Activating somatic mutations in the epidermal growth factor receptor (EGFR) gene define a distinct subgroup of patients with advanced non-small-cell lung cancer (NSCLC), among whom increased responses to EGFR tyrosine-kinase inhibitors (EGFR-TKIs) have been reported [1–3].

Paz-Ares et al. [4] present a weighted pooled analysis of median progression-free survival (PFS) among patients with EGFR mutation-positive advanced NSCLC who had received treatment with erlotinib, gefitinib or chemotherapy. This analysis pooled individual treatment arm median PFS values in a cross-study comparison based on a literature review. Such an approach, unlike a standard meta-analysis of relative treatment effects from randomized controlled trials (RCT), uses only single arm information and the protection of a randomization procedure is lost, potentially introducing bias due to differences in study populations between treatments. The relative efficacies of erlotinib, gefitinib and chemotherapy can only be reliably compared in an RCT or a robust meta-analysis or mixed treatment comparison of relative treatment effects such as hazard ratios from RCTs [5–7].

It is important to note the lack of similarity between the studies included in the review, which encompass prospective and retrospective studies, randomized and single arm studies, large and small studies, with different populations and lines of therapy. Such heterogeneity could lead to subsequent potential bias in the results, and caution should be exercised when interpreting these data. Differences in the distribution of EGFR mutation types between studies may also have biased PFS results; multivariate analysis has indicated that the presence of the L858R mutation significantly correlates with lower PFS versus exon 19 deletions in patients treated with erlotinib (hazard ratio 1.92; 95% confidence interval, 1.19–3.10; \( P = 0.02 \)) [8]. Further influence may have been exerted by the different EGFR mutation assay methods and the definition of EGFR mutation-positive patients employed across the studies. The pooled median PFS value reported for erlotinib by Paz Ares et al. is heavily weighted by the inclusion of one single-arm study which contributed approximately 60% (217/365) of the erlotinib-treated patients [8]; however, this population may not be comparable to the studies of other treatments.

When comparing the relative efficacies of gefitinib and erlotinib versus chemotherapy in patients with EGFR mutation-positive tumours, it is important to note that to date, there is only one recently reported Phase III RCT of erlotinib versus doublet chemotherapy in this patient subgroup [9] and this was not included in Paz-Ares’ analysis; further prospective studies are awaited to confirm the role for erlotinib in this setting. Conversely, four Phase III RCTs have directly compared first-line gefitinib with doublet chemotherapy [3, 10–12], confirming the benefit for gefitinib in patients with EGFR mutation-positive tumours in terms of PFS, response rate, tolerability and health-related quality of life. In June 2009, the European Medicines Agency approved gefitinib for treatment of patients with locally advanced or metastatic NSCLC with activating EGFR mutations.

Paz-Ares et al. chose median PFS/time to progression (TTP) as the efficacy variable in their pooled analysis. Median PFS is a summary statistic that reflects a single time point rather than the true efficacy of a treatment over the whole study. We believe that it would have been more appropriate to choose a relative measure such as hazard ratio. Absolute measures such as medians are highly influenced by patient characteristics, which can vary greatly across studies, particularly in single arm studies from which the majority of the data originate. In addition, PFS and TTP are treated as the same endpoint in the analysis, although TTP may exclude death events when PFS does not. It is also likely that PFS/TTP were not assessed in the same way in all studies and are likely to have been influenced by the frequency and timings of tumour assessment. To help put the PFS data into context, it would have been useful to present other endpoint data (objective response rate, overall survival).

There are a number of other statistical considerations when interpreting Paz Ares et al.’s pooled analysis. As well as differences in patient populations that were not accounted for, the reliability of median PFS estimates can also be strongly influenced by variation in study maturity (the proportion of patients with events). The ‘accuracy intervals’ presented are based on the number of patients, but the number of events is more relevant in defining precision. In addition, the weighted pooled PFS analysis makes assumptions regarding the exponential distribution of PFS data that may not be correct. Finally, the small sample sizes (e.g. only nine chemotherapy studies included) and the large influence that outliers can have on re-sampling technique results detract from the validity of the ‘sensitivity analyses’ performed. Taking into account all of these issues, it is proposed that the medians presented are not directly comparable between treatments and hence the \( P \)-values produced for the treatment comparisons are not statistically appropriate.
In conclusion, this cross-study comparison from Paz Ares et al. does not allow a reliable assessment of the comparative efficacy of erlotinib, gefitinib and chemotherapy in patients with advanced NSCLC with EGFR mutation-positive tumours. Conclusions on the relative efficacy of these agents in the first-line setting will have to wait until results are available from Phase III RCTs comparing all three treatments.

**Conflict of interest**

Claire Watkins is an employee of AstraZeneca and holds stock in AstraZeneca; Yuri Rukazenkov is an employee of AstraZeneca and holds stock in AstraZeneca. We thank Sarah Lewis of Complete Medical Communications for medical writing support funded by AstraZeneca.

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