Editorial

Update on third-generation EGFR tyrosine kinase inhibitors

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Among patients with non-small cell lung cancer (NSCLC), *EGFR* mutations, 90% of which present as an exon 19 deletion or exon 21 point mutation L858R, have been detected in Western and Asian populations at a rate of ~15% and ~40%, respectively. To date, numerous trials have established the efficacy and toxicity profile of single-agent oral EGFR-tyrosine kinase inhibitor (TKI) therapies for EGFR-TKI-naïve NSCLC patients harboring *EGFR* mutations. These trials include IPASS for gefitinib (1), Optimal for erlotinib (2), and LUX-Lung 3 for afatinib (3). Still, the majority of patients will eventually develop resistance.

In the LUX-Lung 4 (4) trial, 61 Japanese patients with lung adenocarcinoma who progressed following gefitinib and/or erlotinib treatment were treated with afatinib 50 mg daily; however, minimal benefit was shown [8.2% confirmed partial response (95% CI, 2.7-18.1%); median progression-free survival (PFS) was 4.4 months (95% CI, 2.8-4.6 months), and median overall survival (OS) was 19.0 months (95% CI, 14.9 months to not achieved)]. Only one patient with a T790M achieved a meaningful outcome (stable disease for 9 months). In both the LUX-Lung 3 and LUX-Lung 4 trials, afatinib showed a higher rate of TKI-related toxicity than has been previously described with gefitinib (1) or erlotinib (2). Toxicities included diarrhea and rash/acne rates of >90% in the LUX-Lung 3, which can impact the ability to safely maintain patients on afatinib treatments and highlights the need for close monitoring and prophylactic medications.

For the AZD9291 trial, a third-generation EGFR-TKI, Janne *et al.* (5) enrolled *EGFR* mutation-positive NSCLC patients with acquired resistance to EGFR-TKI therapy. This trial demonstrated an efficacy benefit with a more amenable side effect profile (AURA; NCT01802632). These findings are likely due to AZD9291 being relatively sparing and selective against wild-type *EGFR* while having better potent activity against mutant *EGFR*, including T790M mutations. More specifically, for all evaluable patients, the overall response rate (ORR) was 51% (91/177), whereas T790M-positive patients (n=89) yielded a 66% ORR (95% CI: 53-74%). The observed ORR of 23% (95% CI: 12-39%) in 43 NSCLC patients whose biopsies tested negative for T790M may have been due to tumor heterogeneity, re-treatment effects (57% of enrolled patients had immediate prior EGFR-TKI), or off-target effects. Age of tumor tissue did not appear to play a role in the results observed in the T790M-negative group as fresh biopsies were required for enrollment to the expansion cohorts. The initial hints of duration of response appear intriguing, but further confirmation is awaited as the trial results continue to mature.

A key aspect of the AZD9291 trial is the improved toxicity profile, which compares favorably with earlier-generation EGFR-TKIs. As expected, the most common EGFR-related adverse events were rash (24%) and diarrhea (30%), both dose dependent and mainly grade 1. Other adverse events included anorexia, dry skin, and nausea. While no dose-limiting toxicities occurred, it is important to note that, in this population previously treated with an EGFR-TKI, side effects also included interstitial lung disease, most of which were grade 1 (n=5), and hyperglycemia, also grade 1 (n=4). Overall, the AZD9291 trial by Janne *et al.* (5) presented at ASCO 2014 demonstrated true clinical significance as there are no FDA-approved drugs for patients who progress after EGFR-TKI resistance, whether or not an acquired resistance molecular

abnormality is identified.

While limitations exist with performing cross trial comparisons, results from this study must be compared to the first-in-human study of CO1686. Similar to AZD9291, CO1686 is an irreversible, third-generation EGFR-TKI therapy that also targets EGFR mutations, including T790M. In the trial, presented by Sequist *et al*. at ASCO 2014 (6) (NCT01526928), 40 T790M-mutant patients with history of progression while on prior EGFR-directed therapy were enrolled. An ORR of 58% was observed, with nausea, fatigue, and impaired glucose tolerance/hyperglycemia as the most common adverse events. The estimated median PFS was >12 months but was ultimately not reached at time of the ASCO presentation. Due to improved bioavailability, the formulation was changed from the free-base capsule to hydrogen bromide salt tablets, with comparable responses reported to date but affecting drug development. Toxicity profile differences between AZD9291 and CO1686 include incidence of hyperglycemia (1% versus 55%), rash (24% versus 4%), and diarrhea (30% versus 23%) (5,6), respectively. These rates are comparable to those shown with erlotinib (25% and 73% for diarrhea and rash, respectively) (2). When choosing between these agents, PFS and OS benefits as well as co-morbidities such as diabetes and patient concerns such as skin toxicity will play a role in the decision-making process. Similar to AZD9291, CO1686 has been granted breakthrough status by the US FDA.

AZD9291 and CO1686 represent very promising therapeutic options for NSCLC patients with resistance to EGFR-TKIs and T790M mutations as well as those limited by severe uncontrolled diarrhea and rash due to targeting of *EGFR* wild-type by earlier generation EGFR TKIs. Still, even with clear demonstration of efficacy and tolerability, alternate treatment options should be evaluated. While a phase I/II trial of erlotinib plus cetuximab failed to reveal any significant clinical benefit in patients with erlotinib resistance (7), preliminary results from Janjigian *et al*. (8,9) (NCT01090011) showed that afatinib 40 mg/m^2 plus cetuximab 500 mg/m^2 in the first 96 patients with defined acquired resistance [Jackman criteria (10)] was efficacious (objective response rate of 30%). In the T790M-positive population, confirmed partial response was 32% versus 28% in the T790M-negative group. With rash and diarrhea occurring in 97%, and 71%, respectively, patients on this combination need to be followed closely. A phase III trial is being planned by SWOG. Other options include intercalating chemotherapy, as is being evaluated in the ongoing trial presented at ASCO 2014 by Schuler *et al*. (11) (NCT01085136). In this trial, 202 patients who had failed prior erlotinib, gefitinib, and afatinib were randomized in a 2:1 ratio of afatinib plus paclitaxel versus investigator choice chemotherapy. Results showed PFS of 5.6 versus 2.8 months (P=0.003), ORR of 32.1% versus 13.2% (P=0.005), and OS of 12.2 versus 12.2 months (P=0.994), along with notable increases in diarrhea and alopecia in the treatment arm. Furthermore, another third-generation EGFR-TKI, HM61713, is under clinical development and may represent another potential option (12) (NCT01588145).

With these promising agents, questions still remain about optimal sequencing, combination strategies, and central nervous system (CNS) penetration. The ongoing trials should provide clarifications. A randomized phase II/III trial of CO1686 versus erlotinib in *EGFR*-mutant NSCLC patients is planned (TIGER 1; NCT02186301), while evaluations of AZD9291 in the EGFR-TKI-naïve population are underway as part of the AURA trial. Combination studies have been initiated such as the trial of AZD9291 plus MEDI4736 (PDL-1 inhibitor), AZD6094 (c-Met inhibitor), or selumetinib led by Astra-Zeneca (NCT02143466), with hopes of further delaying the development of resistance.

CNS relapse remains a risk for patients with NSCLC regardless of *EGFR* mutation status. CNS response with AZD9291 (5) and CO1686 (6) has been reported per their respective ASCO 2014 presentations. Beyond these examples, to our knowledge no data exist specifically detailing the CNS effects of these third-generation EGFR-TKIs. For this class of medications, CNS activity remains uncertain and requires further elucidation.

Findings from the AZD9291 trial along with the CO1686 trial have true clinical significance as there are no FDA-approved drugs for patients who progress on an EGFR-TKI, whether or not a specific acquired resistance molecular abnormality is identified. Moving forward, in the interest of providing more opportunities to our NSCLC patients, all efforts toward rapid and safe clinical development of this compound is imperative. The future of targeting mutant-*EGFR* appears quite promising.

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