Randomized, Phase II Trial of Pemetrexed and Carboplatin with or without Enzastaurin versus Docetaxel and Carboplatin as First-Line Treatment of Patients with Stage IIIB/IV Non-small Cell Lung Cancer

Mark A. Socinski, MD, Robert N. Raju, MD,† Thomas Stinchcombe, MD,* Darren M. Kocs, MD,† Linda S. Couch, MD,† David Barrera, MD,† Steven R. Rousey, MD,† Janak K. Choksi, MD,‡ Robert Jotte, MD, PhD,† Debra A. Patt, MD,† Phillip O. Periman, MD,† Howard R. Schlossberg, MD,† Charles H. Weissman, MD,† Yunfei Wang, MS,† Lina Asmar, PhD,† Sharon Pritchard, RN,† Jane Bromund, MSN, RN,§ Guangbin Peng, MS,§ Joseph Treat, MD,§ and Coleman K. Obasaju, MD, PhD§*

Introduction: Enzastaurin is an oral serine/threonine kinase inhibitor that targets protein kinase C-beta (PKC-β) and the phosphatidylinositol-3-kinase/AKT pathway. This trial assessed pemetrexed-carboplatin ± enzastaurin to docetaxel-carboplatin in advanced non-small cell lung cancer.

Methods: Patients with stage IIIB (with pleural effusion) or IV non-small cell lung cancer and performance status 0 or 1 were randomized to one of the three arms: (A) pemetrexed 500 mg/m^2 and carboplatin area under the curve 6 once every 3 weeks for up to 6 cycles with a loading dose of enzastaurin 1125 or 1200 mg followed by 500 mg daily until disease progression, (B) the same regimen of pemetrexed-carboplatin without enzastaurin, or (C) docetaxel 75 mg/m^2 and carboplatin area under the curve 6 once every 3 weeks for up to six cycles. The primary end point was time to disease progression (TTP).

Results: Between March 2006 and May 2008, 218 patients were randomized. Median TTP was 4.6 months for pemetrexed-carboplatin-enzastaurin, 6.0 months for pemetrexed-carboplatin, and 4.1 months for docetaxel-carboplatin (differences not significant). Median survival was 7.2 months for pemetrexed-carboplatin-enzastaurin, 12.7 months for pemetrexed-carboplatin, and 9.2 months for docetaxel-carboplatin (log-rank $p = 0.05$). Compared with the other arms, docetaxel-carboplatin was associated with lower rates of grade 3 thrombocytopenia and anemia but a higher rate of grade 3 or 4 febrile neutropenia.

Conclusion: There was no difference in TTP between the three arms, but survival was longer with pemetrexed-carboplatin compared with docetaxel-carboplatin. Enzastaurin did not add to the activity of pemetrexed-carboplatin.

Key Words: Pemetrexed, Carboplatin, Enzastaurin, NSCLC, Randomized phase II trial.

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Lung cancer is the leading cause of cancer death worldwide, resulting in more deaths than breast, prostate, and colon cancer combined. In the United States, there will be an estimated 215,000 new cases and 159,000 deaths from cancer of the lung or bronchus in 2009.[1] Approximately 85% of lung cancer patients will have non-small cell lung cancer (NSCLC); most will have advanced stage disease at the time of diagnosis, and 5-year survival is less than 10% in this patient population.[2,3] Platinum-based doublet chemotherapy is the standard of care for patients with good performance status (PS) of 0 or 1 based on modest benefits in survival and quality of life compared with best supportive care alone.[4–7] In otherwise unselected patients, several large clinical trials have failed to establish a specific regimen as standard for advanced NSCLC.[8–11]

Enzastaurin is a selective, oral serine/threonine kinase inhibitor that targets protein kinase C-beta (PKC-β) and the phosphatidylinositol-3-kinase (PI3K)/AKT pathway to inhibit tumor cell proliferation, induce apoptosis, and suppress tumor-induced angiogenesis.[12] PKC and PI3K/AKT are overexpressed and overactive in lung cancer tissues and cell lines.[13–16] A phase IB clinical trial suggested that the combination of pemetrexed plus enzastaurin was well tolerated with preliminary evidence of anticancer activity.[17] In a phase II study of single-agent enzastaurin as second- or third-line

*Multidisciplinary Thoracic Oncology Program, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina; †US Oncology, The Woodlands, Texas; ‡Alamance Cancer Center, Burlington, North Carolina; and §Lilly USA, LLC, Indianapolis, Indiana.

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Address for correspondence: Mark A. Socinski, MD, Multidisciplinary Thoracic Oncology Program, Lineberger Comprehensive Cancer Center, CB# 7305, University of North Carolina, Chapel Hill, NC 27599-7305. E-mail: socinski@med.unc.edu

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therapy in patients with metastatic NSCLC, 13% of patients had disease stabilization for 6 months, and 11% of patients had prolonged stabilization (up to 20 months).[18]

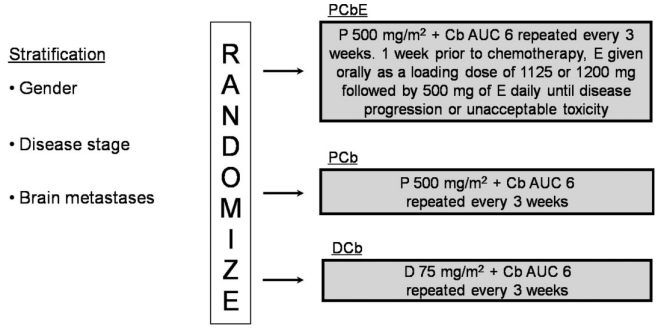
Until recently, histologic subtype was not seen as an important predictor of treatment efficacy, and most trials included patients without selection by histology.[19–21] Subsequent to the initiation of the current trial, results from a phase III trial comparing pemetrexed-cisplatin and gemcitabine-cisplatin were reported.[22] The overall results of the trial showed that pemetrexed-cisplatin provided similar efficacy with improved tolerability compared with gemcitabine-cisplatin. However, a prospectively planned subgroup analysis by histology showed that survival favored the pemetrexed-cisplatin arm among patients with adenocarcinoma or large cell carcinoma (12.6 months versus 10.9 months, $p = 0.03$) but favored gemcitabine-cisplatin among patients with squamous cell carcinoma (9.4 months versus 10.8 months, $p = 0.05$). As a result, pemetrexed-cisplatin has been approved by the Food and Drug Administration as first-line treatment for patients with locally advanced or metastatic NSCLC and nonsquamous histology. Two previous phase II trials have evaluated the combination of pemetrexed-carboplatin.[23,24]

The phase III TAX 326 trial compared three platinum combinations of docetaxel-cisplatin, docetaxel-carboplatin, and vinorelbine-cisplatin. In that trial, docetaxel-carboplatin was associated with a median survival of 9.4 months.[25] The trial showed that docetaxel-platinum combinations were effective treatment options in advanced NSCLC. The combination of docetaxel-carboplatin has not been previously compared with pemetrexed-carboplatin. The current open-label trial was initiated to compare a reference arm of docetaxel-carboplatin with two investigational arms of pemetrexed-carboplatin with and without enzastaurin.

PATIENTS AND METHODS

Patient Eligibility

Patients with a histologic or cytologic diagnosis of NSCLC with stage IIIB (and pleural effusion) or stage IV disease were eligible.[26] Patients had not received prior systemic chemotherapy, immunotherapy, biologic therapy, or radiation therapy. Because this trial was initiated before the treatment-by-histology effect of pemetrexed was known, patients of all NSCLC histologic types were included. Other inclusion criteria included measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST),[27] age 18 years or older, an Eastern Cooperative Oncology Group PS of 0 or 1, a life expectancy ≥12 weeks, and adequate end-organ function and bone marrow reserve (defined as an absolute neutrophil count [ANC] $\geq 1.5 \times 10^9$/L; platelet count $\geq 100 \times 10^9$/L; hemoglobin ≥8 g/dl; bilirubin ≤the institutional upper limit of normal (ULN); alkaline phosphatase ≤2.5 × ULN; aspartate transaminase and alanine transaminase ≤2.5 × ULN; and calculated creatinine clearance [CrCl] ≥45 ml/min using the Cockroft and Gault formula).[28] Patients with documented central nervous system (CNS) metastases that were adequately treated and stable for at least 4 weeks were included. Patients were required to use an appropriate contraceptive method. Prior radiation therapy was allowed to <25% of the bone marrow.



Note: Patients receiving pemetrexed were also administered folic acid, vitamin B12 and steroid prophylaxis. Patients on docetaxel also received steroid prophylaxis. Patients received a maximum of 6 cycles of chemotherapy.

Abbreviations: AUC = under the concentration-time curve; Cb = carboplatin; D = docetaxel; E=enzastaurin; P = pemetrexed

FIGURE 1. Study design.

Exclusion criteria included radiation to the whole pelvis; serious concomitant systemic disorders (e.g., infection); pregnancy or breast-feeding; myocardial infarction within 6 months; weight loss of >10% or 5 kg (whichever was greater) in the past 3 months before study entry; presence of uncontrollable ascites or pleural effusions; and an inability or unwillingness to take folate, vitamin B12, or dexamethasone. Patients with CNS metastases who were receiving warfarin were also excluded.

Treatment Plan

Patients were randomized to one of the following: pemetrexed and carboplatin with enzastaurin (PCbE), pemetrexed and carboplatin (PCb), or docetaxel and carboplatin (DCb) (see Figure 1). For patients receiving PCbE or PCb, pemetrexed was administered at 500 mg/m^2 over 10 minutes and followed by carboplatin at an area under the concentration curve (AUC) of 6 mg/ml/min on day 1 every 3 weeks for six cycles. For patients receiving PCbE, enzastaurin was given as a loading dose of 1125 mg (three 125 mg tablets three times) or 1200 mg (four 100 mg tablets three times) one week before chemotherapy then subsequently daily as 500 mg until disease progression or unacceptable toxicity. Patients in the control treatment arm of DCb received docetaxel at 75 mg/m^2 over 60 minutes followed by carboplatin AUC 6 mg/ml/min on day 1 every 3 weeks for six cycles.

On the days immediately preceding, day of, and immediately after pemetrexed administration, prophylactic dexamethasone (4 mg or equivalent twice daily) was administered to prevent rash. In addition, folic acid (350 to 1000 μg or equivalent daily) and vitamin B12 (1000 μg, every 9 weeks until 3 weeks after the last dose of pemetrexed) supplementation were administered. Dexamethasone (8 mg or equivalent twice daily) was also administered to patients receiving docetaxel.

Hematologic dose adjustments at the start of a subsequent cycle of chemotherapy were based on platelet and neutrophil nadir counts from the preceding cycle of therapy. Before the start of any cycle, ANC had to be $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. Treatment was delayed to allow sufficient time for recovery. For patients receiving

PCbE or PCb, chemotherapy resumed at 75% of the previous dose if ANC nadir was $<0.5 \times 10^9$/L and chemotherapy resumed at 50% of the previous dose if platelets were $<50 \times 10^9$/L. For patients receiving DCb, chemotherapy resumed at 75% of the previous dose if the ANC from the previous cycle was $<0.5 \times 10^9$/L for more than 7 days or was accompanied by fever and platelets were 25 to 50×10^9/L, if ANC was $<0.5 \times 10^9$/L, or if platelets were $<25 \times 10^9$/L. Additional dose adjustment criteria were provided for grade 3 or 4 nonhematologic toxicities. Doses of enzastaurin were to be omitted in the event of an ANC $<0.5 \times 10^9$/L for more than 7 days or $<1.0 \times 10^9$/L and accompanied by fever; platelets $<25 \times 10^9$/L; a grade 3 or 4 nonhematologic toxicity considered clinically relevant; or grade 3 or 4 transaminase elevations.

Any patient who required a dose reduction continued to receive a reduced dose for the remainder of the study. Any patient with two prior dose reductions who experienced a toxicity that would cause a third dose reduction was to be withdrawn from study chemotherapy. Chemotherapy could be delayed for up to 42 days to allow a patient sufficient time to recover from study drug-related toxicity.

Statistical Methods and Study Evaluations

The primary objective of this study was to determine whether or not time to disease progression (TTP) could be improved with PCbE or PCb as compared with a control regimen of DCb. Based on results from TAX 326 trial, the TTP associated with DCb was assumed to be 4.5 months.[25] To provide 80% power to detect a relative improvement in TTP of 3 months for either experimental regimen, a minimum of 126 events were required for each pairwise comparison. Therefore, the target sample size was 70 patients for each treatment regimen or 210 patients in total. The one-sided alpha level for each comparison was 0.025. The planned accrual duration was 36 months, with 12 months of additional follow-up.

TTP was defined as the time from randomization to the first date of disease progression. For patients who did not have documented disease progression and did not receive any other antitumor therapy, TTP was censored at the date of death or date of last visit. TTP was also censored for patients who received other antitumor therapy before disease progression. Secondary end points in this study included overall survival (OS), response rates (evaluated once every 6 weeks by RECIST),[27] toxicities according to the Common Terminology Criteria Version 3.0,[29] resource utilization measured by hospitalization days and reason for hospitalization, and quality of life as measured by the Functional Assessment of Cancer Therapy (FACT)-Lung and FACT-Taxane scales.[30,31] Collection of tissue samples was planned; however, too few were obtained for formal analysis.

OS was defined as the time from the date of randomization to the date of death from any cause. OS was censored at the date of the last follow-up visit for patients who were still alive. TTP and OS were estimated using the Kaplan-Meier method.[32] For response, progression, and survival data, two-sided 95% confidence intervals (CIs) were calculated based on an exact binomial probability. Dose intensity for pemetrexed, carboplatin, and docetaxel was measured as the amount of drug administered as a percentage of planned dose. Compliance with enzastaurin was measured by pill counts, which indicated whether a patient took at least 75% of enzastaurin during the preceding cycle of chemotherapy.

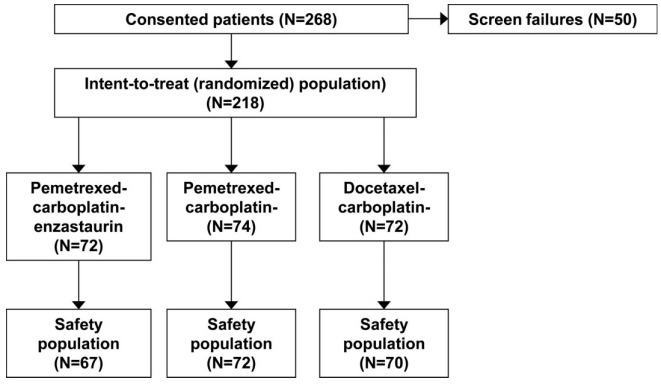


FIGURE 2. CONSORT diagram.

This study was performed in accordance with principles of good clinical practice, applicable laws and regulations, and the Declaration of Helsinki. Before initiation of the study, investigators were responsible for obtaining written consent from participating patients and approval from study sites' ethical review boards.

RESULTS

Patients and Treatment Administration

Between March 2006 and May 2008, 218 patients were enrolled in the United States and randomized to one of the three treatment arms. Patient disposition is shown in Figure 2, and baseline characteristics are summarized in Table 1. Of particular note, histologic distributions were not equal across treatment groups. Compared with the control group of DCb, PCb had a greater percentage of patients with squamous histology (30% versus 19%). Distributions for other variables were similar across treatment groups.

At least one dose of chemotherapy was administered to 67 (93.1%) patients in the PCbE group, 72 of 74 patients in the PCb group (97.3%), and 70 of 72 patients in the DCb group (97.2%). The median (range) number of chemotherapy cycles administered was 4.0 (1–6) for PCbE, 5.5 (1–6) for PCb, and 4.0 (1–6) for DCb. Median relative dose intensity was 97.4% for pemetrexed and 91.0% for carboplatin in PCbE, 97.7% for pemetrexed and 91.9% for carboplatin in PCb, and 99.0% for docetaxel and 93.4% for carboplatin in DCb. In the PCbE group, 67 of 72 patients received at least one dose of enzastaurin (93.1%). The most common reasons for study completion included completion of protocol-defined therapy (which was not defined for PCbE but included 45.9% of PCb and 31.9% of DCb groups), disease progression (65.3% of PCbE, 32.4% of PCb, and 38.9% of DCb), and adverse event (12.5% of PCbE, 12.2% of PCb, and 18.1% of DCb). Differences in reasons for study completion were not significantly different between PCb and DCb. Average compliance with enzastaurin over six cycles of chemotherapy was 77.4% in PCbE.

TABLE 1. Baseline Characteristics for the Intent-to-Treat Population

	PCbE ($N = 72$)	PCb ($N = 74$)	DCb ($N = 72$)
Age, yr			
Median (range)	67 (43–83)	66 (44–84)	65 (46–79)
Gender, *n* (%)			
Male	41 (57)	41 (55)	42 (58)
Female	31 (43)	33 (45)	30 (42)
Race, *n* (%)			
Caucasian	62 (86)	63 (85)	63 (88)
African descent	5 (7)	11 (15)	8 (11)
Hispanic	5 (7)	0 (0)	1 (1)
ECOG performance status, *n* (%)[a]			
0	34 (47)	35 (47)	32 (44)
1	38 (53)	38 (51)	40 (56)
Stage, *n* (%)			
IIIB	6 (8)	5 (7)	6 (8)
IV	66 (92)	69 (93)	66 (92)
Brain metastasis, *n* (%)			
Present	5 (7)	7 (9)	4 (6)
Absent	67 (93)	67 (91)	68 (94)
Histology, *n* (%)			
Adenocarcinoma	46 (64)	43 (58)	43 (60)
Large Cell	2 (3)	3 (4)	3 (4)
Mixed	2 (3)	0 (0)	2 (3)
Squamous	9 (13)	22 (30)	14 (19)
Unknown/NOS	13 (18)	6 (8)	10 (14)
Smoking history			
Ever smoked, *n* (%)	64 (89)	67 (91)	63 (88)
Mean cigarettes per day	25.7	27.9	25.3

[a] Performance status information was missing for one patient receiving PCb.

DCb, docetaxel and carboplatin; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; PCb, pemetrexed and carboplatin; PCbE, pemetrexed, carboplatin, and enzastaurin.

Efficacy

Primary efficacy outcomes by treatment group are summarized in Table 2. Overall censorship rates across treatment groups were 23.8% for TTP and 25.2% for OS end points. Kaplan-Meier curves for TTP and OS are summarized in Figure 3. Median TTP was 4.6 months (95% CI: 3.2–6.7) for PCbE, 6.0 months (95% CI: 4.6–6.5) for PCb, and 4.1 months (95% CI: 2.6–6.3) for DCb. Differences between individual treatment groups were not significant, as indicated by log-rank *p* values. Median survival was 7.2 months (95% CI: 5.7–11.2) for PCbE, 12.7 months (95% CI: 9.3–17.0) for PCb, and 9.2 months (95% CI: 5.9–10.7) for DCb. Comparisons between treatment groups indicated that OS with PCb was significantly longer than with the control group of DCb (after adjusting for histology, hazard ratio = 0.67; 95% CI: 0.45–0.99).

Overall response rates were not significantly different among the three regimens (13.6% for PCbE, 22.2% for PCb, and 27.1% for DCb). Disease control rates (which included all patients with a complete response, partial response, or stable disease) were 65.1% for PCbE, 77.8% for PCb, and 57.1% for DCb. The difference between PCb and DCb in terms of disease control was statistically significant (Fisher's exact test $p = 0.01$).

Toxicity

Toxicity profiles of study drug-related events for the three regimens are summarized in Table 3. In terms of hematologic toxicity, the rates of grade 3 or 4 thrombocytopenia and anemia were greater with PCbE and PCb compared with DCb. Grade 3 or 4 thrombocytopenia was 5.6% for DCb and more than 30% for the other two treatment arms; grade 3 or 4 anemia was 1.4% for DCb and more than 13% for the other two arms. The rate of grade 3 or 4 febrile neutropenia was greatest with DCb (8.3% versus ≤1.5% for the other two arms). The rates of grade 3 or 4 nonhematologic toxicities were generally low. Grade 2 alopecia occurred in 17.1% of DCb patients compared with less than 5% of patients in the other two treatment arms.

Poststudy Therapy/Quality of Life

Table 4 summarizes the use of systemic poststudy therapy. Overall, the most commonly used agents poststudy were erlotonib, docetaxel, carboplatin, and pemetrexed. Final results from the quality of life analysis were previously presented.[33] Using either the FACT-Lung or FACT-Taxane subscales, differences in mean change from baseline scores were not statistically significant across treatment groups. In addition, differences in classification of patients as improved, stable, or worsened were not significant across treatment groups.

DISCUSSION

In this randomized, phase II trial of three regimens in the first-line treatment of stage IIIB/IV NSCLC, differences in the primary end point, TTP, were not statistically significant across treatment arms. Treatment with PCb was associated with significantly longer OS when compared with DCb (12.7 months versus 9.2 months, log-rank $p = 0.05$). Compared with the other two arms, DCb was associated with lower rates of grade 3 thrombocytopenia and anemia but an increased rate of alopecia and a slightly higher rate of grade 3 or 4 febrile neutropenia. The median number of cycles of chemotherapy delivered was greater in the PCb arm (5.5) compared with the DCb arm (4.0).

The disappointing results associated with the PCbE arm in the current trial are consistent with other recent trials using enzastaurin in advanced or metastatic NSCLC. Two previous studies of enzastaurin in advanced NSCLC were terminated for futility at interim analysis. In the second-line setting, a phase II trial ($N = 160$) of the combination of pemetrexed plus enzastaurin did not improve progression-free survival when compared with pemetrexed plus placebo.[34] Similarly, in the first-line setting, a randomized trial conducted by the Hoosier Oncology Group among patients with nonsquamous histology ($N = 40$) failed to show improvement in progression-free survival for the combination of pemetrexed, carboplatin, bevacizumab, and enzastaurin when compared with pemetrexed, carboplatin, bevacizumab, and placebo.[35] Further development of enzastaurin in advanced or metastatic NSCLC is not justified.

TABLE 2. Main Efficacy Parameters

	PCbE (N = 72)	PCb (N = 74)	DCb (N = 72)
Time to disease progression			
Censorship, %	27.8	20.3	23.6
Median, mo (95% CI)	4.6 (3.2–6.7)	6.0 (4.6–6.5)	4.1 (2.6–6.3)
Log-rank pairwise p value	0.40	0.19	Referent
Overall survival			
Censorship, %	22.2	27.0	26.4
Hazard ratios[a] (95% CI)	0.97 (0.67, 1.42)	0.67 (0.45, 0.99)	Referent
Median, mo (95% CI)	7.2 (5.7, 11.2)	12.7 (9.3, 17.0)	9.2 (5.9, 10.7)
1-yr survival rate, % (95% CI)	37.4 (26.0, 48.8)	52.7 (40.4, 63.7)	32.6 (21.5, 44.2)
2-yr survival rate, % (95% CI)	15.0 (7.0, 25.7)	26.8 (16.6, 38.2)	18.9 (10.2, 29.6)
3-yr survival rate, % (95%) CI	0.0	11.5 (3.2, 25.7)	0.0
Log-rank pairwise p value	0.87	0.05	Referent
Response rate			
No. assessed for response	66	72	70
Complete response, n (%)	0 (0.0)	2 (2.8)	0 (0.0)
Partial response, n (%)	9 (13.6)	14 (19.4)	19 (27.1)
Stable disease, n (%)	34 (51.5)	40 (55.6)	21 (30.0)
Progressive disease, n (%)	11 (16.7)	10 (13.9)	10 (14.3)
Unknown/not done, n (%)	12 (18.2)	6 (8.3)	20 (28.5)
Disease control rate,[b] n (%)	43 (65.1)	56 (77.8)	40 (57.1)
p value for disease control rate	0.38	0.01	Referent

[a] Hazard ratios were obtained using Cox model for each pair with adjustment for histologic subgroup.
[b] Disease control rate included patients with complete response, partial response, and stable disease.
CI, confidence interval; DCb, docetaxel and carboplatin; PCb, pemetrexed and carboplatin; PCbE, pemetrexed, carboplatin, and enzastaurin.

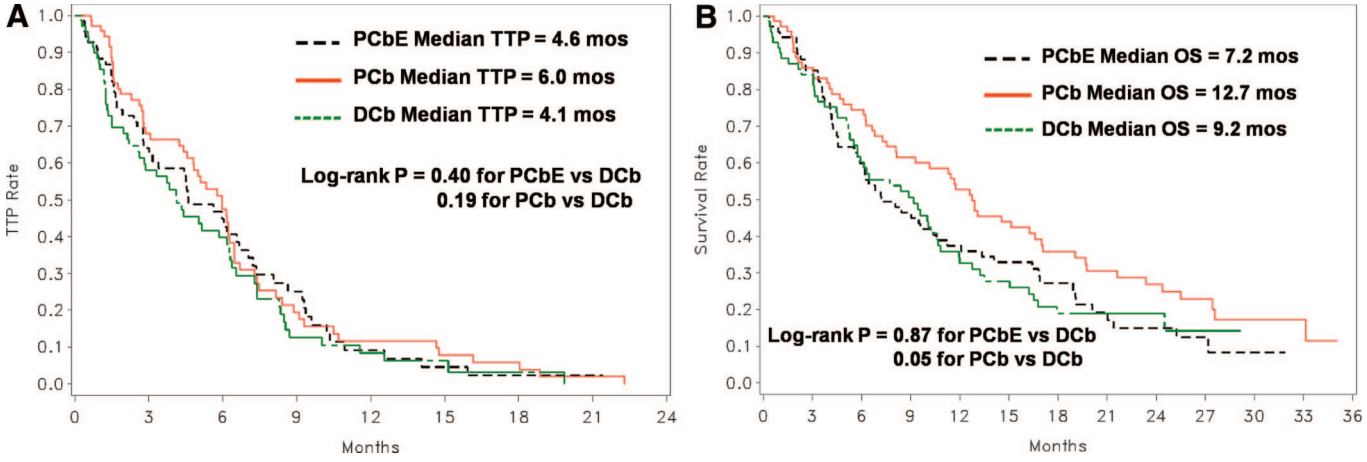


FIGURE 3. *A*, Time to disease progression. *B*, Overall survival. DCb, docetaxel and carboplatin; PCb, pemetrexed and carboplatin; PCbE, pemetrexed, carboplatin, and enzastaurin.

Results with PCb were notable in light of a 2-year survival rate of 26.8% (95% CI: 16.6–38.2). Three-year survival was 11.5% (95% CI: 3.2–25.7). This result is interesting as we continue to strive to identify effective chemotherapy regimens that will help us to achieve our goals of extending long-term survival in metastatic NSCLC. However, conclusions with respect to this trial are limited due to the relatively small sample size associated with the phase II trial design.

Grønberg et al.[36] reported the results of a randomized phase III trial comparing PCb and gemcitabine-carboplatin. In that trial, 219 patients received PCb, and median survival was 7.3 months (95% CI: 6.1–8.6) within that group. The lower survival associated with PCb compared with the current trial in the Grønberg et al.[36] trial may be partly attributed to its less restrictive patient selection criteria, which allowed patients with PS 2, any weight loss, uncontrolled pleural effusions, and progressive CNS metastases. The Grønberg et al. trial also used a lower dose of carboplatin (AUC 5) than the current trial and used prespecified dose reductions based on age.

TABLE 3. Toxicity Summary of Drug-Related Events

	PCbE ($N = 72$)			PCb ($N = 74$)			DCb ($N = 72$)		
Adverse Event	**Any (Grade 1–4)**	**Grade 3**	**Grade 4**	**Any (Grade 1–4)**	**Grade 3**	**Grade 4**	**Any (Grade 1–4)**	**Grade 3**	**Grade 4**
Neutropenia	24 (33.3)	5 (6.9)	4 (5.6)	29 (39.2)	11 (14.9)	2 (2.7)	21 (29.2)	9 (12.5)	5 (6.9)
Febrile neutropenia	1 (1.4)	1 (1.4)	0 (0.0)	1 (1.4)	1 (1.4)	0 (0.0)	6 (8.3)	4 (5.6)	2 (2.8)
Thrombocytopenia	37 (51.4)	16 (22.2)	8 (11.1)	43 (58.1)	18 (24.3)	6 (8.1)	17 (23.6)	3 (4.2)	1 (1.4)
Anemia	33 (45.8)	10 (13.9)	0 (0.0)	48 (64.8)	14 (18.9)	1 (1.4)	34 (47.2)	1 (1.4)	0 (0.0)
Anorexia	9 (12.5)	2 (2.8)	0 (0.0)	10 (13.5)	0 (0.0))	0 (0.0)	14 (19.4)	1 (1.4)	0 (0.0)
Diarrhea	14 (19.4)	3 (4.2)	0 (0.0)	8 (10.8)	1 (1.4)	0 (0.0)	15 (20.8)	4 (5.6)	0 (0.0)
Elevated ALT	3 (4.2)	1 (1.4)	0 (0.0)	7 (9.5)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Thrombosis	10 (13.9)	6 (9.0)	3 (4.5)	4 (5.4)	1 (1.4)	2 (2.8)	6 (8.3)	3 (4.3)	3 (4.3)
Fatigue	25 (34.7)	3 (4.2)	0 (0.0)	31 (41.9)	2 (2.7)	0 (0.0)	31 (43.1)	4 (5.6)	0 (0.0)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (8.3)	3 (4.2)	0 (0.0)
Nausea	33 (45.8)	1 (1.4)	0 (0.0)	30 (40.5)	3 (4.1)	0 (0.0)	22 (30.1)	2 (2.8)	0 (0.0)
Vomiting	15 (20.8)	3 (4.2)	0 (0.0)	14 (18.9)	2 (2.7)	0 (0.0)	13 (18.1)	2 (2.8)	0 (0.0)
Alopecia (grade 2)		1 (1.5)			3 (4.2)			12 (17.1)	

Values are given as *n* (%).
ALT, alanine aminotransferase; DCb, docetaxel and carboplatin; PCb, pemetrexed and carboplatin; PCbE, pemetrexed, carboplatin, and enzastaurin.

TABLE 4. Systemic Poststudy Chemotherapy

	PCbE ($N = 72$)	PCb ($N = 74$)	DCb ($N = 72$)
Patients with any systemic poststudy chemotherapy	42 (58.3)	42 (56.7)	33 (45.8)
Bevacizumab	10 (13.9)	5 (6.8)	5 (6.9)
Carboplatin	12 (16.7)	10 (13.5)	9 (12.5)
Cisplatin	1 (1.4)	3 (4.1)	0 (0.0)
Docetaxel	15 (20.8)	15 (20.3)	4 (5.6)
Erlotinib	10 (13.9)	9 (12.2)	11 (15.3)
Gemcitabine	2 (2.8)	2 (2.7)	4 (5.6)
Paclitaxel	9 (12.5)	7 (9.5)	3 (4.2)
Pemetrexed	4 (5.6)	8 (10.8)	11 (15.3)

Values are given as *n* (%).
DCb, docetaxel and carboplatin; PCb, pemetrexed and carboplatin; PCbE, pemetrexed, carboplatin, and enzastaurin.

Phase II trials of PCb conducted at M. D. Anderson Cancer Center ($N = 50$)[23] and in Europe ($N = 38$)[24] produced median survival times of 13.5 months (95% CI: 10.1–16.8) and 10.5 months (95% CI: 7.6–12.8), respectively. Both those trials excluded patients with PS 2, significant weight loss, uncontrolled pleural effusions, and documented brain metastases.

Histologic subtype has not historically been an important predictor of treatment efficacy, and retrospective analyses of Eastern Cooperative Oncology Group 1594 and Southwest Oncology Group trials suggest that most chemotherapeutic agents do not exhibit a preferential treatment effect by patient histology.[37,38] The phase III first-line trial of pemetrexed-cisplatin[22] as well as phase III trials of single-agent pemetrexed in the second-line[39] and maintenance settings,[40] however, suggest that pemetrexed has preferential activity in nonsquamous patients. In the current trial, the PCb arm had a greater proportion of patients with squamous histology than the DCb arm.

Research to further evaluate PCb with other agents is ongoing. A recent phase II study of initial therapy with PCb and bevacizumab followed by maintenance pemetrexed and bevacizumab resulted in an objective response rate of 55% and a median survival of 14.1 months (95% CI: 10.8–19.6).[41] That regimen is currently being tested in the phase III setting against a regimen of paclitaxel, carboplatin, and bevacizumab followed by maintenance bevacizumab in a trial (NCT00762034) that has a planned accrual of 900 patients.[42] A second ongoing phase III trial (NCT00948675) with a planned sample size of 360 is comparing paclitaxel, carboplatin, and bevacizumab followed by maintenance bevacizumab to PCb followed by maintenance pemetrexed.[43]

Results from this trial with respect to OS should be interpreted cautiously in light of the negative findings with respect to the primary end point and the limitations in generating conclusions from phase II designs. These results, however, support the continued evaluation of PCb with or without novel agents in stage IIIB/IV NSCLC.

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