

EGFR, EGFR TKI, and EMSI: a never-ending story

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Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) such as gefitinib and erlotinib are the first generation of EGFR inhibitors that were developed more than a decade ago. Beginning with the disappointing results of phase III trials that combined EGFR TKIs with chemotherapy in unselected patients with non-small cell lung cancer (NSCLC) (IDEAL-I and IDEAL-II for gefitinib, TALENT and TRIBUTE for erlotinib), both TKIs had a history of ups (BR.21 for erlotinib, INTEREST for gefitinib) and downs (ISEL for gefitinib), until the recent success of pivotal studies comparing EGFR TKIs to doublet chemotherapy in patients with activating *EGFR* mutations (IPASS, NEJ002 and WJTOG3405 for gefitinib, OPTIMAL and EURTAC for erlotinib).

Nowadays, screening for *EGFR* mutations is mandatory prior to selecting a first-line treatment for stage IV adenocarcinoma of the lungs, as EGFR TKIs are the first choice of treatment for NSCLC with activating *EGFR* mutations. If activating mutations are detected on the *EGFR* gene, the disease and symptoms can be controlled by treatment with an EGFR TKI in more than 70% of cases. However, acquired resistance to EGFR TKIs is inevitable after a median response duration of 11 to 14 months.

Second generation EGFR TKIs (afatinib, dacomitinib) were developed to overcome the acquired resistance after the failure of 1st generation EGFR TKIs. However, the Lux lung 1 trial failed to demonstrate any improvement in the overall survival of patients in the afatinib arm compared to the placebo arm. As afatinib monotherapy was not sufficient to overcome resistance caused by *EGFR* T790M mutations in the clinical setting, trials combining afatinib with cetuximab are ongoing, although this combination has higher toxicity.

Subsequently, results of the BR.26 trial comparing

dacomitinib—another second generation EGFR TKI—versus a placebo after the failure of prior EGFR TKI therapy were presented at the 2014 annual meeting of the American Society of Clinical Oncology (ASCO) (1). As with the afatinib therapy, there was no improvement in the overall survival of patients receiving dacomitinib, although the progression free survival improved.

Meanwhile, afatinib therapy was being studied as a potential first-line treatment for NSCLC with activating *EGFR* mutations. In the Lux lung 3 and 6 studies, afatinib was proved superior to doublet therapy with pemetrexed plus cisplatin or gemcitabine plus cisplatin in patients with NSCLC harboring activating *EGFR* mutations. As a result, gefitinib, erlotinib, and afatinib are currently the first-line treatment for NSCLC with activating *EGFR* mutations. The results of a study comparing gefitinib to afatinib therapy in patients with activating *EGFR* mutations are expected to be presented in next year. A similar study comparing the use of dacomitinib with gefitinib as first-line treatment is ongoing (ARCHER 1050).

No standard treatment exists for patients with lung cancer who experience disease progression after the use of 1st or 2nd generation EGFR TKIs. For this reason, the development of EGFR mutant selective inhibitors (EMSI) effective against both EGFR TKI-sensitive and EGFR TKI-resistant (T790M) mutants is eagerly awaited. The EMSIs target not only *EGFR* T790M, the mutant form of EGFR that is associated with clinical resistance to EGFR TKIs, but also the initial activating *EGFR* mutants, including those with exon 19 deletions and L858R. They do so while sparing the wild-type EGFR, and may thus treat refractory NSCLC while minimizing side effects on skin and mucosa. Because the EMSIs target both the sensitive activating mutations as well as the resistance mechanism

(the T790M mutation), they have the potential to be used both as first-line treatment in NSCLC patients with EGFR activating mutations, and as second-line treatment in patients with acquired resistance.

There are various mechanisms of EGFR TKI resistance, such as the presence of the T790M mutation, c-Met amplification, activation of alternative pathways (Insulin-like growth factor 1, Hepatocyte growth factor, Phosphoinositide 3-kinase, AXL), and the transformation to mesenchymal cells or small cell features. Among these, the *EGFR* T790M mutation accounts for more than 60% of the EGFR TKI-resistant cases. As EMSIs have shown efficacy against *EGFR* T790M mutants in a selective manner, it has been suggested that EMSIs only have activity in T790M positive cases, while they have little efficacy against other resistance mechanisms such as the activation of alternative pathways or transformations.

In the 2014 ASCO meeting, three clinical studies examining the use of three different EMSIs were presented (2-4). As expected considering the mechanism of action, all three compounds showed that the therapeutic efficacy is particularly good in patients harboring the *EGFR* T790M mutation. Among the EMSIs presented, AZD-9291 showed the best response rate (64%) in T790M-positive cases when compared with CO-1686 (58%) and HM-61713 (30%).

The response rates of the EMSIs were much lower in T790M negative cases (HM-61713, 12%; AZD-9291, 23%), compared to T790M positive cases. These results suggest that resistance mechanisms that do not involve T790M mutations should be treated by using other strategies. For example, acquired resistance via bypass tract activation (i.e., the MET-HGF pathway) may be blocked in a better way by using a combination of monoclonal antibody targeting molecules of the bypass tract and EGFR TKIs.

It is important to note that there are few toxicities associated with the use of EMSIs compared to 1st and 2nd generation EGFR TKIs. While 1st and 2nd generation EGFR TKIs block both the mutant EGFR in the tumor and the wild-type EGFR in the skin and other organs, often leading to the appearance of debilitating skin rashes, acne, and diarrhea, EMSIs act mostly on the mutant EGFR within the tumor. In the case of AZD9291, no dose limiting toxicities were observed. The most common adverse events were diarrhea (30%), skin rashes (24%), and nausea (17%), all of which were classified as grade 1 under the Common Terminology Criteria for Adverse Events guidelines. Grade 3/4 adverse events occurred in 16% of patients. Six patients (3%) had dose reductions. Five cases of interstitial lung

disease-like events are under investigation.

As EMSIs act mainly on T790M mutant cases, obtaining tumor DNA after the development of acquired resistance is going to be an essential prerequisite. However, a re-biopsy is not always easy to perform in those patients who have already been heavily treated for advanced NSCLC. Interestingly, liquid biopsy using circulating tumor DNA (ctDNA) is becoming available. In the IFUM study, the positive predictive value of mutations detected from ctDNA was very high (98.6%), although the sensitivity was 65.7% (5). Along with the clinical development of EMSIs, companion diagnostic methods are being investigated. For example, for the detection of *EGFR* T790M mutations from ctDNA, digital PCR-based (dPCR) approaches using BioRad ddPCR (MolecularMD) or BEAMing (Inostics) were superior to ARMS-based detection using Roche Cobas and Qiagen Therascreen *EGFR* mutation detection kits (6).

Further studies need to address several issues. Firstly, should we halt the use of EMSIs until after the development of resistance to 1st or 2nd generation EGFR TKIs? Alternatively, should we use the EMSIs as a first-line treatment for NSCLC with activating *EGFR* mutations? To address these questions, the efficacy of EMSIs in EGFR TKI naïve patients is currently under investigation. Furthermore, the direct comparison of EMSIs with 1st or 2nd generation EGFR TKIs as first-line treatment for NSCLC harboring activating *EGFR* mutations will answer this question. Secondly, the development of sensitive, specific diagnostic techniques to detect the mechanisms of acquired resistance should be accompanied by the development of EMSIs. Lastly, clinical resistance to EMSIs is likely to develop eventually. Thus, further research to combat the acquired resistance to EMSIs will be needed, which is why this is going to be a never-ending story.

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References

1. Ellis PM, Liu G, Millward M, et al. NCIC CTG BR.26: A phase III randomized, double blind, placebo controlled trial of dacomitinib versus placebo in patients with advanced/metastatic non-small cell lung cancer (NSCLC) who received prior chemotherapy and an EGFR TKI.

- ASCO Meeting Abstracts. USA, 2014;32:8036.
2. Sequist LV, Soria JC, Gadgeel SM, et al. First-in-human evaluation of CO-1686, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M). ASCO Meeting Abstracts. USA, 2014;32:8010.
 3. Kim DW, Lee DH, Kang JH, et al. Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs). ASCO Meeting Abstracts. USA, 2014;32:8011.
 4. Janne PA, Ramalingam SS, Yang JC, et al. Clinical activity of the mutant-selective EGFR inhibitor AZD9291 in patients (pts) with EGFR inhibitor-resistant non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts. USA, 2014;32:8009.
 5. Douillard JY, Ostoros G, Cobo M, et al. Gefitinib Treatment in EGFR Mutated Caucasian NSCLC: Circulating-Free Tumor DNA as a Surrogate for Determination of EGFR Status. J Thorac Oncol 2014;9:1345-53.
 6. Thress K, Brant R, Carr H, et al. EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of technologies to support the clinical development of AZD9291. ASCO Meeting Abstracts. USA, 2014;32:8092.

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