Keeping our fingers crossed on 2nd generation EGFR TKIs: is better good enough?

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It has been almost a decade since the first generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has been approved for use in non-small cell lung cancer (NSCLC). When EGFR TKIs (gefitinib, erlotinib) were approved, it was based on response rates (gefitinib) or significant improvement in overall survival when compared to placebo (erlotinib) in 2nd line or 3rd line treatment in an unselected NSCLC patient population regardless of histology, gender, or smoking status (1,2). With the advent of the discoveries of activating EGFR mutations (EGFRm), six randomized clinical trials have now unequivocally demonstrated 1st generation EGFR TKIs achieved significant prolongation of progression-free survival (PFS) over standard doublet chemotherapy as 1st line treatment of NSCLC EGFRm patients (3-8).

However, despite the significant PFS prolongation achieved by 1st generation EGFR TKIs in EGFRm patients, the median PFS on average is only about 10-15 months. One of the major resistance mechanisms to 1st generation EGFR TKIs is the generation of T790M gate keeper mutation (9). Thus there is a need for 2nd generation "irreversible" EGFR TKIs that can inhibit the T790M mutation. Currently there are two lead 2nd generation EGFR TKI candidates, afatinib (BIBW2992) and dacomitinib (PF0299804) (10). Afatinib inhibits both EGFR and human epidermal receptor 2 (HER2) while dacomitinib is a pan-HER inhibitor (EGFR, HER2, HER4). However different strategies are being employed by the manufacturers of afatinib (Boehringer Ingelheim) and dacomitinib (Pfizer) in gaining regulatory approval.

Afatinib has successfully demonstrated significant PFS prolongation as 1st line treatment when compared to platinum/pemetrexed doublet combination chemotherapy in NSCLC EGFRm patients from the recently presented LUX Lung 3 trial (11). LUX Lung 6 employs the same design but compares afatinib to cisplatin/gemcitabine doublet chemotherapy in NSCLC EGFRm patients in China, South Korea and Thailand. The LUX Lung 3 (and likely positive LUX Lung 6) results will likely lead to the approval of afatinib as 1st line treatment of NSCLC EGFRm patients worldwide. Nonetheless, the median PFS (13.6 months) (11) achieved by afatinib in EGFRm patients with common (del19/L858R) in the LUX Lung 3 trial is similar to the PFS (13.1 months) achieved by erlotinib in the same patient population in the OPTIMAL trial (8). In addition, the gatekeeper T790M mutation can also develop on progression from afatinib (12). Furthermore, in LUX Lung 1 where advanced NSCLC patients who had failed either erlotinib or gefitinib were randomized to afatinib or placebo, afatinib generated a statistical significant but only an absolute increase in median PFS of about 2.2 months when compared to placebo but no overall survival (OS) benefit [Hazard Ratios (HR)=1.08; 95% confidence interval (CI): 0.86-1.35; P=0.74] (13). Even among EGFRm patients the absolute increase in median PFS is only 2.3 months from afatinib over placebo. Taken together, afatinib may not offer any therapeutic advantage over erlotinib in the 1st line treatment of EGFRm NSCLC patients and offers only modest PFS but no OS benefit in EGFRm patients who failed 1st generation EGFR TKIs regardless of EGFR mutational

status thus limiting its therapeutic benefit in NSCLC.

As the recognition of the efficacy of EGFR TKIs is best for EGFRm patients, the use of erlotinib in the US has been waning for the vast majority of NSCLC patients who did not harbor activating EGFRm. Cetuximab, an antibody against EGFR when added to cisplatin/vinorelbine achieved statistically significant improved overall survival than cisplatin/vinorelbine alone in unselected NSCLC (FLEX trial) (14). However, cetuximab has yet to receive US Food and Drug administration (FDA) approval for use in combination with chemotherapy as 1st line treatment of NSCLC. The recently presented TAILOR trial comparing erlotinib to docetaxel in EGFR wildtype (wt) patients demonstrated docetaxel had superior response rate (RR) [13.9% (docetaxel) versus 2.2% (erlotinib); P=0.004] and PFS [3.4 months (docetaxel) versus 2.4 months (erlotinib); HR=0.69, 95% CI: 0.52-0.93; P=0.014] than erlotinib (15). Take together TAILOR has sown further doubts about the efficacy of EGFR blockade as a therapeutic strategy in EGFR wt NSCLC.

Theoretically, if EGFR pathway blockade is important in the management of EGFR wt NSCLC then a more potent EGFR pathway inhibitor should result in better clinical outcome when compared to a less potent EGFR TKI. Indeed this is the case. Ramalingam *et al.* published a randomized phase II trial comparing dacomitinib to erlotinib as 2nd line treatment in unselected NSCLC patients (16). Dacomitinib achieved significant better PFS among all patients [2.86 months (dacomitinib) versus 1.91 months (erlotinib), HR=0.66; 95% CI: 0.47-0.91; P=0.012], among KRAS wt patients [3.71 months (dacomitinib) versus 1.91 months (erlotinib), HR=0.55; 95% CI: 0.35-0.85; P=0.006], and more importantly among KRAS wt/EGFR wt patients [2.21 months (dacomitinib) versus 1.84 months (erlotinib), HR=0.61; 95% CI: 0.37-0.99; P=0.043]. Overall survival was better but not significant with dacomitinib than erlotinib [9.53 months (dacomitinib) versus 7.44 months (erlotinib), HR=0.80; 95% CI: 0.56-1.13; P=0.205]. Dacomitinib had more frequent treatment related adverse events such as diarrhea (73.1% versus 47.9%), dermatitis acneiform (64.5% versus 57.4%), and stomatitis (29.0% versus 10.6%) than erlotinib (16). The results of this phase II trial results implies that EGFR blockade remains an important therapeutic strategy among in EGFR wt/KRAS wt NSCLC as evidenced that tight or more comprehensive blockade of EGFR signaling pathway resulted in better PFS and OS.

Dacomitinib is being now compared to erlotinib in a global phase III randomized registration trial as 2nd/3rd line treatment in unselected advanced NSCLC patients with improvement in PFS as the primary endpoints in two co-primary populations: all patients with advanced NSCLC and KRAS wt NSCLC (ARCHER 1009, www.clinicaltrials.gov number: NCT01360554). Stratification factors include histology (adenocarcinoma versus non-adenocarcinoma), race (Asian versus non-Asians), Eastern Cooperative Oncology Group (ECOG) performance status (0-1 versus 2), and smoking status (never-smoker versus ever-smoker). Sample size calculations are powered to allow detection of 33% improvement of PFS among all patients receiving dacomitinib over erlotinib and 45% improvement in PFS among KRAS wt patients receiving dacomitinib over erlotinib which were exactly what was achieved by the phase II trial reported by Ramalingam *et al.* (16). A total of 800 patients will be enrolled. Given that the survival benefit in randomized phase III trials is usually less pronounced than in randomized phase II trials it remain to be seen if the PFS improvement observed in dacomitinib-treated patients will hold true. Given there was numerical but no statistical improvement in OS observed by Ramalingam *et al.*, it will be interesting to observe if there is any significant improvement in OS will be achieved in ARCHER 1009. If ARCHER 1009 achieves its primary endpoint, dacomitinib as a 2nd generation EGFR TKI should be available to all NSCLC patients as 2nd line treatment regardless of histology or EGFR mutation status. Interestingly afatinib is also pursuing a similar trial design comparing afatinib to erlotinib as 2nd line treatment in squamous cell carcinoma patients (LUX Lung 8, www.clinicaltrials.gov number NCT01523587).

Finally, subgroup analysis of the 16 patients (8 on dacomitinib arm and 8 on erlotinib arm) harboring EGFR exon 19 deletion on the Ramalingam *et al.* study seemed to indicate dacomitinib may confer significant better PFS [77 weeks (dacomitnib) versus 24 weeks (erlotinib), HR=0.27; 95% CI: 0.076-0.94] on (17). Therefore a direct comparison between dacomitinib and a 1st generation EGFR TKI is warranted to confirm the subgroup analysis of Ramalingam *et al.* (17) so as to provide better therapeutic option for NSCLC EGFRm patients and to provide an alternative option for the regulatory approval of dacomitinib in case ARCHER 1009 fails to achieve its primary endpoints. Thus while the phase II data on dacomitnib is promising, we have to keep our fingers crossed to see if better PFS is good enough.

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