Progression-Free Survival Not Improved With Cabazitaxel Versus Topotecan in Refractory SCLC

Written by Rita Buckley

A randomized, open-label Phase 2 trial with patients who had small cell lung cancer (SCLC) that had progressed during or after first-line platinum-based chemotherapy found no significant difference in progression-free survival (PFS) with cabazitaxel against topotecan, the current standard for comparison [Riemsma R et al. *BMC Cancer* 2010]. The median overall survival (OS) was shorter for patients taking cabazitaxel versus those taking topotecan [NCT01500720].

The authors of the study sought to determine the efficacy of cabazitaxel, a next-generation taxane shown to be safe and effective as second-line treatment of metastatic castrate-resistant prostate cancer (mCRPC) and other advanced solid tumors [de Bono JS et al. *Lancet* 2010; Dieras V et al. *Eur J Cancer* 2013; Fumoleau P et al. *BMC Cancer* 2013; Pivot X et al. *Ann Oncol* 2008] versus topotecan as second-line treatment of SCLC. Two randomized studies demonstrated the efficacy of topotecan in relapsed SCLC [Ardizzoni A et al. *J Clin Oncol* 1997; von Pawel J et al. *J Clin Oncol* 1999]. No other agent has shown superior clinical activity.

One hundred seventy-nine patients with locally advanced or metastatic SCLC were randomly assigned to intravenous (IV) cabazitaxel 25 mg/m^2 (Day 1 every 3 weeks; n=91) or IV topotecan 1.5 mg/m^2 (Days 1 to 5, every 3 weeks; n=88). The patients were divided into 2 subgroups: chemosensitive (progression ≥90 days; n=91) or chemorefractory (progression during or within 90 days; n=88). They were also separated by the presence or the absence of brain metastasis and by plasma concentration of lactate dehydrogenase (LDH; less than or equal to vs greater than the upper limit of normal).

Key eligibility criteria included Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤1, 1 round of prior chemotherapy, and no prior treatment with a taxane or with topotecan.

Tracey L. Evans, MD, Abramson Cancer Center, Philadelphia, PA, USA, presented results for the primary endpoint of improvement in PFS and the secondary endpoints of OS, tumor response rate, and adverse events from this multinational trial. Other secondary endpoints are disease progression-free rate at 12 weeks, duration of response, and health-related quality of life (HRQoL).

The median age of the patients was 61 years. Baseline characteristics were balanced between treatment arms; approximately 50% of patients in each arm were chemorefractory. Patients received a median number of 2 cycles of cabazitaxel and 4 cycles of topotecan.

Median PFS was 1.4 months with cabazitaxel and 3.0 months with topotecan in the intention-to-treat (ITT) analysis. The study failed to meet the primary endpoint of improvement in PFS with cabazitaxel versus topotecan (log-rank test 2-sided, p<0.0001); hazard ratio (HR), 2.169; 95% CI, 1.563 to 3.010). The median PFS was similar to the overall results in the chemosensitive (1.5 vs 3.8 months) and chemoresistant (1.4 vs 2.7 months) subgroups. The tumor response rates by ITT analysis for the overall study population and for the 2 subgroups are detailed in Table 1.

The OS was 5.2 months with cabazitaxel and 6.8 months with topotecan in the ITT population (log-rank test 2-sided, p=0.0125; HR, 1.57; 95% CI, 1.10 to 2.25). Similar results were seen for OS with the

Table 1. The Objective Tumor Response Rate in the Intention-to-Treat Analysis

	Overall		Chemorefractory		Chemosensitive	
Response, n (%)	Cabazitaxel (n=73)	Topotecan (n=79)	Cabazitaxel (n=35)	Topotecan (n=37)	Cabazitaxel (n=38)	Topotecan (n=42)
Complete response	0	0	0	0	0	0
Partial response	0	8 (10.1)	0	3 (8.1)	0	5 (11.9)
Stable disease	16 (21.9)	50 (63.3)	5 (14.3)	21 (56.8)	11 (28.9)	29 (69.0)
Disease progression	51 (69.9)	18 (22.8)	28 (80.0)	11 (29.7)	23 (60.5)	7 (16.7)
Not evaluable/ missing data	6 (8.2)	3 (3.8)	2 (5.7)	2 (5.4)	4 (10.5)	1 (2.4)

subgroups (6.3 vs 7.2 months chemosensitive; 3.4 vs 5.7 months chemorefractory).

Treatment-emergent adverse events (TEAEs) were more frequent with topotecan. Any TEAE of any grade occurred in 94.3% of the topotecan and 88.8% of the cabazitaxel groups, and ≥grade 3 TEAE occurred in 71.6% and 58.4%, respectively. Overall, 29 deaths resulted from TEAEs. TEAEs that led to death and were considered possibly related to treatment were neutropenic infection in 3 patients, febrile neutropenia in 2 patients, neutropenic sepsis in 1 patient, and cardiopulmonary failure in 1 patient.

Randomized, Prospective Trial of Customized Neoadjuvant Versus Standard Chemotherapy Gets Underway

Written by Rita Buckley

The first prospective, multicenter, randomized Phase 2 study to test the use of customized chemotherapy (CT) in locally advanced stage IIIA (N2) non–small cell lung cancer (NSCLC) is currently recruiting patients. The rationale and design of the Customized Neoadjuvant Versus Standard Chemotherapy in NSCLC Patients With Resectable Stage IIIA (N2) Disease trial [CONTEST; NCT01784549] were presented in a poster session.

The most powerful prognostic factor in stage IIIA NSCLC is clearance of mediastinal lymph nodes and pathologic complete response (pCR). A pCR is obtained in 5% to 15% of patients with a significantly prolonged survival. The discovery of predictive molecular tumor biomarkers, such as mutations in the epidermal growth factor receptor (EGFR), has sparked interest in their use for delivery of individualized treatment strategies to increase response rate and survival of patients with NSCLC.

The hypothesis of this study is that NSCLC patients who receive therapy determined by their baseline histology and tumor marker levels will attain higher response rates than patients in the control arm who receive standard CT. At 18 sites, a total of 168 subjects (112 in the investigational arm, and 56 in the standard care arm) with resectable stage IIIA (N2) NSCLC will be centrally randomized in a 2:1 ratio to receive before resection either standard CT with cisplatin (CDDP) plus docetaxel (Doc) or 1 of 6 customized CT arms using predetermined values for excision repair cross-complementation group 1 (ERCC1), ribonucleotide reductase M1 (RRM1), thymidylate synthase (TS), and EGFR mutations. These arms, by biomarker, are

- EGFR+: gefitinib
- EGFR–/nonsquamous (NS)/TS–/ERCC1–: CDDP + pemetrexed
- EGFR–/squamous (S) or NS/TS+/ERCC1–/RRM1+: CDDP + Doc
- EGFR–/S or NS TS+/ERCC1–/RRM1–: CDDP + gemcitabine (Gem)
- EGFR–/S or NS TS+/ERCC1+/RRM1+: Doc + vinorelbine
- EGFR–/S or NS TS+/ERCC1+/RRM1–: Doc + Gem

The primary endpoint is pCR at 30 days, on independent pathology review, using an intention-to-treat analysis. Secondary outcomes are overall survival (OS), disease-free survival (DFS), and overall survival at 1, 2, and 5 years; overall response; and safety. Biological and tissue samples will be collected for exploratory molecular-profiling analyses and biomarker studies.

Specimens will be sent to Response Genetics (Los Angeles, CA, USA) for the evaluation of ERCC1, RRM1, and TS using reverse transcription polymerase chain reaction (RT-PCR). EGFR mutations will be assessed with Sanger sequencing.

Every 4 months for 3 years, and then every 6 months for 2 years following surgery, patients will be assessed for adverse events related to the study drugs, and their therapies received after the study, DFS, and survival will be documented. Periodic evaluation of the trial data will be conducted by an independent data-monitoring committee to ensure patient safety and the validity and scientific merit of the study. The final analysis will be conducted after the targeted number of events (pCR) is reached, or in 24 months, after study initiation.

The study is designed to determine the feasibility of the customized treatment approach and the logistical problems associated with a biomarker-driven strategy in NSCLC.