Combating acquired resistance to EGFR tyrosine kinase inhibitors in lung cancer

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Beginning in 2004, with the initial identification of EGFR mutations in a subset of lung adenocarcinomas, molecular profiling of lung cancer has evolved into a complex spectrum of clinically relevant and therapeutically actionable genomic alterations.[1,2] Treatment for patients with *EGFR*-mutant and *ALK*-rearranged NSCLC with specific tyrosine kinase inhibitors (TKIs) that target the EGFR and ALK tyrosine kinases respectively, has led to remarkable clinical responses, including often-dramatic tumor shrinkage and increased progression-free survival (PFS) compared with standard cytotoxic chemotherapy.[3-8] Unfortunately, virtually every patient will eventually experience disease progression on TKI therapy. The development of drug resistance remains a major limitation to the successful treatment for patients with advanced NSCLC. In an educational session during the 2015 annual ASCO meeting, *Prof Christine Lovly, MD, PhD (Vanderbilt-Ingram Cancer Center, Nashville TN, USA)* discussed several options to overcome acquired EGFR TKI resistance in this disease.

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Acquired resistance to EGFR TKI therapy

Acquired resistance to EGFR TKIs is a complex and heterogeneous phenomenon, with multiple potential mechanisms allowing the tumor to evade the anti-EGFR-directed therapy.[3,4] These mechanisms include modification of the target oncogene (particularly the T790M second-site mutation), upregulation of parallel signalling pathways to circumvent the inhibited EGFR (e.g. HER2, MET), and histologic transformation (e.g. epithelial to mesenchymal transition, small cell transformation). The rest of this report will focus on overcoming resistance mediated by the first of these three mechanisms.

Overcoming resistance mediated by *EGFR* target modification

Genomic alterations in the drug target, such as amplification and/or second-site mutations, have been shown to occur as a common mechanism of resistance in many oncogene-driven cancers treated with kinase inhibitor therapy. In the case of *EGFR*-mutant NSCLC, the most common second-site mutation involves substitution of a methionine in place of a threonine at position 790 (T790M) in the EGFR kinase domain. This T790M gatekeeper mutation is identified in approximately 50% of patients with acquired resistance to the EGFR TKIs erlotinib and gefitinib.[5,6]

In the case of T790M-mediated resistance, one potential strategy to overcome resistance is through the development of novel EGFR inhibitors with increased potency. Erlotinib and gefitinib are first-generation EGFR TKIs that reversibly bind to the EGFR kinase domain. Second-generation inhibitors, such as afatinib, irreversibly bind to the EGFR kinase domain and have activity against other EGFR (ErbB1) family members, including HER2 (ErbB2), HER2 (ErbB3), and/or HER4 (ErbB4). The initial hypothesis was that these second-generation inhibitors would be able to overcome the T790M mutation. Although the second-generation EGFR/HER2 TKI afatinib is FDA approved for first-line therapy in *EGFR*-mutant NSCLC, this agent has not yet proven to be a promising therapy

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in the setting of acquired resistance to first-generation EGFR TKIs, such as erlotinib and afatinib, despite the *in vitro* studies that suggest that afatinib can overcome T790M. In the phase III LUX-lung 1 study, patients with advanced NSCLC who had previously been treated with erlotinib or gefitinib for at least 12 weeks were randomly assigned to receive afatinib or placebo. The response rate and progression-free survival were superior with afatinib, but the study did not meet its primary endpoint of improved overall survival in all study participants or in the subset of patients with known *EGFR*-mutant lung cancer.[7]

These third-generation EGFR TKIs are irreversible inhibitors, analogous to the second-generation EGFR TKIs; however, they have higher specificity for mutant EGFR (including T790M) than wild-type EGFR. The mutant-specific EGFR TKIs with the most clinical data reported to date are AZD9291 and rociletinib (CO-1686). During ASCO 2015, updated results of a phase I study of AZD9291 were presented.[8] The median follow-up overall was 9.6 months, and was slightly longer in the group of patients receiving 80-mg of AZD9291 (11.0 months) than in patients receiving a dose of 160-mg (8.5 months). There were 46 patients in the study who were *T790M*-negative, five were T790M-positive and for nine the T790M status was unknown. Overall, 97% of the cohort received some clinical benefit from the drug (complete response, partial response, or stable disease). The overall response rate was 73%, with a slightly higher rate in the 160-mg group (83%) than the 80-mg group (63%). Data were still too immature to estimate median PFS, but the 12-month PFS-rate was high at 73% for 80-mg patients and a 9-month PFS rate of 78% in the 160-mg group. No adverse event in either group led to death. There were more adverse events leading to dose interruption in the 160-mg group (30%) than the 80-mg group (17%). The same was true for adverse events leading to dose reduction (43% *vs.* 10%). Currently AZD9291 is under evaluation in a larger phase III where the 80-mg dose will be used.

Analogously, promising results were reported for the phase I/II trial of rociletinib (CO-1686). In the TIGER-1 study, 92 evaluable patients with *EGFR*-mutant NSCLC that had progressed on treatment with an EGFR inhibitor who were treated with a free-base form of rociletinib at a dose of 900 mg twice daily or a hydrogen bromide salt form at doses of 500 mg twice daily to 1,000 mg twice daily.[15] A total of 83 patients were evaluable for response. Among 46 patients with centrally confirmed T790M-positive tumors, 59% had a partial response, and 35% had stable disease. Resulting in a disease control rate (DCR) of 93%. Response rates were similar in patients with deletion 19 or L858R *EGFR* mutations. The estimated median PFS at the time of analysis was 13.1 months. Among 17 patients with T790M-negative tumors on central testing, the response rate was 29% and 29% had stable disease (DCR: 59%). The estimated median PFS in these patients was 5.6 months. CO-1686 was well tolerated with hyperglycemia as a frequent adverse event (32%, all grades; 14%, grades 3 to 4).[9]

Despite the excitement surrounding the efficacy of mutant-specific EGFR TKIs in T790M-positive tumors, there still remains a large cohort (40-50%) of patients with T790M-negative tumors who have developed acquired resistance to erlotinib, gefitinib, or afatinib. One potential strategy that has been postulated for this cohort includes a combination of the EGFR monoclonal antibody cetuximab with afatinib in patients with acquired resistance. Among the 126 patients treated with this combination, the objective RR was 29% and was comparable in patients with T790M-positive and T790M-negative tumors (32% *vs.* 25%; p= 0.341). The median PFS was 4.7 months. Sixteen adverse events included expected toxicities of *EGFR* inhibitors, such as rash, diarrhoea, and fatigue. Therapy-related grades 3 and 4 adverse events occurred in 44% and 2% of patients, respectively.

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