Expanding options for EGFR targeting in lung cancer

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The discovery of response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patient with activating mutations in the EGFR gene in 2004 dramatically altered the approach to the treatment of non-small cell lung cancer (NSCLC) (1,2). However, the path to the current treatment paradigm for the use of EGFR TKIs in patients with NSCLC has been circuitous. The first (and to date only) regulatory approval of EGFR inhibitors for NSCLC in the United States was based on data from the BR.21 trial. In this trial, NSCLC patients (without restriction by EGFR mutational status), with one or two prior lines of therapy had a superior progression free survival (PFS) and overall survival (OS) when receiving erlotinib and best supportive care (BSC) as opposed to BSC alone (3). Gefitinib was unable to achieve such a benefit in a similarly designed study (4). However, we have now seen that the first-generation reversible TKIs, gefitinib and erlotinib, lead to superior PFS and response rate (RR) when compared to standard chemotherapy in first-line treatment of EGFR-mutant NSCLC (5-8). Unfortunately, disease progression eventually occurs even in patients that initially benefit due to acquired resistance to the EGFR TKIs after prolonged use. The role of first generation EGFR inhibitors among patients with wild type (WT) EGFR is somewhat unclear, and recent data indicates that such treatment is inferior to docetaxel in second line treatment (9).

The study by Ramalingam and colleagues (10) investigates the role of dacomitinib, a second generation irreversible pan-HER TKI, *vs.* erlotinib as second-/third- line treatment for NSCLC patients. Dacomitinib irreversibly inhibits EGFR/HER1, HER2 and HER4, and it has been shown in preclinical studies to have potent HER kinase inhibition and activity against gefitinib- and erlotinib-resistant NSCLC cell lines (11,12). The study was a randomized, open-label phase II trial involving 188 patients with advanced NSCLC who had progressed after 1-2 prior chemotherapy regimens and had no prior EGFR-directed therapy. Treatment arms were balanced except for baseline ECOG PS 2 (dacomitinib n=19, erlotinib n=3), EGFR mutation (dacomitinib n=19, erlotinib n=11), and number of patients who had received 2 prior chemotherapy regimens (dacomitinib n=40, erlotinib n=29). The primary end point of median PFS was 2.86 months for patients treated with dacomitinib *vs.* 1.91 months for those receiving erlotinib (hazard ratio 0.66; 95% CI, 0.47-0.91; two-sided P=0.012). The RR was 17.0% for dacomitinib *vs.* 5.3% for erlotinib (P=0.011). In the subgroup of patients with KRAS WT/EGFR WT tumors, PFS was 2.21 for patients treated with dacomitinib *vs.* 1.84 months for patients treated with erlotinib (HR 0.61; CI, 0.37-0.99, P=0.043). No significant difference was seen in median overall survival. The most common side effects of diarrhea (73% *vs.* 48%) and dermatologic issues (65% *vs.* 57%) were more frequent in the dacomitinib arm, though largely manageable with grade 1 or 2 severity.

The results of the study suggest that dacomitinib, and potentially other 2nd generation irreversible pan-HER inhibitors, may provide a new treatment option for advanced NSCLC, and may be effective in EGFR WT/KRAS WT patients. However, the significance of the improvement in PFS with dacomitinib *vs.* erlotinib may have been skewed by imbalances in the two treatment arms. Although imbalances in baseline ECOG status and number of prior chemotherapy regimens favored the erlotinib arm, it is known that EGFR mutational status is the best predictor of RR and PFS with EGFR TKIs. The imbalance between the two arms with respect to EGFR mutational status, although numerically small (8 patients), has the

potential to significantly skew the results, particularly RR and PFS. For reference, in the IPASS study (13) which evaluated frontline therapy, the median PFS with gefitinib in EGFR WT patients was 1.5 months *vs.* 9.5 months in EGFR mutant patients, and RR was 1.1% in EGFR WT *vs.* 71.2% in EGFR mutant patients. If the PFS and RR differences based on EGFR mutational status is similar in the Ramalingam study to the IPASS study, having approximately 20% EGFR mutation positive patients in the dacomitinib arm as opposed to approximately 10% in the erlotinib arm would greatly impact PFS and RR between arms. Although statistical superiority was not seen among EGFR WT patients in the Ramalingam study, a benefit was seen when the analysis was restricted to EGFR WT/KRAS WT patients. Although the HR for PFS in the EGFR WT/KRAS WT subgroup appears meaningful (0.61), the absolute magnitude of the benefit was still relatively small (0.37 months).

A phase III study, ARCHER 1009, is currently underway to further evaluate dacomitinib as 2nd/3rd line therapy in advanced NSCLC as well as investigate its role in KRAS WT/EGFR any status patients. This study will specifically answer whether dacomitinib offers benefits over erlotinib in a largely EGFR WT population. The role for dacominitib in patient with EGFR mutations or HER2 alterations will need to be addressed by additional studies.

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