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

Table 1. OS and PFS With Gemcitabine vs BSC

	Gemcitabine	BSC	HR	*P* Value
OS, mo (95% CI)	10 (9.2 to 10.7)	8 (6.7 to 9.2)	0.64 (0.51 to 0.77)	.002
PFS, mo (95% CI)	9 (8.1 to 9.9)	7 (6.3 to 7.7)	0.67 (0.50 to 0.84)	.009

BSC, best supportive care; OS, overall survival; PFS, progression-free survival.
Source: Jakhar SL et al. *Ann Oncol*. 2015 (abstr 100PD).

and not switch therapy; the findings of this trial support results from a larger trial of gemcitabine maintenance therapy [Brodowicz T et al. *Lung Cancer*. 2006] yet stand in contrast to a trial [Belani CP et al. *J Clin Oncol*. 2010] that found no advantage for gemcitabine maintenance plus BSC vs BSC alone.

Patients in the gemcitabine group experienced a higher incidence of grade 3 and 4 adverse events: anemia (12% G; 8.1% BSC), neutropenia (18% G; 4.1% BSC), thrombocytopenia (14% G; 2% BSC), and fatigue (8% G; 2% BSC). Otherwise, the researchers reported that maintenance therapy was well tolerated.

This study has a number of limitations that affect its interpretation. These include the open-label design, which could have influenced the results because the patients and the investigators knew who was receiving active treatment. The histologic subgroups (ie, squamous, nonsquamous) were not reported. Importantly, there is no information about the frequency of follow-up visits or restaging of cancer by imaging for each group and the percentage of patients who eventually had second-line therapy, particularly in the BSC group. The results of this small study may provide a signal that switch maintenance therapy with gemcitabine may extend OS and PFS for patients with advanced NSCLC, a finding that must be interpreted carefully and balanced against the increase in high-grade toxicity.

ASSESS: *EGFR* Mutations Can Be Analyzed With ctDNA

Written by Kathy Boltz, PhD

Circulating tumor DNA (ctDNA) was found to have utility for *EGFR* mutation testing in advanced non–small cell lung cancer (NSCLC) in a real-world setting in the diagnostic ASSESS study [NCT01785888], according to Martin Reck, MD, PhD, Lung Clinic Grosshansdorf, Grosshansdorf, Germany.

The study enrolled 1288 eligible patients, with 997 from Europe and 291 from Japan. Overall, 75.8% of the patients were white and 23.0% were Asian; 19.6% were never-smokers; smokers had 40.0 median pack-years; and the majority of patients (84.6%) had stage IV disease.

The majority of the tissue/cytology samples were obtained during the current diagnosis, derived from the primary tumor, and collected via bronchoscopy. Most samples were prepared as paraffin-embedded tissue blocks and fixed with 4% neutral-buffered formalin. The median turnaround time for *EGFR* mutation testing was 11 days in Europe (95% CI, 14.0 to 17.3) and 8 days in Japan (95% CI, 8.2 to 14.1). The average test success rate was 98.3% in Europe and 99.6% in Japan.

In Japan, the tests used to evaluate tissue/cytology samples and plasma samples for *EGFR* mutations were Cycleave PCR and PNA LNA clamp PCR. In Europe, for tissue/cytology testing, PNA LNA clamp PCR and the older methods of DNA sequencing and pyrosequencing were used, along with newer, more sensitive methods, including the Roche cobas *EGFR* Mutation Test and Sequenom; for plasma testing, the QIAGEN Therascreen RGQ PCR kit and Roche cobas *EGFR* Mutation Test were used.

The overall concordance was 89.1% (1035 of 1162 patients; 95% CI, 87.1 to 90.8) and overall positive predictive value (PPV) was 77.7% (87 of 112; 95% CI, 68.8 to 85.0). In patients in whom the same testing method was used for tissue/cytology and plasma evaluations, the PPV was 92.6% (95% CI, 75.7 to 99.1) compared with 72.9% (95% CI, 62.2 to 82.0) when different testing methods were used for the evaluations. The sensitivity was 46.0% (95% CI, 38.8 to 53.4), specificity was 97.4% (95% CI, 96.2 to 98.3), and the negative predictive value was 90.3% (95% CI, 88.3 to 92.0) in the overall cohort.

The QIAGEN Therascreen RGQ PCR kit had a sensitivity of 72.7%, specificity of 99.1%, and PPV of 94.1% in this trial. A previous trial of white patients, IFUM [Douillard JY et al. *Br J Cancer*. 2014], used the same kit and reported a sensitivity of 65.7%, specificity of 99.8%, and PPV of 98.6%.

False-positive results, meaning an *EGFR* mutation-positive plasma sample and an *EGFR* mutation-negative tissue/cytology sample, were believed to have come from 25 patients. These patients were from multiple sites and countries, indicating no specific laboratory-based