment with erlotinib or pemetrexed had clinical advantages over treatment with placebo or observation in patients with advanced non-small cell lung cancer in terms of overall and progression-free survival. The authors’ conclusions may not be reliable due to unexplained heterogeneity, potential bias in the review process and limited evidence.

Authors’ objectives
To compare the effectiveness of pemetrexed with erlotinib as maintenance therapy for advanced non-small cell lung cancer.

Searching
PubMed, EMBASE and The Cochrane Library were searched from 1980 to October 2011 for relevant studies; limited search terms were reported. Reference lists of retrieved studies or relevant systematic reviews and abstracts from relevant conferences were searched.

Study selection
Randomised controlled trials (RCTs) of patients with advanced non-small cell lung cancer with sufficient data for extraction were eligible for the review. Treatment arms had to include single agent erlotinib or pemetrexed compared to placebo or observation. Outcomes of interest were overall survival and progression-free survival. Studies were excluded if they reported quality of life or economic analysis only or if they were pharmacokinetic studies.

In the included studies, median patient age ranged from 60 to 63 years and the proportion of men ranged from 56% to 75% (where reported). Most patients were ethically white. Patient populations had predominantly stage IV disease with good performance status. Trials compared either erlotinib or pemetrexed mostly against placebo; one trial had an observation control group. Doses of erlotinib were 150mg per day taken orally. Doses of pemetrexed were 500mg per metre squared administered intravenously every three weeks.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
Studies were assessed for quality using the five-point Jadad scale; criteria included randomisation, blinding and description of withdrawals and dropouts.

The authors did not state how many reviewers assessed studies for quality.

Data extraction
Data were extracted on outcomes to enable calculation of hazard ratios (HRs) and standard errors. Where necessary, standard errors were estimated according to the method recommended by the Cochrane Handbook and survival outcomes were read from the graphs by the Parmar method. Where necessary, authors were contacted for clarification.

Two reviewers independently extracted data. Disagreements resolved by consensus.

Methods of synthesis
The results of the studies were pooled in meta-analyses and summary effect hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using a fixed-effect model; where significant heterogeneity was identified, a random-effects model was used. Heterogeneity was assessed with the $X^2$ statistic and the $I^2$ value ($p<0.05$ and $I^2>50\%$ were the cutoffs for significance). Sources of heterogeneity were explored using subgroup stratification analysis. Comparisons between pemetrexed and erlotinib were made indirectly using the Bucher indirect comparison method.
Results of the review
Five RCTs (3,480 patients) were included in the review: three full publications and two conference abstracts. They were all large phase III multicentre trials with explicit inclusion and exclusion criteria. Only one of the five trials was blinded. One trial had a Jadad score of 5 and four trials had a Jadad score of 3.

**Overall survival:** Compared with placebo or observation, erlotinib (HR 0.90, 95% CI 0.83 to 0.98; $I^2=42\%$; three trials) and pemetrexed (HR 0.79, 95% CI 0.65 to 0.95; one trial) were associated with a significant increase in overall survival. An indirect comparison between erlotinib and pemetrexed indicated that there was no evidence of a significant difference in overall survival (HR 0.88, 95% CI 0.71 to 1.08).

**Progression-free survival:** Compared with placebo or observation, erlotinib (HR 0.77, 95% CI 0.70 to 0.84; $I^2=57\%$; two trials) and pemetrexed (HR 0.55, 95% CI 0.48 to 0.64; $I^2=62\%$; two trials) were associated with a significant increase in progression-free survival. An indirect comparison between erlotinib and pemetrexed indicated that patients who took pemetrexed were less likely to progress than those who took erlotinib (HR 0.71, 95% CI 0.60 to 0.85).

**Adverse events:** The frequency of grade 3 or 4 adverse events was 16% in patients treated with pemetrexed compared to a range of 9% to 14% in patients treated with erlotinib.

Authors’ conclusions
Maintenance treatment with erlotinib or pemetrexed had clinical advantages over treatment with placebo or observation in patients with advanced non-small cell lung cancer in terms of overall and progression-free survival.

CRD commentary
The review addressed a clear research question supported by appropriate inclusion criteria. Relevant sources, which included conference abstracts, were searched to identify studies, which minimised the chance of publication bias. Appropriate methods were used to extract data. The authors did not state how many reviewers selected studies or performed quality assessments so reviewer error and bias as a result of these processes could not be ruled out. A valid tool was used for quality assessment. The authors considered the few included studies were of high quality but did not report individual quality characteristics.

Synthesis of the studies in meta-analyses and assessment of heterogeneity were appropriate. However, the authors stated that a random-effects model would be used where significant heterogeneity was identified; for these analyses, the summary effect measures were calculated with a fixed-effect model. There were too few studies to explore the sources of the considerable heterogeneity identified in some of the analyses. The trials compared one or other of the two treatments of interest with either placebo or observation and indirect comparisons were appropriately made between erlotinib and pemetrexed to assess their relative effectiveness and safety.

The authors’ conclusions may not be reliable due to unexplained heterogeneity, potential bias in the review process and limited evidence.

Implications of the review for practice and research
**Practice:** The authors suggested that maintenance therapy for patients with non-small cell lung cancer should be individualised according to whether they had non squamous lung cancer or have epidermal growth factor receptor-positive mutation. Further research would be required to guide treatment.

**Research:** The authors stated that a large phase III RCT was needed to compare pemetrexed in non squamous patients with erlotinib in patients with epidermal growth factor receptor-positive mutation as maintenance therapy in advanced non-small cell lung cancer. More RCTs were required to confirm the results of the review.

Funding
National Natural Science Foundation of China; Science and Technology Commission of Shanghai.

Bibliographic details
Qi WX, Tang LN, He AN, Shen Z, Lin F, Yao Y. Erlotinib and pemetrexed as maintenance therapy for advanced non-small-cell lung cancer: a systematic review and indirect comparison. Current Medical Research and Opinion 2012;
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.