VOLUME 26 · NUMBER 6 · FEBRUARY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Eicosanoid Modulation in Advanced Lung Cancer: Cyclooxygenase-2 Expression Is a Positive Predictive Factor for Celecoxib + Chemotherapy—Cancer and Leukemia Group B Trial 30203

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Submitted August 29, 2007; accepted November 6, 2007.

Supported in part by grants from the National Cancer Institute (CA31946) to the Cancer and Leukemia Group B and to the CALGB Statistical Center (CA33601); and by Grant Nos. CA31983, CA47577, CA77658, CA16450, CA41287, CA45389, CA45418, and CA03927.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2606-848/$20.00

DOI: 10.1200/JCO.2007.13.8081

ABSTRACT

Purpose
Increased expression of eicosanoids in cancer has been associated with adverse prognosis. We performed a randomized phase II trial to test the hypothesis that inhibitors of two eicosanoid pathways (cyclooxygenase-2 [COX-2], celecoxib and 5-lipoxygenase [5-LOX], zileuton) added to chemotherapy would improve outcome in advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Patients with advanced NSCLC, a performance status of 0 to 2, and no prior therapy were eligible. All patients received carboplatin area under the curve (AUC) 5.5 mg/mL · min day 1 + gemcitabine (1,000 mg/m^2) days 1 and 8. Patients were randomly assigned to: (a) zileuton 600 mg PO qid, (b) celecoxib 400 mg PO bid, or (c) celecoxib and zileuton at the same doses. Immunohistochemical staining for COX-2 and 5-LOX was performed without knowledge of outcomes.

Results
One hundred forty patients were entered and 134 were eligible and treated. There was no survival difference between the arms. COX-2 expression was a negative prognostic marker for overall survival (OS; hazard ratio [HR] = 2.51, $P = .019$ for index ≥ 4; HR = 4.16, $P = .005$ for index = 9) for patients not receiving celecoxib. Patients with increased COX-2 expression (index ≥ 4), receiving celecoxib had better survival than did COX-2–expressing patients not receiving drug (HR = .342, $P = .005$ for OS; HR = .294, $P = .002$ for failure-free survival). Multivariate analysis confirmed the interaction of COX-2 and celecoxib on survival. 5-LOX expression was neither prognostic nor predictive.

Conclusion
This study failed to demonstrate the value of dual eicosanoid inhibition or benefit from either agent alone in addition to chemotherapy. However, a prospectively defined subset analysis suggests an advantage for celecoxib and chemotherapy for patients with moderate to high COX-2 expression.

J Clin Oncol 26:848-855. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Recent advances in chemotherapy have improved the outlook for patients with advanced non–small-cell lung cancer (NSCLC). Combinations of platinums with third-generation drugs (eg, paclitaxel, gemcitabine, vinorelbine) demonstrate improved survival and/or reduced toxicity compared with older combinations, but have not identified a preferred regimen.[1-5] Recently, the Eastern Cooperative Oncology Group (ECOG) presented data demonstrating that bevacizumab was beneficial in selected patients with advanced NSCLC.[6] Even in this population, the 1-year mortality is approximately 50%.

Eicosanoids are a diverse group of small–molecular weight lipids derived from arachidonic acid that act as local signaling molecules. They include prostaglandins, prostacyclins, leukotrienes, thromboxanes and lipoxins. Recent evidence strongly supports a fundamental role for dysregulation of these molecules in carcinogenesis, progression, and drug resistance.[7]

Zileuton is a 5-lipoxygenase (5-LOX) inhibitor initially developed for asthma treatment. It has been demonstrated to prevent lung tumorigenesis in carcinogen-treated mice.[8] Inhibition of 5-LOX has also been demonstrated to reduce production of vascular endothelial growth factor (VEGF), indicating a possible antiangiogenic

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effect. Zileuton is devoid of myelotoxicity, neurotoxicity, or emetogenecity. Celecoxib is an inhibitor of cyclooxygenase-2 (COX-2), the enzyme that converts arachidonic acid to prostaglandins. Inhibition of COX-2 results in reduced proliferation of cancer cells in vitro.[9] The drug has been approved for prevention of colorectal polyps in patients with familial adenomatous polyposis.[10]

In vitro and animal data support the concept that altering eicosanoid metabolism at multiple sites may be of benefit.[9] Carboplatin/paclitaxel and celecoxib have been combined at full doses in a preoperative study of stage I and II NSCLC with no evidence of overlapping toxicities.[11] Given the nonoverlapping toxicities of celecoxib and zileuton, we believed that this combination would be well tolerated. A pilot trial (UMGCC 0226) at the University of Maryland (Baltimore, MD) confirmed that full doses of carboplatin/paclitaxel or carboplatin/gemcitabine could be combined with the chemopreventative dose of celecoxib and the approved antiasthma dose of zileuton (unpublished results).

Cancer and Leukemia Group B (CALGB) trial 30203 was developed to test the concept of eicosanoid inhibition in advanced lung cancer. The hypothesis was that eicosanoid inhibition in addition to chemotherapy would potentially increase failure-free survival (FFS). Furthermore, the concept of single versus double pathway inhibition was tested with inhibitors of COX-2 and 5-LOX.

PATIENTS AND METHODS

Patient Eligibility

Eligible patients had, histologically documented NSCLC, stage IIIb on the basis of malignant effusion or supraclavicular adenopathy or stage IV disease and a performance status of 0 to 2. Patients had not received prior chemotherapy. Adequate hematologic status was required and was defined as absolute neutrophil count (ANC) of at least 1,500/mm^3, hemoglobin of at least 10 g/dL, and platelets of at least 100,000/mm^3. Adequate hepatic and renal function defined as AST or ALT no more than 4× the upper limit of normal, total bilirubin no more than 1.5 mg/dL, and serum creatinine no more than 1.5 mg/dL were required. Surgery or radiotherapy must have been completed 2 weeks before enrollment. Patients with brain metastases were eligible. Those with symptomatic metastases must have completed therapy, be neurologically stable, and not require seizure medication or steroids. Patients with a recent history (ie, < 6 months) of ulcer disease, coronary artery disease, cerebrovascular disease, or venous thromboembolic disease, or who chronically utilized nonsteroidal anti-inflammatory drugs (NSAIDs) or leukotriene antagonists were excluded. Patients could enter onto the study if NSAID use was discontinued 1 week before enrollment. Paraffin-embedded blocks were required for entry, although this could be waived by permission of the principal investigator.

Treatment Plan

All patients received carboplatin area under the curve (AUC) 5.5 mg/mL · min intravenously (IV) day 1 and gemcitabine 1,000 mg/m^2 IV days 1 and 8.[5] A total of six courses of chemotherapy were permitted. Patients were randomly assigned to receive one of three eicosanoid regimens: arm A, zileuton 600 mg PO qid; arm B, celecoxib 400 mg PO bid; or arm C: both agents (Fig 1). Eicosanoid modulators were begun with chemotherapy and continued until progression of disease. Drug diaries were not required. The study was approved by local institutional review boards before patient enrollment.

Adverse events were graded according to the National Cancer Insitute Common Toxicity Criteria, version 2.0. Doses of carboplatin and gemcitabine were modified on the day of therapy as follows: for ANC no more than 1,500/mm^3 but at least 1,000/mm^3 or platelet count no more than 100,000/mm^3 but at least 75,000/mm^3, 50% of the agents were administered. Both drugs were withheld if ANC was 1,000/mm^3 or lower or if platelet count was 75,000/mm^3 or lower. Neurotoxicity grade 2 or worse would result in a 25% decrease in carboplatin dose. Ototoxicity grade 3 or worse would result in discontinuation of carboplatin. For nonhepatic GI toxicity grade 3 or worse, gemcitabine and carboplatin were to be reduced 25%. Grade 3 toxicity would result in removal from protocol therapy. For hepatotoxicity grade 3 or worse, therapy was to be held until resolution to grade 1 or better, at which time therapy could be resumed. Zileuton would resume at 50%. For all other toxicities grade 2 or worse, all drugs would be reduced by 25%, but could be re-escalated with resolution of the toxicity.

Clinical Assessment and Response Criteria

All patients underwent history and physical examination before entry and every 3 weeks during therapy. CBCs and chemistry panels (including hepatic enzymes) were performed weekly. Computerized tomographic scans of the chest were obtained every 6 weeks. Additional scans, tests, and other evalutations were obtained as clinically indicated. Patients were removed from the study for unacceptable toxicity or progression of disease. Response was defined according to the National Cancer Institute Response Criteria in Solid Tumor (RECIST).

Immunohistochemistry

Paraffin-embedded tissue was cut at 4 μm and placed on positively charged slides. Slides were then placed in a 60°C oven for 1 hour, cooled, and deparaffinized and rehydrated through xylene and graded ethanol solutions to water. All slides were quenched for 5 minutes in a 3% hydrogen peroxide solution in water to block for endogenous peroxidase. Antigen retrieval was performed using Dako's TRS, pH 6.1, in a vegetable steamer (Dako Cytomation, Carpinteria, CA). Slides were then placed on a Dako Autostainer. Nonspecific antibody binding was inhibited by incubating sections with Dako's serum-free protein block for 15 minutes. For 5-LOX, an antibody to 5-LOX

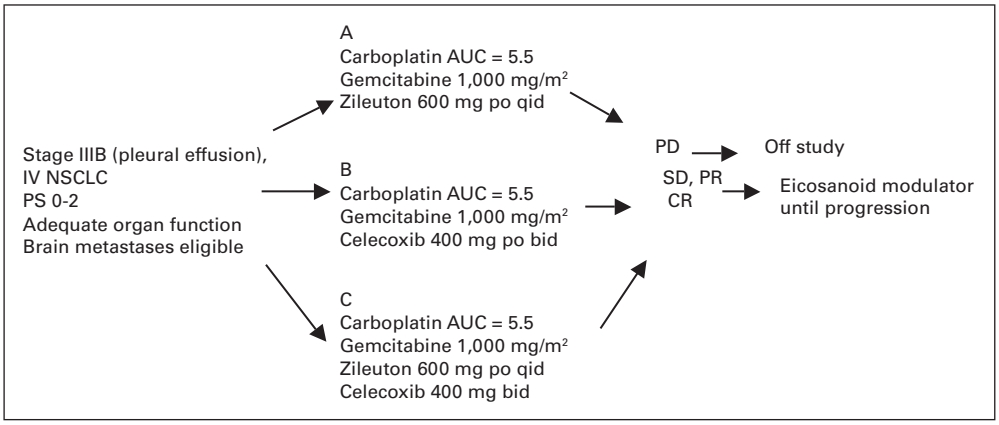

Fig 1. Schema for Cancer and Leukemia Group B trial 30203. AUC, area under the curve; NSCLC, non–small-cell lung cancer; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

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(5-lipoxygenase, clone 33; BD Transduction Labs, San Jose, CA) was diluted 1:2,000 and incubated for 1 hour at room temperature. For COX-2 an antibody to COX-2, clone SP21 (Lab Vision Corp, Fremont, CA) was diluted 1:50 and incubated for 1 hour at room temperature. The detection system was the Biocare Medical (Concord, CA) MACH 3 mouse polymer kit. Lastly, sections were incubated with Dako's DAB+ chromogen for 5 minutes, counterstained with hematoxylin, dehydrated through graded ethanol solutions, and coverslipped. All slides were reviewed by a pathologist without knowledge of patient history or treatment. The slides were scored for intensity of staining (0 to 3) and the percentage of cells scored 0 (0%), 1 (1% to 9%), 2 (10% to 49%), 3 (50% to 100%). The immunohistochemistry (IHC) index (0-9) was defined as the product of the intensity and percentage of cells.

Statistical Considerations

The objective was to examine the efficacy of three regimens for the treatment of patients with advanced NSCLC. Each treatment was to be

Table 1. Patient Characteristics and Baseline Variables by Treatment Arm

Characteristics and Variables	Arm A (n = 44)		Arm B (n = 45)		Arm C (n = 45)		Total (N = 134)		*P*
	No.	%	No.	%	No.	%	No.	%	
Patient demographics									
Sex									
Male	31	70	24	53	29	64	84	63	
Female	13	30	21	47	16		50	37	
Age, years									
< 40	2	5	2	4	0	0	4	3	
40-49	2	5	3	7	4	9	9	7	
50-59	11	25	21	47	15	33	47	35	
60-69	16	36	12	27	15	33	43	32	
70-79	11	25	6	13	9	20	26	19	
80+	2	5	1	2	2	4	5	4	
Race/ethnicity									
White	40	91	37	82	35	78	112	84	
Black	2	5	7	16	8	18	17	13	
Other	2	5	1	2	2	4	5	4	
Histology									
Adenocarcinoma	22	50	23	51	22	49	67	50	
Squamous	10	23	7	16	11	24	28	21	
Undifferentiated	9	20	12	27	10	22	31	23	
Other	3	7	3	7	2	4	8	6	
Performance status									
0	8	18	14	31	20	44	42	31	
1	31	70	28	62	20	44	79	59	
2	5	11	3	7	5	11	13		
Stage								10	
IIIB	6	14	3	7	6	13	15	11	
IV	35	80	40	89	37	82	112	84	
Recurrent	3	7	2	4	2	4	7	5	
Baseline variables for patients with tissue data									
Performance									
0	7	24	10	40	14	48			.1559
1-2	22	76	15	60	15	51			
Sex									
Male	22	76	13	52	17	59			.1673
Female	7	24	12	48	12	41			
Stage									
IIIB	3	10	3	12	1	3			.5384
IV	19	66	15	60	16	55			
Other	7	24	7	28	12	41			
Histology									
Adenocarcinoma	15	52	12	48	12	41			.6502
Squamous	8	28	4	16	8	28			
Other	6	21	9	36	9	31			
Age, years									
< 65	21	72	17	68	14	48			.1321
≥ 65	8	28	8	32	15	52			
COX-2 expression									
< 4	18	62	17	68	16	55			.6215
≥ 4	11	38	8	32	13	45			

Abbreviation: COX-2, cyclooxygenase-2.

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individually screened to determine whether the regimen merited inclusion in a larger phase III trial. Exploratory comparisons of the arms and subsets were to generate new hypotheses, not to reach definitive conclusions. The primary end point of this study and basis for sample size determination was the percentage of patients who remained alive and failure-free at 9 months. With 39 patients enrolled in each arm, the study had 90% power to differentiate a true 9-month FFS of 30% or less versus 50% or more at a one-sided significance level of 0.10.

The balance of demographic and clinical variables across study arms were tested by χ^2 tests for categoric variables and Wilcoxon rank sum tests for continuous variables. All *P* values were two-sided without adjusting for multiple comparisons.

Patients were followed for response, FFS, and overall survival (OS). The response rate and its 95% CI were estimated. The difference of response rates between arms were tested by χ^2 tests and by logistic regression with adjustment for significant prognostic factors. FFS was defined as the time from study entry to the date of disease progression or death, whichever came first. OS was defined as the time from study entry to the date of death resulting from any cause. Kaplan-Meier curves were used to characterize OS and FFS. Median survival and survival rate at certain landmark times as well as their 95% CIs were computed. Log-rank tests were used to test the survival difference between study arms. Cox proportional hazard models were used to estimate unadjusted and adjusted hazard ratios (HRs) for treatment effects.

The relationship between levels of COX-2 and 5-LOX expression and response were evaluated utilizing χ^2 tests and logistic regression. The significance of the correlation between expression and survival was tested by the log-rank test with expression dichotomized at different levels. The corresponding HRs and CIs were computed by fitting a Cox proportional hazard model for the predictor. The interaction between expression levels and treatment on survival were tested in a multivariate Cox proportional hazard regression model. Stepwise variable selection was used to identify significant prognostic predictors to be adjusted.

Members of the Data Audit Committee of the CALGB reviewed the records of a subgroup of 46 (32.9%) of the 140 patients entered onto this study.

RESULTS

Demographics

Between December 5, 2003, and September 30, 2004, 140 patients were enrolled, and 134 patients were eligible and treated (Table 1). Of six ineligible patients, one had brain metastases felt to require immediate therapy, two had thromboembolic disease, and three withdrew without receiving treatment. Eight-four percent of patients had stage IV disease; the remainder were stage IIIB (pleural effusion) or recurrent. Ninety percent had a performance status of 0 to 1, and approximately half had adenocarcinoma histology.

Toxicity

Treatment in all three arms was well tolerated (Table 2). Hematologic toxicity was similar to that demonstrated in prior studies of carboplatin and gemcitabine.[12] Nonhematologic toxicity was also not different from that seen for the cytotoxic agents alone. There were no cardiac events attributed to therapy. One fatal cardiac event occurred in arm A and one fatal thrombotic event in arm B.

Response and Survival

The median follow-up time for all patients was 29 months. None of the three arms met the primary end point of 50% FFS at 9 months (Fig 2). Overall, the entire study population demonstrated a 9-month FFS of 14%, median FFS of 4.9 months, OS of 10.3 months, and 1-year survival of 42%. There were no significant differences in OS (log-rank $P = .7469$) and FFS (log-rank $P = .0763$) between the three arms. An exploratory comparison of arm C versus arms A and B demonstrated an advantage of 7.3 months versus 4.3 months (log-rank $P = .032$) for median FFS, but when this was adjusted for known prognostic factors of stage and performance status, this difference decreased to a borderline significance (Wald $P = .054$). There was no trend towards benefit of overall survival for arm C versus arms A and B (log-rank $P = .49$). No complete responses occurred on any arm. For arms A, B, and C, the response and stable disease rates were 25% and 50%, 24% and 49%, and 36% and 44%, respectively. Overall, the response rate was 28% and stable disease rate 48%.

IHC

Tissue was submitted from 107 (76%) of the 140 patients. Of 134 eligible patients, eighty-three (61%) of the specimens were adequate for analysis with 29 in arm A, 25 in arm B, and 29 in arm C (Table 3). There were no significant imbalances in baseline variables across the treatment arms in the cohort assessable by IHC. We wished to explore whether the expression of either 5-LOX or COX-2 would be prognostic or would potentially predict for activity of the specific inhibitor or combination. Patients were grouped into those who did or did not receive the specific inhibitor and compared. For evaluation of the

Table 2. Toxicity

	Grade																	
	Arm A (n = 44)						Arm B (n = 45)						Arm C (n = 44)					
	3		4		5		3		4		5		3		4		5	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hemoglobin	13	30	3	7	0	0	10	22	4	9	0	0	10	23	1	2	0	0
Absolute neutrophil count	12	27	11	25	0	0	12	27	11	24	0	0	15	34	12	27	0	0
Platelets	5	11	12	27	0	0	8	18	14	31	0	0	9	20	15	34	0	0
Neutropenic fever	1	2	1	2	0	0	2	4	0	0	0	0	1	2	0	0	0	0
Hemorrhage	1	2	0	0	0	0	0	0	2	4	0	0	4	9	0	0	0	0
Cardiac ischemia	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0
Thrombosis/embolism	1	2	0	0	0	0	0	0	1	2	1	2	0	0	0	0	0	0
Nausea	1	2	0	0	0		4	9	0	0	0		5	11	0	0	0	0
Vomiting	1	2	0	0	0		3	7	0	0	0		5	11	0	0	0	0

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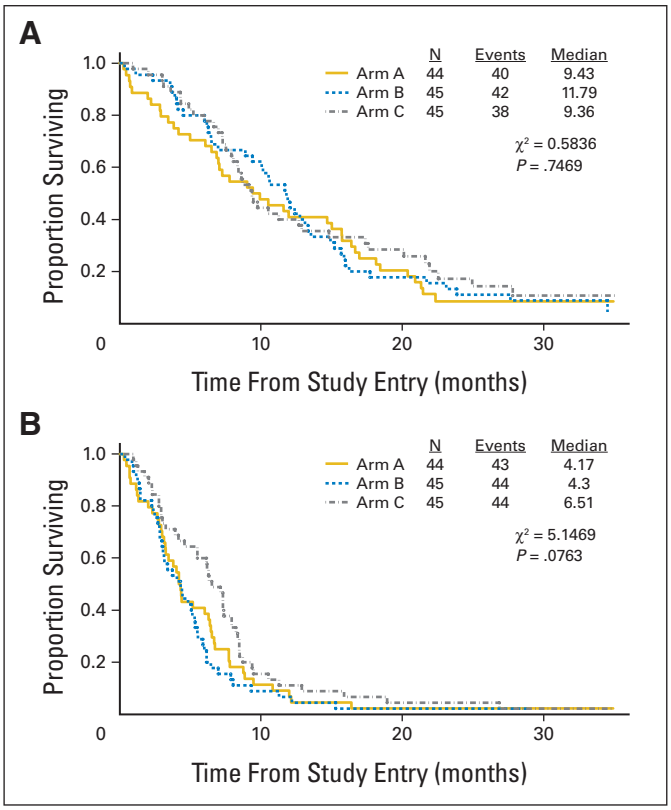

Fig 2. (A) Overall and (B) failure-free survival by treatment.

prognostic value of 5-LOX, arm B (celecoxib alone) was evaluated. For evaluation of whether 5-LOX expression correlated with response to zileuton, arms A and B (both containing zileuton) were compared with arm B. For evaluation of the prognostic value of COX-2, arm A (zileuton alone) was evaluated. For the predictive value of whether COX-2 expression correlated with response to celecoxib, arms B and C were compared with arm A. Expression was tabulated with outcome, and cut points were established by visual inspection of the data.

Analysis of arm A (chemotherapy + zileuton, the 5-LOX inhibitor) demonstrated that patients with moderate to high (defined as an index of ≥ 4) expression of COX-2 had a worse overall survival than did those who did not have moderate or high (HR = 2.51; 95% CI, 1.14 to 5.56; $P = .019$; Table 3; Fig 3A). For those with high levels of expression (index = 9) the result was even more dramatic with an HR of 4.16 (95% CI, 1.44 to 12.01; $P = .005$). However, if patients with moderate to high COX-2 expression received the COX-2 inhibitor celecoxib, the outcome was dramatically improved (Table 3; Fig 3B). Patients receiving celecoxib (± zileuton) who had moderate to high expression of COX-2 had a superior outcome in terms of overall survival (HR = .342; $P = .005$) compared with patients with moderate to high expression who did not receive celecoxib. A trend was apparent that the greater the degree of COX-2 expression, the greater the degree of benefit from celecoxib (Table 3). Patients who did not demonstrate expression of COX-2 (index < 1) and received celecoxib seemed to have an inferior OS outcome compared with those who expressed COX-2 and received celecoxib (HR = 1.43; 95% CI, 0.64 to 3.20), but the difference is not statistically significant ($P = .384$; Table 3). Similar analysis for 5-LOX expression failed to demonstrate that it was either prognostic by itself or predictive of response to zileuton.

To test for possible imbalances in known prognostic factors (eg, age, sex, and performance status) a multivariate analysis using a Cox regression model was performed (Table 4). COX-2 expression, whether a patient received celecoxib and their interaction are forced in the Cox model, whereas stepwise algorithm is used to select significant covariates and their pairwise interactions with COX-2 expression (≥ 4, < 4) and whether the patient received celecoxb (yes, no). For OS, the final model confirmed that the interaction of receiving celecoxib and COX-2 expression was highly significant, with a P value of .0026 (adjusted HR = 0.21; 95% CI, 0.07 to 0.58). The only other factors that significantly associated with OS were sex, with an adjusted HR of 2.79 (95% CI, 1.56 to 4.99; $P = .0005$) in favor of female sex and the interaction of COX-2 overexpression and age in disfavor of COX-2 overexpression (≥ 4) and older patients (> 65 years), with an adjusted HR of 2.50 (95% CI, 0.87 to 7.21), $P = .0888$. Similar results are found with FFS, with an adjusted HR of 0.31 (95% CI,

Table 3. COX-2 As a Prognostic and Predictive Marker

Marker	End Point	COX-2 Index (prognostic) Cut Point	COX-2 Index (prognostic) Arm A	COX-2 Index (predictive) Cut Point	COX-2 Index (predictive) Arm A	COX-2 Index (predictive) Arm B/C	HR	95% CI	Log-Rank P	Low Expression MST (months)	Low Expression 95% CI	High Expression MST (months)	High Expression 95% CI	Did Not Receive Celecoxib MST (months)	Did Not Receive Celecoxib 95% CI	Did Receive Celecoxib MST (months)	Did Receive Celecoxib 95% CI
Prognostic (evaluation of COX-2 expression on arm A)*	OS	≥ 1	17				1.647	0.752 to 3.611	.208	13.3	7.3 to 18.4	7.1	3.4 to 15.7				
	OS	≥ 4	11				2.514	1.138 to 5.555	.019	13.3	9.4 to 18.4	3.8	0.9 to 10.5				
	OS	9	6				4.155	1.437 to 12.010	.005	12.0	7.3 to 16.7	4.0	3.4 to 6.5				
	FFS	≥ 1	17				0.600	0.273 to 1.315	.198	3.9	3.1 to 5.2	4.2	2.9 to 7.7				
	FFS	≥ 4	11				2.000	0.883 to 4.530	.091	4.7	3.2 to 6.7	3.4	0.8 to 6.4				
	FFS	9	6				1.680	0.641 to 4.403	.286	4.3	3.1 to 6.7	3.8	3.3 to 4.2				
Predictive (evaluation of celecoxib effect on arm A v B/C)†	OS			< 1	12	18	1.429	0.638 to 3.201	.384					13.3	7.3 to 18.4	8.6	4.9, 14.9
	OS			≥ 4	11	21	0.342	0.155 to 0.752	.005					3.8	0.9 to 10.5	11.3	9.2, 17.6
	OS			9	6	14	0.177	0.066 to 0.576	.002					4.0	3.4 to 6.5	12.1	8.0, 16.0
	FFS			< 1	12	18	0.819	0.382 to 1.755	.608					3.9	3.1 to 5.2	4.0	2.8,15.5
	FFS			≥ 4	11	21	0.294	0.127 to 0.678	.002					3.4	0.8 to 6.4	6.5	4.8,8.4
	FFS			9	6	14	0.199	0.063 to 0.621	.002					3.8	3.3 to 4.2	7.2	5.5,11.3

Abbreviations: COX-2, cyclooxygenase; OS, overall survival; FFS, failure-free survival; HR, hazard ratio; MST, median survival.
*HR of high *v* low COX-2.
†HR of received *v* did not receive celecoxib.

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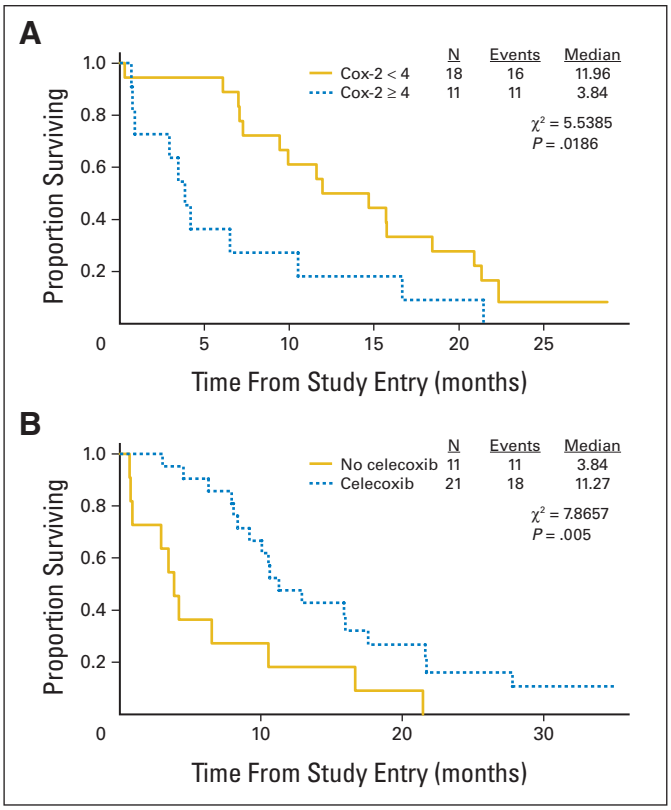

Fig 3. Cyclooxygenase-2 (COX-2) expression as a prognostic predictive marker. (A) COX-2 expression and survival for patients who did not receive celecoxib (arm A, n = 29). (B) Receiving celecoxib and survival for patients with moderate or high COX-2 expression (index ≥ 4, n = 32).

0.12 to 0.82; $P = .0185$) for the interaction of receiving celecoxib and COX-2 expression.

DISCUSSION

Dysregulation of eicosanoids is thought to play a role in carcinogenesis, tumor progression and drug resistance. We evaluated two eicosanoid pathway–modifying agents: zileuton and celecoxib. Zileuton, an agent developed and approved for the treatment of asthma, inhibits 5-LOX. Inhibition of 5-LOX reduces production of 5HETE, leukotriene B4 (LTB4), and other metabolites of 5HPETE. Increased LTB4 stimulates the growth of a wide range of human carcinomas. 5-LOX inhibition has been demonstrated to prevent lung tumorigenesis in carcinogen-treated mice.[8] In addition, inhibition of 5-LOX has been demonstrated to potently reduce production of VEGF, indicating a possible antiangiogenic effect.

Overexpression of COX-2 is common in NSCLC and is associated with poor prognosis.[13-15] COX-2 overexpression occurs not only in the tumor cells but also in the tumor vasculature.[16] Therefore, selective COX-2 inhibitors such as celecoxib have the potential to inhibit tumor angiogenesis and metastases and might serve as ideal agents for long-term maintenance therapy. Intratumoral levels of COX-2 increase in response to carboplatin/paclitaxel chemotherapy.[17] Concurrent treatment with a COX-2 inhibitor has the potential to abrogate this adverse effect.

Dual eicosanoid inhibition has been evaluated in several experimental models and found to be potentially beneficial.[18-20] This trial failed to confirm the value of dual eicosanoid inhibition in NSCLC. However, a predefined analysis evaluating COX-2 and/or 5-LOX expression as prognostic or predictive markers indicates that COX-2 overexpression (defined as an index of ≥ 4) dramatically correlates with both prognosis and benefit. This level of expression was seen in 32 of 83 assessable specimens (95% CI, 28% to 50%). Patients with COX-2 overexpression who did not receive celecoxib in addition to chemotherapy demonstrated a markedly inferior outcome. This result is similar to others reported and is now confirmed for the first time in a prospective trial. Of greater significance is the predictive value of COX-2 expression and benefit from celecoxib. There is also a possible adverse effect for those who receive celecoxib and do not overexpress COX-2. This finding may explain recent negative results utilizing celecoxib and other COX-2 inhibitors in lung and other malignancies, because any positive effect in the COX-2–expressing patients may have been obscured by the negative effects on patients whose tumors did not express COX-2.[21-23] Interestingly, a similar finding for COX-2 has been reported in renal cell carcinoma in which a study (n = 25) of interferon alfa + celecoxib demonstrated superior results for the COX-2 overexpressing patients.[24] A large retrospective study (N = 130,274) demonstrated that aspirin, a nonselective COX inhibitor, suppressed growth of only COX-2 expressing colorectal cancers.[25] Importantly, there are supporting data from two other lung cancer studies: Urinary levels of a COX-2 dependent metabolite, PGE-2, correlated with survival in patients treated with celecoxib + docetaxel as second-line chemotherapy,[26] and Bonomi has recently reported that COX-2–overexpressing patients receiving erlotinib + celecoxib as second-line therapy had significantly better survival than did patients whose tumors did not express COX-2.[27]

Table 4. Multivariate Modeling of the Relationship of OS/FFS and COX-2, Receiving Celecoxib, Baseline Variables and Their Interactions (N = 82)

	OS			FFS		
Parameter	Wald *P*	Hazard Ratio	95% CI	Wald *P*	Hazard Ratio	95% CI
COX-2 (≥ 4)	.2443	1.67	0.71 to 3.96	.2900	1.58	0.68 to 3.72
Celecoxib (yes)	.1469	1.59	0.85 to 2.96	.7471	1.10	0.61 to 1.99
Celecoxib × COX-2	.0026	0.21	0.07 to 0.58	.0185	0.31	0.12 to 0.82
Sex (male)	.0005	2.79	1.56 to 4.99	.3336	1.28	0.78 to 2.10
Age (≥ 65 years)	.3882	1.31	0.71 to 2.42	.5416	1.20	0.67 to 2.15
COX-2 × age	.0888	2.50	0.87 to 7.21	.5293	1.36	0.52 to 3.57

Abbreviations: OS, overall survival; FFS, failure-free survival; COX-2, cyclooxygenase-2.

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Although CALGB 30203 failed to achieve its primary objective, the prospectively planned analysis of patient specimens has confirmed retrospective observations that COX-2 expression is a negative prognostic factor in NSCLC. More importantly, it has generated a new hypothesis, that COX-2 inhibition may be beneficial in the approximately 35% of patients with advanced NSCLC whose tumors have moderate to high COX-2 expression. Confirmation of this approach will require prospective randomized trials that will select patients for therapy based on COX-2 status. Such a study is currently under consideration by the CALGB.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Martin J. Edelman, Eli Lilly, Pfizer (C); Mark J. Green, Tragara Pharmaceuticals (C) **Stock Ownership:** Mark J. Green, Tragara Pharmaceuticals **Honoraria:** Martin J. Edelman, Eli Lilly, Pfizer; Ajeet Gajra, Eli Lilly **Research Funding:** Martin J. Edelman, Eli Lilly, Pfizer; Ajeet Gajra, Eli Lilly **Expert Testimony:** None **Other Remuneration:** None

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Acknowledgment

We thank Susie Jones for technical assistance with immunohistochemistry.

Appendix

The following institutions participated in this study: Christiana Care Health Services, Inc. CCOP, Wilmington, DE—Stephen Grubbs, MD, supported by CA45418; University of North Carolina at Chapel Hill, Chapel Hill, NC—Thomas C. Shea, MD, supported by CA47559; University of Chicago, Chicago, IL —Gini Fleming, MD, supported by CA41287; Duke University Medical Center, Durham, NC—Jeffrey Crawford, MD, supported by CA47577; Georgetown University Medical Center, Washington, DC, Minetta Liu, MD, supported by CA77597; Greenville CCOP, see above Cancer Center of Carolinas; University of Iowa, Iowa City, IA—Gerald Clamon, MD, supported by CA47642; University of Maryland Greenebaum Cancer Center, Baltimore, MD—Martin Edelman, MD, supported by CA31983; University of Minnesota, Minneapolis, MN—Bruce A. Peterson, MD, supported by CA16450; University of Missouri/Ellis Fischel Cancer Center, Columbia, MO—Michael C. Perry, MD, supported by CA12046; Missouri Baptist Medical Center, St Louis, MO, Alan P. Lyss, MD, supported by CA114558-02; Rhode Island Hospital, Providence, RI—William Sikov, MD, supported by CA08025; Roswell Park Cancer Institute, Buffalo, NY—Ellis Levine, MD, supported by CA02599; Southeast Cancer Control Consortium Inc. CCOP, Goldsboro, NC—James N. Atkins, MD, supported by CA45808; Southern Nevada Cancer Research Foundation CCOP, Las Vegas, NV—John Ellerton, MD, supported by CA35421; State University of New York Upstate Medical University, Syracuse, NY—Stephen L. Graziano, MD, supported by CA21060; Syracuse Hematology-Oncology Assoc. CCOP, Syracuse, NY—Jeffrey Kirshner, MD, supported by CA45389; University of California at San Diego, San Diego, CA—Joanne Mortimer, MD, supported by CA11789; University of California at San Francisco, San Francisco, CA—Alan P. Venook, MD, supported by CA60138; The University of Texas Southwestern Medical Center, Dallas, TX—Debasish Tripathy, MD; Vermont Cancer Center, Burlington, VT—Hyman B. Muss, MD, supported by CA77406; and Washington University School of Medicine, St Louis, MO—Nancy Bartlett, MD, supported by CA77440.

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