Veliparib Plus Platinum Therapy Promising in NSCLC Phase 2 Trial

Written by Francesca Coltrera

A phase 2 randomized trial [NCT01560104] suggests that combining carboplatin and paclitaxel with veliparib—an oral poly (ADP-ribose) polymerase (PARP) inhibitor—may modestly extend progression-free survival (PFS) in certain patients with advanced non–small cell lung cancer (NSCLC), and a phase 3 trial has been initiated. Giorgio V. Scagliotti, MD, PhD, University of Turin, Turin, Italy, discussed the results of a study based on a poster by Julien Mazières, MD, PhD, Larrey Hospital-CHU, Toulouse, France, and colleagues.

PARP enzymes are essential to DNA repair pathways. PARP inhibitors act to undermine repairs to chemotherapy-induced DNA damage. In preclinical models, veliparib boosted efficacy of DNA-damaging platinum therapies. Some previous clinical trials—such as ECLIPSE [Spigel D et al. *J Thorac Oncol*. 2013], which combined iniparib with gemcitabine and carboplatin—indicated that PARP inhibitors may have only a marginal role to play in treating lung cancer, Prof Scagliotti commented. However, he added, BRCA-like behavior seen in certain tumors suggests potentially wider applications for PARP inhibitors.

Patients eligible for this multicenter double-blind trial had squamous or nonsquamous NSCLC, ≥ 1 measurable NSCLC lesion on computed tomography scan, no history of metastasis to the brain or primary central nervous system tumors on baseline magnetic resonance imaging, and an ECOG performance status ≤ 1. The investigators stratified patients by histology (49% squamous NSCLC) and smoking history (60% reported smoking within a year of beginning the study). Sixty-four percent of participants were men.

Among the study exclusions were 2 confirmed EGFR mutations (either exon 19 deletion or L858R mutation in exon 21), although patients with wild-type EGFR, status unknown, or other EGFR mutations were deemed eligible.

The primary end point was the effect of veliparib vs placebo on PFS. Secondary end points were overall survival (OS), objective response rate, duration of overall response, and regimen safety and tolerability.

In a 2:1 ratio, 158 patients were randomly assigned to receive carboplatin + paclitaxel (CP; n = 53) or veliparib + carboplatin + paclitaxel (VCP; n = 105; Table 1). Full chest and abdomen computed tomography scans were performed every 6 weeks and at the last visit to assess response based on the RECIST version 1.1 criteria [Eisenhauer EA et al. *Eur J Cancer*. 2009].

Table 1. Dose Regimen and Cycles

Dose regimen	Veliparib 120 mg or placebo BID on days 1 to 7 of 21 Carboplatin: 6 mg/mL/min on day 3 of 21 Paclitaxel: 200 mg/m^2 on day 3 of 21
Cycle	Up to six 21-day cycles
Mean no. of cycles	CP: 4.5 for carboplatin + 4.5 for paclitaxel VCP: 4.5 for carboplatin + 4.3 for paclitaxel

CP, carboplatin + paclitaxel; VCP, veliparib + carboplatin + paclitaxel.

Table 2. Trend in Squamous Subgroup Favors Veliparib

End Point	CP	VCP	HR (95% CI)
Progression-free survival	4.2	5.8	0.71 (0.50 to 1.13)
Nonsquamous	5.0	4.3	0.94 (0.52 to 1.71)
Squamous	4.1	6.1	0.50 (0.24 to 1.04)

CP, carboplatin + paclitaxel; VCP, veliparib + carboplatin + paclitaxel.

Adverse events (AEs) were common in the CP and VCP groups (any grade AE: 89% and 96%, respectively; ≥ grade 3 AE: 58% and 67%, respectively). Discontinuation due to AEs was 17% (CP) and 13% (VCP).

When data were analyzed, there was a statistically nonsignificant trend toward improvement in the primary end point, PFS, in favor of the veliparib-containing arm, with most of that improvement apparently coming in patients with squamous cell carcinoma (Table 2). There was also a trend toward improvement in OS favoring veliparib, although this also failed to reach statistical significance (9.1 months with CP vs 11.7 months with VCP; HR, 0.80; 95% CI, 0.54 to 1.18). Furthermore, duration of response was 3.3 and 6.9 months in the CP and VCP groups, respectively (HR, 0.11; 95% CI, 0.03 to 0.50).

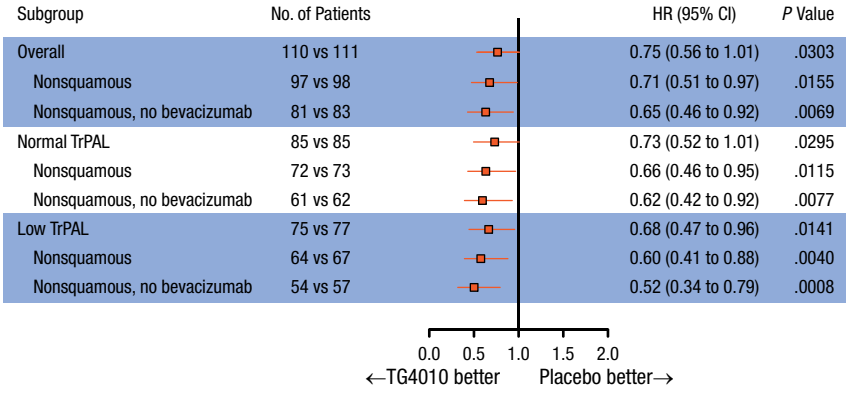
Combining veliparib with carboplatin and paclitaxel was well tolerated and offered modest though statistically insignificant improvements in PFS and OS in patients with squamous NSCLC. Given this encouraging trend, a phase 3 trial for this subgroup has begun.

TIME Trial: Efficacy of TG4010 Immunotherapy With First-Line Chemotherapy in NSCLC

Written by Anita Misra-Press, PhD

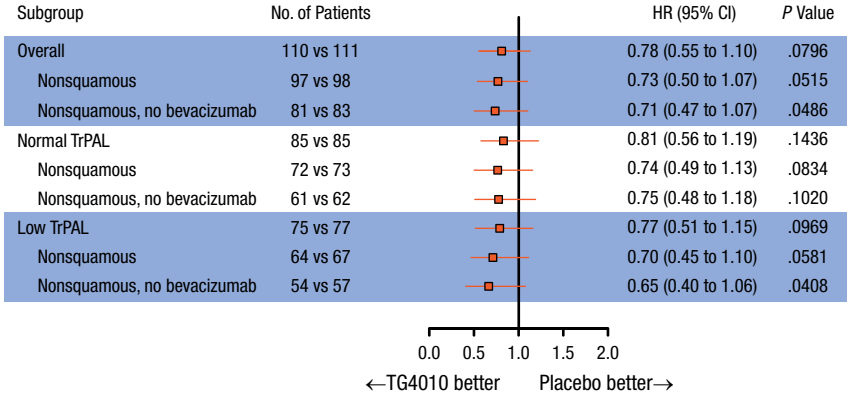
Lung cancer is emerging as a promising target for immunotherapy, with the PD-1 inhibitor nivolumab just recently approved by the FDA. Two categories of novel immunotherapies being evaluated include

Figure 1. Progression-Free Survival by Subgroup



The HR is from the unstratified Cox proportional hazards model. The *P* value (one-sided) is from the unstratified log-rank test.
TrPAL, triple-positive activated lymphocyte.
Reproduced with permission from E Quoix, MD.

Figure 2. Overall Survival by Subgroup



The HR is from the unstratified Cox proportional hazards model. The *P* value (one-sided) is from the unstratified log-rank test.
TrPAL, triple-positive activated lymphocyte.
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cancer vaccines and checkpoint inhibitors [Guibert N et al. *Ther Adv Respir Dis.* 2015]. Elisabeth Quoix, MD, The University Hospitals of Strasbourg, Strasbourg, France, and colleagues shared phase 2b results from TIME, a phase 2b/3 randomized, double-blind, placebo-controlled study comparing the efficacy of adding TG4010, a therapeutic cancer vaccine, to first-line treatment for stage IV non–small cell lung cancer (NSCLC) [Quoix E et al. *Ann Oncol.* 2015]. TG4010 is a modified attenuated poxvirus (Ankara strain) coding for MUC1 tumor-associated antigen and interleukin-2. The aim of the phase 2b study was to validate a normal level of triple-positive activated lymphocytes (TrPALs; including $CD16^+$, $CD56^+$, and $CD69^+$) as a predictive biomarker for TG4010 efficacy. The primary end point was progression-free survival (PFS) assessed by RECIST 1.1, while the secondary end points included overall response rates, safety, overall survival (OS), and subgroup analysis.

The trial enrolled 221 patients with untreated NSCLC and an *MUC1* mutation. Patients were stratified by TrPAL levels (normal vs high) and then randomized 1:1 to receive TG4010 (subcutaneous injection, 10^8 PFU weekly over 6 weeks, once every 3 weeks thereafter until progression) or placebo in combination with chemotherapy (21-day cycles for 4-6 cycles). Bayesian analysis of PFS in patients with normal TrPAL levels (n = 170) treated with

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