EGFR inhibition and more: a new generation growing up

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The discovery of activating epidermal growth factor receptor (*EGFR*) mutations in non-small cell lung cancer (NSCLC) has led to a shift in treatment paradigm for some patients with advanced disease. Mutations in exons 18-21 in the tyrosine kinase domain are associated with improved clinical outcomes following treatment with tyrosine kinase inhibitors (TKIs). The first-generation EGFR TKIs erlotinib and gefitinib are most effective in the presence of *EGFR* mutations (1). However, despite the fact that the majority of patients with *EGFR* mutations benefit from these drugs, in excess of 20% of patients experience *de novo* resistance, and all tumours will ultimately develop resistance following initial response (2). This has driven research into the mechanisms of EGFR TKI resistance and the development of new approaches to overcome this. The study by Ramalingham *et al*. recently published in the Journal of Clinical Oncology is the first trial directly comparing a first generation EGFR TKI with one of the more potent and broadly-specific new generation of drugs in this class (3). It is useful to review EGFR TKI resistance mechanisms to understand some of the rationale driving the development of these newer drugs.

Both primary and *de novo* resistance to TKIs can occur even in the presence of activating *EGFR* mutations. A variety of molecular events is responsible for this, many of which can now be targeted using new agents in development. While many mutations in exons 18, 19 and 21 are predictive of response to TKIs, insertions, duplications or point mutations in exon 20 are observed in around 5% of all NSCLCs which result in a low response rates to first generation TKIs (4). The commonest of these is T790M. Although this mutation is more commonly seen in acquired resistance, varying allele frequencies can be detected prior to TKI exposure in some patients. Besides T790M mutation, alterations in parallel signalling pathways explain a significant further proportion of primary resistant tumours, which are often mutually exclusive with EGFR activation. Around 25% of lung adenocarcinomas harbour activating *KRAS* mutations, and are associated with lack of sensitivity to TKIs presumably because the driving oncogenic molecular event is acting downstream from the EGFR protein (5). Another 5% of tumours harbour a translocation of anaplastic lymphoma kinase (*ALK*) resulting in a fusion kinase (6). This rearrangement results in constitutive fusion activity contributing to carcinogenesis and resulting in resistance to drugs targeting other kinases. Other tumour genomic alterations driving *de novo* resistance to EGFR TKIs include *BRAF*, *PI3K* mutations and amplification of *MET* (2).

The clinical definition of acquired resistance to erlotinib or gefitinib includes patients with known sensitising *EGFR* mutations, and/or with objective clinical benefit from these drugs, progressing despite at least 30 days' continuous therapy. This definition is required to facilitate accurate reporting and the development of potential new agents that might overcome this problem. In contrast to *de novo* resistance, acquired resistance to EGFR TKIs is most often due to T790M mutations, which abrogate the inhibitory effect of first generation TKIs. This secondary *EGFR* mutation (exon 20) was found in nearly 50% of repeat tumour biopsies obtained from patients who developed acquired resistance against first generation TKIs (7). This T790M mutation results in the substitution of a bulky methionine side chain, which affects drug binding in the ATP pocket of *EGFR*.

Alterations in parallel signalling pathways, rather than *EGFR* mutations, can also play an important role in acquired resistance. Independent of T790M mutations, amplification of the *MET* oncogene can be observed in up to 20% of *EGFR*-mutant tumours following TKI failure (2). Amplification of this receptor tyrosine kinase activates *PI3K* signalling via HER3, independent of *EGFR* activity. In addition mutations in *PIK3CA*, encoding PI3K, can result in tumour resistance to EGFR TKIs (8). Surprisingly, other cases of acquired resistance can be explained by dramatic phenotypic change within tumours. Repeat tumour biopsies upon TKI failure showed transformation to small cell lung cancer (SCLC) in 14% of patients in one series, and a smaller proportion showed evidence of epithelial-to-mesenchymal transition (EMT) (7). The molecular genetic

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mechanism of this is poorly understood.

New-generation EGFR TKIs such as dacomitinib and afatinib have superior potency *in vitro* and broader specificity, with low nanomolar inhibitory concentrations against HER2 and HER4 as well as EGFR. Irreversible binding by these newer pan-HER TKIs can overcome T790M-induced resistance in preclinical models through covalent binding at Cys-797 of EGFR (9,10). Afatinib was shown to improve progression-free survival (PFS) compared with placebo in the second or third line setting after gefitinib or erlotinib failure in the LUX-Lung 1 trial (11). Although no benefit was recorded in terms of overall survival, significant post-study crossover from the control arm to treatment with with TKIs occurred. These results suggest meaningful clinical activity, and afatinib is likely to become a treatment option for patients with acquired resistance to first generation drugs.

Dacomitinib is another example of a new generation EGFR TKI, which also irreversibly targets EGFR, HER2 and HER4 and has in vitro activity in T790M-mutated cells (9). The phase II study reported by Ramalingham *et al*. is the first trial to directly compare an irreversible pan-HER TKI with a first generation TKI in advanced NSCLC (3). Patients with one or two prior chemotherapy regimens were included, but no previous HER-directed therapy was allowed. Despite randomization, there were imbalances in baseline characteristics with higher numbers of ECOG performance status 2, *EGFR* mutations, and patients receiving two prior chemotherapy regimens in the dacomitinib arm. The primary end point was met with median PFS of 2.9 months for dacomitinib and 1.9 months for erlotinib (hazard ratio =0.66, 95% CI, 0.47 to 0.91, P=0.012), and this effect was seen across all molecular subtypes. These results could possibly have been confounded by an imbalance in baseline characteristics including differences in the number of patients with *KRAS* wild-type/*EGFR*-any status tumours. Nevertheless, after correcting for this a stratified log-rank test favoured superiority of dacomitinib over erlotinib for PFS. No significant difference was seen in overall survival. Treatment-related side effects were as expected, with frequently reported adverse events including diarrhoea, acneiform rash and mucositis. Although treatment withdrawal due to toxicity was uncommon for both arms, treatment-related dose reductions were significantly higher in the dacomitinib group (41%) compared to erlotinib group (17%).

Both this latest study and LUX-Lung 1 suggest clinical benefit from this new generation of irreversible pan-HER TKIs. Their proposed role in deferring or counteracting the most common mechanism of resistance to EGFR TKI therapy is supported by pre-clinical data, although clinical confirmation of this hypothesis is so far inconclusive. Ramalingham *et al*. do not provide data on mechanisms of acquired resistance to either drug in their randomised study. Ongoing phase III studies should clarify the position of the newer agents in the treatment algorithm for NSCLC, and molecular analysis continues to play an increasingly important part in guiding treatment decisions.

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