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PRONOUNCE: Randomized, Open-Label, Phase III Study of First-Line Pemetrexed + Carboplatin Followed by Maintenance Pemetrexed versus Paclitaxel + Carboplatin + Bevacizumab Followed by Maintenance Bevacizumab in Patients ith Advanced Nonsquamous Non–Small-Cell Lung Cancer

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Introduction: PRONOUNCE compared the efficacy and safety of pemetrexed+carboplatin followed by pemetrexed (Pem+Cb) with paclitaxel+carboplatin+bevacizumab followed by bevacizumab (Pac+Cb+Bev) in patients with advanced nonsquamous non–small-cell lung cancer (NSCLC).

Methods: Patients ≥18 years of age with stage IV nonsquamous NSCLC (American Joint Committee on Cancer v7.0), and Eastern Cooperative Oncology Group performance status 0/1 were randomized (1:1) to four cycles of induction Pem+Cb (pemetrexed, 500 mg/m^2, carboplatin, area under the curve = 6) followed by Pem maintenance or Pac+Cb+Bev (paclitaxel, 200 mg/m^2, carboplatin, area under the curve = 6, and bevacizumab, 15 mg/kg) followed by Bev maintenance in the absence of progressive disease or discontinuation. The primary objective was progression-free survival (PFS) without grade 4 toxicity (G4PFS). Secondary end points were PFS, overall survival (OS), overall response rate (ORR), disease control rate (DCR), and safety. Resource utilization was also assessed.

Results: Baseline characteristics of the patients randomized to Pem+Cb (N = 182) and Pac+Cb+Bev (N = 179) were well balanced between the arms. Median (months) G4PFS was 3.91 for Pem+Cb and 2.86 for Pac+Cb+Bev (hazard ratio = 0.85, 90% confidence interval, 0.7–1.04; p = 0.176); PFS, OS, ORR, or DCR did not differ significantly between the arms. Significantly more drug-related grade 3/4 anemia (18.7% versus 5.4%) and thrombocytopenia (24.0% versus 9.6%) were reported for Pem+Cb. Significantly more grade 3/4 neutropenia (48.8% versus 24.6%), grade 1/2 alopecia (28.3% versus 8.2%), and grade 1/2 sensory neuropathy were reported for Pac+Cb+Bev. Number of hospitalizations and overall length of stay did not differ significantly between the arms.

Conclusions: Pem+Cb did not produce significantly better G4PFS compared with Pac+Cb+Bev. Pem+Cb was not superior in PFS, OS, ORR, or DCR compared with Pac+Cb+Bev. Both regimens were well tolerated, although, toxicity profiles differed.

Key Words: Advanced nonsquamous non–small-cell lung cancer, Efficacy, Safety, Combination therapy, Pemetrexed, Carboplatin, Paclitaxel, Bevacizumab.

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Lung cancer is the leading cause of cancer mortality in the United States accounting for more than a quarter of cancer deaths for both men and women.[1] Non–small-cell lung cancer (NSCLC) accounts for ~85% of the lung cancer histologies in the United States, and 70% of the patients with NSCLC present with inoperable, locally advanced (stage III) or metastatic (stage IV) disease.[2]

Patients with stage IV NSCLC and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 benefit in survival and quality of life from standard platinum doublet chemotherapy.[3–6] No randomized trial has demonstrated superiority of one platinum-based doublet over another for unselected patients.[7–10] The three-drug regimen of carboplatin/paclitaxel/bevacizumab induction followed by bevacizumab maintenance was approved for nonsquamous NSCLC based on the well-known ECOG 4599 clinical trial.[11] This regimen has been adopted as the new ECOG standard for patients eligible to receive bevacizumab.[11] Currently in the United States, less than half of all the new lung cancer diagnoses are made in patients who would have met the eligibility criteria for ECOG 4599 and it is usually estimated that no more than a third of the lung cancer patients in the United States are treated with this regimen.[12]

Pemetrexed is a multitargeted antifolate approved for first-line, second-line, and maintenance treatment of nonsquamous NSCLC.[13–16] A prespecified analysis of a large phase III first-line study showed that pemetrexed/cisplatin produced superior overall survival (OS) to gemcitabine/cisplatin for patients with nonsquamous NSCLC.[14,17] In first-line maintenance, pemetrexed was superior to placebo for OS in large phase III studies after initial chemotherapy with pemetrexed or taxane-based regimens.[15–17] Superior OS with pemetrexed versus docetaxel also was confirmed in a post hoc analysis of second-line study data for nonsquamous histologies.[18] In the US, cisplatin doublets are less often used than carboplatin doublets, and although it has not been directly compared in a phase III trial, pemetrexed/carboplatin is more often used in clinical practice in the US.[19,20]

PRONOUNCE was designed to assess the efficacy and safety of pemetrexed+carboplatin followed by pemetrexed maintenance (Pem+Cb) versus paclitaxel+carboplatin+bevacizumab followed by bevacizumab maintenance (Pac+Cb+Bev) in patients with advanced nonsquamous NSCLC. PRONOUNCE was designed as a supportive study for the PointBreak study and has similar patient eligibility and monitoring.[21]

A maximum of four cycles of induction therapy was chosen based on recent reviews and meta-analyses confirming four cycles as the optimal duration of first-line platinum combination therapy.[22–25] G4PFS defined by the Common Terminology Criteria for Adverse Events (CTCAE) is a composite end point that includes both efficacy and safety outcomes. The G4PFS primary end point is reasonable for clinical trials comparing regimens where efficacy is likely to be similar, making a less toxic regimen clinically relevant, particularly in the noncurative setting.[21,26] The hypothesis for PRONOUNCE trial was that Pem+Cb would be superior to Pac+Cb+Bev for G4PFS.

MATERIALS AND METHODS

Eligibility Criteria

Chemotherapy naïve adults (≥18 years of age) with histologically or cytologically confirmed stage IV (American Joint Committee on Cancer, version 7) nonsquamous NSCLC, ECOG PS 0 or 1, measurable disease by Response Evaluation Criteria in Solid Tumors,[27] and adequate organ function were eligible. Stable, treated brain metastases were allowed. Patients were required to be eligible for both pemetrexed and bevacizumab. Women of childbearing potential were required to have a negative pregnancy test, and all the patients for whom pregnancy was a risk were required to use effective contraception. The patients were excluded for any contraindications for pemetrexed or bevacizumab or for general radiotherapy within 2 weeks, stereotactic brain radiotherapy within 7 days, major surgery within 28 days, minor surgery within 7 days, neurosurgical resection or brain biopsy within 3 months before day 1, cycle 1. Additional exclusions included the use of an investigational agent within 30 days of randomization and any serious concomitant disorder that could compromise the ability to adhere to the protocol.

The study protocol was approved by ethical review boards at each of the participating investigational sites and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All the patients signed written informed consent before the initiation of any study interventions.

Study Design, Treatment, and End points

In this multicenter, randomized, open-label, US-only phase III trial, the eligible patients with nonsquamous NSCLC were randomized in a 1:1 ratio to Pem+Cb or Pac+Cb+Bev by standard protocols including B12 and folate supplementation for pemetrexed and dexamethasone premedication for both the arms. Patients in the Pac+Cb+Bev arm received additional standard prophylaxis against allergic reactions according to the paclitaxel label. Randomization was stratified for disease stage (M1a versus M1b), ECOG PS, and sex. After four cycles of induction therapy every 21 days, maintenance continued until disease progression or intolerance. Planned chemotherapy doses were pemetrexed 500 mg/m^2; carboplatin, area under the curve = 6, (as of December 31, 2010, maximum possible dose of 900 mg), paclitaxel 200 mg/m^2; bevacizumab 15 mg/kg.

Any required dose reductions, per label indication for each drug or regimen, were maintained for the remainder of the study per CTCAE.[28] A maximum of two dose reductions were permitted before the patients were discontinued from the study therapy. Bevacizumab doses were not reduced due to toxicity but bevacizumab was interrupted for any unresolved

adverse events (AEs). Upon resolution of select AEs, bevacizumab was resumed at the full dose at the next cycle. The maximum allowable length of any study treatment interruption was 42 days.

The primary objective of this trial was to compare G4PFS between the two treatment arms in the intent-to-treat (ITT) population.[29] G4PFS was measured from the date of randomization to the earliest occurrence of the first of grade 4 AEs, disease progression, or death from any cause, regardless of whether or not the event leads to discontinuation. Secondary end points included PFS (gated secondary end point), OS, overall response rate (ORR), disease control rate (DCR = complete response + partial response + stable disease), and safety. Associated resource use data were also collected.

If a patient discontinued study therapy without disease progression, the tumor measurements were performed at 30 days and subsequently every 6 weeks (± 2 weeks) until objective disease progression. Thereafter, the patient was followed every 90 days (± 14 days) for survival.

As a post hoc analysis of the AEs that are important to patients, we have reviewed the symptoms described by Dubey et al.[30] in their analysis of data from a questionnaire answered by 464 patients with lung cancer (registered in the Alliance for Lung Cancer Advocacy, Support, and Education database from 2000 to 2002).

Statistical Plan and Analyses

The study was powered for G4PFS; assuming a hazard ratio (HR) of 0.75, approximately 360 randomized patients (180 per arm) were needed for 80% power to detect superiority of the Pem+Cb arm over the Pac+Cb+Bev arm with a two-sided type I error of 0.10. PFS (gated end point) and OS were key secondary end points. Efficacy data were analyzed by ITT using all randomized patients, and safety data were evaluated using CTCAE v3 for patients who received ≥ 1 dose of study treatment (grouped as treated).

All other tests of treatment effects were conducted at a two-sided alpha level of 0.05 and all confidence intervals (CIs) were given at a two-sided 95% level, unless otherwise specified.

For the time-to-event end points, including G4PFS, PFS, and OS, Kaplan-Meier estimates and (nonstratified) log-rank test were employed. Cox regression model (non-stratified) was used to estimate the treatment HR. Fisher's exact tests were used to compare differences in the ORR and DCR between the two treatment arms. The safety analysis included the maximum grade CTCAEs of laboratory and nonlaboratory events, serious AEs, treatment-emergent AEs, hospitalizations, transfusions, and the use of concomitant medications. Comparisons of the incidences of toxicities and resources use between the two treatment arms were performed using Fisher's exact test.

RESULTS

Patient Disposition

A CONSORT diagram depicting the patient enrollment and disposition is presented in Figure 1. A total of 496 patients were screened from September 2009 to January 2013 with data cutoff January 31, 2013; 135 patients were excluded for eligibility (n = 105), death (n = 3), or subject decision (n = 27); and 361 patients were randomized (Pem+Cb = 182; Pac+Cb+Bev = 179). Twelve patients in each arm did not receive study treatment after randomization, and the most common reasons included patient decision, entry criteria exclusion, and AEs. At the time of data cutoff (January 31, 2013), 352 patients (n = 177 on Pem+Cb; n = 175 on Pac+Cab+Bev) had discontinued study therapy, and nine patients (n = 5 on Pem+Cb; n = 4 on Pac+Cab+Bev) were continuing study therapy.

Patient Baseline Characteristics

Patient baseline demographic and disease-related characteristics (ITT population) are presented in Table 1. Baseline

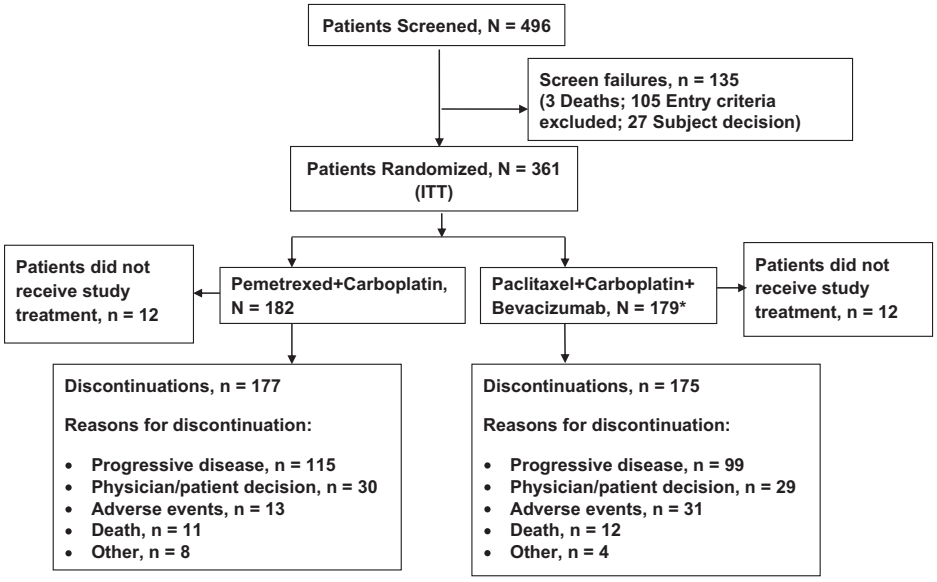


FIGURE 1. Patient CONSORT flow diagram. ITT, Intent-to-treat. *1 patient randomized to Pac+Cb+Bev but received Pem+Cb, analyzed per ITT population.

TABLE 1. Patient Baseline Demographic and Disease Characteristics of Intent-to-Treat Population

Characteristic	Pem+Cb N = 182 n (%)	Pac+Cb+Bev N = 179 n (%)
Age, years, median (range)	65.8 (38.4–84.1)	65.4 (41.2–86.2)
>70 years	59 (32.4)	51 (28.5)
Gender		
Female	77 (42.3)	75 (41.9)
Race/ethnicity		
White[a]	165 (90.7)	157 (87.7)
African American	11 (6.0)	20 (11.2)
Asian	4 (2.2)	0 (0.0)
American Indian	0 (0.0)	2 (1.1)
Multiple	2 (1.1)	0 (0.0)
ECOG PS		
0	85 (46.7)	84 (46.9)
1	96 (52.7)	95 (53.1)
Disease stage IV	181 (99.5)	179 (100.0)
M1a	52 (28.6)	53 (29.6)
Histology		
Adenocarcinoma	152 (83.5)	137 (76.5)
Large cell	1 (0.5)	9 (5.0)
Other or indeterminate	28 (15.4)	33 (18.4)
Smoking status		
Ever	164 (90.1)	172 (96.1)
No previously treated brain metastasis	159 (87.4)	147 (82.1)

Some patients had missing values for these characteristics; percentage calculated accordingly.

[a]Includes four (2.2%) in Pem+Cb and five (2.8%) in Pac+Cb+Bev arm who were patients of Hispanic ethnicity.

Bev, bevacizumab; Cb, carboplatin; ECOG, Eastern Cooperative Oncology Group; Pac, paclitaxel; Pem, pemetrexed; PS, performance status.

characteristics were well balanced between the treatment arms. Most patients were white (89.2%) with median age of 65.6 (range, 38.4–86.2) years. No *p* values were calculated for these characteristics between the arms as the data were descriptive.

Treatment

The ITT population included 182 in Pem+Cb and 179 in Pac+Cb+Bev. The median number of cycles (defined as 50% of the patients stay on study treatment) administered was six (range, 1–36$^+$ Pem+Cb and 1–31$^+$ Pac+Cb+Bev). The number of patients completing four cycles of treatment were similar between the two treatment arms: 121 patients (70.8%) in Pem+Cb arm and 113 patients (68.1%) in Pac+Cb+Bev arm. The mean dose intensities in the safety (treated) population were similar for both the arms (%, standard deviation): pemetrexed 92.3 (10.8) and carboplatin 94.1 (11.1) for the Pem+Cb arm; paclitaxel 91.5 (14.9), carboplatin 92.8 (15.5), and bevacizumab 93.3 (15.5) for the Pac+Cb+Bev arm.

Efficacy Measures

In the ITT population, 296 G4PFS events occurred with 152 in Pem+Cb and 144 in Pac+Cb+Bev. Median G4PFS was not statistically significantly different between the two treatment arms as shown by Kaplan-Meier curves (Fig. 2*A*). For Pem+Cb versus Pac+Cb+Bev, the median G4PFS was 3.91 versus 2.86 months (HR, 0.85, 90% CI, 0.7–1.04, $p = 0.176$). The median PFS was 4.44 months for Pem+Cb versus 5.49 months for Pac+Cb+Bev (HR, 1.06; 95% CI, 0.84–1.35; $p = 0.610$) (Fig. 2*B*). The median OS for Pem+Cb was 10.5 months versus 11.7 months for Pac+Cb+Bev (HR, 1.07; 95% CI, 0.83 to 1.36; $p = 0.615$) (Fig. 2*C*). One- and 2-year survival rates were not significantly different between the arms and were 43.7% and 18.0% for Pem+Cb and 48.8% and 17.6% for Pac+Cb+Bev (Fig. 2*C*). Response rate and DCR were 23.6% and 59.9% for Pem+Cb and 27.4% and 57.0% for Pac+Cb+Bev ($p = 0.414$ and 0.575, respectively) (Fig. 2*B*).

Additional analysis of which G4PFS event (G4AE, progressive disease [PD], or death) occurred first in the ITT population is shown in Table 2. A total of 296 G4PFS events were reported in both the arms. Among these G4PFS events, those occurring first were: 101 (34.1%) G4 AEs; 163 (55.1%) PD; 32 (10.8%) deaths. The most common G4PFS toxicities observed were neutropenia, thrombocytopenia, and thrombosis/embolism (Table 2). The *p* values for the differences between the two treatment arms were not calculated as the data were descriptive (Table 2).

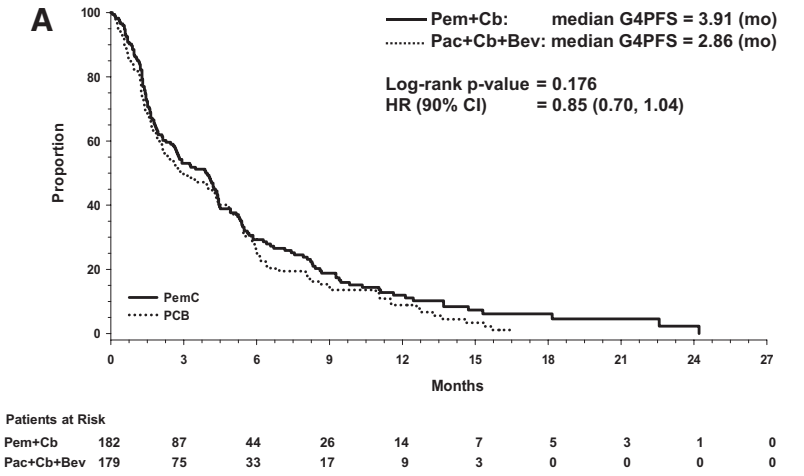
A sensitivity analysis was performed to evaluate the efficacy outcome for patients who received at least one cycle of study treatment (safety population). The efficacy results based on safety population are similar to that based on the ITT population (data not shown).

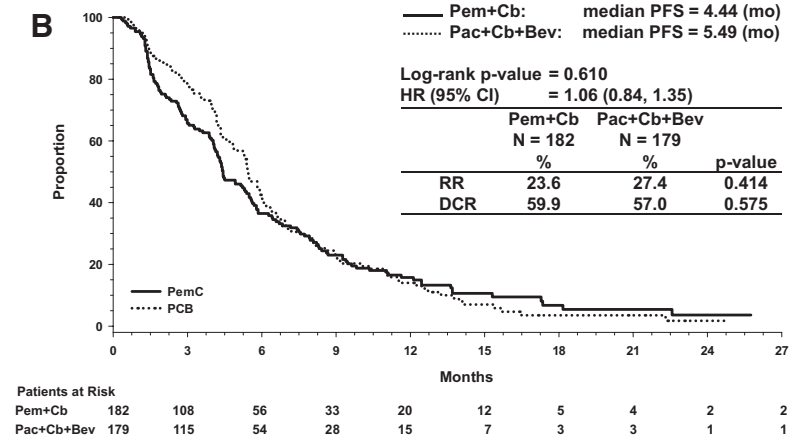
The preplanned subgroup analyses are shown as Forest plots for G4PFS (Fig. 3*A*) and for OS (Fig. 3*B*). The unadjusted HRs (with 95% CIs) shown in these plots do not favor any treatment subgroup.

Safety Measures

Grade 3/4 drug-related toxicities that were significantly different between the treatment arms in the safety population were (Pem+Cb versus Pac+Cb+Bev): anemia (18.7% versus 5.4%, $p < 0.001$), neutropenia (24.6% versus 48.8%, $p < 0.001$), and thrombocytopenia (24.0% versus 9.6%, $p < 0.001$). Hemorrhage was numerically higher in the Pem+Cb arm (1.2% versus 0.00%), and thrombosis/embolism was numerically higher in the Pac+Cb+Bev arm (0.0% versus 2.4%); these differences did not reach statistical significance. Grade 3 and grade 4 drug-related AEs in each treatment arm are presented in Table 3.

Drug-related events considered most important to patients such as nausea, vomiting, infections, alopecia, and sensory neuropathy[30] were analyzed post hoc in this study. Grade 1 (21.7% versus 7.6%), and 2 (8.4% versus 0.6%), sensory neuropathy were significantly more common with Pac+Cb+Bev compared with Pem+Cb ($P < 0.001$). Grade 1 nausea was significantly ($p = 0.003$) higher in Pem+Cb (29.8%) compared with Pac+Cb+Bev (15.7%). However, grade 2 nausea was not significantly different between the two arms (17.0% versus 13.3%, $p = 0.365$). Grade 1 (16.3% versus 5.8%) and 2 (12.0% versus 2.3%) alopecia were significantly more common with Pac+Cb+Bev compared with Pem+Cb ($p < 0.001$). The other nonhematological grade 3/4 events





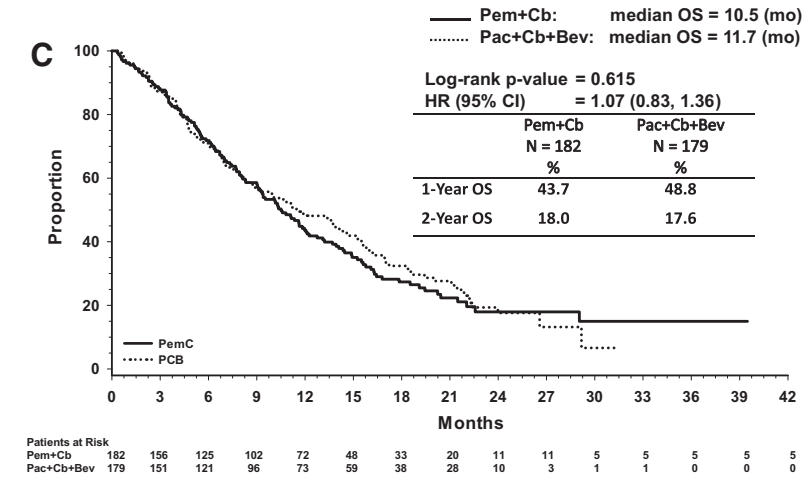


FIGURE 2. *A*, Kaplan-Meier plot of primary end point G4 progression-free survival, (*B*), Kaplan-Meier plot showing the progression-free survival in intent-to-treat population, (*C*), Kaplan-Meier plot showing the overall survival in intent-to-treat population. Bev, bevacizumab; Cb, carboplatin; G4PFS, grade 4 progression-free survival; HR, hazard ratio; OS, overall survival; Pac, paclitaxel; Pem, pemetrexed; PFS, progression-free survival.

including fatigue, febrile neutropenia, nausea, and vomiting were similar between the treatment arms. For patients with G4PFS other than PD as the initial event, the incidence of subsequent PD was 18 of 37 for arm A and 22 of 64 for arm B.

The patients who developed G4AEs during the induction phase (one to four cycles) were 33 of 37 (89.2%) in Pem+Cb and 60 of 64 (93.6%) in Pac+Cb+Bev and in the maintenance phase (> 4 cycles), 4 of 37 (10.8%) in Pem+Cb and 3 of 64 (4.8%) in Pac+Cb+Bev.

Forty-nine patients died during the study or within 30 days of discontinuation (Pem+Cb, n = 24 [14.0%]; Pac+Cb+Bev, n = 25 [15.1%]). Possible drug-related deaths

TABLE 2. First Occurrences of G4PFS Events in Intent-to-Treat Population

Event	Pem+Cb N = 182	Pac+Cb+Bev N = 179
G4PFS	*n* = 152 (%)	*n* = 144 (%)
G4 events	37 (24.3)	64 (44.4)
Progressive disease	95 (62.5)	68 (47.2)
Death	20 (13.2)	12 (8.3)
G4 events	*n* = 37 (%)	*n* = 64 (%)
Neutropenia	6 (16.2)	46 (71.9)
Thrombocytopenia	13 (35.1)	4 (6.3)
Thrombosis/thrombus/embolism	3 (8.1)	3 (4.7)
Leukopenia	1 (2.7)	3 (4.7)
Hyperglycemia	2 (5.4)	1 (1.6)
Confusion	1 (2.7)	1 (1.6)
Vascular access thrombosis	1 (2.7)	1 (1.6)
Others[a]	10 (27.0)	5 (8.0)

[a]Other isolated events include allergic reaction, cardiac ischemia, troponin T elevation, left ventricular dysfunction, creatinine elevation, diarrhea, muscle weakness, neurology nonspecific, joint pain, back pain, pericarditis, hyperkalemia, hyponatremia, renal failure.

Bev, bevacizumab; Cb, carboplatin; G4, Grade 4; Pac, paclitaxel; Pem, pemetrexed; PFS, progression free survival.

were one patient (0.6%) in Pem+Cb due to neutropenia and two patients (1.2%) in Pac+Cb+Bev due to myocardial infarction and pulmonary embolism. Deaths not deemed to be related to study drug by the investigator were attributed to progression of lung cancer (8.2% versus 12.0%) and AEs of other causes (5.3% versus 1.8%) including pneumonia, respiratory failure, myocardial infarction, stroke, and renal failure in the Pem+Cb arm; and respiratory failure, intracranial bleeding, and nonspecific AEs in the Pac+Cb+Bev arm.

In the safety population, the number of patients with at least one hospitalization was not significantly different between the treatment arms (Pem+Cb, $n = 59$ [34.5%]; Pac+Cb+Bev, $n = 53$ [31.9%], $p = 0.645$). Similarly, the mean (SD) number of hospitalized days did not differ between the arms (Pem+Cb, 8.2 [6.79]; Pac+Cb+Bev, 8.8 [7.33], $p = 0.682$). Significantly, more patients treated with Pem+Cb received at least one red blood cell transfusion compared with Pac+Cb+Bev (35.7% versus 12.7%, $p < 0.001$). No differences were observed for platelet transfusions between the treatment arms (Pem+Cb, 5.8% versus Pac+Cb+Bev, 4.2%, $p = 0.621$).

Use of rescue antiemetics (64.3% in Pem+Cb versus 60.8% in Pac+Cb+Bev, $p = 0.574$), analgesics (88.9% in Pem+Cb versus 92.2% in Pac+Cb+Bev, $p = 0.355$), and antibiotics (53.2% in Pem+Cb versus 59.0% in Pac+Cb+Bev, $p = 0.323$) did not differ significantly between the treatment arms. Use of erythropoetic stimulating agents was significantly higher in Pem+Cb (19.9%) compared with Pac+Cb+Bev (7.2%) ($p < 0.001$), whereas the use of granulocyte colony stimulating factors was significantly lower in Pem+Cb (17.0%) compared with Pac+Cb+Bev (30.1%) ($p = 0.005$).

Postdiscontinuation Therapies

Second-line therapy and beyond was determined by the treating physician. Among the ITT population, the use of second-line treatment was similar between the two treatment arms (47.3% in Pem+Cb versus 52.5% in Pac+Cb+Bev, $p = 0.344$). Treatments were similar between the two treatment arms except for docetaxel (26.4% in Pem+Cb versus 6.1% in Pac+Cb+Bev, $p < 0.001$) and pemetrexed (8.8% in Pem+Cb versus 34.1% in Pac+Cb+Bev, $p < 0.001$). Other therapies administered to ≥5% of the patients but not significantly different in Pem+Cb versus Pac+Cb+Bev included: bevacizumab (7.7% versus 12.8%), carboplatin (9.9% versus 16.2%), erlotinib (9.3% versus 7.8%), gemcitabine (5.5% versus 5.0%), and paclitaxel (6.0% versus 7.3%).

DISCUSSION

The randomized phase III PRONOUNCE study demonstrated that Pem+Cb was not superior to Pac+Cb+Bev for either the primary end point of G4PFS ($p = 0.176$) or for the secondary efficacy end points of PFS, OS, ORR, and DCR. This trial attempted for the first time to prospectively measure the novel primary end point of G4PFS. Although G4PFS has not been validated, a previous clinical trial that showed similar survival with pemetrexed versus docetaxel[13] was retrospectively analyzed for OS without grade 3/4 toxicity and suggested a benefit-to-risk favoring pemetrexed compared with docetaxel in the second-line treatment of patients with NSCLC.[26] A similar primary end point (survival without grade 3/4 toxicity) was also used in a phase III clinical trial comparing pemetrexed/carboplatin with docetaxel/carboplatin as first-line treatment for advanced, nonsquamous NSCLC.[31] This end point (survival without grade 3/4 toxicity) also has been analyzed post hoc in a large phase III trial.[32] The current study prospectively evaluated PFS without grade 4 toxicity and did not show superior benefit-to-risk for Pem+Cb compared with Pac+Cb+Bev. Both the treatments showed similar severity and temporal onset of toxicity, although the specific toxicities differed between the arms. The G4PFS end point as applied here did not discriminate between different, similarly graded AEs that may have different significance for patient quality of life.[30]

The G4PFS end point was hoped to provide an indication of toxicity and efficacy. A substantial number of patients met this end point from a toxicity standpoint although still responding to their assigned regimen and continued on study. As might be expected, the majority of non-PD G4PFS end points occurred in the first four cycles of therapy during platinum doublet/triplet treatment. This provides some reassurance about the tolerability of maintenance with either pemetrexed or bevacizumab.

Regular weekly complete blood cell counts in the experimental setting compared with clinical practice may have contributed to the observed higher incidences of laboratory toxicities, sometimes referred to as paper toxicities. If the G4PFS end point is used in future studies, consideration should be given to excluding nonclinically significant laboratory toxicities and to including some lower grade toxicities such as grade 2 neuropathy or alopecia, that are considered clinically relevant to the patients. The practice of weekly laboratory testing in asymptomatic participants in clinical trials where this is not standard in a nonstudy population treated

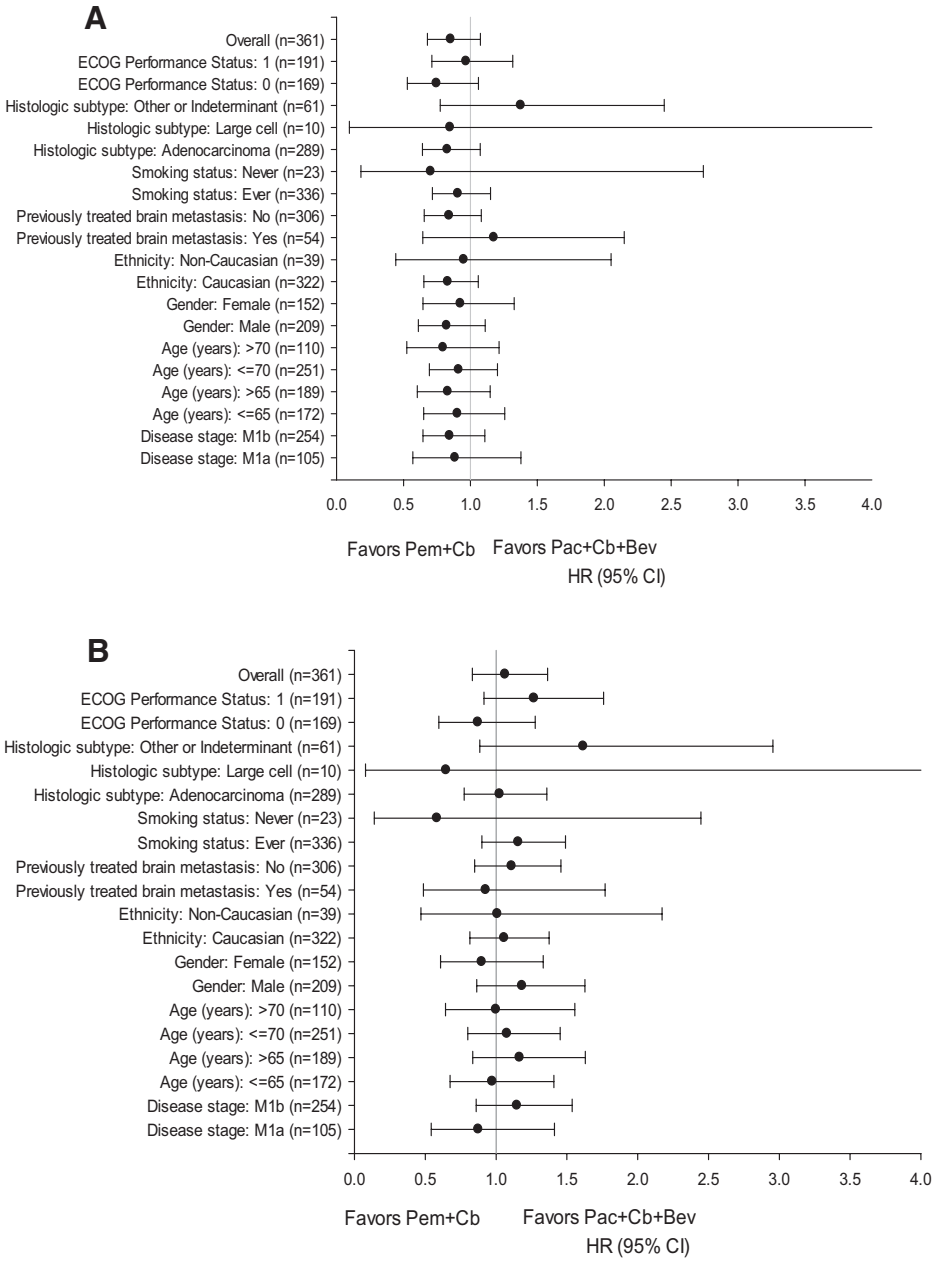


FIGURE 3. *A*, Subgroup analysis of G4 progression-free survival, and (*B*), overall survival, hazard ratio (95% CI). Bev, bevacizumab; Cb, carboplatin; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; Pac, paclitaxel; Pem, pemetrexed; CI, confidence interval.

with similar regimens should be carefully considered for future studies.

The PFS and OS values reported here are comparable with other recently reported phase III trials with pemetrexed and platinum combinations and with other chemotherapy and bevacizumab combinations.[11,14,21,33] Because of the small number of patients, we did not evaluate the differences in safety and efficacy in the >70 years age subgroup. Earlier studies have shown conflicting outcomes with or without differences by age groups.[34,35] These data when analyzed will be reported elsewhere.

The efficacy of the control arm (Pac+Cb+Bev) in this study showed lower median survivals compared with previous trials[11,21] possibly due to differences in the study populations and smaller sample size. The estimation of median OS in the control arm was 11.66 months with 95% CI (9.17–14.32), which is similar to the outcome in the ECOG 4599 study (12.3 months).[11]

Patients experienced acceptable and expected toxicities on both the arms of this study based upon comparable rates of total AEs reported in previous pemetrexed plus platinum-based regimens[21,33] and bevacizumab combinations.[11]

Several AEs considered most important to patients[30] including grade 1 and 2 alopecia and sensory neuropathy were significantly more common with Pac+Cb+Bev than with Pem+Cb ($p < 0.001$), whereas grade 1 nausea was significantly more common in patients receiving Pem+Cb ($p = 0.003$). Other grades of sensory neuropathy, febrile neutropenia,

TABLE 3. Drug-Related Grade 3 and 4 Common Terminology Criteria for Adverse Events in Patients (Safety Population)

	Grade 3 AEs			Grade 4 AEs		
Event	Pem+Cb N = 171 n (%)	Pac+Cb+Bev N = 166 n (%)	*p* Value	Pem+Cb N = 171 n (%)	Pac+Cb+Bev N = 166 n (%)	*p* Value
Anemia	31 (18.1)	9 (5.4)	< 0.001	1 (0.6)	0 (0.0)	1.000
Neutropenia	36 (21.1)	37 (22.3)	0.793	6 (3.5)	44 (26.5)	< 0.001
Thrombocytopenia	26 (15.2)	7 (4.2)	< 0.001	15 (8.8)	9 (5.4)	0.291
Febrile neutropenia	0 (0.0)	2 (1.2)	0.242	0 (0.0)	1 (0.6)	0.493
Hypertension	0 (0.0)	4 (2.4)	0.058	0 (0.0)	0 (0.0)	N/A
Thrombosis/embolism	0 (0.0)	3 (1.8)	0.118	0 (0.0)	1 (0.6)	0.493
Any hemorrhagic events	2 (1.2)	0 (0.0)	0.499	0 (0.0)	0 (0.0)	N/A
Sensory neuropathy	0 (0.0)	4 (2.4)	0.058	0 (0.0)	0 (0.0)	N/A

Grade 5 AEs: One death (neutropenia) in Pem+Cb and two deaths (myocardial infarction and pulmonary embolism) in Pac+Cb+Bev occurred.
AEs, adverse events; Bev, bevacizumab; Cb, carboplatin; N/A, not available; Pac, paclitaxel; Pem, pemetrexed.

fatigue, nausea, and vomiting were similar between the treatment arms. The specific toxicity profiles and resource use differed by regimen.

In addition to the traditionally measured toxicities, financial burden is becoming recognized as an additional toxicity that may affect a patient's potential course of treatment or quality of life.[36–39] Using data from the PRONOUNCE trial, a post hoc cost analysis estimated differences in costs of treatment and related patient care between the two study regimens. Clinical data, resource use, and postdiscontinuation therapy data were used to estimate preprogression and postprogression inputs to which the respective 2013 unit costs were applied. The costs were obtained from three sources: Truven Health Analytics (drug wholesale acquisition costs), Centers for Medicare and Medicaid Services (drug administration and transfusion costs), and HCUPnet (hospital charges for treating toxicities). Results suggest that the average total cost of treatment with Pem+Cb was $4,690 less than Pac+Cb+Bev ($30,334 versus $35,024), and Pem+Cb was cost-saving in 99% of 10,000 iterations of a probabilistic sensitivity analysis that used Monte Carlo methods.[40]

The recently published results for the PointBreak study comparing Pem+C+Bev followed by Pem+Bev to Pac+C+Bev followed by Bev showed no statistical difference in OS, though PFS was statistically longer in the pemetrexed arm; different toxicities were noted between the two study arms. Similarly, this PRONOUNCE trial that compared Pem+Cb followed by Pem to Pac+Cb+Bev followed by Bev demonstrated no significant difference of efficacy for OS and PFS between the treatment arms, and again different toxicities were noted. Comparison of the results of these two studies are informative when choosing a chemotherapy regimen for a given patient who may not tolerate certain regimens and reassures the clinicians that the standard of care therapy is being offered to each patient based upon individual preferences and comorbid conditions.

In conclusion, the PRONOUNCE study objective of superiority of G4PFS was not met; no superiority was observed for the standard end points such as PFS, OS, ORR, or DCR in Pem+Cb compared with Pac+Cb+Bev. The safety profiles of both the treatment regimens are reasonable, though different. Differing toxicity profiles are often a deciding factor considered by treating oncologists when choosing an effective regimen for nonsquamous NSCLC.

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