

# Japanese-US Common-Arm Analysis of Paclitaxel Plus Carboplatin in Advanced Non-Small-Cell Lung Cancer: A Model for Assessing Population-Related Pharmacogenomics

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## ABSTRACT

### Purpose

To explore whether population-related pharmacogenomics contribute to differences in patient outcomes between clinical trials performed in Japan and the United States, given similar study designs, eligibility criteria, staging, and treatment regimens.

### Methods

We prospectively designed and conducted three phase III trials (Four-Arm Cooperative Study, LC00-03, and S0003) in advanced-stage, non-small-cell lung cancer, each with a common arm of paclitaxel plus carboplatin. Genomic DNA was collected from patients in LC00-03 and S0003 who received paclitaxel (225 mg/m<sup>2</sup>) and carboplatin (area under the concentration-time curve, 6). Genotypic variants of CYP3A4, CYP3A5, CYP2C8, NR1I2-206, ABCB1, ERCC1, and ERCC2 were analyzed by pyrosequencing or by PCR restriction fragment length polymorphism. Results were assessed by Cox model for survival and by logistic regression for response and toxicity.

### Results

Clinical results were similar in the two Japanese trials, and were significantly different from the US trial, for survival, neutropenia, febrile neutropenia, and anemia. There was a significant difference between Japanese and US patients in genotypic distribution for *CYP3A4\*1B* ( $P = .01$ ), *CYP3A5\*3C* ( $P = .03$ ), *ERCC1* 118 ( $P < .0001$ ), *ERCC2* K751Q ( $P < .001$ ), and *CYP2C8* R139K ( $P = .01$ ). Genotypic associations were observed between *CYP3A4\*1B* for progression-free survival (hazard ratio [HR], 0.36; 95% CI, 0.14 to 0.94;  $P = .04$ ) and *ERCC2* K751Q for response (HR, 0.33; 95% CI, 0.13 to 0.83;  $P = .02$ ). For grade 4 neutropenia, the HR for *ABCB1* 3425C→T was 1.84 (95% CI, 0.77 to 4.48;  $P = .19$ ).

### Conclusion

Differences in allelic distribution for genes involved in paclitaxel disposition or DNA repair were observed between Japanese and US patients. In an exploratory analysis, genotype-related associations with patient outcomes were observed for *CYP3A4\*1B* and *ERCC2* K751Q. This common-arm approach facilitates the prospective study of population-related pharmacogenomics in which ethnic differences in antineoplastic drug disposition are anticipated.

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## INTRODUCTION

Results may vary between different clinical trials that evaluate the same treatment regimen for many reasons, including trial design, eligibility criteria, patient characteristics, and subtle alterations in the treatment regimens themselves. An additional explanation for divergence of outcomes is host-related genetic differences associated with ethnicity, which is particularly pertinent when trials that are performed in different parts of the world are compared.

More than 10 years ago, the Southwest Oncology Group (SWOG) established a collaboration with Japanese investigators of lung cancer to provide a forum for exchange of research data, to facilitate standardization of clinical trial design and conduct, and to establish areas for joint collaboration.<sup>1</sup> We hypothesized that outcome differences between trials performed in Japan and the United States that evaluated similar treatment regimens in advanced-stage, non-small-cell lung cancer (NSCLC) could be explained by population-related

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pharmacogenomics. To evaluate this possibility, we prospectively designed three phase III trials, (Four-Arm Cooperative Study [FACS], LC00-03, and S0003), each with similar patient eligibility criteria, staging, and treatment with a common arm of paclitaxel plus carboplatin. We have reported previously that, despite this effort at trial standardization, differences in clinical outcomes were observed in Japanese versus US patients treated on these studies.<sup>2,3</sup> Herein, we report the results of a clinical and pharmacogenomic analysis that involved patients from two of the three clinical trials (LC00-03 and S0003), and we report implications for additional studies by using this clinical research approach in which population-related differences in drug disposition are anticipated.

## METHODS

### Patients

The clinical trial methodology employed was prospective design of three separate-but-equal, randomized, phase III trials in advanced-stage NSCLC, each with its own comparator regimens but linked by a common treatment arm of paclitaxel plus carboplatin. In FACS, patients were randomly assigned to a standard treatment in Japan (irinotecan plus cisplatin) versus experimental arms of paclitaxel plus carboplatin, gemcitabine plus cisplatin, and vinorelbine plus cisplatin. LC00-03 compared paclitaxel plus carboplatin to the nonplatinum regimen of sequential vinorelbine plus gemcitabine followed by docetaxel, whereas patients on S0003 were randomly assigned to paclitaxel plus carboplatin with or without the hypoxic cytotoxin tirapazamine.

Clinical results for the three trials have been previously presented and published separately.<sup>4-6</sup> Common elements of eligibility criteria are summarized here. All patients had histologically or cytologically confirmed chemotherapy-naïve NSCLC with stage IV (ie, no brain metastases) or selected stage IIIB disease (ie, positive pleural or pericardial effusion or multiple ipsilateral lung nodules); measurable or assessable disease, performance status (PS) of 0 or 1; and adequate hematologic, hepatic, and renal function. All patients gave written informed consent in accordance with institutional regulations, and each protocol was approved by the respective institutional review boards; trials were conducted with adherence to the Helsinki Declaration.

### Treatment Schedule, Dose Modifications, and Toxicity Assessment

Study elements of S0003, FACS and LC00-03 were designed to be as similar as possible: each study contained a common arm of paclitaxel plus carboplatin, which was repeated on a 21-day schedule. In all three studies, carboplatin was dosed at an area under the concentration-time curve (AUC) of 6.0 mg/mL/min on day 1. Paclitaxel was dosed at 225 mg/m<sup>2</sup> in S0003 and LC00-03 and at 200 mg/m<sup>2</sup> in FACS because of regulatory requirements for this study; in each study, paclitaxel was delivered as a 3-hour infusion on day 1. Premedication to prevent paclitaxel-related allergic reactions were similar. Prophylactic granulocyte colony-stimulating factor was not utilized. A complete blood count and chemistries were performed on day 1 of each cycle. Dose modifications occurred as previously described.<sup>4</sup> Patients were evaluated every two cycles for objective response by using RECIST (Response Evaluation Criteria in Solid Tumors) criteria.<sup>7</sup> Toxicity grading was performed in accordance with the National Cancer Institute Common Toxicity Criteria, version 2.0, in each study.<sup>8</sup>

### DNA Extraction and Genotyping

Specimens were not available from FACS; therefore, this analysis compares pharmacogenomic results from LC00-03 with S0003. Whole-blood specimens were collected from consenting patients at the time of enrollment on to LC00-03 and S0003. For S0003, DNA was extracted from patient plasma by using the Gentra PureGene Blood Kit (Gentra, Minneapolis, MN) and the QIAamp DNA Blood midi kit (Qiagen, Valencia, CA), and DNA was recon-

stituted in a buffer that contained 10 mmol/L Tris (pH 7.6) and 1 mmol/L EDTA, as previously described.<sup>9</sup> For LC00-03, DNA was extracted from buffy coats by using the GenElute Blood Genomic DNA Kit (Sigma-Aldrich, St Louis, MO). Selected genotypic variants related to paclitaxel disposition (ie, the ABC transporter superfamily [multidrug resistance {MDR} transporter 1 P-glycoprotein, *ABCB1* 3435C→T], the pregnane X receptor (PXR, NR1I2-206 deletion), *CYP3A4* (*CYP3A4\*1B* 392A→G, 5' untranslated region), *CYP3A5* (*CYP3A5\*3C* 6986A→G, splice variant), *CYP2C8* (*CYP2C8\*3* 416G→A, R139K) or to platinum-related DNA repair enzymes *ERCC1* (118C→T, silent) and *ERCC2* (XPD, K751Q) previously reported to be of functional consequence were analyzed by polymerase chain reaction (PCR) or pyrosequencing, as previously described.<sup>9-13</sup> Briefly, PCR was conducted by using Amplitaq Gold PCR master mix (ABI, Foster City, CA), 5 pmol of each primer, and 5 to 10 ng of DNA. Pharmacogenetic analysis was conducted by using the Pyrosequencing hsAPSQ96 instrument and software (Biotage, Uppsala, Sweden). The genotype was considered variant if it differed from the Reference Sequence consensus sequence for the single-nucleotide polymorphism (SNP) position (<http://www.ncbi.nlm.nih.gov/RefSeq/>). The *ERCC1* polymorphism was analyzed by PCR restriction fragment length polymorphism, as previously described.<sup>14</sup>

### Statistical Methods

Comparison of clinical results among the three trials was prospectively planned and was coordinated through the SWOG statistical center. Pharmacogenomic results were assessed by Cox model for progression-free survival (PFS) and overall survival and by logistic regression for response and toxicity, adjusted for sex and histology.<sup>15</sup> Comparisons of patient demographics, toxicity, and efficacy parameters were made, when applicable, from the available data sets, by two-sample *t* tests, log-rank tests, and Wilcoxon rank sum tests.

## RESULTS

### Clinical Results Summary

Clinical results are presented for all three trials to document similarities between the two Japanese trials compared with the US S003 trial, whereas pharmacogenomic information was derived only from LC00-03 and S0003. Table 1 summarizes characteristics of patients on the paclitaxel-plus-carboplatin arms of each of the three trials. The median ages and age ranges were similar, and there were no significant differences in sex, stage, or histology. In S0003, 3% of patients self-reported Asian heritage, not additionally specified. Toxicity, efficacy, and dose delivery comparisons are listed in Table 2, which compares S0003 versus FACS/LC00-03 when applicable. Grades 3 to 4 neutropenia and febrile neutropenia were comparable

**Table 1.** Patient Demographic and Clinical Characteristics

Characteristic	Trial						P
	FACS (n = 145)		LC00-03 (n = 197)		S0003 (n = 184)		
	No.	%	No.	%	No.	%	
Age, years							.03*
Median	63		65		63		
Range	33-74		33-81		28-80		
Female sex	46	32	61	31	68	37	.42
Disease stage IV	117	81	162	82	161	87	.20
Nonsquamous tumor type	114	79	167	85	152	83	.17

Abbreviation: FACS, four-arm cooperative study.

\*Two-sample *t* test to compare LC00-03 and S0003 data. Patient-level data not available for FACS.

**Table 2.** Toxicity Comparisons

Toxicity	Trial						P
	FACS (n = 148)		LC00-03 (n = 197)		S0003 (n = 184)		
	No.	%	No.	%	No.	%	
Neutropenia grades 3-4	130	88	137	70	70	38	< .0001
Febrile neutropenia grades 3-4	27	18	24	12	4	2	< .0001
Thrombocytopenia grades 3-4	16	11	14	7	12	6.5	.31
Anemia grades 3-4	22	15	16	8	12	7	.03
Neuropathy grades 2-4	25	17	32	16	30	16	.99

Abbreviation: FACS, four-arm cooperative study.

in FACS and LC00-03 and were significantly greater than in S0003. Anemia was more frequent in FACS compared with the two other trials (Table 2). Efficacy comparisons are summarized in Table 3. Response rates were similar between the three trials and ranged from 32% to 36%. Median PFS rates were 4.5, 6, and 4 months in FACS, LC00-03, and S0003, respectively. Median survival rates were higher in the Japanese studies at 12 and 14 months, versus 9 months in S0003, and 1-year survival was significantly higher in FACS and LC00-03 than in S0003 ( $P = .0004$ ). Dose delivery, summarized in Table 4, was lower in FACS than in S0003 and LC00-03. Dose reductions were similar between LC00-03 and S0003. Dose reduction data were not available from FACS.

### Pharmacogenomic Results

Table 5 lists allelic distributions of patients with common, heterozygous, and variant alleles in the Japanese (LC00-03) and US (S0003) trials. Fisher's exact test was used to determine whether allele distributions were different between the populations. There were significant differences between patients from Japan (LC00-03) and the United States (S0003) in genotype distribution for *CYP3A4\*1B* ( $P = .01$ ), *CYP3A5\*3C* ( $P = .03$ ), *ERCC1 118* ( $P < .0001$ ), *ERCC2 K751Q* ( $P < .001$ ), and *CYP2C8\*3* ( $P = .01$ ).

Across populations, genotypic correlations were observed between *CYP3A4\*1B* for PFS (hazard ratio [HR], 0.36; 95% CI, 0.14 to 0.94;  $P = .04$ ) and *ERCC2 K751Q* for response (HR, 0.33; 95% CI, 0.13 to 0.83;  $P = .02$ ). There were no other significant associations noted

(Table 6). For grade 4 neutropenia, the HR for *ABCB1 3425C→T* was 1.84 (95% CI, 0.77 to 4.48;  $P = .19$ ). The relationship between the *ERCC2* polymorphism and patient response stems principally from US patients. All but one Japanese patient was homozygous for the common allele (A/A). Those who harbored one or more variant alleles were significantly more likely to respond to treatment compared with those who had the common genotype. The response rate for patients with variant alleles was 51% versus 19% for patients homozygous for the common allele ( $P = .004$ ). However, no differences were observed in overall survival when stratified by this locus.

In S0003 (ie, the US trial), there were seven African American patients who had specimens available for genotyping. African American patients accounted for all seven patients who were heterozygous or homozygous for the *CYP3A4\*1B* allele (Table 5). Additionally, the three patients with the common allele for *CYP3A5\*3C* were African American.

## DISCUSSION

This report describes the culmination of a unique multinational and multistudy collaboration that explores the hypothesis that clinical differences in treatment outcomes between Japanese and US patients with NSCLC may be explained, in part, by pharmacogenomic factors. Potential differences in drug disposition related to ethnic variability in distribution of relevant single nucleotide polymorphisms are well recognized. To our knowledge, however, the current project represents the first attempt to prospectively incorporate study of this topic into a joint clinical trial design. To preplan such a multinational endeavor required a high level of collaboration and compromise among all participants, including, in the case of FACS, Japanese regulatory authorities. Nevertheless, this report demonstrates the overall feasibility of using a common-arm methodology to investigate this research topic, in which a single, prospectively planned, joint study cannot be conducted. Considering the limitations of the clinical and pharmacogenomic data sets generated in this effort, and considering the multiple comparisons generated, the results reported here should be viewed as exploratory only and as primarily useful for refining this common-arm model of multinational collaboration. Even so, the clinical results are remarkably consistent with those anticipated, in which expectations were for both improved efficacy and higher levels of toxicity in Japanese patients who received a similar treatment regimen. Observation of clinical differences despite reduced paclitaxel

**Table 3.** Efficacy Comparisons

Parameter	Trial			P
	FACS (n = 145)	LC00-03 (n = 197)	S0003 (n = 184)	
Response				.55
No.	47	73	61	
%	32	37	33	
PFS, months	4.5	6	4	.04*
MST, months	12	14	9	.0006*
1-year survival	51%	57%	37%	.0004

Abbreviations: FACS, four-arm cooperative study; PFS, progression-free survival; MST, median survival time.

\*Log-rank test to compare LC00-03 and S0003. Patient-level data not available for FACS.

Table 4. Treatment Delivered

Treatment Data	Trial						P
	FACS (n = 145)		LC00-03 (n = 197)		S0003 (n = 184)		
	No.	%	No.	%	No.	%	
Median cycles delivered	3.5		4		4		.07
Received > three cycles	35	24	118	60	100	54	< .0001
Received six cycles	16	11	58	29	68	36.5	< .0001
Dose was reduced	No data	No data	100	51	98	26	.63*

Abbreviation: FACS, four-arm cooperative study.

\*Wilcoxon rank sum test to compare LC00-03 and S0003. Patient-level data not available for FACS.

dosing and drug delivery of paclitaxel plus carboplatin in the FACS Japanese study highlights the contrast.

The rationale for conducting this common-arm project specifically in collaboration with Japanese investigators was based on several factors, including the established SWOG interaction described earlier, the high quality of lung cancer investigation by Japanese cooperative groups, and prior literature that suggested that overall, Japanese patients achieve better results than their US counterparts. However, the most compelling rationale was prior pharmacogenomic literature, which suggested that relevant drug disposition differences might exist between US and Japanese populations treated with cancer chemotherapeutic agents. Well recognized here are alterations in irinotecan metabolism as a result of variability in the allelic distribution of UDP-glucuronosyltransferases, particularly *UGT1A1\*28* in different

ethnic groups, as Asians have a much lower frequency of variant alleles. Recently, a comparative analysis of patient-level data from phase III trials in small-cell lung cancer in Japan (J9511) and the United States (S0124) demonstrated significant differences in toxicity profiles between the two groups. In addition, a pharmacogenomic analysis of S0124 showed significant associations between genotypic variants and toxicity levels.<sup>16,17</sup>

The genes evaluated in this study were selected on the basis of their potential to influence paclitaxel disposition or DNA damage repair. Paclitaxel is principally eliminated through multiple hydroxylation reactions mediated by cytochrome isoforms *CYP2C8*, *CYP3A4*, and *CYP3A5*.<sup>18,19</sup> The *CYP2C8\*3* variant (R139K), which is associated with decreased metabolism of paclitaxel, occurs at a frequency of 9% to 15% in white patients but is rare in African and Asian populations.<sup>20-23</sup> In this study, the allele frequency in the US population was 12%, which was significantly different from the less-than-1% frequency in the Japanese cohort ( $P = .01$ ). *CYP2C8* genotypic variability at R139K was not significantly associated with patient outcome. *CYP3A* isozymes account for 45% to 60% of paclitaxel metabolism.<sup>24</sup> In white patients, the *CYP3A5* allele is commonly nonfunctional as a result of a transition in intron 3 that produces a truncated splice variant.<sup>25</sup> Our findings are consistent with that of Hustert et al,<sup>25</sup> who reported frequencies of functional *CYP3A5* as 5% in white patients, 29% in Japanese patients, and 73% in African American patients. Of patients enrolled onto the S0003 trial conducted in the US, three of three with the functional allele (indicated as common in Table 5) were African Americans, as were three of the seven heterozygous patients. Although trends were observed, *CYP3A5\*3C* genotypic variability was not significantly associated with patient outcome (overall survival  $P = .07$ ; PFS  $P = .09$ ), perhaps related to the small sample size. Similarly, the *CYP3A4\*1B* allele was observed in seven of seven African American patients but was absent in white and Japanese patients. In vitro studies suggest that the *CYP3A4\*1B* variant has enhanced activity over common allele.<sup>26</sup> An association was observed between occurrence of the *CYP3A4\*1B* and PFS ( $P = .04$ ); however, this association should be interpreted in the context that only African American patients harbored this allele. Thus, it remains unclear whether this potential relationship with outcome is associative or causative. The PXR (*NR1I2*-206 deletion) is a master regulator of genes involved in xenobiotic detoxification and influences transcription of *CYP3A4*, *CYP3A5*, *CYP2C8*, and *MDR-1 (ABCB1)*.<sup>27-29</sup> Paclitaxel can activate PXR, which enhances drug clearance through increased activity of MDR1.<sup>30</sup> No significant differences by genotype were observed for PXR or ABCB1, although there was a trend toward

Table 5. Genotype Profiles in Japanese and US Patients on LC00-03 and S0003

Polymorphism by Trial Location	No. of Patients			P
	Com	Het	Var	
<i>CYP3A4*1B</i>				
Japan	73	0	0	.01
United States	64	4	3	
<i>CYP3A5*3C</i>				
Japan	7	16	50	.03
United States	3	7	66	
<i>CYP2C8 (R139K)</i>				
Japan	69	2	0	.01
United States	57	7	5	
<i>ABCB1 (3435C→T)</i>				
Japan	33	21	17	.11
United States	24	23	29	
<i>NR1I2 (206 deletion)</i>				
Japan	51	19	5	.25
United States	40	25	8	
<i>ERCC1 (118)</i>				
Japan	8	27	43	< .0001
United States	23	33	19	
<i>ERCC2 (K751Q)</i>				
Japan	73	1	0	< .001
United States	37	27	8	

NOTE. LC00-03 is the trial in Japan; S0003 is the trial in the United States. Fisher's exact test was used to determine whether allele distributions were different between the populations.

Abbreviations: Com, common allele; Het, heterozygous allele; Var, variant allele.

**Table 6.** Cox Model to Compare Outcomes by Polymorphism

Outcome by Polymorphism	Comparison	Analyses		
		HR	95% CI	P
<i>ABCB1</i> 3425				
Overall survival	Com v Het/Var (CC v CT/TT)	1.09	0.71 to 1.67	.69
PFS		1.04	0.70 to 1.56	.82
Response		0.97	0.39 to 2.38	1.00
Neutropenia		0.54	0.22 to 1.30	.19
<i>CYP2C8</i> R139K				
Overall survival	Com v Het/Var (GG v GA/AA)	1.09	0.61 to 1.96	.76
PFS		1.12	0.63 to 2.00	.69
Response		1.92	0.46 to 11.11	.51
Neutropenia		1.30	0.35 to 5.00	.87
<i>CYP3A4*</i> 1B				
Overall survival	Com v Het/Var (AA v AG/GG)	0.74	0.32 to 1.72	.48
PFS		0.36	0.14 to 0.94	.04
Response		0.63	0.10 to 4.76	.84
Neutropenia		0.44	0.04 to 2.94	.58
<i>CYP3A5*</i> 3C				
Overall survival	Com/Het v Var (AA/AG v GG)	1.64	0.95 to 2.86	.07
PFS		1.56	0.93 to 2.63	.09
Response		1.61	0.53 to 4.76	.47
Neutropenia		1.30	0.44 to 3.85	.78
<i>ERCC1</i> (118)				
Overall survival	TT v TC/CC	1.20	0.74 to 1.96	.45
PFS		1.11	0.69 to 1.82	.65
Response		1.45	0.48 to 4.17	.61
Neutropenia		0.57	0.20 to 1.61	.35
<i>ERCC2</i> K751Q				
Overall survival	Com v Het/Var (AA v AC/CC)	0.97	0.63 to 1.49	.89
PFS		0.85	0.55 to 1.30	.45
Response		0.33	0.13 to 0.83	.02
Neutropenia		0.75	0.30 to 1.85	.63
<i>nr1I2-206</i> del				
Overall survival	Com v Het/Var 206 deletion	0.82	0.53 to 1.25	.35
PFS		0.93	0.63 to 1.39	.75
Response		0.82	0.34 to 2.00	.77
Neutropenia		0.88	0.37 to 2.08	.90

Abbreviations: HR, hazard ratio; PFS, progression-free survival; Com, common allele; Het, heterozygous allele; Var, variant allele.

neutropenia ( $P = .19$ ) for patients who harbored the *ABCB1* 3435 common allele.

The *ERCC2* gene, also known as xeroderma pigmentosum complementation group D, encodes a DNA helicase which complexes with TFIIH, a transcription factor essential for replication and nucleotide excision repair.<sup>31</sup> Several nonsynonymous SNPs have been described in this gene, including an Asp→Asn (G→A) at codon 312 in exon 10 and a Lys→Gln (A→C) at codon 751 in exon 23 and are likely in linkage disequilibrium with each other.<sup>32,33</sup> The functional consequences of these SNPs are still in contention, and the majority of studies indicate that variants in these alleles result in reduced DNA repair capacity.<sup>34-41</sup> Additionally, most studies indicate that *ERCC2* variants confer an increased risk of lung cancer.<sup>32,34,35,42-48</sup> In this study, 51% of patients (ie, 37 of 72 patients) from the US were homozygous wild type for the common (A) allele. These patients were significantly less likely to respond to treatment compared with US patients who had one or more variant alleles (A/C or C/C). However, no differences in overall survival were observed on the basis of *ERCC2* K751Q allele frequencies. In addition, this allele cannot

account for the improved survival experienced by Japanese patients, as they uniformly harbored the common A/A genotype (and only one patient harbored A/C). The *ERCC1* 118 C→T SNP does not result in an amino acid substitution, although studies have nevertheless identified associations with patient outcome in various tumor types.<sup>49</sup> It has been suggested that this variant may modulate *ERCC1* mRNA and protein expression and/or may be in linkage disequilibrium with other functional SNPs.<sup>14,50,51</sup> However, three reports in NSCLC found no associations between the *ERCC1* 118 and patient outcome.<sup>52-54</sup> Here, we found a highly significant divergence in allele frequency between Japanese and US patients ( $P < .0001$ ); however, no impact on patient outcome was observed.

In summary, the results of cancer clinical trials to test the same regimen may differ for a variety of reasons, including differences related to ethnicity. FACS, LC00-03, and S0003 were prospectively designed to facilitate a comparison of patient outcomes and pharmacogenomic results, in a setting where joint clinical trials sponsored by the US National Cancer Institute were not possible. Our

results suggest that global clinical trials (ie, those conducted internationally) should be carefully designed and conducted to account for potential genetic differences in the patient populations studied. This common-arm approach provides a model for the prospective study of population-related pharmacogenomics in which ethnic differences in antineoplastic drug disposition are anticipated.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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