

# Phase III Trial Comparing Paclitaxel Poliglumex (CT-2103, PPX) in Combination with Carboplatin Versus Standard Paclitaxel and Carboplatin in the Treatment of PS 2 Patients with Chemotherapy-Naïve Advanced Non-small Cell Lung Cancer

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**Introduction:** Performance status (PS) 2 patients with non-small cell lung cancer (NSCLC) experience more toxicity, lower response rates, and shorter survival times than healthier patients treated with standard chemotherapy. Paclitaxel poliglumex (PPX), a macromolecule drug conjugate of paclitaxel and polyglutamic acid, reduces systemic exposure to peak concentrations of free paclitaxel and may lead to increased concentrations in tumors due to enhanced vascular permeability.

**Methods:** Chemotherapy-naïve PS 2 patients with advanced NSCLC were randomized to receive carboplatin (area under the curve = 6) and either PPX (210 mg/m<sup>2</sup>/10 min without routine steroid premedication) or paclitaxel (225 mg/m<sup>2</sup>/3 h with standard premedication) every 3 weeks. The primary end point was overall survival.

**Results:** A total of 400 patients were enrolled. Alopecia, arthralgias/myalgias, and cardiac events were significantly less frequent with PPX/carboplatin, whereas grade  $\geq 3$  neutropenia and grade 3 neuropathy showed a trend of worsening. There was no significant difference in the incidence of hypersensitivity reactions despite the

absence of routine premedication in the PPX arm. Overall survival was similar between treatment arms (hazard ratio, 0.97; log rank  $p = 0.769$ ). Median and 1-year survival rates were 7.9 months and 31%, for PPX versus 8 months and 31% for paclitaxel. Disease control rates were 64% and 69% for PPX and paclitaxel, respectively. Time to progression was similar: 3.9 months for PPX/carboplatin versus 4.6 months for paclitaxel/carboplatin ( $p = 0.210$ ).

**Conclusion:** PPX/carboplatin failed to provide superior survival compared with paclitaxel/carboplatin in the first-line treatment of PS 2 patients with NSCLC, but the results with respect to progression-free survival and overall survival were comparable and the PPX regimen was more convenient.

**Key Words:** Non-small cell lung cancer, Paclitaxel poliglumex, PPX, CT-2103, PS 2, Toxicity.

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Patients with non-small cell lung cancer (NSCLC) usually present with inoperable, advanced disease. Untreated, these patients have a 1-year survival rate of approximately 10%.<sup>1</sup> Combination chemotherapy regimens provide a statistically significant survival benefit, with 1-year survival rates of 30% to 40% in performance status (PS) 0 to 1 individuals and 2-year survival rates exceeding 10%.<sup>2–5</sup> Retrospective reviews and meta-analyses of phase III trials have shown that patients with compromised PS (e.g., PS 2) have significantly impaired survival compared with PS 0 to 1 patients.<sup>6–8</sup> This may be due to highly aggressive disease or comorbid conditions and impaired organ function, which can exacerbate chemotherapy toxicity. Consequently, PS 2 patients are often excluded from chemotherapy trials. Toxicity may deter clinicians from using standard platinum-based combination regimens for PS 2 patients, who often receive palliative care or single-agent, non-platinum therapy instead.

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A recent, prospectively planned subanalysis of Cancer and Leukemia Group B (CALGB) 9730, however, demonstrated that PS 2 patients benefited from platinum-based combination therapy compared with a single agent.<sup>9</sup> Of the nearly 600 patients enrolled in CALGB 9730, 99 were PS 2. Within this cohort, overall response rate, median survival, and 1- and 2-year survival rates were 24%, 4.7 months, 18%, and 9% for the paclitaxel/carboplatin regimen versus 10%, 2.4 months, 10%, and 0% for single-agent paclitaxel.

Paclitaxel poliglumex (PPX) is an anionic, polymeric macromolecule consisting of paclitaxel conjugated to glutamic acid residues.<sup>10</sup> The large number of anionic charges renders this molecule water soluble. The ester bond between paclitaxel and the polyglutamate backbone is stable and resistant to spontaneous hydrolysis; therefore, PPX is not broken down by plasma esterases. Consequently, the circulating polymer is relatively less toxic to normal tissue and theoretically better at delivering paclitaxel to the target cells.<sup>11</sup> Aqueous solubility also permits rapid intravenous administration and obviates the need for toxic solubilizing agents such as Cremophor. Finally, this molecule capitalizes on enhanced tumor permeability and retention of macromolecules to maximize tumor paclitaxel exposure.

Preclinical models demonstrated activity in NSCLC lines and synergy with platinating agents, including carboplatin.<sup>12,13</sup> In a phase II trial of 28 patients with treatment-naïve advanced NSCLC, PPX at a dose of 175 mg/m<sup>2</sup> every 3 weeks yielded a median survival of 8.1 months in a PS 0 to 1 population and 5.4 months in a PS 2 cohort. In phase I trials, PPX has been combined at doses as high as 225 mg/m<sup>2</sup> every 3 weeks with carboplatin (area under the curve [AUC] = 6) without untoward short-term toxicity.<sup>14</sup> Based on cumulative neurotoxicity, the recommended phase II dose in this setting was 210 mg/m<sup>2</sup>.

The observations from the phase II single-agent trial, the ability to combine PPX at full dose with standard doses of carboplatin, its convenient administration, and the potential of decreased toxicity compared with standard paclitaxel laid the groundwork for a phase III trial, PGT303. This trial, also known as Selected Targeted Efficacy in Lung Cancer to Lower Adverse Reactions 3 (STELLAR 3), compared standard paclitaxel/carboplatin with PPX/carboplatin in PS 2 patients.

## MATERIALS AND METHODS

### Study Design

This open-label, phase III study compared paclitaxel 225 mg/m<sup>2</sup> with PPX at 210 mg/m<sup>2</sup> each in combination with carboplatin (AUC = 6) given every 3 weeks for up to 6 cycles. Patients were excluded from the study for disease progression (PD), intolerable toxicity, withdrawal of consent, or investigator discretion.

Randomization was stratified based on disease stage (IV versus other), gender, history of brain metastases, and geographic location (US versus Western Europe/Canada versus Eastern Europe).

Antiemetic prophylaxis was permitted for carboplatin including dexamethasone to prevent delayed nausea and

vomiting. The paclitaxel arm required routine hypersensitivity prophylaxis; however, the use of routine antihistamines or hypersensitivity prophylaxis was prohibited on the PPX arm. Hematopoietic growth factor support was permitted according to American Society of Clinical Oncology guidelines.<sup>15</sup>

### End Points

The primary study end point was survival. Secondary objectives included response rate, time to progression (TTP), safety, and quality of life. Radiographic response was assessed every 2 cycles. For patients who completed therapy without evidence of PD, indicator lesions were re-evaluated every 8 weeks until documentation of PD or start of second-line therapy.

Safety data were collected on all patients. Disease-related symptoms were measured by the Functional Assessment of Cancer Therapy Lung Cancer Subscale (FACT-LCS) at baseline and within 3 days of each treatment.

### Eligibility Criteria

All enrollees had histologically or cytologically confirmed NSCLC, an Eastern Cooperative Oncology Group (ECOG) PS 2 and stage IV, stage IIIB (but not candidates for combined modality therapy with curative intent), or locally advanced or recurrent disease previously treated with radiation and/or surgery. Eligibility stipulated age  $\geq 18$  years; adequate organ function, including baseline absolute neutrophil count  $\geq 1500/\mu\text{L}$ ; platelet count  $\geq 100,000/\mu\text{L}$ ; creatinine  $\leq 1.5$  times the upper limit of normal (ULN); bilirubin  $\leq$  ULN; transaminases  $\leq 2.5$  times ULN ( $\leq 5$  times ULN in patients with hepatic metastases); and alkaline phosphatase  $\leq 2.5$  times ULN, unless bone metastases were present. Patients with stable, treated brain metastases were eligible. Adequate contraception was required for female patients of reproductive potential.

Exclusion criteria included any small cell or carcinoma histology; prior systemic therapy for NSCLC; active, untreated brain metastases; other active primary invasive malignancies requiring treatment; grade  $\geq 2$  neuropathy; clinically significant infection; exposure to other investigational agents within 4 weeks of study entry; and unstable concomitant medical conditions. The protocol was approved by the institutional review board at each participating institution. All patients gave informed consent.

Representative case report forms were carefully reviewed to make certain that patient characteristics supported PS 2 designations.

### Efficacy Parameters and Statistical Considerations

Overall survival was defined as the interval between randomization and death from any cause. Patients remaining alive, including those lost to follow-up, were censored at the date of last contact. Nonstratified log-rank testing was used for the formal primary comparison of survival. This study targeted accrual of 370 evaluable patients with 80% power and 0.05 type I error to show a 1.5-month improvement in median survival from a projected baseline of 4 to 5.5 months. In addition, secondary analyses were conducted using Cox



regression models of prognostic factors associated with survival in patients with NSCLC.

Response was assessed by response evaluation criteria in solid tumors.<sup>16</sup> Disease control was determined by the percentage of patients alive without PD for at least 12 weeks. A two-sided Fisher exact test with an  $\alpha$  level of 0.05 for statistical significance was used. TTP was defined as the interval between randomization and PD and was analyzed using an unstratified log-rank test. Toxicities were compared between the treatment arms using the Fisher's exact test.

### Quality of Life

Disease-related symptoms were measured by the FACT-LCS, a validated, five-point Likert-type scale ranging from 0 (not at all) to 4 (very much). The total LCS score ranged from 0 to 28, with higher scores indicative of fewer symptoms. The percentage of patients with at least two-point improvements in their LCS scores at the beginning of cycle 2 was compared by treatment arm.

## RESULTS

### Disposition of Patients

Four hundred patients were enrolled between December 2002 and December 2003; 199 patients were assigned to the PPX arm and 201 to the paclitaxel arm. Three patients, all in the paclitaxel treatment arm, did not receive study treatment: one developed PD before starting therapy, a second had an elevated baseline bilirubin and did not meet eligibility criteria, and a third was withdrawn from the study due to rapid PD and intercurrent pneumonitis.

The arms were well balanced with regard to baseline characteristics (Table 1). Seventy-seven percent of patients were male, 94% white, and 63% from Eastern Europe. Median age was 61 years on the PPX arm and 63 years on the paclitaxel arm. Seventy-three percent of patients had stage IV disease, and 7% had brain metastases at baseline. Russia contributed the largest proportion of patients (35%), followed by the United States (23%). The differences between Eastern European enrollees and their Western European, US, and Canadian counterparts are delineated in Table 2.

### Treatment Completion Rates

The median number of cycles was four in each arm. In the PPX arm, 27% of patients completed six cycles of therapy compared with 36% in the paclitaxel arm ( $p = 0.0411$ ; Fisher's exact test). The most frequent reasons for stopping treatment were PD (36% versus 34%, respectively) and adverse effects (27% versus 20%, respectively). Nine percent of patients withdrew consent in the PPX arm compared with 6% in the paclitaxel arm.

### Efficacy

Median overall survival was 7.8 months in the PPX arm and 7.9 months in the paclitaxel arm (Fig. 1A). One-year survival was identical at 31%. The 18- and 24-month survival rates were numerically higher in the PPX arm (20 and 13%, respectively) compared with the paclitaxel arm (11 and 11%, respectively), but these differences were not statistically significant.

**TABLE 1.** Demographic and Baseline Characteristics

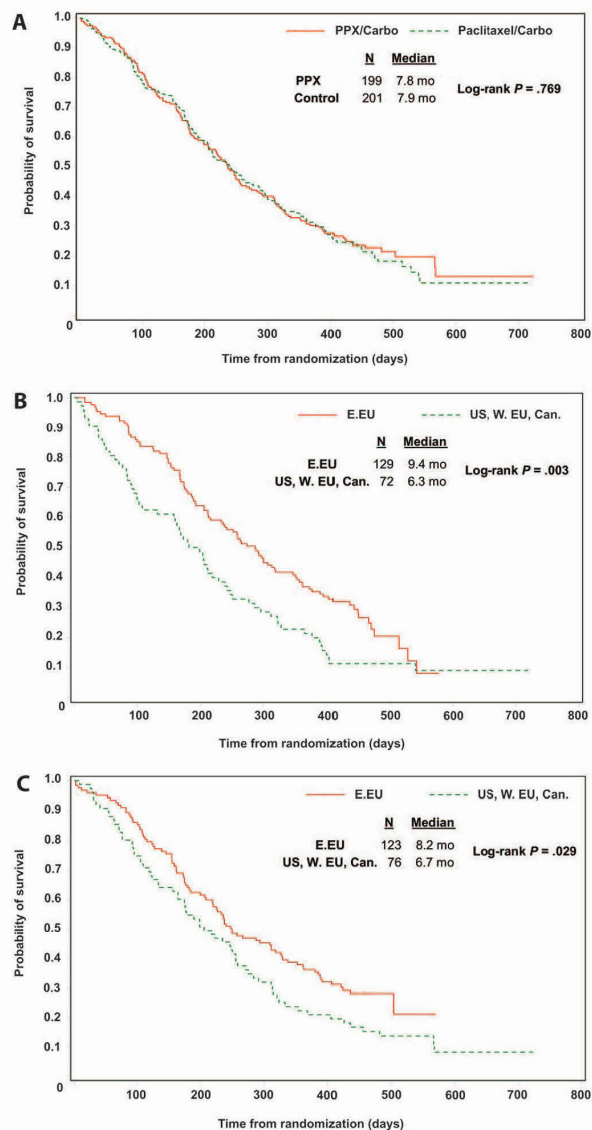
	PPX/Carboplatin (n = 199)	Paclitaxel/Carboplatin (n = 201)
Gender		
Male	151 (76%)	156 (78%)
Female	48 (24%)	45 (22%)
Race		
White	189 (95%)	188 (94%)
Black	8 (4%)	9 (5%)
Asian	2 (1%)	1 (<1%)
Hispanic	0 (0%)	2 (1%)
Other	0 (0%)	1 (<1%)
Age at randomization, (yr)		
Mean (SD)	61.1 (10.6)	61.5 (10.1)
Median (range)	61.0 (35–86)	63.0 (36–89)
Geographic site		
United States	46 (23%)	45 (22%)
Western Europe and Canada	30 (15%)	27 (13%)
Eastern Europe	123 (62%)	129 (64%)
Stage at randomization		
IIIa	2 (1%)	0 (0%)
IIIb	51 (26%)	55 (27%)
IV	146 (73%)	146 (73%)
History of brain metastases		
Yes	14 (7%)	15 (7%)
No	185 (93%)	186 (93%)
Smoking history		
Yes	170 (85%)	171 (85%)
No	29 (15%)	30 (15%)

PPX, paclitaxel poliglumex; SD, standard deviation.

**TABLE 2.** Demographic and Baseline Characteristics at Entry Based on Region

Region	US/Western Europe/Canada (n = 148)	Eastern Europe (n = 252)
≥5% weight loss within 6 mo of randomization	58 (39%)	104 (41%)
Histologic diagnosis		
Squamous cell carcinoma	43 (29%)	134 (53%)
Adenocarcinoma	78 (53%)	72 (29%)
Other	27 (18%)	46 (18%)
Stage at enrollment		
Stage IV/recurrent	122 (82%)	170 (67%)
Stage IIIb	26 (18%)	80 (32%)
History of brain metastases	21 (14%)	8 (3%)
Prior radiation	47 (32%)	40 (16%)
Median FACT-LCS score	18.7	17.0
Current use of tobacco	46 (31%)	113 (45%)
Baseline opioid use	19 (13%)	12 (5%)
Baseline hemoglobin ≥11 g/dL	110 (74%)	220 (87%)

FACT-LCS, functional assessment of cancer therapy lung cancer subscale.



**FIGURE 1.** Overall survival using Kaplan-Meier estimation. (A) Paclitaxel poliglumex/carboplatin versus paclitaxel/carboplatin. (B) Paclitaxel/carboplatin—United States/Western Europe/Canada versus Eastern Europe. (C) PPX/carboplatin—United States/Western Europe/Canada versus Eastern Europe.

Prespecified analyses by stratification factors (Table 3) demonstrated that median survival in the paclitaxel arm was significantly better in Eastern Europe and Russia than in the United States and Western Europe (9.4 versus 6.3 months;  $p = 0.003$ ; Fig. 1B). There was less difference in median survival on the PPX arm (8.2 versus 6.7 months;  $p = 0.029$ ; Fig. 1C). Women on the paclitaxel arm had a median survival similar to those in the experimental arm (8.3 versus 7.9 months). However, at 12, 18, and 24 months, survival rates

were better on PPX compared with paclitaxel (37 versus 25%, 26 versus 5%, and 13 versus 5%, respectively). Survival for men was similar in both arms with virtually identical median survival (7.9 versus 7.9 months) and 1- (29 versus 33%) and 2-year (13 versus 13%) survival rates.

Cox multivariate stepwise modeling, with all other factors constant, demonstrated that weight loss before study entry, tobacco use, elevated lactate dehydrogenase levels, and elevated calcium levels significantly increased the probability of death.

### Response and TTP

The overall response rate was 20% for the PPX arm with 1% complete responses and 37% for the paclitaxel arm with 2% complete responses; these results significantly favored the paclitaxel arm (Table 4). Blended response rates differed by geographic region: 35% for Eastern Europe, 23% for Western Europe and Canada, and 14% for the United States. Disease control rate was 64% in the PPX arm, compared with 69% in the paclitaxel arm.

Median TTP was 3.9 months in the PPX arm and 4.6 months on the paclitaxel arm ( $p = 0.210$ ). The proportion of patients receiving subsequent therapy and the type of therapy administered were not different in the 2 arms. Eighteen percent of those enrolled in the PPX arm went on to radiation therapy, compared with 13% in the paclitaxel arm. Nearly 50% in each arm received additional chemotherapy; no specific agents predominated. Roughly 7% of patients received epidermal growth factor receptor tyrosine-kinase inhibitors as second-line or subsequent therapy.

### Quality of Life

FACT-LCS evaluations were completed by 180 patients on the PPX/carboplatin arm and 172 patients on the paclitaxel/carboplatin arm. No significant difference in the FACT-LCS scores was seen.

### Toxicity

#### Drug Delivery

Patients received nearly 90% of planned doses during the second and subsequent cycles. The mean delivered dose intensity per cycle was comparable in both arms. In Eastern Europe, 75% of patients received 4 to 6 cycles, compared with 44 and 49% in the United States and Western Europe/Canada, respectively. The mean normalized carboplatin dose per cycle per patient was the same for both arms (AUC = 5.6).

#### Relative Toxicities

Patients enrolled in the paclitaxel arm were significantly more likely to experience cardiac toxicity, alopecia, and musculoskeletal toxicity (Table 5). However, those in the PPX arm experienced significantly more nausea and vomiting. More grade 3/4 neuropathy was seen on the PPX arm (17 versus 10%), but this difference was not statistically significant. Time to first manifestation of neuropathy was generally later in the PPX arm—a median of 89 days compared with 54 days for the paclitaxel arm (log-rank  $p < 0.001$ ). By day 100, the incidence was equal. Fatigue was higher in the PPX arm than the paclitaxel arm: 15 versus 8% ( $p = 0.05$ ); however,



**TABLE 3.** Subgroup Analysis of Overall Survival

Subgroup	PPX/Carboplatin		Paclitaxel/Carboplatin		Hazard Ratio <sup>a</sup>	Log-Rank Test; <i>p</i>
	<i>n</i>	Median Survival, d (95% CI)	<i>n</i>	Median Survival, d (95% CI)		
Overall	199	237 (205–271)	201	239 (206–287)	0.97 (0.78–1.21)	0.769
Gender						
Male	151	237 (199–275)	156	239 (204–288)	1.04 (0.80–1.34)	0.780
Female	48	236 (174–380)	45	248 (167–323)	0.76 (0.48–1.20)	0.239
Geographic location						
United States	46	217 (164–291)	45	173 (100–248)	0.79 (0.50–1.23)	0.298
Western Europe/Canada	30	188 (118–275)	27	206 (103–322)	1.08 (0.63–1.86)	0.773
Eastern Europe	123	249 (219–326)	129	287 (233–347)	1.00 (0.75–1.33)	0.992
Disease stage at randomization						
IV	146	237 (189–283)	146	236 (205–277)	0.92 (0.71–1.19)	0.528
Other	53	246 (182–311)	55	274 (181–404)	1.09 (0.70–1.70)	0.715
History of brain metastases						
Yes	14	207 (145–320)	15	229 (87–328)	1.13 (0.51–2.50)	0.770
No	185	237 (206–275)	186	239 (206–292)	0.97 (0.77–1.22)	0.778

<sup>a</sup> Hazard ratio (CT-2103 to paclitaxel) was estimated by Cox regression with treatment arm as a single covariate. PPX, paclitaxel poliglumex; CI, confidence intervals.

**TABLE 4.** Efficacy Results in the Intent-to-Treat Population

	PPX/Carboplatin	Paclitaxel/Carboplatin
No. patients	199	201
Survival		
Median (d)	237	239
95% CI	205–271	206–287
Hazard ratio (95% CI); log-rank <i>p</i> value	0.97 (0.78–1.21); 0.769	
1-yr survival rate (%)	31	31
95% CI	24–37	25–38
2-yr survival rate (%)	13	11
95% CI	5–22	4–18
Time to progression		
Median (d)	118	139
95% CI	100–129	118–156
Hazard ratio (95% CI); log-rank <i>p</i> value	1.14 (0.93–1.40); 0.210	
Disease control, % (95% CI)	64 (57–70)	69 (62–75)
Response rate (patients with measurable disease only)		
No. patients	191	192
PR + CR, % (95% CI)	20 (15–27)	37 (30–44)
Confirmed PR + CR, % (95% CI)	13 (9–19)	28 (22–35)

PPX, paclitaxel poliglumex; CI, confidence intervals; PR, partial response; CR, complete response.

grade 3/4 fatigue was similar between arms: 2 versus 3% ( $p = 0.66$ ).

The incidence of grade 3/4 thrombocytopenia was significantly higher in the PPX arm ( $p < 0.001$ ) but was not associated with more thrombocytopenic bleeding or higher transfusion requirements. Five percent of patients on the PPX

arm required platelet transfusions, compared with 3% on the paclitaxel arm ( $p = 0.42$ ). The incidence of febrile neutropenia was 6% in the PPX arm versus 3% in the paclitaxel arm ( $p = 0.32$ ). The reported incidence of neutropenia in Eastern Europe was 24%, compared with 47% in the United States and 42% in Western Europe/Canada. The use of supportive care, including transfusions, erythropoietin, and granulocyte colony-stimulating factor, was similar between treatment arms but different based on geographic regions. The use of red blood cell growth factor support in the United States/Western Europe/Canada was 38% compared with less than 1% in Eastern Europe ( $p < 0.001$ ); the use of white blood cell growth factor support in the United States/Western Europe/Canada was 31% compared with 7% in Eastern Europe ( $p < 0.001$ ). Seven percent of those in Eastern Europe required red blood cell transfusions compared with 16% in the United States/Western Europe/Canada ( $p = 0.006$ ).

Twelve percent of patients in each arm died within 30 days of treatment, but only 1% of all deaths were attributable to study drugs. There were 7.5% disease-related deaths, and 3.5% were due to comorbidities.

Total infusion time for the PPX combination was 48 minutes, compared with 224 minutes for the paclitaxel combination. The incidence of hypersensitivity reactions was 2% for the paclitaxel/carboplatin arm with standard premedications of steroids and H1 and H2 blockers, compared with 1% for the PPX/carboplatin arm without routine hypersensitivity reaction prophylaxis. However, 28% of PPX patients, mostly in the United States and Canada, received steroid prophylaxis and/or antihistamines beginning in cycle 1 as antiemetic prophylaxis for carboplatin.

## DISCUSSION

STELLAR 3 is the first dedicated phase III trial ever conducted and reported in treatment-naïve PS 2 patients with

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