Randomized Phase III Trial Comparing Single-Agent Paclitaxel Poliglumex (CT-2103, PPX) with Single-Agent Gemcitabine or Vinorelbine for the Treatment of PS 2 Patients with Chemotherapy-Naïve Advanced Non-small Cell Lung Cancer

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Background: Patients with advanced non-small cell lung cancer (NSCLC) and impaired performance status (PS ≥ 2) have limited life expectancies and decreased tolerance for drug-induced toxicities. Current treatment guidelines indicate that PS 2 patients benefit from systemic therapy. Further refinement of treatment in these patients requires reduction of treatment-associated toxicities while maintaining or improving efficacy. Paclitaxel poliglumex (PPX), a macromolecular polymer–drug conjugate of paclitaxel and poly-L-glutamic acid, may enhance the therapeutic index of paclitaxel.

Methods: Chemotherapy-naive PS 2 patients with advanced NSCLC randomly received single-agent PPX (175 mg/m^2) or a comparator (single-agent vinorelbine or gemcitabine). The primary end point of this study was overall survival.

Results: Overall survival was similar between treatment arms (hazard ratio [HR] = 0.95; log-rank p = 0.686). Median and 1-year survival were 7.3 months and 26%, respectively, for PPX versus 6.6 months and 26% for the control arm. There was a nonsignificant trend toward improved survival in women in the PPX arm compared with standard single agents (HR = 0.65; p = 0.069). The most frequent grade 3/4 adverse events in the treatment versus control arm were dyspnea (13% versus 17%, respectively) and fatigue (10% versus 9%). Grade 3/4 neutropenia and anemia were reduced in the PPX arm (2% versus 8% and 3% versus 9%, respectively). Neuropathy, a taxane-specific toxicity, was more common in the PPX arm; grade 3 neuropathy was limited to 3%.

Conclusions: Single-agent PPX, dosed at 175 mg/m^2, is active and well tolerated in PS 2 patients with advanced NSCLC. Patients on PPX required fewer red blood cell transfusions, hematopoietic growth factors, opioid analgesics, and clinic visits than patients receiving gemcitabine or vinorelbine.

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

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Nonsmall cell lung cancer (NSCLC) is one of the most common malignancies worldwide and is the leading cause of cancer-related deaths in western countries.[1–3] Of the approximately 172,000 new cases and 164,000 lung cancer-related deaths, an estimated 90% were due to NSCLC for the year 2005 in the United States.[4,5] Most patients present with disease beyond the scope of surgical cure.

Performance status (PS) 2 patients have significantly shorter survival than less symptomatic patients, and most

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TABLE 1. Outcome of PPX and Comparators Used in PS 2 Patients: Trial Results Compared with Historical Results

Reference	Drug	*N*	Median Survival, mo	1-yr Survival
Lilenbaum et al.[6]	Paclitaxel	50	2.4	10%
Perrone et al.[7]	Vinorelbine	45	3.5	20%
Perrone et al.[7]	Gemcitabine	41	4.2	18%
Neubauer et al.[18]	Gemcitabine	42	4.8	20%
Kosmidis et al.[19]	Gemcitabine	47	4.8	18%
Current study	Vinorelbine	32	6.1	7%
Current study	Gemcitabine	155	6.7	29%
Current study	PPX	191	7.3	26%

PPX indicates paclitaxel poliglumex; PS, performance status.

chemotherapy trials exclude these patients because of reports of increased toxicities. The median survival for single-agent first-line therapy for PS 2 patients with advanced NSCLC ranges from 2.4 months for paclitaxel[6] to 3.5 months for vinorelbine[7] and 4.8 months for gemcitabine[7] (Table 1). This is not much different than the reported survival benefit achieved with combination therapy, but the trade-off is a lower incidence of toxicities.[6,8–10] One study demonstrated a survival benefit for carboplatin/paclitaxel versus paclitaxel alone in a prospectively defined subset analysis of 99 PS 2 patients (median survival = 4.7 versus 2.4 months, respectively).[6] In a PS 2 subset analysis of a study of gemcitabine, vinorelbine, or a combination of the two, there was no survival benefit for the combination (median survival = 3.5 versus 4.2 months, respectively).[7] Because PS 2 patients are less tolerant of therapy and only receive limited clinical benefit, American Society of Clinical Oncology, European, and National Comprehensive Cancer Network guidelines and a European expert panel suggest that single-agent therapy with drugs having demonstrated activity is appropriate in PS 2 patients.[11–13] In a phase II trial of 28 elderly patients or treatment-naive PS 2 patients with advanced NSCLC, PPX at a dose of 175 mg/m^2 every 3 weeks yielded a median survival of 8.1 month in a PS 0-1 population and 5.4 months in a PS 2 cohort.

Paclitaxel poliglumex (PPX) is a conjugate that links paclitaxel to a biodegradable polymeric backbone consisting of L-glutamic acid residues.[14] PPX is water soluble and minimally immunogenic, allowing administration by 10- to 20-minute peripheral vein infusion without routine premedication. Following infusion of PPX, plasma concentrations of conjugated taxanes decline biphasically with a distribution phase of approximately 48 hours, followed by a long terminal half-life of 108 to 261.5 hours. PPX is relatively stable in circulation; the area under the curve of unconjugated paclitaxel is 1 to 2% of the area under the curve of conjugated paclitaxel. The total systemic exposure to unconjugated paclitaxel is similar after administration of equivalent doses of PPX and standard paclitaxel; however, the C_{max} values for paclitaxel are significantly lower in patients treated with PPX,[15] resulting in lower observed levels of alopecia and neutropenia when PPX is used as a single agent.

Because of the observations from the phase II trial, its convenient administration, and the potential of decreased toxicity, this trial, PGT304 (also known as Selected Targeted Efficacy in Lung Cancer to Lower Adverse Reactions 4), was conducted to determine if PPX would improve survival compared with standard single-agent therapy with either gemcitabine or vinorelbine in chemotherapy-naive PS 2 patients with advanced NSCLC. Secondary objectives included surrogate measures of efficacy and safety.

PATIENTS AND METHODS

Patient Selection

Patients were recruited from 83 centers in 10 countries and randomly assigned in a 1:1 ratio. Randomization was stratified by gender, geographic location, disease stage, and history of brain metastases. Eligible patients were PS 2 and had histologically or cytologically confirmed diagnoses of NSCLC that were either recurrent disease previously treated with radiation and/or surgery or stage IIIb/IV disease suitable for palliative treatment only. Additional inclusion criteria were absolute neutrophil count $\geq$1500/μl, platelet count $\geq$100,000/μl, creatinine $\leq$1.5 times upper limit of normal (ULN), bilirubin $\leq$ ULN, and transaminases and alkaline phosphatase $\leq$2.5 times ULN (unless liver/bone metastases were present, in which case $\leq$5.0 times ULN was allowed). Patients with stable or treated brain metastases were eligible. Patients were excluded if they had had any prior systemic chemotherapy for the treatment of lung cancer; concurrent primary malignancies except for carcinoma in situ or nonmelanoma skin cancer; $\geq$ grade 2 neuropathy; evidence of unstable neurologic symptoms within the 4 weeks before study randomization, or clinically significant active infections. The protocol was approved through institutional ethics review boards, and all patients provided written informed consent.

Treatment Plan

Patients were randomized to receive either PPX or comparator drug (investigator's choice of gemcitabine or vinorelbine). Each site chose the comparator and used the drug for all patients treated. PPX (175 mg/m^2) was administered on day 1 of each 21-day cycle. At study initiation, the dose of PPX was 235 mg/m^2. The data monitoring committee noted an increased incidence of deaths resulting from neutropenia in patients treated with 235 mg/m^2 PPX after 96 patients had been treated. As a result of these observations, the dose was reduced to 175 mg/m^2 PPX. Randomization continued such that there was a 1:1 ratio between the PPX at 175 mg/m^2 arm and the comparator arm.

Gemcitabine (1000 mg/m^2) was administered on days 1, 8, and 15 of each 28-day cycle. Vinorelbine (30 mg/m^2) was administered on days 1, 8, and 15 of each 21-day cycle.

Patients were treated for up to 6 cycles. Patients were not retreated until significant toxicities had resolved to $\leq$ grade 1. Retreatment could be delayed for up to 2 weeks. The PPX dose was reduced if any of the following were observed: febrile neutropenia; grade 4 neutropenia lasting $>$7 days; absolute neutrophil count $<$1500/μl at the assessment

before dosing; ≥ grade 2 neuropathy at the time of dosing; or any drug-related grade 3/4 nonhematologic toxicities except manageable nausea, vomiting, hypersensitivity reactions, and fatigue (persistent grade 3/4 nausea or vomiting uncontrolled by medication required dose reduction). Two dose reductions were allowed. Treatment was discontinued for patients with persistent peripheral neuropathy ≥ grade 3, grade 3 hypersensitivity reactions despite adequate prophylaxis, and grade 4 hypersensitivity reactions.

Doses for gemcitabine and vinorelbine were adjusted according to the respective package inserts.

Patients were withdrawn for disease progression, intolerable toxicity, patient withdrawal of consent, or investigator decision to withdraw the patient.

Assessments

Evaluations at baseline, before each cycle, and at the end of treatment included medical history, physical examination, assessment of PS, electrocardiogram, tumor status, laboratory evaluations, and Functional Assessment of Cancer Therapy Lung Cancer Subscale (FACT-LCS).

Hematology was assessed 8 days after PPX administration and before each administration of comparator drug. Hematologic adverse events were recorded from laboratory events. All other toxicities were tabulated from investigator-reported adverse events.

Computed tomography (CT) scans were assessed in the last week of every second study cycle (every 6 weeks for PPX and vinorelbine and every 8 weeks for gemcitabine). Efficacy was assessed by the investigator; no central reviews of images were performed. In patients who ended study treatment with stable disease, partial response, or complete response, CT scans were to be obtained every 8 weeks until documentation of the first occurrence of one of the following: disease progression, date of first nonstudy treatment for NSCLC, or death. After the end of study treatment, patients were followed to obtain the dates of disease progression, initiation of subsequent treatment regimens, and death.

Statistical Analysis

The original sample size was 370 patients (185 per treatment arm). Before the dose was reduced for the PPX arm, approximately 91 patients had been randomized to the comparator arm based on a 1:1 allocation over an accrual period of 12 months. To maintain the original number of patients in each final treatment arm (175 mg/m^2 PPX and comparator) after the PPX dose reduction, the randomization ratio was adjusted to 2:1 (175 mg/m^2 PPX to comparator). An unstratified log-rank test of overall survival showed similar survival in patients randomized to the comparator arm before and after the dose reduction; therefore, these patients were grouped together for the analysis. A survival analysis of patients randomized to the comparator arm after the dose reduction and patients who received the reduced dose of CT-2103 yielded similar survival results as the analysis including all patients randomized to the comparator arm [p = 0.939, hazard ratio (HR) = 1.01].

With the assumption that a 1.5-month median survival difference between the 2 treatment arms was of clinical significance, an additional 279 patients (185 randomized to PPX and 94 randomized to the comparator) were accrued over 6 months (with 9 months follow-up), together with the 91 patients already randomized to the comparator arm. This number of patients would result in 80% power to detect a HR of 1.375.

The unstratified log-rank test without adjustments for covariates was used in the primary evaluation of survival differences between the PPX arm (patients dosed at 175 mg/m^2) and the comparator arm using a two-sided $\alpha = 0.05$ test. All randomized patients were included in this analysis. Additional secondary analyses were performed using the Cox regression techniques with covariates determined to be clinically meaningful to the survival of patients with NSCLC.

The fraction retention method described by Rothmann[16] was used to evaluate whether PPX maintains 50% of the effect of the control drugs. Because there is limited historical data available comparing gemcitabine or vinorelbine with best supportive care in PS 2 NSCLC patients, the log of the relative HR observed in the current trial was used in the calculation.

Disease response was assessed according to response evaluation criteria in solid tumors.[17] The comparison was made by randomized treatment group using the Fisher exact test. Disease control was defined as the percentage of patients alive without documented disease progression for ≥12 weeks after randomization. All randomized patients were included. The comparison was made by randomized treatment group using the Fisher exact test. The analysis of time to progression (TTP) was made using an unstratified log-rank test.

Toxicities were evaluated at each patient visit using the National Cancer Institute Common Toxicity Criteria, version 2. All patients who received any amount of study drug were included in the safety analyses.

Disease-related symptoms were measured by the FACT-LCS, a validated, 5-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 Fisher exact test for equal proportions of patients achieving at least a 2-point increase in FACT-LCS score from baseline to week 3 was performed in the overall sample and by each baseline covariate strata. Patients with missing FACT-LCS scores at week 3 were classified as having less than a 2-point increase in the primary analysis data but classified as missing and excluded from the supplemental analysis.

RESULTS

A total of 477 patients were enrolled from December 2002 to June 2004: 199 were randomized to the comparator arm, 190 were randomized to the PPX arm at the dose of 175 mg/m^2, and 96 were randomized to the PPX arm at the dose of 235 mg/m^2. In the comparator arm, 32 patients received vinorelbine and 155 received gemcitabine. The analysis presented here includes only the PPX 175 mg/m^2 and comparator arms. Baseline characteristics were generally well matched between treatment arms (Table 2).

TABLE 2. Demographic and Baseline Characteristics

	PPX (175 mg/m^2) (n = 191)	Gemcitabine or Vinorelbine (n = 190)
Gender (%)		
Male	142 (74.3)	134 (70.5)
Female	49 (25.7)	56 (29.5)
Race (%)		
White	170 (89.0)	170 (89.5)
Black	3 (1.6)	9 (4.7)
Asian	2 (1.0)	1 (0.5)
Hispanic	13 (6.8)	7 (3.7)
Other	3 (1.6)	3 (1.6)
Age at randomization		
Mean (SD)	61.4 (9.85)	62.8 (10.29)
Median (range)	61.0 (36–86)	64.0 (30–90)
Geographic site (%)		
United States	16 (8.4)	24 (12.6)
Western Europe and Canada	16 (8.4)	25 (13.2)
Other	159 (83.2)	141 (74.2)
Histology (%)		
Squamous	86 (45)	102 (54)
Adenocarcinoma	70 (37)	61 (32)
Bronchoalveolar	5 (3)	1 (<1)
Other	30 (16)	26 (14)
Stage at randomization (%)		
IIIa	1 (<1)	2 (1)
IIIb	60 (31)	59 (31)
IV	130 (68)	129 (68)
History of brain metastases	3 (8)	1 (2)
Extrathoracic metastases	75 (39)	84 (44)
Prior radiotherapy	30 (16)	39 (21)
>5% weight loss	60 (31)	66 (35)
Never smoked	36 (19)	34 (18)

PPX indicates paclitaxel poliglumex; SD, standard deviation.

TABLE 3. Efficacy Results in the Intent-to-Treat Population

	PPX (n = 191)	Gemcitabine or Vinorelbine (n = 190)
Survival		
Median, d	220	198
95% CI	198, 263	173, 220
Hazard ratio (95% CI); log-rank p	0.95 (0.76, 1.20); 0.686	
1-yr survival rate, %	26	26
95% CI	20, 33	19, 32
2-yr survival rate, %	15	10
95% CI	5, 25	3, 16
Time to progression		
Median, d	87	107
95% CI	81, 122	87, 112
Hazard ratio (95% CI); log-rank p	1.08 (0.87, 1.33); 0.480	
Disease control, % (95% CI)	52 (45, 59)	59 (52, 67)
Response rate (patients with measurable disease only)		
No. of patients	180	179
PR + CR, % (95% CI)	11 (6, 16)	15 (10, 21)
Confirmed PR + CR, % (95% CI)	5 (2, 9)	7 (4, 12)

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

Extent of Exposure

The median number of cycles administered was 4 in the PPX arm compared with a median of 3.5 in the control arm. The total number of cycles administered was 754 in the PPX arm and 652 in the comparator arm. More patients received 6 cycles of treatment in the PPX arm than in the comparator arm (38% versus 23%; $p = 0.002$). The most frequent reason for not completing all 6 cycles was progressive disease (55 and 59% in the experimental and comparator arms, respectively). An additional 12% of patients in the PPX arm and 17% of patients in the comparator arm discontinued therapy due to adverse events.

Efficacy

Survival, TTP, and response rates were similar in both arms (Table 3). Survival was similar between treatment arms (HR = 0.95; $p = 0.686$; Figure 1). The median overall survival was 7.3 months in the PPX arm and 6.6 months in the control arm. The estimated 1-year survival rate was the same in both arms (26%). The estimated 2-year survival rate was higher in the PPX arm (15%) compared with the control arm (10%). With the Rothmann method[18] for determination of noninferiority, PPX retained at least 50% of the efficacy of the control arm ($p = 0.039$).

The results of the Cox modeling process suggested that, holding all other factors constant, significant predictors of survival were the presence of extrathoracic metastases, excluding brain metastases (HR = 1.61; $p < 0.001$); lactate dehydrogenase (HR = 1.46; $p = 0.003$); FACT-LCS score (HR = 1.50; $p = 0.001$); and tobacco use (HR = 1.78; $p = 0.001$). The treatment arm did not impact survival (HR = 0.95; $p = 0.686$).

Prespecified analyses of survival by stratification factors including gender, geographic location, disease stage, and history of brain metastases were performed (Table 4). Survival was similar between treatment groups in all subgroups; however, there was a nonsignificant trend toward improved survival in women in the PPX arm compared with women in the comparator arm (10 versus 7 months, respectively; HR = 0.65; $p = 0.069$). The number of patients who received poststudy chemotherapy was similar between treatment arms (36% versus 39%). No major differences were noted in the types of therapy administered between the 2 arms. Less than 5% of patients in either arm received subsequent therapy with epidermal growth factor receptor antagonists. Survival was similar between the study arms in patients who did not receive poststudy chemotherapy (5.8 versus 5.9 months; HR = 1.13; $p = 0.390$).

Assessment times were 2 weeks longer for gemcitabine than for vinorelbine or PPX, making direct comparison problematic. However, TTP was similar between treatment groups (87 days for PPX versus 107 days for the comparator; HR = 1.08; $p = 0.480$). Response rate (11% for PPX versus 15%

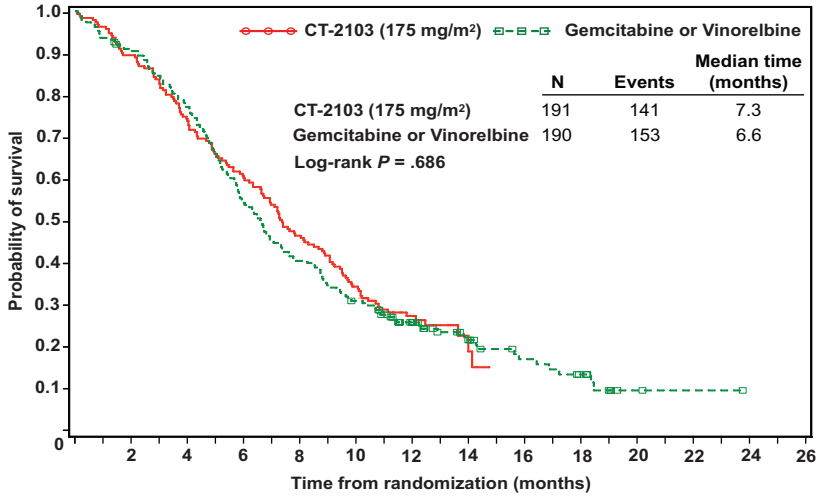

FIGURE 1. Overall survival using Kaplan-Meier estimation: Paclitaxel poliglumex versus gemcitabine or vinorelbine.

TABLE 4. Subgroup Analysis of Overall Survival

	PPX (n = 191)		Gemcitabine or Vinorelbine (n = 190)			
Subgroup	***n***	**Median OS, d (95% CI)**	***n***	**Median OS, d (95% CI)**	**Hazard Ratio**	***p****
Overall	191	220 (198, 263)	190	198 (173, 220)	0.95 (0.76, 1.20)	0.686
Gender						
Male	142	208 (168, 234)	134	190 (165, 220)	1.08 (0.82, 1.41)	0.579
Female	49	312 (216, 408)	56	209 (169, 271)	0.65 (0.40, 1.04)	0.069
Geographic location						
United States	16	203 (127, 373)	24	163 (109, 234)	0.70 (0.34, 1.43)	0.324
Western Europe and Canada	16	164 (96, 271)	25	155 (132, 306)	1.29 (0.65, 2.57)	0.464
Other	159	228 (201, 271)	141	201 (177, 255)	0.99 (0.76, 1.29)	0.946
History of brain metastases						
Yes	6	294 (221, 373)	6	187 (90, 206)	0.17 (0.03, 0.88)	0.020
No	185	217 (197, 259)	184	198 (174, 228)	0.98 (0.77, 1.24)	0.841
Disease stage at randomization						
IV	130	216 (168, 244)	129	177 (150, 206)	0.89 (0.67, 1.17)	0.392
Other	61	266 (189, 285)	61	247 (193, 334)	1.10 (0.72, 1.68)	0.660

*Log-rank test.
PPX indicates paclitaxel poliglumex; OS, overall survival; CI, confidence intervals.

for the comparator) and disease control (52% for PPX versus 59% for the comparator) were also similar.

Supportive Care

In the PPX arm compared with the comparator arm, there was a decreased use of red blood cell transfusions (p = 0.001), erythropoietin (p = 0.014), myeloid growth factors (p = 0.032), and new narcotic analgesics (p = 0.034).

Quality of Life

FACT-LCS evaluations were completed by 178 patients on the PPX arm and 165 patients on the comparator arm. No significant difference in the FACT-LCS scores was seen.

Toxicity

Adverse events are summarized in Table 5. Lower rates of hematologic ($p < 0.001$) and gastrointestinal (p = 0.004) adverse events were observed in the PPX arm. Neuropathy occurred more frequently in the PPX arm compared with control (30% versus 5%, ($p < 0.001$). Grade 3 neuropathy occurred in 4% of patients in the PPX arm; however, no grade 4 neuropathy occurred. Alopecia occurred less frequently in the PPX arm compared with the comparator arm (2% versus 9%, respectively, p = 0.085), as did fatigue (42% versus 55%, p = 0.055), asthenia (11% versus 16%, p = 0.169), and weight loss (7% versus 12%, p = 0.121). There were no treatment-related deaths in either arm. The number of patients who withdrew due to

TABLE 5. No. (%) of Patients with Select Adverse Events

Adverse Event Toxicity	PPX (175 mg/m^2) (n = 190)		Gemcitabine or Vinorelbine (n = 187)		
	All	Grade 3/4	All	Grade 3/4	p*
Anemia NOS	27 (14%)	5 (3%)	68 (36%)	17 (9%)	<0.001
Neutropenia	11 (6%)	4 (2%)	27 (14%)	15 (8%)	0.006
Leukopenia NOS	14 (7%)	4 (2%)	20 (11%)	5 (3%)	0.285
Febrile neutropenia	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)	1.000
Anorexia	27 (14%)	4 (2%)	27 (14%)	2 (1%)	1.000
Dehydration	3 (2%)	2 (1%)	8 (4%)	3 (2%)	0.138
Neuropathy NOS	57 (30%)	8 (4%)	10 (5%)	0	
Dyspnea NOS	41 (22%)	25 (13%)	56 (30%)	32 (17%)	0.077
Nausea	37 (19%)	0	54 (29%)	2 (1%)	0.041
Vomiting NOS	16 (8%)	0	32 (17%)	3 (2%)	0.013
Diarrhea NOS	15 (8%)	2 (1%)	12 (6%)	0	0.691
Arthralgia	10 (5%)	1 (<1%)	9 (5%)	3 (2%)	1.000
Fatigue	79 (42%)	19 (10%)	103 (55%)	16 (9%)	0.055
Asthenia	20 (11%)	13 (7%)	29 (16%)	14 (7%)	0.169
Weight decrease	14 (7%)	1 (<1%)	23 (12%)	2 (1%)	0.121
Alopecia	3 (2%)	NA	9 (5%)	NA	0.085

*p value based on Fisher exact test for difference in all adverse events between treatment groups.
PPX indicates paclitaxel poliglumex; NOS, not otherwise specified; NA, not applicable.

adverse events was similar between treatment arms, and most were events resulting from disease progression. Adverse events resulted more frequently in dose reduction in the comparator arm (13%) compared with the PPX arm (4%). The dose reductions most frequently resulted from hematologic events in the comparator arm. Neuropathy resulted in dose reduction in 4 (2%) patients in the PPX arm; neuropathy did not occur in the comparator arm.

DISCUSSION

Despite patients having PS 2 being relatively common in clinical situations, remarkably few studies have been dedicated to this topic (Table 1). This is the largest series of patients with PS 2 in a clinical trial. In the present study, PPX, an active macromolecular paclitaxel conjugate, was compared with gemcitabine or vinorelbine in a randomized, controlled international study in PS 2 chemotherapy-naive patients with advanced NSCLC. The accrual period was 30 months, during which a total of 487 patients were enrolled, demonstrating that such studies are feasible. The primary objective was to compare survival with secondary objectives of other efficacy measures and tolerability. After a dose reduction of PPX to 175 mg/m^2, 190 patients were accrued at this dose and 191 to gemcitabine or vinorelbine, and these patients are analyzed in this report. Median survival was similar for the 2 study arms (7.3 months for the PPX arm versus 6.6 months for the control arm). This survival duration is considerably longer than prior reports for single-agent therapy in PS 2 patients (Table 1). The longer survival observed in this study was observed across all geographic regions. The demographics of the population under study were similar to those reported in other PS 2 trials with respect to age, percent weight loss, stage, and presence of extrathoracic metastases. In a Cox multivariate linear regression model, important negative survival factors were the presence of extrathoracic metastases, a FACT-LCS score <18, lactate dehydrogenase ≥200 U/L, and a history of smoking. Treatment arm was not significant. Response rates were similar between the 2 arms (11% for the PPX arm versus 15% for the comparator arm), and TTP was 20 days longer in the gemcitabine/vinorelbine arm (HR = 1.08; p = 0.480).

The analysis plan specified that survival would be examined by each of the stratification factors. When survival was analyzed by geography, stage, or presence of brain metastases, there were no apparent effects on survival. However, there was a strong nonsignificant trend toward improved survival for women treated with PPX (HR = 0.65; p = 0.069). Recent preclinical data indicate that PPX efficacy in human tumor xenograft models expressing estrogen receptor β is enhanced by estradiol.

Both PPX and gemcitabine/vinorelbine were well tolerated with relatively few grade 3 nonhematopoietic toxicities. The median number of cycles administered was 4.0 and 3.5 for the PPX and comparator arms, respectively. Grade 3 neutropenia and anemia occurred more frequently in the gemcitabine/vinorelbine arm and was associated with a higher red blood cell transfusion requirement and use of more growth factor support. Neuropathy was more common in the PPX arm, but only 4% of patients had grade 3 despite administration of 6 cycles of therapy to 38% of the patients.

CONCLUSIONS

Patients in both arms of this study had comparable survival rates, and both treatments represent reasonable alternatives for PS 2 patients. Both therapies were well tolerated with no drug-associated deaths and relatively few non-

hematopoietic 3/4 toxicities. Patients on PPX required fewer red blood cell transfusions, hematopoietic growth factors, and opioid analgesics than patients receiving gemcitabine or vinorelbine and because the agent was administered once every 3 weeks, they required substantially fewer clinic visits than those patients receiving either gemcitabine or vinorelbine. The intriguing exploratory finding that women may have an improved outcome with PPX will be evaluated in a phase III study.

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