What phase III trials are needed to improve the treatment of advanced non-small-cell lung cancer?

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Platinum-based doublets are standard treatments for stage IV non-small-cell lung cancer (NSCLC). Several doublets that include new drugs improve survival, but no one regimen is clearly superior to the others, as previously discussed by Scagliotti¹ and Govindan² in *Nature Clinical Practice Oncology*.

Numerous molecular-target-based drugs have been introduced for the treatment of NSCLC, but can they replace or be used as an adjuvant to current therapy, and can they be combined with other chemotherapeutic agents, radiotherapy and/or surgery? We hypothesize that incorporation of novel molecular-target-based therapies into current treatment paradigms will improve outcomes. However, carefully designed clinical trials and translational science will be required to identify the subsets of patients likely to benefit. If these treatment strategies are to be used, we must first answer the following critical questions. First, will patients lacking the target still respond? It is still unclear why responses occur in those lacking the correct molecular target. Second, what expression levels of the target are sufficient for a response, and can we measure the target in a biologically relevant and/or technologically valid way? Third, does the agent inhibit the proposed target at the dose and schedule utilized? Fourth, is the target a critical driving force for cell growth in the tumor type in question?

Various molecular-target-based drugs for advanced NSCLC have been evaluated in randomized controlled trials, but the majority, including a matrix metalloproteinase inhibitor, a protein kinase C inhibitor, and trastuzumab, have yielded negative results.^{3,4} Gefitinib (Iressa®) and erlotinib (Tarceva™) are orally available selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) that exhibit antitumor activity in patients with previously treated advanced NSCLC. However, both drugs failed to show additive or synergistic effects when combined with platinum-based chemotherapy as a first-line treatment for NSCLC. On 17 December 2004,

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AstraZeneca announced the preliminary results of their ISEL (Iressa® Survival Evaluation in Lung Cancer) study of 1,692 patients with advanced recurrent or refractory NSCLC. Unfortunately, gefitinib failed to prolong survival significantly compared with placebo (hazard ratio 0.89, $P=0.11$) in the overall patient population or among patients with adenocarcinoma (hazard ratio 0.83, $P=0.07$). A retrospective analysis of patients treated with gefitinib showed that tumor response was associated with distinct subgroups: women, patients with no history of smoking, patients with adenocarcinoma, and Japanese patients. Survival in the gefitinib group in the ISEL study was significantly higher for non-smokers ($P<0.01$) and Asians ($P<0.01$) than in the placebo group. The survival curves of the two treatment groups were the same for non-Asians. The results of similar randomized trials of erlotinib (the BR21 study) were presented at the American Society of Clinical Oncology meeting in 2004. Erlotinib significantly prolonged survival in patients with advanced, previously treated, refractory or recurrent NSCLC. The survival of non-smokers in the erlotinib group in the BR21 study was extremely good and contributed to the improvement in overall survival. The presence of an *EGFR* mutation has been demonstrated to be a strong predictor of a favorable response to EGFR-TKI. Mutations have recently been reported to be significantly more frequent in women, in patients with adenocarcinoma, and in those who had never smoked, and these findings are consistent with the clinical predictors of tumor response in patients treated with EGFR-TKI. Mitsudomi *et al.* reported that patients with *EGFR* mutations survived longer after the initiation of gefitinib treatment than those without mutations.⁵ It can be concluded that translational studies are extremely important for the development of molecular-target-based drugs.

Supplementary information, in the form of a reference list, is available on the *Nature Clinical Practice Oncology* website.

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Competing interests

The author declared he has no competing interests.

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