ARCHER 1009 Subset Analysis and LUX-8 Lung: Erlotinib Compared With Dacomitinib or Afatinib

Written by Kathy Boltz, PhD

Results of 2 trials comparing erlotinib, a first-generation reversible tyrosine kinase inhibitor, with second-generation irreversible tyrosine kinase inhibitors (dacomitinib and afatinib) in patients with either advanced non–small cell lung cancer (NSCLC) or squamous cell carcinoma (SCC) were presented in one session.

EGFR MUTANT SUBSET ANALYSIS OF ARCHER 1009 COMPARING DACOMITINIB AND ERLOTINIB

The ARCHER 1009 trial was a randomized, double-blind, phase 3 study in which patients (n = 878) with locally advanced or metastatic NSCLC who had progressed after 1 to 2 prior lines of therapy were randomized 1:1 to receive either dacomitinib 45 mg/d or erlotinib 150 mg/d. Among these patients, 47 treated with dacomitinib and 44 treated with erlotinib had *EGFR*-mutant NSCLC, and 37 treated with dacomitinib and 39 treated with erlotinib had an *EGFR*-activating mutation in exon 19 or 21.

It has been previously reported that for the overall study population, dacomitinib was not superior to erlotinib for patients with advanced NSCLC or in patients with *KRAS* wild-type tumors [Ramalingam SS et al. *Lancet Oncol.* 2014]. In the present session, Luis Paz-Ares, MD, PhD, Hospital Universitario Virgen del Rocio, Seville, Spain, discussed a subset analysis of patients with *EGFR*-activating mutations [Paz-Ares L et al. *Ann Oncol.* 2015].

Among the 91 patients with *EGFR* mutations, the median progression-free survival (PFS) per independent review was 11.1 months (95% CI, 5.6 to 21.9) with dacomitinib and 10 months (95% CI, 7.4 to 16.6) with erlotinib (HR, 0.935; 95% CI, 0.539 to 1.624; one-sided $P = .403$). Among the 76 patients with *EGFR*-activating mutations in exon 19 or 21, the median PFS per independent review was 14.6 months (95% CI, 7.6 to not reached [NR]) with dacomitinib and 9.6 months (95% CI, 7.3 to 16.6) with erlotinib (HR, 0.707; 95% CI, 0.380 to 1.315; one-sided $P = .136$). Notably, the PFS values per independent review were not mature, as the event rate was 56%.

When PFS was determined per investigator's assessment, the median PFS for all *EGFR* mutations was 10.9 months for patients treated with dacomitinib (95% CI, 7.5 to 18.2) and 10 months for patients treated with erlotinib (95% CI, 7.4 to 12.8), with an HR of 0.874 (95% CI, 0.542 to 1.408; one-sided $P = .286$). Among the 76 patients with *EGFR*-activating mutations in exon 19 or 21, the median PFS per investigator's assessment was 13.4 months (95% CI, 9.0 to 19.6) with dacomitinib and 10.0 months (95% CI, 7.4 to 12.8) with erlotinib (HR, 0.749; 95% CI, 0.440 to 1.275; one-sided $P = .142$). The PFS data by the investigator's assessment were mature.

For patients with *EGFR* mutations, overall survival (OS) was 26.6 months (95% CI, 21.6 to NR) with dacomitinib and 28.0 months (95% CI, 16.4 to NR) with erlotinib (HR, 0.976; 95% CI, 0.534 to 1.786; one-sided $P = .472$). For patients with *EGFR*-activating mutations in exon 19 or 21, OS was 26.6 months (95% CI, 21.6 to NR) with dacomitinib and 23.2 months (95% CI, 16.0 to NR) with erlotinib (HR, 0.796; 95% CI, 0.405 to 1.565; one-sided $P = .256$). These OS data were not mature as the trial was still < 50% deaths. The toxicity profile was similar between the *EGFR* mutation population and the overall patient population.

Overall, the subgroup of patients with the *EGFR*-activating mutation in exon 19 or 21 appeared to show a trend in favor of dacomitinib for PFS. The activity of dacomitinib in NSCLC with *EGFR*-activating mutations as a second- and third-line treatment is being reviewed for future presentation.

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LUX-LUNG 8: AFATINIB VS ERLOTINIB FOR SQUAMOUS CELL CARCINOMA

Afatinib has shown activity in patients with SCC of the head/neck and lung. Silvia Novello, MD, PhD, San Luigi Hospital, Orbassano, Italy, discussed the results of the LUX-Lung 8 phase 3 trial [Goss GD et al. *Ann Oncol.* 2015], based on a poster by Glendwood D. Goss, MD, University of Ottawa, Ottawa, Canada, and colleagues. The LUX-Lung 8 trial prospectively compared afatinib and erlotinib in patients with SCC of the lung after failure of platinum-based first-line chemotherapy. Prof Novello explained that early trial data led researchers to expect that afatinib would have a different efficacy, safety profile, pharmacokinetic interactions, and activity in different mutations, as well as a specific role in overcoming resistance and ability to target other receptors, but not all of the above-mentioned characteristics have been clinically demonstrated.

In the LUX-Lung 8 trial, patients with stage IIIB/IV SCC were randomized 1:1, after being stratified by race to avert any possible imbalance in *EGFR* mutation. The primary analysis was based on 414 PFS events when 669 patients had been randomized (afatinib n = 335; erlotinib n = 334).

The median PFS was significantly higher for afatinib vs erlotinib (2.4 months vs 1.9 months; HR, 0.822; 95% CI, 0.676 to 0.998; log-rank $P = .043$). Novello noted that an HR of 0.822 is much less than that required by recent American Society of Clinical Oncology guidelines that define clinically meaningful outcomes [Ellis LM et al. *J Clin Oncol.* 2014], but she raised the question of how to meet that goal in SCC.

The overall response rate (4.8% vs 3%; $P = .23$) and disease control rate (45.7% vs 36.8%; $P = .02$) were higher with afatinib vs erlotinib.

The overall adverse event (AE) profiles were similar, with grade 3 or higher AEs occurring in 50.2% of patients receiving afatinib and in 49.1% of patients receiving erlotinib. Afatinib had a higher incidence of drug-related grade 3 or higher diarrhea (9.7% vs 2.4%) and grade 3 stomatitis (3.3% vs 0%), while erlotinib had a higher incidence of grade 3 rash/acne (5.5% vs 9%). The drug was discontinued due to AEs in 8.8% of the afatinib arm and 4.2% of the erlotinib arm.

Notably, Prof Novello stated that the toxicity was not negligible. At 2 months, 50% of the patients did not benefit from one treatment vs the other. This raises the question of how to select patients who can really benefit from treatment.

More patients had improved global health status (36.4% vs 27.1%; $P = .03$) and cough (44% vs 33%; $P = .01$) with afatinib than with erlotinib. Changes in mean scores over time favored afatinib over erlotinib for cough, dyspnea, and physical and role functioning.

Overall, LUX-Lung 8 is the largest prospective trial comparing afatinib vs erlotinib in patients with relapsed/refractory SCC. PFS, tumor shrinkage, overall response rate, and disease control rate were significantly better for afatinib than erlotinib. Afatinib had drug-related AEs more frequently and severely than erlotinib, but rates of discontinuation from AEs were comparable. Notably, this trial was still recruiting when this data analysis occurred.

Gemcitabine Switch Maintenance Superior to Supportive Care in Advanced NSCLC

Written by Francesca Coltrera

Roughly two-thirds of people with non–small cell lung cancer (NSCLC) are diagnosed at stage IIIB or IV and can benefit only from palliative chemotherapy. This prospective randomized trial found that switch maintenance therapy outperformed best supportive care (BSC) alone when following platinum doublet chemotherapy in these patients [Jakhar SL et al. *Ann Oncol.* 2015]. Christian Manegold, MD, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany, discussed the results of a study based on a poster by Shankar Lal Jakhar, MD, Acharya Tulsi Regional Cancer Treatment & Research Institute, Bikaner, Rajasthan, India, and colleagues.

For switch maintenance after platinum-paclitaxel chemotherapy, gemcitabine (G) was chosen as a different active agent aimed at preventing replication of clonal variants that slipped through first-line palliative treatment. Overall survival (OS) was the primary end point of this open-label study. The secondary end point was progression-free survival (PFS).

Patients with stage IIIB and IV NSCLC (N = 134; median age, 50 years) were enrolled in the trial between July 2011 and January 2012. None had received chemotherapy. Roughly half (50.7%) had stage IV disease, and 76.8% were men. Two-thirds (67.9%) were ECOG performance status 0/1, and the remainder were status 2.

Participants underwent 6 three-week cycles of cisplatin (40 mg/m^2, cycle days 1 and 2) and paclitaxel (175 mg/m^2, cycle day 1). Following this, the 99 nonprogressing patients were randomly assigned 1:1 to maintenance gemcitabine (1000 mg/m^2, cycle days 1 and 8) every 3 weeks or BSC until their disease progressed.

Gemcitabine significantly lengthened OS and PFS compared with BSC alone (Table 1). Prof Manegold mentioned other trials of gemcitabine as maintenance