LUX-Lung: determining the best EGFR inhibitor in NSCLC?

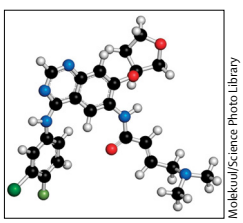
The frequency and characteristics of *EGFR* mutations in patients with non-small-cell lung cancer, and their correlation with outcome in patients receiving tyrosine kinase inhibitors, have been previously reported in the scientific literature.[1] In *The Lancet Oncology*, James Chih-Hsin Yang and colleagues now report overall survival (a secondary endpoint) from two phase 3 trials: LUX-Lung 3 (n=345) and LUX-Lung 6 (n=364). Both trials compared afatinib, a second-generation EGFR tyrosine kinase inhibitor, with platinum-based first-line chemotherapy in patients with lung adenocarcinoma harbouring *EGFR* mutations.[2] In each trial, both in the intention-to-treat population and in patients with tumours harbouring common mutations (exon 19 deletion [del19] or Leu858Arg), the overall survival difference between treatment groups was not found to be statistically significant. This finding was not surprising, and in line with the lack of significant difference in overall survival reported with the first-generation EGFR inhibitors, gefitinib and erlotinib, in the same setting.[3]

However, in both trials, exploratory subgroup analyses showed a statistically significant improvement in overall survival with afatinib in patients with tumours harbouring del19 whereas no overall survival difference was reported in patients with Leu858Arg.[2] Furthermore, in the pooled exploratory analysis based on the combined individual data of patients with tumours harbouring common mutations from both trials, afatinib was associated with a significant overall survival benefit (HR 0·81 [95% CI 0·66–0·99], p=0·037).

Should afatinib be regarded as the only EGFR tyrosine kinase inhibitor associated with a significant overall survival benefit, and in particular the first choice for treating lung adenocarcinoma with del19 mutations? From a methodological point of view, subgroup and post-hoc analyses can be informative, but should be interpreted with caution.[4] Progression-free survival was chosen as the primary endpoint in all trials done in this setting; the investigators of LUX-Lung 3 and LUX-Lung 6, not surprisingly, stated in the trial protocols that the overall survival difference was expected to be masked by treatments received after progression. However, even with no difference in overall survival between treatment groups, median overall survival reported with all the three EGFR inhibitors has never before been reported in advanced non-small-cell lung cancer, emphasising the importance of the results obtained with these drugs in this subpopulation of patients with oncogene-addicted tumours. Crossover was high for afatinib and erlotinib, and very high for gefitinib, making the statistical power for analysis of overall survival very low.[5] Moreover, the finding of an overall survival benefit with afatinib in the pooled analysis and in particular in patients with del19 mutations does not definitely prove that a similar benefit is not produced by gefitinib or erlotinib. For example, if three parallel, randomised trials with a similar design testing the same drug, were conducted, but all three trials had low statistical power, one positive result but two negative results would easily be ascribed to the low power. However, if the three trials were similar but tested different drugs, whether the differences were drug related or simply due to chance cannot be determined.

Apart from chance, other possible explanations might account for the overall survival results obtained with afatinib. The number of patients in LUX-Lung 3 and LUX-Lung 6 trials was larger than the number of patients in trials that investigated gefitinib or erlotinib (additionally, most studies with these EGFR inhibitors were stopped early, after interim analyses), implying a difference in statistical power. Afatinib is also active against HER2 (also known as ERBB2)—the preferred dimerisation partner of EGFR—and through its irreversible, covalent binding leads to longer suppression of receptor kinase activity than with reversible first-generation EGFR inhibitors, because kinase activity is suppressed until new receptors are synthesised.[6] Furthermore, patients randomly assigned to afatinib and receiving further EGFR inhibitors in subsequent treatment lines, thus prolonging the overall exposure to EGFR inhibition, could potentially have produced overall survival benefits. This hypothesis is in agreement with that proposed for reversible EGFR inhibitors.[7]

As emphasised by the investigators themselves, the impressive advantage in overall survival reported in patients with lung adenocarcinoma harbouring del19 mutations strongly suggests that the two most common mutations (del19 and Leu858Arg) represent



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two distinct subclasses of non-small-cell lung cancer. This idea has similarly been suggested by findings from trials of other EGFR inhibitors.[8,9]

Are these data sufficient to address whether afatinib is better than first-generation EGFR inhibitors? Only head-to-head trials can definitively answer this question and LUX-Lung 7 (NCT01466660), a phase 2b randomised trial comparing afatinib with gefitinib for first-line treatment of lung adenocarcinoma with *EGFR* common mutations, should provide the first comparative evidence of efficacy and safety in this setting. In the absence of direct comparisons, for each patient the choice among the available EGFR inhibitors should take into account all the clinically relevant endpoints, including disease control, survival prolongation, tolerability, and quality of life.

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