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ORIGINAL REPORT

Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
Cisplatin plus gemcitabine is a standard regimen for first-line treatment of advanced non–small-cell lung cancer (NSCLC). Phase II studies of pemetrexed plus platinum compounds have also shown activity in this setting.

Patients and Methods
This noninferiority, phase III, randomized study compared the overall survival between treatment arms using a fixed margin method (hazard ratio [HR] < 1.176) in 1,725 chemotherapy-naive patients with stage IIIB or IV NSCLC and an Eastern Cooperative Oncology Group performance status of 0 to 1. Patients received cisplatin 75 mg/m^2 on day 1 and gemcitabine 1,250 mg/m^2 on days 1 and 8 (n = 863) or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 on day 1 (n = 862) every 3 weeks for up to six cycles.

Results
Overall survival for cisplatin/pemetrexed was noninferior to cisplatin/gemcitabine (median survival, 10.3 *v* 10.3 months, respectively; HR = 0.94; 95% CI, 0.84 to 1.05). Overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (n = 847; 12.6 *v* 10.9 months, respectively) and large-cell carcinoma histology (n = 153; 10.4 *v* 6.7 months, respectively). In contrast, in patients with squamous cell histology, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (n = 473; 10.8 *v* 9.4 months, respectively). For cisplatin/pemetrexed, rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia ($P \leq .001$); febrile neutropenia ($P = .002$); and alopecia ($P < .001$) were significantly lower, whereas grade 3 or 4 nausea ($P = .004$) was more common.

Conclusion
In advanced NSCLC, cisplatin/pemetrexed provides similar efficacy with better tolerability and more convenient administration than cisplatin/gemcitabine. This is the first prospective phase III study in NSCLC to show survival differences based on histologic type.

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INTRODUCTION

In advanced-stage (stage IIIB or IV) non–small-cell lung cancer (NSCLC), doublet combinations of platinum compounds (cisplatin or carboplatin) with gemcitabine, vinorelbine, or taxanes (paclitaxel or docetaxel) are reference regimens.[1] When compared head-to-head in phase III studies, these doublets have shown comparable efficacy, with differences in toxicity profiles.[2-5] Cisplatin plus gemcitabine, in a 3-week schedule, is an effective widely used regimen for first-line treatment of NSCLC.[3,6]

Pemetrexed is a potent inhibitor of thymidylate synthase[7,8] and other folate-dependent enzymes, including dihydrofolate reductase and glycinamide ribonucleotide formyl transferase.[9] Pemetrexed is currently approved in combination with cisplatin for first-line treatment of malignant pleural mesothelioma[10] and as a single agent for second-line treatment of advanced NSCLC.[11]

In phase II studies in chemotherapy-naive patients with NSCLC, pemetrexed in combination with cisplatin or carboplatin has yielded efficacy results comparable with other platinum doublets.[12-15]

In addition, pemetrexed has an excellent safety profile and a convenient administration schedule.

More recently, the addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor, to paclitaxel and carboplatin led to a significant survival benefit; however, this efficacy benefit was seen with an increased risk of treatment-related deaths.[16] In a confirmatory study, the addition of bevacizumab to cisplatin/gemcitabine led to a statistically significant improvement in progression-free survival (PFS).[17] In both of these studies, safety issues that emerged from a previous phase II randomized study were considered,[18] and consequently, restrictive eligibility criteria were adopted. The primary objective of this phase III noninferiority study was to compare the overall survival of cisplatin/pemetrexed with cisplatin/gemcitabine in chemotherapy-naive patients with advanced NSCLC.

PATIENTS AND METHODS

Patients

Chemotherapy-naive patients with histologically or cytologically confirmed NSCLC, classified as stage IIIB not amenable to curative treatment or stage IV, with at least one unidimensionally measurable lesion according to the Response Evaluation Criteria in Solid Tumors,[19] with an Eastern Cooperative Oncology Group performance status of 0 or 1,[20] and at least 18 years of age were eligible. Patients had adequate bone marrow reserve and organ function including calculated creatinine clearance $\geq$ 45 mL/min based on the standard Cockcroft and Gault formula.[21] Prior radiation therapy was permitted if it was completed at least 4 weeks before study treatment and patients had fully recovered from its acute effects.

Exclusion criteria included peripheral neuropathy $\geq$ National Cancer Institute Common Toxicity Criteria[22] grade 1, progressive brain metastases, or uncontrolled third-space fluid retention before study entry. Patients were also excluded if they were unable to interrupt aspirin and other nonsteroidal anti-inflammatory drugs or if they were unable or unwilling to take folic acid, vitamin B_{12}, or corticosteroids.

The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines[23] and was approved by each participating institutional ethics review board. All patients signed written informed consent before treatment.

Study Design and Treatment Plan

Eligible patients were randomly assigned to receive either cisplatin 75 mg/m^2 on day 1 plus gemcitabine 1,250 mg/m^2 on days 1 and 8 or cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 on day 1. Pocock and Simon[24] random assignment was used according to disease stage (IIIB *v* IV), performance status (0 *v* 1), history of brain metastases (yes *v* no), sex (male *v* female), pathologic diagnosis (histologic *v* cytologic), and investigative center.

Chemotherapy was repeated every 3 weeks for a maximum of six cycles (unless there was earlier evidence of disease progression or intolerance of the study treatment). Patients on both arms received dexamethasone prophylaxis of 4 mg orally twice per day on the day before, the day of, and the day after each day-1 treatment. All patients received oral folic acid (350 to 1,000 μg) daily and a vitamin B_{12} injection (1,000 μg) every 9 weeks, beginning 1 to 2 weeks before the first dose and continuing until 3 weeks after the last dose of study treatment.

Patients requiring a day-1 dose reduction of pemetrexed, gemcitabine, or cisplatin received the reduced dose for the remainder of the study. Patients who had two dose reductions on day 1 and who experienced toxicity requiring a third dose reduction were discontinued from study therapy. Cycle delays of up to 42 days were permitted for recovery from adverse events. Within-cycle (day 8) dose reductions and omissions were allowed for gemcitabine. Concomitant supportive therapies, such as erythropoietic agents or granulocyte colony-stimulating factors, were allowed according to the American Society of Clinical Oncology guidelines.[25]

The study protocol requested, in a nonmandatory way, the collection of tumor samples for assessment of candidate biomarkers. Details about these data will be reported separately.

Baseline and Treatment Assessments

Before entering the study, patients underwent a medical history, physical examination, and tumor measurements of palpable lesions as well as lesions assessed by imaging techniques (positron emission tomography and ultrasound scans were not permitted). The baseline assessment method was repeated every other cycle and then every 6 weeks after treatment discontinuation until disease progression. Disease status was assessed according to Response Evaluation Criteria in Solid Tumors.[19]

Randomly assigned patients who met the eligibility criteria and who had baseline imaging and at least one scan after starting chemotherapy were considered assessable for tumor response and duration of response. All patients who received at least one dose of pemetrexed, gemcitabine, or cisplatin were considered assessable for safety. Patients were assessed for toxicity according to

Table 1. Baseline Patient and Disease Characteristics for Randomly Assigned Patients

Characteristic	Cisplatin/Pemetrexed (n = 862)		Cisplatin/Gemcitabine (n = 863)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	61.1		61.0	
Range	28.8-83.2		26.4-79.4	
Age < 65 years	541	62.8	577	66.9
Age ≥ 65 years	321	37.2	286	33.1
Sex				
Female	257	29.8	258	29.9
Male	605	70.2	605	70.1
Smoking status				
Former/current smoker	629	73.0	637	73.8
Never-smoker	128	14.8	122	14.1
Unknown	105	12.2	104	12.1
Stage of disease				
Stage IIIB, dry	138	16.0	159	18.4
Stage IIIB, wet	67	7.8	51	5.9
Stage IV	657	76.2	653	75.7
ECOG performance status				
0	305	35.4	307	35.6
1	556	64.5	554	64.2
Unknown	1	0.1	2	0.2
Pathologic diagnosis				
Histologic	573	66.5	575	66.6
Cytologic	289	33.5	288	33.4
Race				
African descent	18	2.1	18	2.1
White	669	77.6	680	78.8
East/South East Asian	116	13.5	104	12.1
Other	59	6.8	61	7.1
Histologic type*				
Adenocarcinoma	436	50.6	411	47.6
Large-cell carcinoma	76	8.8	77	8.9
Squamous cell carcinoma	244	28.3	229	26.5
Other: NSCLC, NOS	106	12.3	146	16.9

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell lung cancer; NOS, not otherwise specified.
*Histologic type was reported by the investigative site.

the National Cancer Institute Common Toxicity Criteria, version 2.0.[22] Efficacy analyses, including the primary end point of overall survival, incorporated all randomly assigned patients on an intent-to-treat basis. Secondary end points included PFS, time to progressive disease, time to treatment failure, objective tumor response rate, duration of response, and toxicity.

Statistical Analyses

Using a noninferiority design, this study compared overall survival between the two treatment arms using a fixed margin method. Assuming a hazard ratio (HR) of 1.0 and including all randomly assigned patients, when at least 1,190 deaths occurred, the analysis provided 80% power to reject the null hypothesis (H_0). The H_0 assumed that cisplatin/gemcitabine would provide a $\geq$ 15% reduction in the risk of death over cisplatin/pemetrexed, corresponding to a fixed margin of 1.176. Using the Cox proportional hazards model[26] (with preplanned adjustments for sex, diagnosis [histologic *v* cytologic], disease stage, and performance status) and two-tailed 95% CIs for the HR, rejection of the H_0 occurred when the upper bound of the HR's 95% CI was less than 1.176.

Cox proportional hazard models were also used to compare the other time-to-event end points between the treatment arms and to test for treatment-by-histology interaction; the Kaplan-Meier[27] method was used to estimate the medians for time-to-event parameters. Tests were conducted as follows: noninferiority tests at one-sided $\alpha = .025$ level; superiority tests at two-sided $\alpha = .05$ level; and two-sided CIs at 95%. Tumor response was compared using the normal approximation test for superiority. The incidences of toxicities, hospitalizations, and supportive care were analyzed using Fisher's exact test and analysis of variance (as appropriate). Prespecified analyses of overall survival by random assignment factors included age group, race, smoking status, and histology. All HRs are reported as adjusted, unless otherwise specified. *P* values were not adjusted for multiple comparisons.

RESULTS

Patient Characteristics

From July 2004 to December 2005, a total of 1,725 patients were randomly assigned (863 patients to cisplatin/gemcitabine and 862 patients to cisplatin/pemetrexed). The baseline patient and disease-related characteristics were well balanced between the two treatment arms (Table 1).

All 1,725 patients were evaluated for efficacy, whereas 1,669 patients (cisplatin/gemcitabine, n = 830, 96.2%; cisplatin/pemetrexed, n = 839, 97.3%) were eligible for the safety analyses (Fig 1). As of March 2007, 1,270 of 1,725 patients had died, 647 (75.0%) on the cisplatin/gemcitabine arm and 623 (72.3%) on the cisplatin/pemetrexed arm.

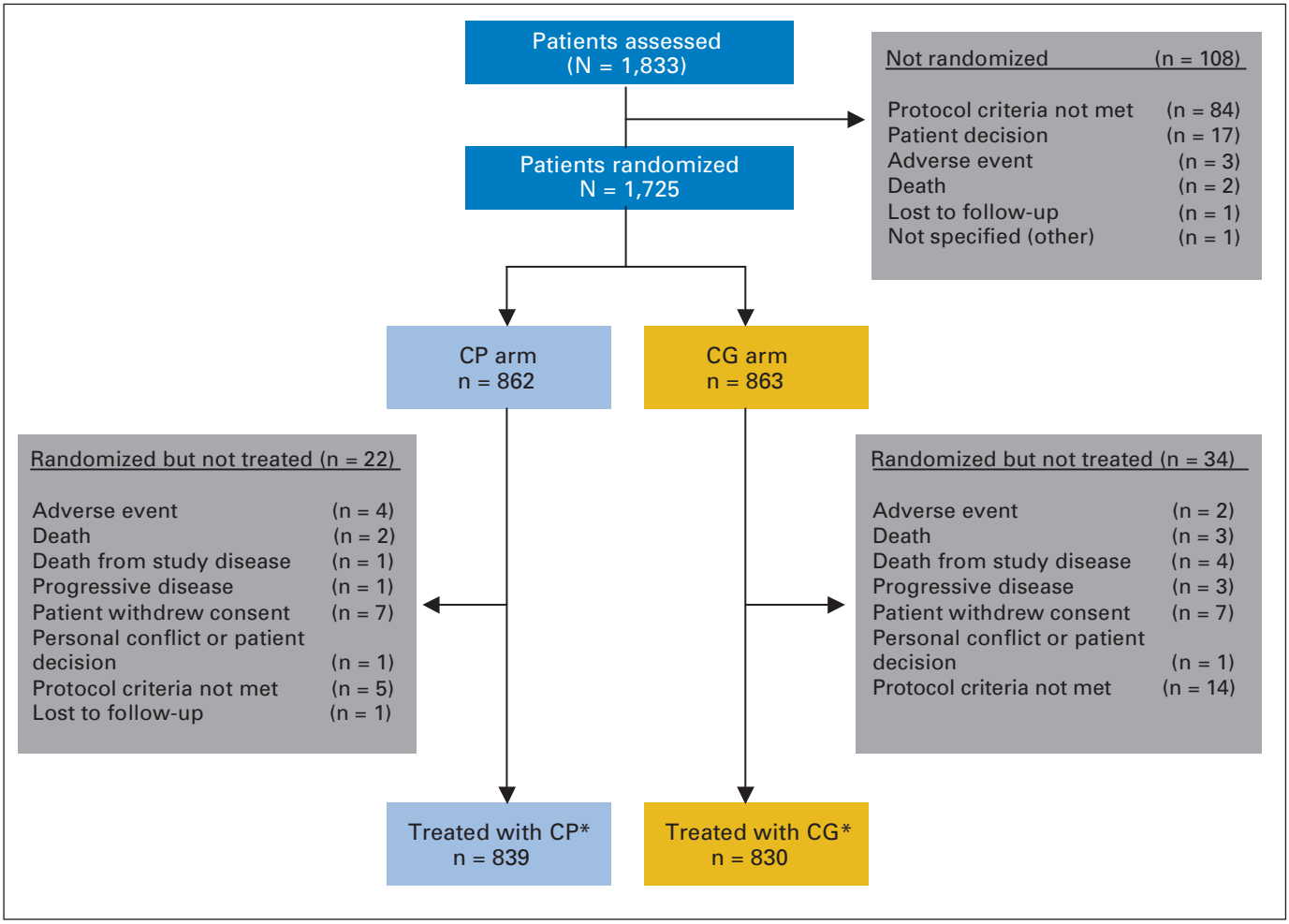

Fig 1. CONSORT diagram of the study. A total of 1,669 patients (96.8%) received study treatment consisting of at least one dose of cisplatin/pemetrexed (CP; n = 839) or cisplatin/gemcitabine (CG; n = 830). (*) One patient was assigned to the CP arm but received CG treatment. This patient was included in the CG arm for the safety analysis.

Treatment

Table 2 indicates that a median number of five cycles was administered on both arms. Dose adjustments (delays, reductions, and omissions) were less frequent in patients treated with cisplatin/pemetrexed compared with cisplatin/gemcitabine, even when considering the more frequent gemcitabine dosing (days 1 and 8 for gemcitabine *v* only day 1 for pemetrexed). On day 1, cisplatin/pemetrexed dose reductions were much less frequent (cisplatin, n = 64; pemetrexed, n = 54 *v* cisplatin, n = 154; gemcitabine, n = 362) and were mainly caused by neutropenia, whereas cisplatin/gemcitabine dose reductions were most commonly attributable to neutropenia, thrombocytopenia, febrile neutropenia, and leukopenia. On day 8, 339 gemcitabine doses (9.3%) were omitted. Delivered dose-intensities were higher for cisplatin/pemetrexed (95.0% and 94.8%, respectively) than for cisplatin/gemcitabine (93.5% and 85.8%, respectively).

Efficacy

Overall survival for patients randomly assigned to cisplatin/pemetrexed was noninferior to the overall survival of patients assigned to cisplatin/gemcitabine (median overall survival, 10.3 *v* 10.3 months; HR = 0.94, 95% CI, 0.84 to 1.05), with the CIs for the HR well below the 1.176 noninferiority margin. Figure 2 shows the Kaplan-Meier curve for overall survival. Survival rates at 12 and 24 months were 43.5% and 18.9% for cisplatin/pemetrexed, respectively, and 41.9% and 14.0% for cisplatin/gemcitabine, respectively.

Table 2. Dose Adjustments: Reductions, Omissions, and Delays

Cycles and Dose Adjustments	Cisplatin/ Pemetrexed (n = 839)	Cisplatin/ Gemcitabine (n = 830)
No. of cycles per patient		
Median	5.0	5.0
Range	1-7*	1-8†
Total No. of cycles administered	3,648	3,626
Cycles delayed		
No.	315	408
% total cycles	8.6	11.3
Dose adjustments		
Doses reduced on day 1		
Cisplatin		
No.	64	154
%	1.8	4.2
Pemetrexed		
No.	54	—
%	1.5	—
Gemcitabine		
No.	—	362
%	—	10.0
Doses omitted on day 8	Not applicable	
Gemcitabine		
No.	—	339
%	—	9.3
Relative dose-intensity, %		
Cisplatin	95.0	93.5
Pemetrexed	94.8	—
Gemcitabine	—	85.8

*One patient on the cisplatin/pemetrexed arm received more than six cycles.
†Four patients on the cisplatin/gemcitabine arm received more than six cycles.

PFS was also noninferior (cisplatin/pemetrexed median PFS, 4.8 months; cisplatin/gemcitabine median PFS, 5.1 months; HR = 1.04; 95% CI, 0.94 to 1.15; Fig 2), as was time to progressive disease. Objective response rates were comparable for the two arms (cisplatin/pemetrexed = 30.6%; cisplatin/gemcitabine = 28.2%), whereas duration of response was longer for cisplatin/gemcitabine than cisplatin/pemetrexed (4.5 *v* 5.1 months), although neither comparison was statistically significant.

In a Cox adjusted analysis (similar to the primary analysis of survival) to which smoking status was added, current/former smokers had a significantly higher risk of death compared with never-smokers (HR = 1.74, test for superiority $P < .001$), even after controlling for treatment and the other four covariates. This effect of smoking status was also demonstrated in unadjusted analyses, in which the median survival time for never-smokers was 15.9 months compared with 10.0 months for former/current smokers on the cisplatin/pemetrexed arm and the median survival time for never-smokers was 15.3 months compared with 10.3 months for former/current smokers on the cisplatin/gemcitabine arm.

Figure 3 shows a plot of Cox adjusted survival HRs (with 95% CIs) for the preplanned analyses that evaluated differences in overall survival with respect to baseline characteristics. The effect on survival of cisplatin/pemetrexed relative to cisplatin/gemcitabine was significantly different according to nonsquamous (large-cell carcinoma plus adenocarcinoma) versus squamous histology. The treatment-by-histology interaction analysis ($P = .0011$) also showed that overall survival for patients with nonsquamous histology was significantly improved on the cisplatin/pemetrexed arm compared with the overall survival for all other patients with nonsquamous or squamous histology, thus confirming the analysis shown in Figure 3.

The analyses of overall survival by treatment arm for each of three histologic groups (large-cell carcinoma, adenocarcinoma, and squamous) demonstrated that cisplatin/pemetrexed in patients with adenocarcinoma and large-cell carcinoma resulted in significantly better survival than cisplatin/gemcitabine (adenocarcinoma: n = 847, 12.6 *v* 10.9 months, respectively; HR = 0.84; 95% CI, 0.71 to 0.99; $P = .03$; large-cell carcinoma: n = 153, 10.4 *v* 6.7 months, respectively; HR = 0.67; 95% CI, 0.48 to 0.96; $P = .03$; nonsquamous: n = 1,000, 11.8 *v* 10.4 months, respectively; HR = 0.81; 95% CI, 0.70 to 0.94; $P = .005$). Patients with squamous histology assigned to cisplatin/pemetrexed (n = 244) had a median survival time of 9.4 months, whereas patients assigned to cisplatin/gemcitabine (n = 229) had a median survival time of 10.8 months (HR = 1.23; 95% CI, 1.00 to 1.51; $P = .05$). Figure 2 shows the Kaplan-Meier overall survival by treatment arm for the nonsquamous and the squamous histologic groups. The overall survival for a fourth group, consisting of all those patients in whom a generic cytologic diagnosis of NSCLC without further subtype classification was made (n = 252), did not show a significant difference between the two arms; in this group, patients assigned to cisplatin/pemetrexed had a median survival time of 8.6 months compared with 9.2 months for patients assigned to cisplatin/gemcitabine (HR = 1.08; 95% CI, 0.81 to 1.45; $P = .586$). When analyzed according to other baseline and disease characteristics, survival was consistent with the overall study results (Table 3). Factors that had a statistically significant ($P < .05$) prognostic impact on survival (independent of treatment) included sex, race, performance status, disease stage, and histology.

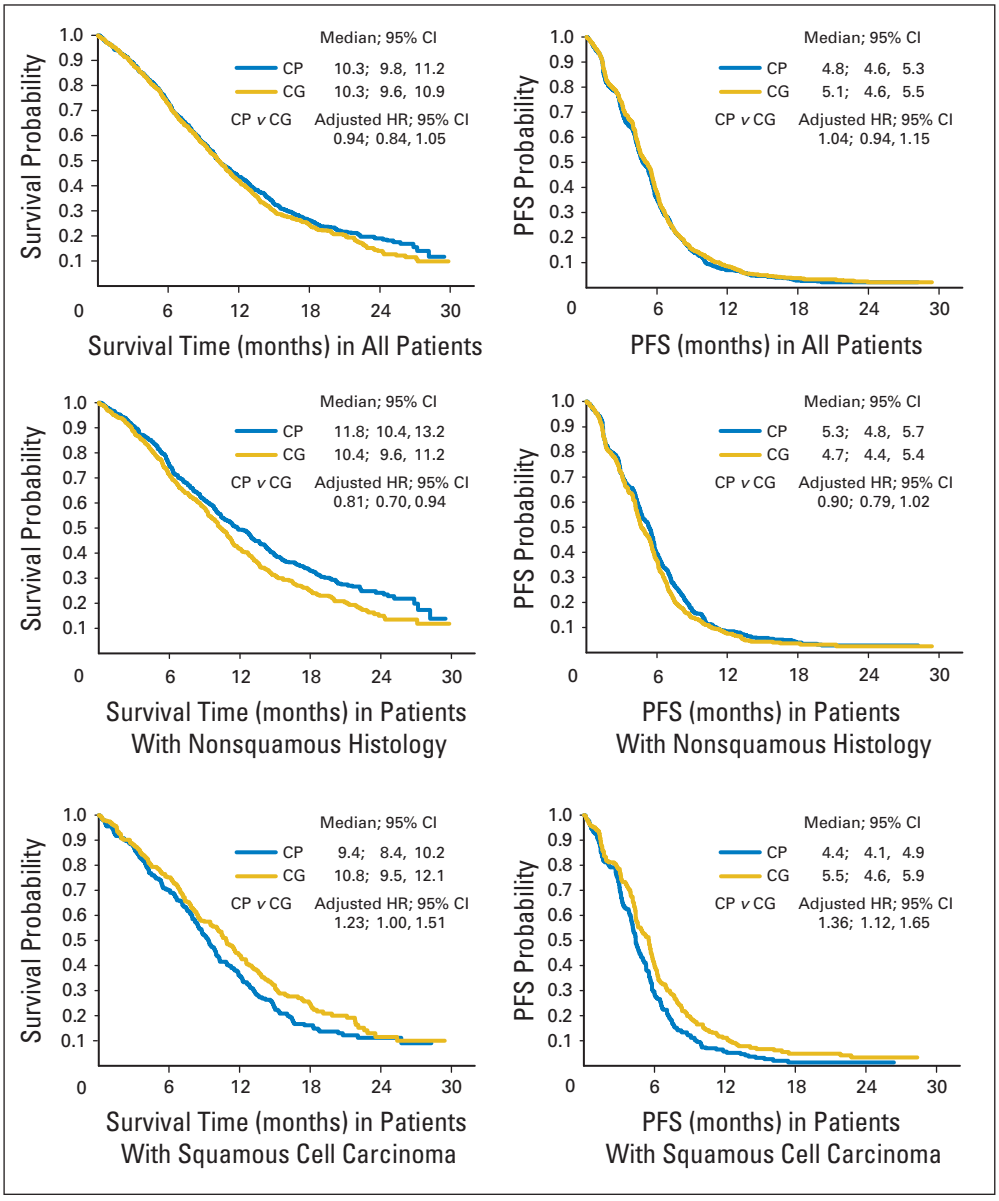

Fig 2. Kaplan-Meier overall survival and progression-free survival (PFS) curves for the entire population, patients with nonsquamous histology (adenocarcinoma plus large cell), and patients with squamous histology. CP, cisplatin/pemetrexed; CG, cisplatin/gemcitabine; HR, hazard ratio.

Safety

Key hematologic grade 3 or 4 drug-related toxicities were significantly ($P \leq .001$) lower for cisplatin/pemetrexed compared with cisplatin/gemcitabine (neutropenia, 15% *v* 27%; anemia, 6% *v* 10%, and thrombocytopenia, 4% *v* 13%, respectively). For cisplatin/pemetrexed versus cisplatin/gemcitabine, drug-related grade 3 or 4 febrile neutropenia (1% *v* 4%, respectively; $P = .002$) and alopecia (all grades; 12% *v* 21%, respectively; $P < .001$) were also significantly lower, whereas drug-related grade 3 or 4 nausea (7% *v* 4%, respectively; $P = .004$) was higher (Table 4). Safety within the histology groups was generally consistent with the overall safety results.

There were no statistically significant differences in hospital admissions or hospital days per patient observed between the study arms. Patients on the cisplatin/pemetrexed arm versus the cisplatin/gemcitabine arm received significantly fewer transfusions (16.4% *v* 28.9%, respectively; $P < .001$), including RBC transfusions (16.1% *v* 27.3%, respectively; $P < .001$) and platelet transfusions (1.8% *v* 4.5%, respectively; $P = .002$); the administration of erythropoietic (10.4% *v* 18.1%, respectively; $P < .001$) and granulocyte colony-stimulating factors (3.1% *v* 6.1%, respectively; $P = .004$) was significantly lower in favor of cisplatin/pemetrexed.

There was no significant difference ($P = .387$) between treatment arms in the incidence of or reason for the 116 deaths (7%) that occurred during study treatment. Each investigator categorized the deaths as caused by study disease, possibly caused by study drug, or as a result of other causes. Deaths attributed to study drug toxicity were low and were similar between arms (nine patients [1.0%] for cisplatin/pemetrexed, and six patients [0.7%] for cisplatin/gemcitabine).

Postdiscontinuation Therapies

Data regarding additional lines of therapy were prospectively collected; decisions regarding which therapies to use were made by the

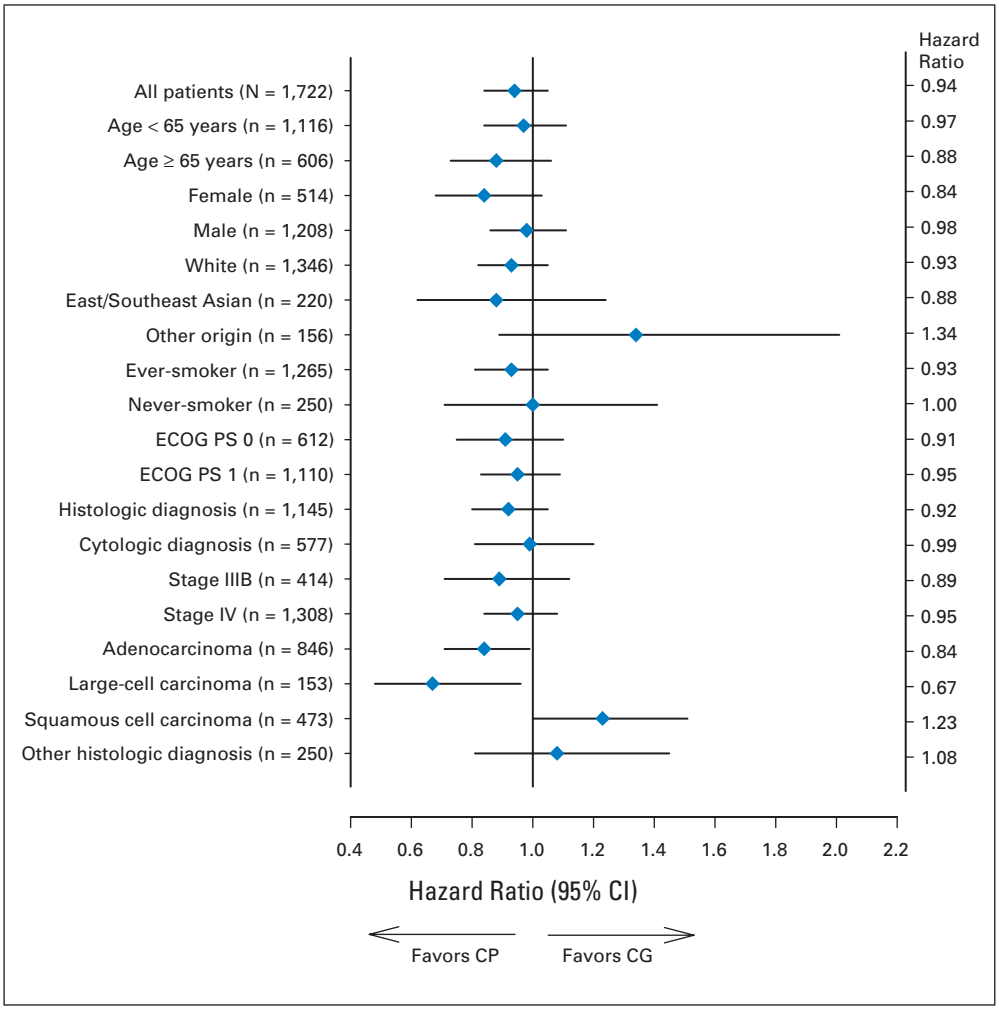

Fig 3. Survival hazard ratios (cisplatin/pemetrexed over cisplatin/gemcitabine) in groups according to baseline characteristics. Results based on Cox adjusted analyses for Eastern Cooperative Oncology Group performance status (ECOG PS), disease stage, sex, and basis for diagnosis (histologic *v* cytologic). In the analysis by group, pertaining to each of these four covariates, the variable predicting the group was excluded from the model. Three patients were missing ECOG PS and are excluded from the Cox adjusted analyses; 209 patients were missing smoking status. CP, cisplatin/pemetrexed; CG, cisplatin/gemcitabine.

individual investigators. Overall, 56.1% of cisplatin/gemcitabine patients and 52.6% of cisplatin/pemetrexed patients received an additional line of therapy. The types of agents administered were well balanced on the two arms, with the exception of more frequent pemetrexed use on the cisplatin/gemcitabine arm (13.4% *v* 3.5% on the cisplatin/pemetrexed arm; $P < .001$) and more frequent gemcitabine use on the cisplatin/pemetrexed arm (16.7% *v* 8.6% on the cisplatin/gemcitabine arm; $P < .001$). Docetaxel was administered in 27.6% and 25.4% of patients and epidermal growth factor receptor tyrosine kinase inhibitors were administered in 22.5% and 24.9% of patients on the cisplatin/gemcitabine and cisplatin/pemetrexed arms, respectively. The distribution of postdiscontinuation therapies in each histologic group was similar to that of the overall study group.

DISCUSSION

In this randomized study, to our knowledge the largest ever conducted in the first-line setting of advanced NSCLC, cisplatin/pemetrexed was noninferior to cisplatin/gemcitabine. Survival, as well as other efficacy outcomes (PFS, 1- and 2-year survival rates, and response rates), for cisplatin/pemetrexed compares favorably with recent, first-line, NSCLC randomized clinical trials evaluating other platinum doublets (median survival time ranging from 7.4 to 10.1 months).[2-5] The modest improvement in survival observed on both arms of this study compared with previous studies of platinum-based regimens[2-4] may have been influenced by several factors including improvements in NSCLC clinical staging, a relatively higher proportion of stage IIIB patients, or the exclusion of patients with a performance status of 2. In addition, enrollment onto this study reflects the relative increase in the proportion of adenocarcinoma,[28] a favorable prognostic factor observed in the overall NSCLC population, which was confirmed in this study. The combination of cisplatin/pemetrexed demonstrated a better safety profile compared with cisplatin/gemcitabine as documented by fewer dose adjustments, lower incidences of drug-related grade 3 or 4 hematologic toxicities, and a significantly lower incidence of febrile neutropenia, even though patients on both arms received a similar number of treatment cycles. In addition, patients treated with cisplatin/gemcitabine required significantly more transfusions and supportive care interventions (ie, hematopoietic growth factor support) than did patients on the cisplatin/pemetrexed arm.

An intriguing aspect of this study occurred in the prespecified analyses for survival with respect to histology, in which a significant survival difference in favor of cisplatin/pemetrexed occurred in

Table 3. Survival Based on Baseline Patient and Disease Characteristics

Characteristic	No. of Patients	Survival (months)				Adjusted Hazard Ratio	95% CI
		Cisplatin/Pemetrexed		Cisplatin/Gemcitabine			
		Median	95% CI	Median	95% CI		
Age							
< 65 years	1,118	10.3	9.6 to 11.3	10.3	9.6 to 11.3	0.97	0.84 to 1.11
≥ 65 years	607	10.1	9.2 to 12.0	10.2	8.5 to 11.2	0.88	0.73 to 1.06
Sex							
Males	1,210	9.6	8.8 to 10.2	9.9	9.1 to 10.6	0.98	0.86 to 1.11
Females	515	13.3	12.3 to 15.0	11.4	10.2 to 12.7	0.84	0.68 to 1.03
Race							
White	1,349	10.0	9.3 to 10.8	10.1	9.3 to 10.8	0.93	0.82 to 1.05
East/South East Asian	220	13.8	10.2 to 17.1	11.9	9.0 to 14.7	0.88	0.62 to 1.24
All other	156	9.9	8.6 to 12.8	11.5	9.6 to 14.1	1.34	0.89 to 2.01
Smoking status*							
Former/current smoker	1,266	10.0	9.4 to 11.1	10.3	9.5 to 10.9	0.93	0.81 to 1.05
Never-smoker	250	15.9	13.8 to 20.2	15.3	12.1 to 22.9	1.00	0.71 to 1.41
Disease stage							
IIIB	415	11.9	10.0 to 14.2	11.3	9.6 to 13.1	0.89	0.71 to 1.12
IV	1,310	10.0	9.3 to 10.8	10.1	9.3 to 10.8	0.95	0.84 to 1.08
Performance status†							
0	612	13.4	11.9 to 14.9	12.2	11.3 to 13.4	0.91	0.75 to 1.10
1	1,110	9.1	8.1 to 9.9	9.0	8.3 to 9.8	0.95	0.83 to 1.09

*Two hundred nine patients with unknown smoking history were not included in the smoking history analysis.
†Three patients with unknown Eastern Cooperative Oncology Group performance status were not included in the performance status analysis.

two histologic groups (adenocarcinoma, n = 847; and large-cell carcinoma, n = 153). For patients with adenocarcinoma randomly assigned to cisplatin/pemetrexed, survival was significantly better than for those assigned to cisplatin/gemcitabine (12.6 *v* 10.9 months, respectively; $P = .03$). One potential explanation may relate to thymidylate synthase expression levels in NSCLC histologic types. Preclinical data have indicated that overexpression of thymidylate synthase correlates with reduced sensitivity to pemetrexed.[29,30] A recent study in chemotherapy-naive patients with adenocarcinoma or squamous cell carcinoma of the lung demonstrated that the baseline expression of the thymidylate synthase gene and protein were significantly higher in squamous cell carcinoma compared with adenocarcinoma ($P < .0001$).[31] In addition, thymidylate synthase and S phase kinase–associated protein (Skp2) are transcriptionally regulated in the S phase of the cell cycle by the transcription factor E2F-1.[32,33] Like thymidylate synthase, elevated expression of Skp2 has been more commonly found in patients with squamous cell carcinoma of the lung than in patients with adenocarcinoma.[34]

Table 4. Randomly Assigned and Treated Patients with Common Toxicity Criteria Grade 3 or 4 Drug-Related Toxicities (worst grade)*

Toxicity	Cisplatin/Pemetrexed (n = 839)		Cisplatin/Gemcitabine (n = 830)		*P*
	No. of Patients	%	No. of Patients	%	
Hematologic					
Neutropenia	127	15.1	222	26.7	< .001
Anemia, hemoglobin	47	5.6	82	9.9	.001
Thrombocytopenia, platelets	34	4.1	105	12.7	< .001
Leukopenia	40	4.8	63	7.6	.019
Nonhematologic					
Febrile neutropenia	11	1.3	31	3.7	.002
Alopecia, any grade	100	11.9	178	21.4	< .001
Nausea	60	7.2	32	3.9	.004
Vomiting	51	6.1	51	6.1	1.000
Dehydration, any grade	30	3.6	17	2.0	.075
Fatigue	56	6.7	41	4.9	.143

*Only toxicities reported in at least 3% of patients on at least one arm are listed.

In a large, randomized, phase II trial of 441 patients that compared docetaxel/gemcitabine with docetaxel/cisplatin, no statistical difference in the efficacy outcomes was seen, but histology was the main predictive factor for response rate in each treatment group.[35] In our study, significantly improved overall survival for cisplatin/pemetrexed compared with cisplatin/gemcitabine was also observed in patients with large-cell carcinoma histology (10.4 *v* 6.7 months, respectively; $P = .03$). To our knowledge, levels of thymidylate synthase expression in large-cell carcinoma of the lung have not been previously described. Despite the uncommon prevalence of this histologic type, further investigation of this association is warranted.

Although direct comparisons of efficacy across different randomized clinical studies may lead to biased conclusions as a result of differing patient populations, clinicians may consider cisplatin/pemetrexed to be an attractive alternative to bevacizumab-containing regimens (with either paclitaxel/carboplatin[16] or gemcitabine/cisplatin[17]) for patients with nonsquamous tumors. The evaluation of treatment options for these patients must consider both the efficacy of these regimens and the different safety profiles of these combinations.

Definitive answers to these relevant clinical questions will only come from controlled clinical trials.

In conclusion, cisplatin/pemetrexed provides similar efficacy to cisplatin/gemcitabine, with better tolerability, a reduced need for supportive therapies, and more convenient administration than cisplatin/gemcitabine, for first-line treatment of patients with advanced NSCLC. Furthermore, to our knowledge, this is the first phase III study in NSCLC to prospectively report survival differences between platinum doublets according to histology. These results are hypothesis generating and warrant a prospective study that is specifically designed to evaluate histology findings, which may potentially guide the selection of patients most likely to benefit from cisplatin/pemetrexed therapy. Lastly, it could be argued that the efficacy to date of cisplatin/pemetrexed in nonsquamous histology should allow it to be a preferred regimen for future studies testing molecular targeted therapies in nonsquamous histology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

