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