TG4010 (n = 85) or placebo (n = 85) was conducted after 144 events of disease progression.

In the patients with normal TrPAL levels, the primary end point of PFS was achieved in 70 patients (82.4%) receiving TG4010 and 74 patients (87.1%) receiving placebo. The observed hazard ratio (HR) for PFS was 0.74 (95% CI, 0.53 to 1.02), which corresponded to a 98.6% Bayesian probability that the true HR was < 1 and thus passed the necessary threshold of 95% to have met the efficacy end point in the normal TrPAL patient population. In patients with normal TrPAL levels, median PFS favored the TG4010 treatment arm compared with standard chemotherapy alone (5.7 vs 5.1 months, respectively; HR, 0.78; 95% CI, 0.53 to 1.02; $P = .078$). The overall response rate was 37.6% in the TG4010 treatment arm compared and 30.6% in the placebo arm of the patients with a normal TrPAL level. The analysis of patients with high TrPAL levels is still pending.

Most grade 3/4 adverse events were similar between the treatment arms and included neutropenia, thrombocytopenia, fatigue, anemia, and febrile neutropenia with higher TG4010-related adverse events at the injection site (31.4% vs 4%).

Subgroup analyses in patients with nonsquamous NSCLC (n = 195) showed a significant improvement in PFS when treated with TG4010 (HR, 0.71; 95% CI, 0.51 to 0.97; $P = .016$), with an increase in OS (HR, 0.73; 95% CI, 0.50 to 1.07). In the 75% of patients with the lowest baseline TrPAL levels (low TrPAL; n = 152), the HR for PFS was 0.66 (95% CI, 0.46 to 0.96; $P = .014$). In the patients with nonsquamous NSCLC and low TrPAL levels (n = 131), PFS was significantly increased in the TG4010 arm vs placebo (HR, 0.60; 95% CI, 0.41 to 0.88) and OS was increased with TG4010 vs placebo (HR, 0.70; 95% CI, 0.45 to 1.10). Forest plots of PFS and OS in the stratified subgroups are shown in Figures 1 and 2.

Prof Quoix concluded that the results of the phase 2b portion of the TIME study provided evidence of the efficacy and safety of TG4010 in stage IV NSCLC, especially in patients with nonsquamous tumors and low TrPAL levels.

LUX-Lung 5: Afatinib Plus Paclitaxel Improves Outcomes for Metastatic NSCLC

Written by Anita Misra-Press, PhD

Patients with advanced non–small cell lung cancer (NSCLC) who have wild-type *EGFR* fare better with conventional chemotherapy instead of tyrosine kinase inhibitors (TKIs) as first-line treatment [Lee JK et al. *JAMA*. 2014]. In contrast, 70% of patients with NSCLC harboring *EGFR* mutations show tumor regression from the EGFR TKIs erlotinib and gefitinib [Jackman D et al. *J Clin Oncol*. 2010]. The majority of these patients eventually acquire resistance to erlotinib and gefitinib, contributing to disease progression.

Because of tumor cell heterogeneity, inclusion of an EGFR TKI in postprogression therapy improves outcomes. For instance, a combination of gefitinib or erlotinib plus pemetrexed has been shown to improve outcomes in 27 patients with EGFR mutation-positive NSCLC who had disease progression on gefitinib/erlotinib monotherapy; an overall response rate of 25.9% (95% CI, 62.1% to 95.5%) was achieved with the combination [Yoshimura N et al. *J Thorac Oncol*. 2013]. Afatinib, an irreversible ErbB TKI (including EGFR, HER2, HER4), increases survival outcomes as monotherapy and overcomes resistance in patients who had disease progression after gefitinib/erlotinib [Katakami N et al. *J Clin Oncol*. 2013; Sequist LV et al. *J Clin Oncol*. 2013].

Martin Schuler, MD, West German Cancer Center, Essen, Germany, shared results of LUX-Lung 5 [Schuler M et al. *Ann Oncol*. 2015], a randomized, open-label, 2-stage design, phase 3 trial that assessed continued afatinib plus paclitaxel vs investigator's choice of single-agent chemotherapy (ICC). The study consisted of 2 parts. In part A, patients with NSCLC who had failed ≥ 1 line of chemotherapy (including platinum/pemetrexed) and erlotinib/gefitinib after ≥ 12 weeks of treatment (n = 1154) were treated with afatinib 50 mg/d. In part B, patients who had been treated with afatinib for ≥ 12 weeks followed by disease progression after part A of the study were eligible to be randomized 2:1 to afatinib 40 mg/d plus paclitaxel 80 mg/m^2/wk or ICC. The primary end point was progression-free survival, whereas the secondary end points included overall survival, objective response rate, safety, and health-related quality-of-life outcomes.

Of the 1154 patients who had disease progression on erlotinib/gefitinib and afatinib 50 mg/d, 202 patients derived ≥ 12 weeks of benefit on afatinib monotherapy. These selected patients were randomized 2:1 to receive afatinib plus paclitaxel (n = 134; 40 mg/d; 80 mg/m^2/wk) or ICC (n = 68). Baseline patient characteristics (included sex, age, ECOG performance status, race, smoking status, clinical stage, and tumor histology) were well balanced between both arms. Progression-free survival increased from 2.8 months with ICC to 5.6 months with afatinib plus paclitaxel (HR, 0.60; 95% CI, 0.43 to 0.85; $P = .0031$). Afatinib plus paclitaxel, as fourth-line treatment, was also more effective than ICC in reducing tumor size (15.1% vs 1.2%).

Although disease control rate (OR, 3.4; $P < .0001$) and objective response rate (OR, 3.1; $P = .0049$) were superior

with afatinib plus paclitaxel, overall survival did not show any statistical difference between the 2 treatment arms (12.2 months in each arm; HR, 1.00; 95% CI, 0.70 to 1.43; $P = .994$), possibly attributed to differences in postprogression treatment between the arms. More patients in the ICC arm received 2 postprogression lines of therapy compared with the afatinib plus paclitaxel arm (36% vs 15%).

Despite prolonged exposure time to afatinib plus paclitaxel compared with ICC (133 vs 51 days), discontinuation due to treatment-related adverse events was low, and quality of life was comparable between arms (HR, 0.97; 95% CI, 0.6 to 1.5). The most common adverse events in afatinib plus paclitaxel vs ICC arms included diarrhea (53.8% vs 6.7%), alopecia (32.6% vs 15%), and asthenia (27.3% vs 28.3%).

Prof Schuler concluded that afatinib plus paclitaxel was superior to ICC and improved outcomes in patients who had an acquired resistance to erlotinib/gefitinib and had disease progression on afatinib monotherapy after an initial benefit. It should, however, be noted that this study did not include a mutational analysis. Future studies should include a mutational status analysis (including *EGFR* mutations) to evaluate how the efficacy of treatments differs based on mutational status.

Age-Stratified Subgroup Analysis of SQUIRE in Patients With Stage IV Squamous NSCLC

Written by Anita Misra-Press, PhD

The current treatment for advanced non–small cell lung cancer (NSCLC), the leading cause of cancer death, is a combination of a platinum agent with third-generation therapies [Socinski MA et al. *J Clin Oncol.* 2012]. However, with survival differences related to histology, the paucity of data for patients with squamous NSCLC underscores an unmet need for more effective treatment.

Nicholas Thatcher, PhD, The Christie NHS Foundation Trust, Manchester, United Kingdom, previously reported results from the SQUIRE trial [Thatcher N et al. *J Clin Oncol.* 2014], a multinational, randomized, open-label, phase 3 study demonstrating increased overall survival (OS), progression-free survival (PFS), and disease control rates by adding necitumumab (N) to gemcitabine/cisplatin (GC) as first-line treatment for stage IV squamous NSCLC.

Changing the prevalence of comorbidities (and associated toxicities) across the age spectrum may influence outcomes, particularly for the elderly squamous NSCLC population [Piccirillo JF et al. *Crit Rev Oncol Hematol.* 2008]. In the present poster, Prof Thatcher presented efficacy results from an age-stratified subgroup analysis of the SQUIRE trial (N + GC or GC alone) in elderly patients with stage IV squamous NSCLC [Thatcher N et al. *Ann Oncol.* 2015].

Prespecified subgroup analyses (< 70 years: N + GC [n = 437], GC [n = 451] vs ≥ 70 years: N + GC [n = 108], GC [n = 97]) for efficacy were based on the randomized intent-to-treat population. Baseline patient characteristics were comparable between the subgroups. Exposure to N and GC treatment cycles was slightly lower in the ≥ 70-year subgroup; N continuation monotherapy was initiated in 53% of the < 70-year subgroup and in 43% of the ≥ 70-year subgroup. Both subgroups showed predictable toxicities with similar grade ≥ 3 adverse events (AEs) in both arms; however, the higher incidence of serious AEs in the N plus GC arm in both age groups was likely responsible for the higher proportion of patients discontinuing treatment in that arm.

Kaplan–Meier curves for OS of the < 70-year subgroup demonstrated a significant increase from 9.9 months (GC) to 11.7 months (N + GC; HR, 0.81; 95% CI, 0.70 to 0.94; $P = .006$). However, OS in the ≥ 70-year subgroup showed no significant benefit from the addition of N (9.7 months GC vs 10 months N + GC; HR, 1.03; 95% CI, 0.75 to 1.42; $P = .858$).

PFS in the < 70-year subgroup increased slightly (5.5 months GC to 5.7 months N + GC; HR, 0.82; 95% CI, 0.70 to 0.95; $P = .007$). However, PFS in the ≥ 70-year subgroup demonstrated no change in the 2 treatment arms (5.5 months GC vs 5.6 months N + GC; HR, 1.07; 95% CI, 0.77 to 1.49; $P = .686$). This age-related decrease in survival response is consistent with previous studies in patients with advanced NSCLC [Pirker R et al. *Lancet.* 2009; Ramalingam SS et al. *J Clin Oncol.* 2008].

Prof Thatcher concluded that treatment benefit with N plus GC was observed for patients aged < 70 years; however, for the ≥ 70-year subgroup of elderly patients (representing 19% of the SQUIRE population), there was no significant difference in OS or PFS between the treatment arms.

Novel Compound Beneficial as Adjunct to Antibody-Based Therapy for Stage IV NSCLC Patients

Written by Anita Misra-Press, PhD

Recent reports show that PGG beta-glucan, a novel immune cell modulator, increased objective response rates in patients with stage IV non–small cell lung cancer (NSCLC) when added to the first-line regimen of carboplatin/paclitaxel (C/P) chemotherapy and cetuximab, an EGFR-targeted antibody [Schneller F. *J Thorac Oncol.* 2014]. Bevacizumab is a vascular endothelial growth factor