A Comparison of White and African American Outcomes from a Three-Arm, Randomized, Phase III Multicenter Trial of Advanced or Metastatic Non-small Cell Lung Cancer

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Purpose: To investigate the effect of race on the efficacy and safety of standard chemotherapy doublet regimens in African American patients, we conducted a subgroup analysis of a phase III randomized trial.

Patients and Methods: Chemonaïve patients with a performance status of 0 or 1 and stage IIIB or IV non-small cell lung cancer were randomized to arm A: gemcitabine 1000 mg/m^2 on days 1 and 8 plus carboplatin area under the curve 5.5 on day 1; arm B: the same schedule of gemcitabine plus paclitaxel 200 mg/m^2 on day 1; or arm C: paclitaxel 225 mg/m^2 on day 1 plus carboplatin area under the curve 6.0 on day 1. Cycles were repeated every 21 days up to 6. A site selection tool identified institutions with potential to recruit a minority population. Outcome and toxicity data of white and African American patients were compared.

Results: Of 1135 total patients, 972 were white (85.6%) and 138 were African American (12.2%). Median survival was 8.3 months for white patients (95% confidence interval [CI]: 7.7–9.3) and 9.1 months for African American patients (95% CI: 8.2–11.1). Response rates were 29.1 and 29.0%, respectively. Rates of grade 3 or 4 toxicities were comparable. Among African Americans, median survival was 7.2 months (95% CI: 5.1–10.1) for gemcitabine-carboplatin ($n = 47$), 10.5 months (95% CI: 7.1–15.4) for gemcitabine-paclitaxel ($n = 42$), and 10.2 months (95% CI: 8.5–13.2) for paclitaxel-carboplatin ($n = 49$).

Conclusion: Whites and African Americans had similar outcomes, although there was some variability in survival among African Americans across the three treatment groups.

Key Words: NSCLC, Phase III, African American, Nonplatinum doublets, Accrual, Race.

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The annual burden of non-small cell lung cancer (NSCLC) was estimated in 2007 at ~181,000 new cases and 136,000 deaths in the United States.[1] At the time of diagnosis, most patients (>80%) have locally advanced stage III or metastatic stage IV disease and are ineligible for potentially curative surgery; and 5-year survival is <10% in this patient population.[2,3] Palliative chemotherapy has become standard therapy for patients with advanced NSCLC, with platinum-based or nonplatinum doublets producing a modest survival benefit and improvement in quality of life compared with best supportive care alone.[4–9]

Compared with whites, African Americans have a greater occurrence and worsened prognosis from lung cancer. In the United States, incidence rates for cancer of the lung and bronchus are 112.2 per 100,000 among African Americans compared with 81.7 per 100,000 among whites.[10] African Americans are more likely than whites to be diagnosed with lung cancer of all stages, with the greatest differential for advanced or metastatic stage disease.[11,12] Surveillance databases indicate that survival for NSCLC of similar stages is less for African Americans than for whites.[13,14] Differences in outcomes between African Americans and whites have largely been attributed to disparities in socioeconomic status and access to health care.[15,16] In an analysis of Eastern Cooperative Oncology Group (ECOG) studies, African Americans presented with greater weight loss and worsened performance status when compared with non-African Americans, suggesting that diagnosis may occur in later stages of the disease course.[17] When controlling for factors associated with access to care, patient outcomes by race are similar.[18–21]

Although participation in cancer clinical trials is low across all demographic categories, African American accrual

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to trials is especially lower than that of whites.[22,23] Disparities in accrual persist in spite of the National Institutes of Health Revitalization Act of 1993, which mandated inclusion of a valid subset of women and minorities in phase III clinical trials as a condition of National Institutes of Health funding.[24] This law was based on the recognition that clinical trial findings from one population cannot necessarily be extrapolated to others. Despite this federal imperative, few robust subset analyses of trial outcomes by race have been published. As a result, the optimal treatment of African Americans and whites with advanced or metastatic NSCLC is not clear.

The primary objective of the current phase III study was to compare the outcomes associated with a reference regimen of paclitaxel and carboplatin to an alternative platinum regimen of gemcitabine and carboplatin and a nonplatinum regimen of gemcitabine and paclitaxel in patients with advanced or metastatic NSCLC. The overall clinical results of this trial have been previously reported.[25,26] Additional components of this trial assessed whether the use of a site selection tool could result in a patient population that more accurately reflected patient characteristics in the Surveillance Epidemiology and End Results database[10] and a retrospective analysis of whether outcomes from the trial differed by race and if any treatment-by-race interaction was present.

PATIENTS AND METHODS

Investigative Site Selection

Alpha Oncology (AO) is a subsidiary of the Coalition of National Cancer Cooperative Groups. This trial used a site selection tool created by AO with the goal of recruiting a diverse patient population that accurately represented the population of the National Cancer Institute's (NCI's) Surveillance Epidemiology and End Results database, which is ~11.5% African American.[10] Six characteristics indicated that a site was favorable for minority participation: (1) an organized multimodality approach to lung cancer with dedicated program combining participation in cancer clinical trials with delivery of cancer treatment, (2) a dedicated clinical trial support staff that was separate from clinical support staff, (3) minority representation within the research staff (investigators and clinical research associates), (4) geographic locations with representative minority population, (5) university medical centers or community centers with university affiliations, and (6) Active participation in one of the three NCI-sponsored multimodality cooperative group programs (including Cancer and Leukemia Group B, ECOG, or Southwest Oncology Group [SWOG]). In addition to including sites with these characteristics, AO targeted a series of programs toward minority-based community physician practices with the goal of overcoming misconceptions and mistrust associated with clinical trial participation. These programs included a public awareness campaign and the distribution of educational brochures.

Patient Selection/Study Design

Detailed information with respect to patient selection and study design of this trial is included in a separate publication.[25] Briefly, patients with a histologically confirmed diagnosis of stage IIIB (with pleural or pericardial effusion), stage IV, or recurrent NSCLC were enrolled in this study.[27] Mixed tumors were categorized by the predominant cell type unless small cell anaplastic elements were present, in which case the patient was ineligible. All patients were required to be 18 years or older and have measurable or evaluable disease (according to ECOG solid tumor criteria); an ECOG performance status of 0 or 1; and adequate bone marrow reserve (neutrophils $>1500/mm^3$ and platelets $>100{,}000/mm^3$), adequate hepatic function (aspartate transaminase ≤ 5 times institutional upper limit of normal and serum bilirubin ≤ 1.5 mg/dL times institutional upper limit of normal), and adequate renal function (creatinine clearance ≥ 40 mL/min or serum creatinine ≤ 1.5 mg/dL). Stage IV patients with brain metastases were eligible provided the brain metastases were, in the opinion of the site investigator, clinically stable after treatment with surgery or radiation therapy.

Patients who met all eligibility criteria were randomly allocated to receive one of the following three treatment regimens: arm A: gemcitabine 1000 mg/m^2 infused over 30 minutes on days 1 and 8 plus carboplatin area under the curve 5.5 over 15 to 30 minutes on day 1; arm B: gemcitabine 1000 mg/m^2 infused over 30 minutes on days 1 and 8 plus paclitaxel 200 mg/m^2 infused over 3 hours on day 1; or arm C: paclitaxel 225 mg/m^2 infused over 3 hours on day 1 plus carboplatin area under the curve 6.0 over 15 to 30 minutes on day 1. Treatment cycles for all three treatment arms were repeated every 21 days for six cycles, or until unacceptable toxicity or disease progression. At randomization, patients were stratified by baseline weight loss, stage of disease, and presence or absence of brain metastasis. In arms B and C, patients received prophylactic dexamethasone 20 mg orally 12 and 6 hours before paclitaxel infusion, diphenhydramine 50 mg intravenously (or equivalent) ≤ 1 hour before paclitaxel infusion, and cimetidine 300 mg intravenously (or equivalent; ranitidine 50 mg or famotidine 20 mg) ≤ 1 hour before paclitaxel infusion. Patients who developed brain metastases as the only evidence of progressive disease were able to be treated with whole brain radiation and corticosteroids for brain metastases and remained on study. Chemotherapy was resumed 2 weeks after the completion of brain irradiation. However, if the patient failed to meet entry criteria after radiation therapy, the patient was removed from the study. No other chemotherapy, immunotherapy, antitumor hormonal therapy (excluding contraceptives and replacement steroids), or experimental medication was permitted while the patient was on the study, and appropriate supportive care was provided.

This study was reviewed and approved by an ethical review board at each participating institution, and it was conducted in accordance with the precepts established by the Declaration of Helsinki. Patients who were eligible for participation provided written informed consent consistent with all applicable governing regulations before undergoing any study procedure or receiving any study drug.

Statistical Analysis

The sample size for this study was 1134 patients. The large number of patients accrued in this study allowed for retrospective statistical analyses of outcomes by specific patient subgroups. To assess whether a difference in outcome by ethnicity was present, overall survival (OS), response rates (RRs), time to progression (TTP), and tolerability results were compared between whites (non-Hispanic) and African Americans. Survival and TTP were assessed using the intention-to-treat population and calculated from the date of randomization to the date of death or documented progression. The Kaplan-Meier product limit method was used to construct survival and TTP curves and calculate unadjusted medians.[28] RECISTs criteria were used for response evaluation.[29] RRs were calculated by summing the number of patients with complete responses and partial responses, and clinical benefit rates were calculated by summing the number of patients with complete responses, partial responses, and stable disease. Safety was assessed by calculating the percentage of patients experiencing grade 3 or 4 toxicities using NCI Common Terminology Criteria version 2.0.[30] All tests were two-sided.[31]

To further compare outcomes by ethnicity and test for potential treatment-by-ethnicity interaction, Cox proportional hazard models[32] and a logistic regression model were created. The reported multivariate models were cofactor adjusted for weight loss, gender, performance status, brain metastasis, and disease stage and included main effects terms for treatment and ethnicity and a treatment-by-ethnicity interaction term.

TABLE 1. Accrual from Sites with ≥4 Characteristics Favorable for Minority Participation

Site	Total Accrual, *N* = 1135	White, *N* = 972	African American, *N* = 138
East Carolina University	24	10 (41.7)	14 (58.3)
VA Medical Center, Atlanta	18	8 (44.4)	10 (55.6)
Temple University Cancer Center	33	11 (33.3)	18 (54.5)
Hahnemann University Hospital, PA	7	3 (42.9)	3 (42.9)
University of Maryland Greenebaum Cancer Center	22	14 (63.6)	7 (31.8)
Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill	48	35 (72.9)	12 (25.0)
Kimmel Cancer Center, PA	24	18 (75.0)	6 (25.0)
South Carolina Oncology Associates	16	12 (75.0)	4 (25.0)
University of Virginia Cancer Center	59	51 (86.4)	8 (13.6)
Loma Linda, CA	31	24 (77.4)	3 (9.7)
Northern Indiana Cancer Research Consortium	118	104 (88.1)	12 (10.2)
University of Pittsburgh	129	123 (95.3)	6 (4.7)
Total from 12 sites listed above	529 (46.6)	413 (42.5)	103 (74.6)
Total from all other sites	606 (53.3)	559 (57.5)	35 (25.4)

N, number of patients.

RESULTS

Accrual

Between July 2000 and November 2005, 1135 patients were screened for eligibility/entry into this trial at 105 investigative sites in the United States. Of these, 972 patients were white (85.6%), 138 patients were African American (12.2%), and 25 were of a different ethnicity. Table 1 summarizes accrual from sites that had ≥4 of the six characteristics associated with favorable minority participation. The 12 sites that had ≥4 favorable characteristics for minority participation enrolled 46.6% of patients in the trial, but 74.6% of all African Americans. The percentage of African Americans at sites with ≥4 characteristics for favorable minority participation was 19.5% compared with 5.6% at all other sites. Nine of 12 sites with favorable characteristics exceeded the targeted African American accrual representation of 11.5%.

Patient Characteristics

Table 2 compares patient characteristics between white and African American patients enrolled in the trial. Compared with white patients, African American patients were younger and a smaller percentage had stage IV disease. The median age of white patients was 65 years compared with 58 for African American patients. The percentage of patients 70 years or older was 32.1% for whites and 14.5% for African Americans. The percentage of patients with stage IV or recurrent disease was 90.8% for whites and 81.9% for African Americans. Similar percentages of white and African American patients were assigned to each treatment group.

Dose Administration

Of the 1110 white or African American patients who were screened, 48 (4.3%) did not receive any study therapy; thus, 1052 patients were included in the safety analysis population. The median number of cycles of chemotherapy was 4.0 for both white and African American patients, and the percentage of patients receiving six cycles of chemotherapy was 34.3% for white patients and 33.1% for African American patients. Relative dose intensity (percentage of planned dose that was administered) of gemcitabine (86.8% versus 89.9%), carboplatin (90.1% versus 97.1%), and paclitaxel (98.8% versus 99.0%) were similar in white patients compared with African American patients.

Efficacy

Table 3 summarizes the main efficacy parameters in the trial by ethnicity. Median survival was 8.3 months for white patients (95% confidence interval [CI]: 7.7–9.3) and 9.1 months for African American patients (95% CI: 8.2–11.1). RRs were nearly identical between the two ethnicities (29.1 and 29.0%, respectively). Median TTP was 4.6 months for white patients (95% CI: 4.3–5.1) and 4.3 months for African American patients (95% CI: 3.3–5.7). Kaplan-Meier curves for OS and TTP by ethnicity are summarized in Figure 1.

Table 4 summarizes a logistic regression model with response as the outcome variable and two Cox regression models with OS and TTP as outcome variables, respectively. Unadjusted efficacy outcomes were similar across strata of treatments and ethnicities with one notable exception. Afri-

TABLE 2. Patient Characteristics

Characteristic	White, $N = 972$	African American, $N = 138$
Age (yr)		
Median	65	58
Range	32, 88	37, 86
Age ≥70 yr, *n* (%)	312 (32.1)	20 (14.5)
Gender, *n* (%)		
Male	592 (60.9)	82 (59.4)
Female	380 (39.1)	56 (40.6)
Performance status, *n* (%)		
0	373 (38.4)	42 (30.4)
1	590 (60.7)	96 (69.6)
2	4 (0.4)	0 (0.0)
Brain metastases, *n* (%)	162 (16.7)	26 (18.8)
Histology, *n* (%)		
Squamous	170 (17.5)	27 (19.6)
Nonsquamous	802 (82.5)	111 (80.4)
Weight loss, *n* (%)		
<5%	613 (63.1)	81 (58.7)
≥5%	359 (36.9)	57 (41.3)
Disease stage, *n* (%)		
IIIB with effusion	89 (9.2)	25 (18.1)
IV or recurrent disease	883 (90.8)	113 (81.9)
Assignment to treatment, *n* (%)		
Gemcitabine-carboplatin	326 (33.5)	47 (34.1)
Gemcitabine-paclitaxel	329 (33.8)	42 (30.4)
Paclitaxel-carboplatin	317 (32.6)	49 (35.5)

N, number of patients; *n*, number in group.

TABLE 3. Main Efficacy Parameters

Variable	White, $N = 972$	African American, $N = 138$
Best overall response, *n* (%)		
Complete response	11 (1.1)	2 (1.4)
Partial response	272 (28.0)	38 (27.5)
Stable disease	328 (33.7)	48 (34.8)
Progressive disease	186 (19.1)	37 (26.8)
Unknown/Not done	175 (18.0)	13 (9.4)
Response rate (CR + PR), *n* (%)	283 (29.1)	40 (29.0)
(95% CI)	(26.3–32.1)	(21.6–37.3)
Clinical benefit rate (CR + PR + SD), *n* (%)	611 (62.9)	88 (63.8)
(95% CI)	(59.7–65.9)	(55.2–71.8)
Overall survival		
Failed, *n* (%)	882 (90.7)	129 (93.5)
Censored, *n* (%)	90 (9.3)	9 (6.5)
Median, mo (95% CI)	8.3 (7.7–9.3)	9.1 (8.2–11.1)
1 yr, % (95% CI)	34.6 (31.6–37.7)	39.1 (30.9–47.3)
2 yr, % (95% CI)	13.0 (10.8–15.2)	11.9 (6.4–17.5)
3 yr, % (95% CI)	6.3 (4.6–8.0)	5.4 (1.2–9.5)
Time to progression		
Failed, *n* (%)	898 (92.4)	134 (97.1)
Censored, *n* (%)	74 (7.6)	4 (2.9)
Median, mo (95% CI)	4.6 (4.3–5.1)	4.3 (3.3–5.7)

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; *N*, number of patients; *n*, number in group.

can Americans receiving gemcitabine-carboplatin had the lowest RR (17.0%), OS (7.2 months), and TTP (3.6 months) of any strata. Among African Americans, patients receiving gemcitabine-carboplatin were marginally less likely to experience a response than patients receiving paclitaxel-carboplatin (17.0% versus 34.7%, $p = 0.07$). In the cofactor adjusted model of OS, African Americans receiving gemcitabine-carboplatin had an hazard ratio of 1.40 (compared with African Americans receiving paclitaxel-carboplatin; 95% CI: 0.92–2.12). The treatment-by-race interaction effect on OS was marginally significant when comparing gemcitabine-carboplatin to paclitaxel-carboplatin ($p = 0.09$).

Toxicity

Chemotherapy safety is summarized for whites and African Americans in Table 5. Rates of grade 3 or 4 hematologic toxicities were comparable, although whites had a nonsignificantly higher frequency of grade 3 or 4 thrombocytopenia (28.5% versus 21.1%, $p = 0.08$). Rates of nonhematologic events were also generally similar. The rate of grade 1 to grade 4 gastrointestinal disorders was significantly greater among whites compared with African Americans (74.5% versus 64.7%, $p = 0.02$). Within gastrointestinal disorders, the rates of grade 1 to grade 4 diarrhea (24.5% versus 16.5%, $p = 0.05$) and grade 1 to grade 4 constipation (33.1% versus 24.2%, $p = 0.04$) were significantly greater among whites. When considering only grade 3 or 4 nonhematologic toxicities, differences between ethnicities were not statistically significant.

DISCUSSION

The primary clinical results from this trial have been previously presented.[25,26] They demonstrated that all three regimens produced similar efficacy in terms of OS, RR, and TTP and that each regimen produced a distinct toxicity profile, with the reference arm of paclitaxel-carboplatin being associated with more neurotoxicity and alopecia, whereas the gemcitabine-carboplatin arm was associated with greater myelosuppression and reduced median dose intensity. The current analysis indicates that African Americans enrolled in the trial experienced efficacy outcomes that were similar to whites with slightly different toxicity profiles. This finding is consistent with previous analyses of ECOG advanced NSCLC trials.[18] Despite the similarities in overall results between African Americans and whites, there was some variability in efficacy outcomes by treatment arm among African Americans.

This trial showed that minority representation in advanced or metastatic NSCLC trials may be enhanced by selective targeting of institutions with favorable characteristics as defined by the site selection tool employed by this trial. Minority patients have been underrepresented in many of the reported clinical trials defining the evidence-based practice standard of modern doublets used as front-line treatment for

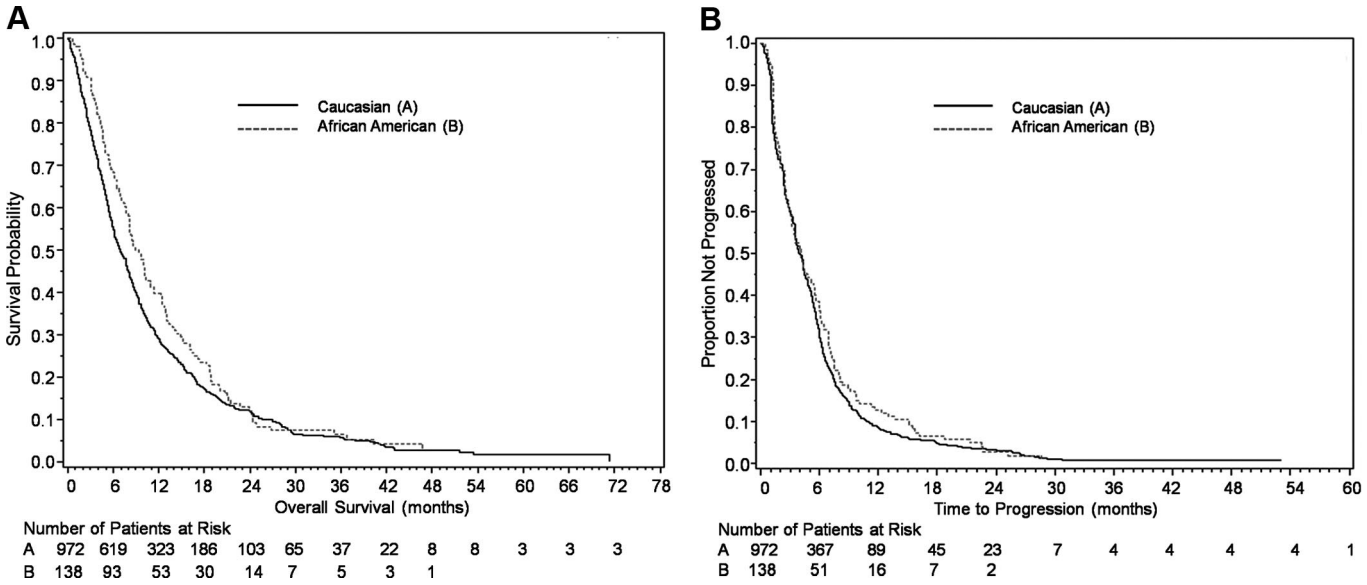

FIGURE 1. Kaplan-Meier estimates of overall survival (*A*) and time to progression of disease (*B*).

TABLE 4. Regression Analyses with Treatment by Race Interaction Effect

Race Subgroup	*N*	Response Rate, % (95% CI)	Cofactor Adjusted OR (95% CI)	*p* for OR	Treatment × Race Interaction *p*
White					
Gemcitabine/carboplatin	326	26.4 (21.7–31.5)	0.87 (0.61–1.23)	0.44	0.12 comparing gemcitabine/carboplatin and paclitaxel/carboplatin
Gemcitabine/paclitaxel	329	31.6 (26.6–36.9)	1.11 (0.79–1.56)	0.55	
Paclitaxel/carboplatin	317	29.3 (24.4–34.7)	1.0 (Reference)	Reference	
African American					
Gemcitabine/carboplatin	47	17.0 (7.7–30.8)	0.41 (0.15–1.09)	0.07	0.81 comparing gemcitabine/paclitaxel and paclitaxel/carboplatin
Gemcitabine/paclitaxel	42	35.7 (21.6–52.0)	1.09 (0.45–2.64)	0.85	
Paclitaxel/carboplatin	49	34.7 (21.7–49.6)	1.0 (Reference)	Reference	
Race Subgroup	***n***	**Median Survival, mo (95% CI)**	**Cofactor Adjusted HR (95% CI)**	***p* for HR**	**Treatment × Race Interaction *p***
White					
Gemcitabine/carboplatin	326	8.2 (7.1–9.4)	0.99 (0.84–1.16)	0.87	0.09 comparing gemcitabine/carboplatin and paclitaxel/carboplatin
Gemcitabine/paclitaxel	329	8.4 (7.4–9.7)	0.97 (0.83–1.15)	0.75	
Paclitaxel/carboplatin	317	8.7 (7.4–9.9)	1.0 (Reference)	Reference	
African American					
Gemcitabine/carboplatin	47	7.2 (5.1–10.1)	1.40 (0.92–2.12)	0.12	0.32 comparing gemcitabine/paclitaxel and paclitaxel/carboplatin
Gemcitabine/paclitaxel	42	10.5 (7.1–15.4)	1.14 (0.72–1.80)	0.57	
Paclitaxel/carboplatin	49	10.2 (8.5–13.2)	1.0 (Reference)	Reference	
Race Subgroup	***n***	**Median TTP, mo (95% CI)**	**Cofactor Adjusted HR (95% CI)**	***p* for HR**	**Treatment × Race Interaction *p***
White					
Gemcitabine/carboplatin	326	4.6 (4.2–5.3)	0.95 (0.81–1.12)	0.570	0.33 comparing gemcitabine/carboplatin and paclitaxel/carboplatin
Gemcitabine/paclitaxel	329	4.6 (4.0–5.4)	0.97 (0.83–1.14)	0.723	
Paclitaxel/carboplatin	317	5.0 (4.2–5.6)	1.0 (Reference)	Reference	
African American					
Gemcitabine/carboplatin	47	3.6 (2.8–5.3)	1.20 (0.79–1.83)	0.395	0.73 comparing gemcitabine/paclitaxel and paclitaxel/carboplatin
Gemcitabine/paclitaxel	42	4.3 (2.1–6.7)	1.02 (0.66,1.57)	0.931	
Paclitaxel/carboplatin	49	4.5 (3.2–6.3)	1.0 (Reference)	Reference	

CI, confidence interval; HR, hazard ratio; *n*, number in group; OR, odds ratio; TTP, time to progression.

TABLE 5. Toxicity According to Treatment Group (Safety Population)

Type of Toxicity	White, $N = 919$		African American, $N = 133$		p for Overall Comparison
	Grade 3	Grade 4	Grade 3	Grade 4	
Hematologic events, n (%)					
Neutropenia	150 (16.3)	134 (14.6)	27 (20.3)	22 (16.5)	0.20
Febrile neutropenia	26 (2.8)	7 (0.8)	2 (1.5)	0 (0.0)	0.30
Thrombocytopenia	209 (22.7)	53 (5.8)	23 (17.3)	5 (3.8)	0.08
Platelet transfusion	29 (3.2)		1 (0.8)		0.16
Anemia	100 (10.9)	3 (0.9)	16 (12.0)	0 (0.0)	0.77
Red blood cell transfusion	5 (0.5)		0 (0.0)		1.0
Transfusion	46 (5.0)		4 (3.0)		0.39
Nonhematologic events, n (%)					
Infection	18 (2.0)	5 (0.5)	3 (2.3)	0 (0.0)	1.0
Sensory neuropathy	59 (6.4)	2 (0.2)	6 (4.5)	1 (0.8)	0.71
Arthralgia (grade 3 or 4)	20 (2.2)		3 (2.3)		1.0
Alopecia (grade 2)	359 (39.1)		57 (42.9)		0.51
Diarrhea (grade 1 to grade 4)	225 (24.5)		22 (16.5)		0.05
Nausea (grade 1 to grade 4)	508 (55.3)		65 (48.9)		0.19
Constipation (grade 1 to grade 4)	304 (33.1)		32 (24.2)		0.04
Fatigue (grade 1 to grade 4)	667 (72.6)		89 (66.9)		0.18
Any nervous system disorder (grade 1 to grade 4)	546 (59.4)		85 (63.9)		0.35

N, number of patients; n, number in group.

patients with advanced NSCLC.[8,33–35] In the current trial, however, African American accrual was 12.2%, greater than rates achieved by NCI trials from 1991 to 1994 (9.8%)[36] and from 2000 to 2002 (7.4%).[23] Based on the accrual observed in this trial, the site selection tool was effective at ensuring patient diversity. The current number of sites able to demonstrate the required number of favorable characteristics is limited and achievement by additional institutions may fall outside the monetary infrastructure setup within the traditional clinical trial system. Previous research has demonstrated that long-term meaningful improvement in minority representation must be a multifocal, cooperative effort between research sponsors, investigators, and the communities and institutions in which they serve.[37,38]

In the overall analysis of efficacy parameters, median survival (8.3 months versus 9.1 months), TTP (4.6 months versus 4.3 months), and RR (29.1% versus 29.0%) were similar between white and African American patients, respectively. This is consistent with previous research that suggests that whites and African Americans who have uniform access to health care have similar outcomes in advanced NSCLC.[18–21] However, there was some indication of a treatment-by-race interaction, suggesting that the effect of individual treatment arms was not consistent within African Americans. Among whites, median survival ranged from 8.2 to 8.7 months by treatment arm. Among African Americans, median survival was 7.2 months for gemcitabine-carboplatin, 10.5 months for gemcitabine-paclitaxel, and 10.2 months for paclitaxel-carboplatin. The worsened outcomes associated with gemcitabine-carboplatin and improved outcomes in the other two arms for African Americans were also observed with RR and TTP endpoints. The reduced RR associated with gemcitabine-carboplatin (17.0%) compared with paclitaxel-carboplatin (34.7%) among African Americans approached significance ($p = 0.07$) and in a cofactor adjusted Cox model of OS, the treatment-by-race interaction term was marginally significant compared with paclitaxel-carboplatin ($p = 0.09$).

Collaborations between SWOG and Japanese institutions have examined the comparability of results of trials performed in the United States versus Japan among patients uniformly treated with the same dose and schedule of paclitaxel-carboplatin.[39–41] In the analyses, US and Japanese patients had similar characteristics in terms of age, gender, disease stage, and histology. However, the US SWOG trial resulted in an OS of 9 months compared with 12 to 14 months in the Japanese trials.[39,40] The authors hypothesized that these differences may have been a result of genotypic differences, which were statistically significant between ethnicities.[41] There is some indication that the frequency of pharmacogenomic biomarkers that predict response to specific chemotherapy regimens (such as ERCC1 and RRM1)[42] may vary by ethnicity within the US population.[43,44] Similarly, research indicates that epidermal growth factor receptor mutations are not uniform across ethnicities,[45] and the activity of epidermal growth factor receptor inhibitors seems to vary across ethnicities.[46,47] Unfortunately, no pharmacogenomic samples were collected for analysis in the current trial.

Although the current article addresses methods to increase diversity within clinical trials, it does not address broader issues of access to screening or treatment. It is possible that racial disparities in the broader population are attributable to factors such as disease stage or performance

status at diagnosis or access to health care services. Soon after the initiation of the current trial, approved therapy for the second-line setting became available. Information on poststudy chemotherapy was not collected. Similarities in OS by race in this trial, however, make it unlikely that second-line therapy was disproportionately administered by race.

Conclusions from this retrospective analysis are hypothesis generating, not definitive. Differences in African American outcomes by treatment did not reach statistical significance nor were treatment arms powered for such an analysis. The significance of interaction terms within regression models is often limited because of sample size requirements within subgroups.[48] Definitive results with respect to differences in outcome by race require prospectively designed studies. A phase III study of the effectiveness of pemetrexed by race in the second-line NSCLC setting is currently accruing. Enrollment will include 200 African Americans, 200 Asians, 200 Hispanics, and 400 whites.[49] A phase II trial of second-line erlotinib in African Americans is also currently recruiting patients.[50]

Minority accrual in advanced or metastatic NSCLC trials will continue to be of interest. This trial showed that selective targeting of institutions, combined with other interventions, can ensure a diverse patient population. Whites and African Americans generally had similar outcomes in the current trial, although there was some variability of outcome among African Americans across the three treatment groups.

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REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43–66.
2. Shepherd FA. Screening, diagnosis, and staging of lung cancer. *Curr Opin Oncol* 1993;5:310–322.
3. Walling J. Chemotherapy for advanced non-small-cell lung cancer. *Respir Med* 1994;88:649–657.
4. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ* 1995; 311:889–890.
5. Grilli R, Oxman AD, Julian JA. Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? *J Clin Oncol* 1993;11: 1866–1872.
6. Marino P, Pampallona S, Preatoni A, et al. Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. *Chest* 1994;106:861–865.
7. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. *Lancet* 1993; 342:19–21.
8. Rajeswaran A, Trojan A, Burnand B, et al. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. *Lung Cancer* 1997;59:1–11.
9. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol* 2005;23: 2926–2936.
10. Ries L, Melbert D, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2005. Bethesda, MD: National Cancer Institute, 2008. Available at: http://seer.cancer.gov/csr/1975_2005/.
11. Gadgeel SM, Severson RK, Kau Y, et al. Impact of race in lung cancer: analysis of temporal trends from a surveillance, epidemiology, and end results database. *Chest* 2001;120:55–63.
12. American Cancer Society. Cancer Facts & Figures for African Americans 2007–2008. Atlanta, GA: American Cancer Society, 2008.
13. Abidoye O, Ferguson MK, Salgia R. Lung carcinoma in African Americans. *Nat Clin Pract Oncol* 2007;4:118–129.
14. Ries LA. Influence of extent of disease, histology, and demographic factors on lung cancer survival in the SEER population-based data. *Semin Surg Oncol* 1994;10:21–30.
15. Lathan CS, Neville BA, Earle CC. The effect of race on invasive staging and surgery in non-small-cell lung cancer. *J Clin Oncol* 2006;24:413–418.
16. Blackstock AW, Herndon JE II, Paskett ED, et al. Outcomes among African-American/non-African-American patients with advanced non-small-cell lung carcinoma: report from the Cancer and Leukemia Group B. *J Natl Cancer Inst* 2002;94:284–290.
17. Evans T, Wang W, Schiller J. Survival outcome of African American versus non-African American patients with advanced non-small cell lung cancer in first-line treatment studies by the Eastern Cooperative Oncology Group (ECOG). *J Clin Oncol* 2005 ASCO Annual Meeting Proceedings Part I;23(Abstract 7154).
18. Ikpeazu C, Vangel M, Schiller J, et al. Survival in advanced non-small cell lung cancer (NSCLC) with platinum-based chemotherapy in two Eastern Cooperative Group trials: the influence of race. *J Clin Oncol* 2003 ASCO Annual Meeting Proceedings;22:(Abstract 2593).
19. Mulligan CR, Meram AD, Proctor CD, et al. Unlimited access to care: effect on racial disparity and prognostic factors in lung cancer. *Cancer Epidemiol Biomarkers Prev* 2006;15:25–31.
20. Bryant AS, Cerfolio RJ. Impact of race on outcomes of patients with non-small cell lung cancer. *J Thorac Oncol* 2008;3:711–715.
21. Kallab A, Jillela A, Dainer P, et al. Influence of race and gender on non-small cell lung cancer (NSCLC) survival. *J Clin Oncol* 2001 ASCO Annual Meeting Proceedings;20:(Abstract 2756).
22. Du W, Gadgeel SM, Simon MS. Predictors of enrollment in lung cancer clinical trials. *Cancer* 2006;106:420–425.
23. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA* 2004;291:2720–2726.
24. Freedman LS, Simon R, Foulkes MA, et al. Inclusion of women and minorities in clinical trials and the NIH Revitalization Act of 1993—the perspective of NIH clinical trialists. *Control Clin Trials* 1995;16:277–285; discussion 286–289, 293–309.
25. Treat J, Gonin R, Socinski M, et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. *Ann Oncol* 2010;21:540–547.
26. Treat J, Belani C, Edelman M, et al. A randomized phase III trial of gemcitabine (G) in combination with carboplatin (C) or paclitaxel (P) versus paclitaxel plus carboplatin in advanced (Stage IIIB, IV) non-small cell lung cancer (NSCLC): update of the Alpha Oncology trial (A1-99002L). *J Clin Oncol* 2005 ASCO Annual Meeting Proceedings (Post-Meeting Edition);23:(Abstract 7025).
27. Fleming I, Cooper J, Henson D. AJCC Cancer Staging Manual, 5th Ed. Philadelphia: Lippincott-Raven, 1997.
28. Kaplan E, Meier P. Nonparametric estimation of incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
29. Therasse P, Arbuck S, Eisenhauer E. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92:205–216.
30. NCI Common Terminology Criteria Version 2.0. Cancer Therapy Evaluation Program. 1999.
31. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549–556.
32. Cox D, Snell E. Analysis of Binary Data, 2nd Ed. London: Chapman & Hall, 1989.
33. Kosmidis PA, Kalofonos HP, Christodoulou C, et al. Paclitaxel and gemcitabine versus carboplatin and gemcitabine in patients with advanced non-small-cell lung cancer. A phase III study of the Hellenic Cooperative Oncology Group. *Ann Oncol* 2008;19:115–122.

34. Murphy WK, Fossella FV, Winn RJ, et al. Phase II study of taxol in patients with untreated advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1993;85:384–388.
35. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
36. Tejeda HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. *J Natl Cancer Inst* 1996;88:812–816.
37. Sateren WB, Trimble EL, Abrams J, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *J Clin Oncol* 2002;20:2109–2117.
38. Wujcik D, Ikpeazu C, Chinratanalab W, et al. Strategies to improve minority patient accrual to cancer clinical trials. *J Clin Oncol* 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition);22:(Abstract 6017).
39. Gandara D, Ohe Y, Kubota K, et al. Japan-SWOG common arm analysis of paclitaxel/carboplatin in advanced stage non-small cell lung cancer (NSCLC): a model for prospective comparison of cooperative group trials. *J Clin Oncol* 2004 ASCO Annual Meeting Proceedings Part I;22:(Abstract 7007).
40. Crowley J, Furuse K, Kawahara M, et al. Second Japan-SWOG common arm analysis of paclitaxel/carboplatin in advanced stage non-small cell lung cancer (NSCLC): a model for testing population-related pharmacogenomics. *J Clin Oncol* 2006 ASCO Annual Meeting Proceedings Part I;24:(Abstract 7050).
41. Gandara D, Kawaguchi T, Crowley J, et al. Pharmacogenomic (PG) analysis of Japan-SWOG common arm study in advanced stage non-small cell lung cancer (NSCLC): A model for testing population-related pharmacogenomics. *J Clin Oncol* 2007 ASCO Annual Meeting Proceedings Part I;25:(Abstract 7500).
42. Ceppi P, Volante M, Novello S, et al. ERCC1 and RRM1 gene expressions but not EGFR are predictive of shorter survival in advanced non-small-cell lung cancer treated with cisplatin and gemcitabine. *Ann Oncol* 2006;17:1818–1825.
43. Gao R, Price DK, Sissung T, et al. Ethnic disparities in Americans of European descent versus Americans of African descent related to polymorphic ERCC1, ERCC2, XRCC1, and PARP1. *Mol Cancer Ther* 2008;7:1246–1250.
44. Bepler G, Zheng Z, Gautam A, et al. Ribonucleotide reductase M1 gene promoter activity, polymorphisms, population frequencies, and clinical relevance. *Lung Cancer* 2005;47:183–192.
45. Nomura M, Shigematsu H, Li L, et al. Polymorphisms, mutations, and amplification of the EGFR gene in non-small cell lung cancers. *PLoS Med* 2007;4:e125.
46. Calvo E, Baselga J. Ethnic differences in response to epidermal growth factor receptor tyrosine kinase inhibitors. *J Clin Oncol* 2006;24:2158–2163.
47. Ho C, Murray N, Laskin J, et al. Asian ethnicity and adenocarcinoma histology continues to predict response to gefitinib in patients treated for advanced non-small cell carcinoma of the lung in North America. *Lung Cancer* 2005;49:225–231.
48. Peterson B, George SL. Sample size requirements and length of study for testing interaction in a 2 x k factorial design when time-to-failure is the outcome [corrected]. *Control Clin Trials* 1993;14:511–522.
49. An observational study of the ethnic impact of patients undergoing 2nd line treatment for non-small cell lung cancer using pemetrexed. NCT00497770: Available at: http://www.clinicaltrials.gov/ct2/show/NCT00497770?term=pemetrexed+observational&rank=1, 2008.
50. OSI-774 in African American patients with advanced and previously treated non-small cell lung cancer. NCT00230126: Available at: http://clinicaltrials.gov/ct2/show/record/NCT00230126, 2008.