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ORIGINAL REPORT

Phase III Randomized, Placebo-Controlled, Double-Blind Trial of Celecoxib in Addition to Standard Chemotherapy for Advanced Non–Small-Cell Lung Cancer With Cyclooxygenase-2 Overexpression: CALGB 30801 (Alliance)

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ABSTRACT

Purpose

Tumor overexpression of cyclooxygenase-2 (COX-2) has been associated with worse outcome in non–small-cell lung cancer (NSCLC). In Cancer and Leukemia Group B (CALGB) 30203, we found that the selective COX-2 inhibitor celecoxib in addition to chemotherapy in advanced NSCLC improved progression-free and overall survival in patients with moderate to high COX-2 expression by immunohistochemistry (IHC). CALGB 30801 (Alliance) was designed to prospectively confirm that finding.

Patients and Methods

Patients with NSCLC (stage IIIB with pleural effusion or stage IV according to American Joint Committee on Cancer [sixth edition] criteria) were preregistered, and biopsy specimens were analyzed for COX-2 by IHC. Patients with COX-2 expression ≥ 2, performance status of 0 to 2, and normal organ function were eligible. Chemotherapy was determined by histology: carboplatin plus pemetrexed for nonsquamous NSCLC and carboplatin plus gemcitabine for squamous histology. Patients were randomly assigned to celecoxib (400 mg twice per day; arm A) or placebo (arm B). The primary objective was to demonstrate improvement in progression-free survival in patients with COX-2 index ≥ 4 with hazard ratio of 0.645 with approximately 85% power at two-sided significance level of .05.

Results

The study was halted for futility after 312 of the planned 322 patients with COX-2 index ≥ 2 were randomly assigned. There were no significant differences between the groups (hazard ratio, 1.046 for COX-2 ≥ 4). Subset analyses evaluating histology, chemotherapy regimen, and incremental COX-2 expression did not demonstrate any advantage for COX-2 inhibition. Elevation of baseline urinary metabolite of prostaglandin E2, indicating activation of the COX-2 pathway, was a negative prognostic factor. Values above the third quartile may have been a predictive factor.

Conclusion

COX-2 expression by IHC failed to select patients who could benefit from selective COX-2 inhibition. Urinary metabolite of prostaglandin E2 may be able to identify patients who could benefit from COX-2 inhibition.

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ASSOCIATED CONTENT

Appendix
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Data Supplement
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INTRODUCTION

Overexpression of cyclooxygenase-2 (COX-2) is common in non–small-cell lung cancer (NSCLC) and is associated with poor prognosis.[1-3] COX-2 has been shown to be expressed not only in the tumor cells but also in the tumor vasculature.[4] Celecoxib, a selective inhibitor of COX-2, inhibits tumor growth of Lewis lung carcinoma implanted in mice in a dose-dependent manner.[5] COX-2 is associated with overexpression of phosphoglycoprotein, and its inhibition therefore could potentially reverse drug resistance.[6]

Several trials in lung cancer have evaluated cyclooxygenase inhibition in general and COX-2

inhibition specifically. Csiki et al[7] evaluated the combination of celecoxib and docetaxel for second-line treatment of metastatic NSCLC. There was no overall survival (OS) benefit; however, patients who had evidence of inhibition of urinary metabolite of prostaglandin E2 (PGE-M) levels (PGE2 is the product of COX-2) demonstrated prolonged survival. Part of this benefit may have come from inhibition of COX-2 expression induced by chemotherapy. Altorki et al[8] evaluated COX-2 expression after neoadjuvant chemotherapy (carboplatin plus paclitaxel) in localized lung cancer and found that intratumoral levels were three-fold higher than those in patients who did not receive chemotherapy. This effect was abrogated when celecoxib was administered concurrently with chemotherapy. A randomized phase III trial of celecoxib in addition to carboplatin plus docetaxel in an unselected population was negative for OS.[9]

Cancer and Leukemia Group B (CALGB) 30203 was a randomized phase II trial that tested the concept of eicosanoid inhibition in advanced NSCLC. The hypothesis was that eicosanoid inhibition (COX-2 and/or 5-lipoxygenase inhibition with celecoxib and/or zileuton) in addition to standard chemotherapy would potentially improve survival.[10] CALGB is now part of the Alliance for Clinical Trials in Oncology. Although the overall results were negative, a preplanned analysis of tissue specimens submitted as part of the trial demonstrated that, for patients who did not receive celecoxib, those with overexpression of COX-2 had worse OS than those who did not have overexpression (hazard ratio [HR] for moderate overexpression (index ≥ 4), 2.68; $P = .018$). For those with high levels of overexpression (index ≥ 9), there was an HR of 4.16 ($P = .009$). Patients who received celecoxib who had overexpression of COX-2 had a superior outcome compared with patients with overexpression who did not receive celecoxib. There seemed to be a steadily increasing level of benefit with increased COX-2 expression. Patients who did not demonstrate overexpression of COX-2 (ie, COX-2 index = 0) and received celecoxib seemed to have an inferior outcome (HR, 1.84; $P = .178$). Multivariable analysis confirmed the independent predictive value of COX-2 expression and response to celecoxib (HR, 0.17; 95% CI, 0.06 to 0.49; $P = .001$). 5-lipoxygenase expression was neither prognostic nor predictive. On the basis of the results of CALGB 30203, we undertook a prospective randomized trial in patients with COX-2 overexpression to determine the value of COX-2 inhibition in addition to standard chemotherapy in stage IV NSCLC.

PATIENTS AND METHODS

Eligibility

Patients were eligible if they were ≥ 18 years of age; had an Eastern Cooperative Oncology Group performance status of 0 to 2, with pathologically documented, measurable, or evaluable NSCLC, either stage IIIB (with malignant effusion) T4N2 disease not amenable to curative therapy or stage IV disease (according to American Joint Committee on Cancer [sixth edition] criteria); and had normal organ function. No prior

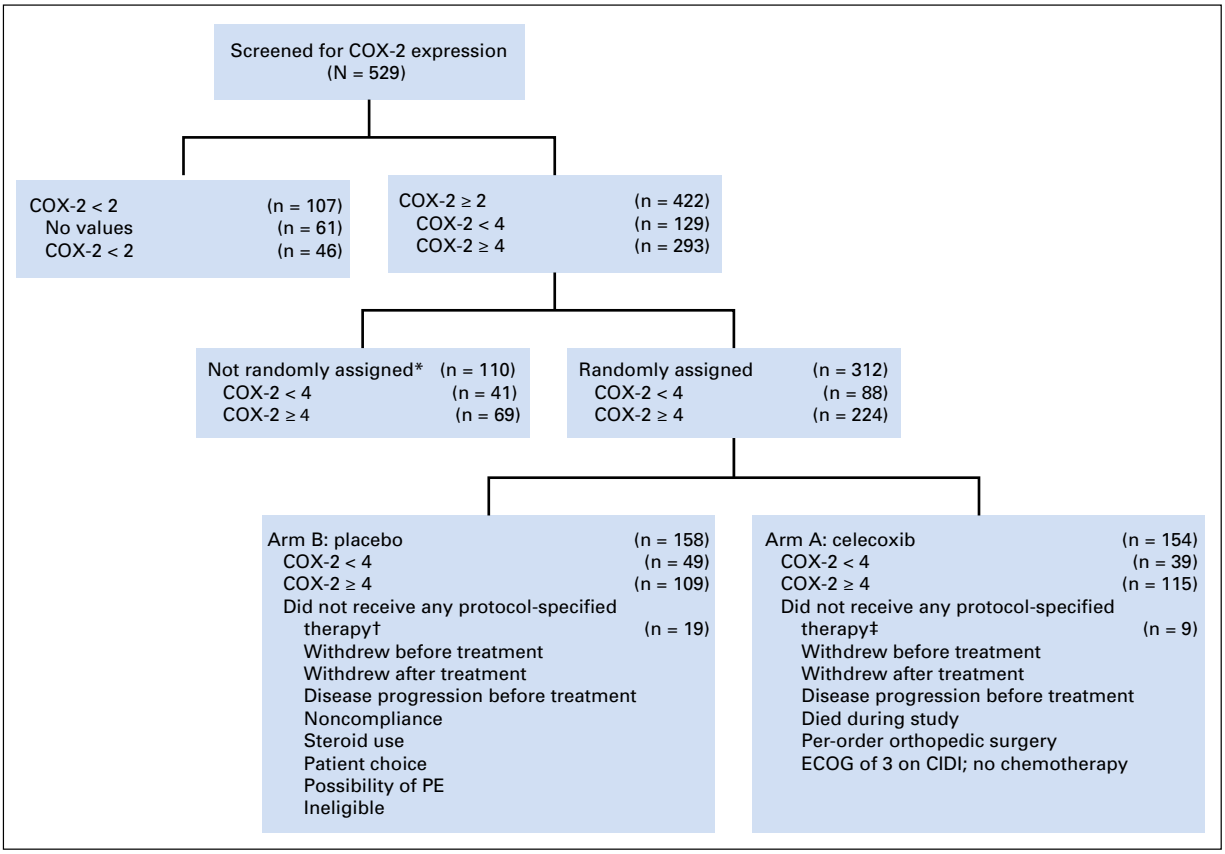

Fig 1. CALGB 30801 CONSORT diagram. COX-2, cyclooxygenase-2; CIDI, Composite International Diagnostic Interview; ECOG, Eastern Cooperative Oncology Group; PE, pulmonary embolism. (*) Not eligible for this trial per protocol. (†) Received carboplatin or pemetrexed (n = 7) or no protocol treatment (n = 12). (‡) Received carboplatin or pemetrexed (n = 3) or no protocol treatment (n = 6).

Table 1. Demographic and Stratification Factors

Factor	No. (%) Celecoxib (n = 154)	Placebo (n = 158)	Total (N = 312)	*P*
Age, years				.7540
Mean	63.6	64.0	63.8	
SD	9.5	10.0	9.7	
Median	64.0	64.0	64.0	
Q1-Q3	57.0-70.0	57.0-71.0	57.0-70.5	
Range	38.0-83.0	36.0-89.0	36.0-89.0	
Race				.9580
White	133 (86.4)	131 (82.9)	264 (84.6)	
Black or African American	14 (9.1)	19 (12.0)	33 (10.6)	
Asian	3 (1.9)	3 (1.9)	6 (1.9)	
Native Hawaiian or Pacific Islander	1 (0.6)	1 (0.6)	2 (0.6)	
American Indian or Alaska Native	2 (1.3)	2 (1.3)	4 (1.3)	
Not reported	1 (0.6)	2 (1.3)	3 (1.0)	
Sex*				.7475
Male	82 (53.2)	87 (55.1)	169 (54.2)	
Female	72 (46.8)	71 (44.9)	143 (45.8)	
Performance status				.7488
0	61 (39.6)	62 (39.2)	123 (39.4)	
1	82 (53.2)	81 (51.3)	163 (52.2)	
2	11 (7.1)	15 (9.5)	26 (8.3)	
Histology*				.7894
Nonsquamous	110 (71.4)	115 (72.8)	225 (72.1)	
Squamous	44 (28.6)	43 (27.2)	87 (27.9)	
Stage*				.0735
IIIB	6 (3.9)	14 (8.9)	20 (6.4)	
IV	148 (96.1)	144 (91.1)	292 (93.6)	
Smoker*				.6962
Yes	133 (86.4)	134 (84.8)	267 (85.6)	
No	21 (13.6)	24 (15.2)	45 (14.4)	
COX-2*				.2643
≥ 2 and < 4	39 (25.3)	49 (31.0)	88 (28.2)	
≥ 4	115 (74.7)	109 (69.0)	224 (71.8)	

Abbreviations: COX-2, cyclooxygenase-2; Q, quartile; SD, standard deviation.
*Stratification factors.

chemotherapy, immunotherapy, or systemic treatment for NSCLC was allowed. Patients using nonsteroidal anti-inflammatory drugs were eligible only if they discontinued all nonsteroidal anti-inflammatory drugs 7 days before and for the duration of the trial. A full description of eligibility criteria is provided in the study protocol.

A tumor specimen (recent biopsy or archival specimen) from a primary or metastatic site was submitted for COX-2 analysis by immunohistochemistry (IHC). Only those patients with COX-2 index ≥ 2 were registered and randomly assigned. The study was approved by the central institutional review board and institutional review boards of each

Table 2. PFS Analysis

PFS	Celecoxib	Placebo	*P** Unstratified	*P** Stratified†
All patients with COX-2 ≥ 2 (n = 312)				
No. of patients	154	158		
Observed events	146	143		
Median PFS, months (95% CI)	5.16 (4.40 to 5.78)	5.26 (4.40 to6.08)	.5346	.3862
HR of celecoxib/placebo (95% CI)‡	1.076 (0.853 to 1.367)			
All patients with COX-2 ≥ 4 (n = 224)				
No. of patients	115	109		
Observed events	108	98		
Median PFS, months (95% CI)	5.16 (4.40 to 5.91)	5.45 (4.27 to 6.80)	.7502	.6415
HR celecoxib/placebo (95% CI)‡	1.046 (0.794 to 1.377)			

Abbreviations: COX-2, cyclooxygenase-2; HR, hazard ratio; PFS, progression-free survival.
*Log-rank test.
†Strata included: sex (male *v* female), histology (squamous *v* nonsquamous), stage (IIIB *v* IV), smoking status (yes *v* no), and COX-2 (< 4 *v* ≥ 4).
‡HRs were from single-variable model.

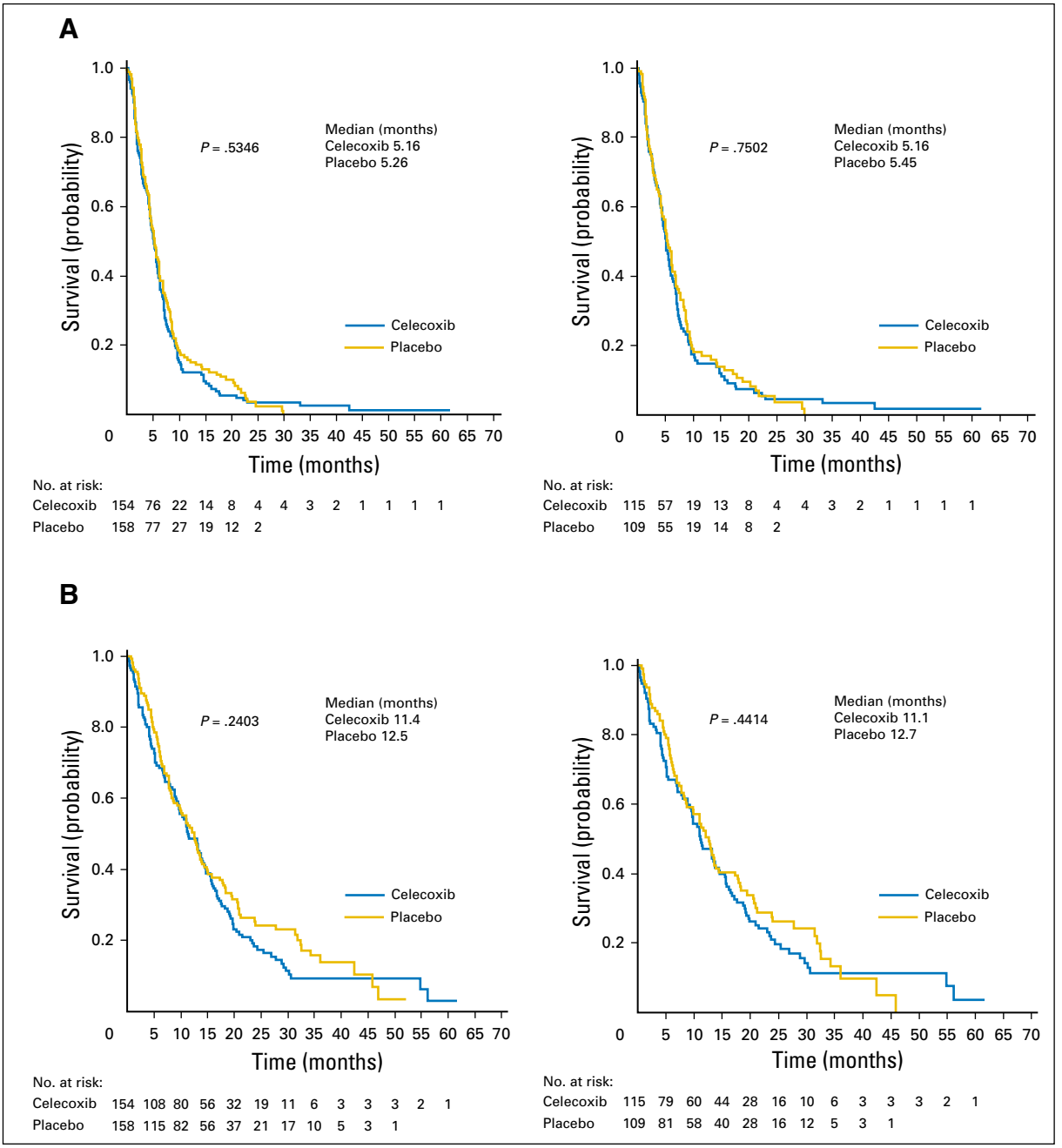

Fig 2. Treatment effect (celecoxib *v* placebo) in cyclooxygenase-2 (COX-2) subgroups. (A) Progression-free and (B) overall survival in all patients (left) and those with COX-2 ≥ 4 (right).

participating institution. Each patient provided written informed consent before any study-specific procedures.

COX-2 IHC

The method for COX-2 determination used in CALGB 30203 was also used in the current trial and was performed at the Clinical Laboratory Improvement Amendments–approved CALGB Molecular Pathology Reference Laboratory.[11] Images of the slides along with the pathology reports were interpreted by study pathologists employing a virtual microscopy system (AperioScanscope XT; Aperio, Vista, CA). The slides were reviewed and scored by at least two and usually three certified anatomic pathologists. The neoplastic cells for any given patient represented by one stained slide were scored for intensity (range of scores, 0 to 3) and percentage of cells staining (0 [0%], 1 [1% to 9%], 2 [10% to 49%], or 3 [50% to 100%]). An IHC index (range of scores, 0 to 9) is defined as the product of the intensity and percentage of cells staining. Controls for the assay included both negative and positive controls as well as an isotype negative control. Specimens were processed and results were reported within 3 business days.

Treatment

Chemotherapy was determined by histology: carboplatin (area under the curve, 6) and pemetrexed (500 mg/m^2) on day 1, every 21 days, for nonsquamous NSCLC; carboplatin (area under the curve, 5.5) on day 1 and gemcitabine (1,000 mg/m^2) on days 1 and 8 for squamous histology. Patients were randomly assigned to celecoxib (400 mg twice per day;

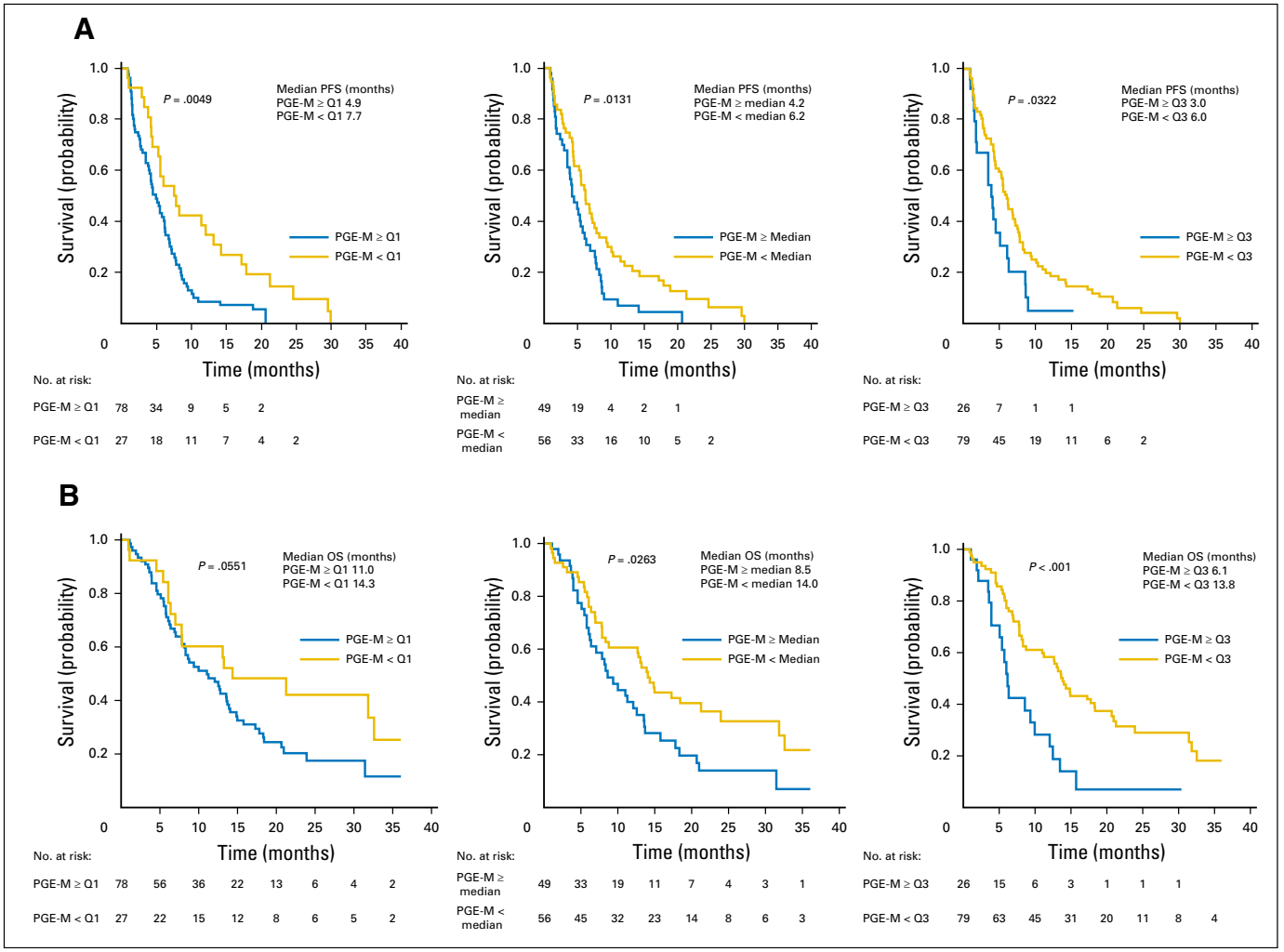

Fig 3. Prognostic effect of baseline urinary metabolite of prostaglandin E2 (PGE-M) in (A, B) placebo (n = 105) and (C, D) celecoxib (n = 106) arms on (A, C) progression-free (PFS) and (B, D) overall survival (OS) with quartile 1 (Q1; left), median (middle), and Q3 cutoffs (right). PGE-M normal (± standard deviation): male, 10.4 ± 1.5; female, 6.0 ± 0.7 ng/mg chromium-11. Q1: PGE-M ≤ 10: placebo, n = 27; celecoxib, n = 26. Q2: PGE-M > 10 and ≤ 15.4: placebo, n = 31; celecoxib, n = 24. Q3: PGE-M > 15.4 and ≤ 26.1: placebo, n = 21; celecoxib, n = 29. Q4: PGE-M > 26.1 and ≤ 27: placebo, n = 26; celecoxib, n = 27.

arm A) or placebo (arm B). Dose modifications are described in the appended protocol.

Urinary PGE-M

PGE2 has been identified as the prostaglandin most involved in the neoplastic process and can be measured by a urinary metabolite, PGE-M.[11] Urine specimens were collected at baseline and 8 days after the start of celecoxib or placebo before treatment on day 8. The PGE-M assay was performed in the Eicosanoid Core Laboratory at Vanderbilt University Medical Center (Nashville, TN) and has been previously described.[12]

Statistical Considerations

The primary objective of this placebo-controlled, double-blind phase III trial was to evaluate the benefit of COX-2 inhibition combined with chemotherapy (arm A) versus chemotherapy only (arm B) in patients with advanced NSCLC with a COX-2 index ≥ 4. The secondary objectives were to determine response rate and toxicity, to evaluate the survival benefit of arm A compared to arm B in patients with COX-2 index ≥ 2, and to verify the adverse prognostic value of COX-2 expression and/or urinary PGE-M levels. Random assignment was performed through a stratified random permuted-blocks procedure, with balanced assignments to each treatment arm. Random assignment was stratified by sex (female *v* male), stage (IIIB *v* IV), histology (squamous *v* nonsquamous), smoking status (never/light smoker [ie ≤ 10 pack years and quit > 1 year ago] *v* smoker), and COX-2 expression status (COX-2 index ≥ 4 *v* ≥ 2 but < 4).[12]

The study was powered to detect benefit for patients with overexpression (COX-2 ≥ 4) in arm A against those in arm B in terms of progression-free survival (PFS). Based on CALGB 30203, COX-2 overexpression selected for patients with an unfavorable prognosis when not treated with celecoxib. We conservatively estimated, based on CALGB 30203, that patients with COX-2 expression index of ≥ 4 would have a median PFS of 4.0 months and OS of 6.0 months. Our hypothesis was that this median PFS would increase to 6.2 months and that the median OS would increase to 9.2 months with the addition of celecoxib. We anticipated a total of 792 patients would be preregistered for the study, of whom 594 would be COX-2 evaluable and 208 would have COX-2 ≥ 4, and would be randomly assigned with equal allocation to arms A and B. At the time of final analysis, a total of 192 events were expected in the celecoxib arm (93 events) and in the placebo arm (99 events) under the alternative hypotheses. Under fixed sample-size design, the power to detect the expected PFS benefit for arm A over arm B would be at least 85% using a log-rank test at a two-sided significance level of .05, and approximately 81% power would be required to detect a median OS of 9.2 months for arm A and 6 months for arm B (HR, 0.652).

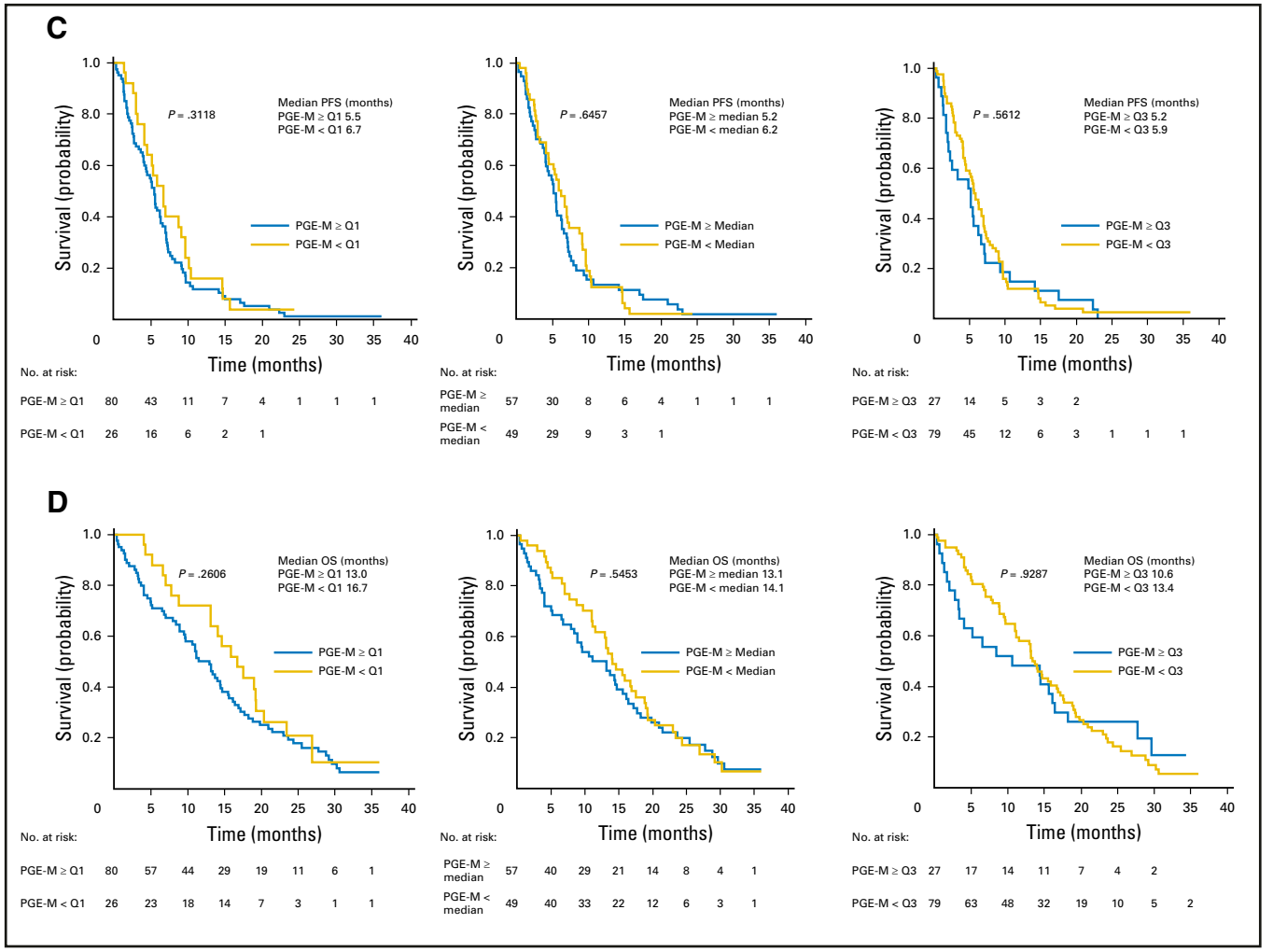

Fig 3. (Continued).

PFS was defined as the time from the date of random assignment to the date of disease progression or death resulting from any cause, whichever came first. Progression was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. OS was defined as the time from the date of random assignment to death resulting from any cause. Reassessment imaging was performed every 6 weeks during treatment. For efficacy analyses, all randomly assigned patients were included in an intention-to-treat analysis. Kaplan-Meier curves were used to characterize PFS and OS.[13] Median survival times and their 95% CIs were computed. Log-rank testing was used to evaluate survival differences between treatments of patients with COX-2 ≥ 4 and COX-2 ≥ 2.[14] The Cox proportional hazards model was used to estimate the HRs and their 95% CIs of celecoxib relative to placebo. Multivariable Cox regression models were used to examine the effect of celecoxib relative to placebo and the effect of biomarker (COX-2 or PGE-M level) and their interaction while adjusting for significant prognostic factors at baseline.[15] Potential prognostic factors included sex, histology and chemotherapy, smoking status, stage, age group, and performance status. The correlation and agreement between PGE-M and COX-2 was evaluated with multiple methods, including Pearson's, intraclass, and concordance correlation coefficients. All reported *P* values are two sided. All statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC) and R (version 3.2.2; R Foundation, Vienna, Austria) software.

This phase III therapeutic trial was monitored twice annually by the Alliance Data and Safety Monitoring Committee, a standing committee composed of individuals from within and outside of the Alliance. Details about the early stopping boundaries for futility and superiority are provided in the study protocol. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

RESULTS

After reviewing the data from CALGB 30801 on November 8, 2013, the Alliance Data and Safety Monitoring Committee voted to terminate accrual because the prespecified futility boundary had been passed. From February 15, 2010, to November 15, 2013, 529 patients were registered, of whom 312 with COX-2 index ≥ 2 (224 patients had COX-2 index ≥ 4) were randomly assigned (Fig 1). The data for the final analysis were locked on January 8, 2016. All randomly assigned patients were included in the intention-to-treat analysis, and the median follow-up time was 31 months. The demographics of the randomly assigned patients were well balanced (Table 1). No significant differences were noted for PFS or OS, whether in the overall population or for patients who had tumors with COX-2 expression ≥ 4 (Table 2; Figs 2A and 2B). Nor were

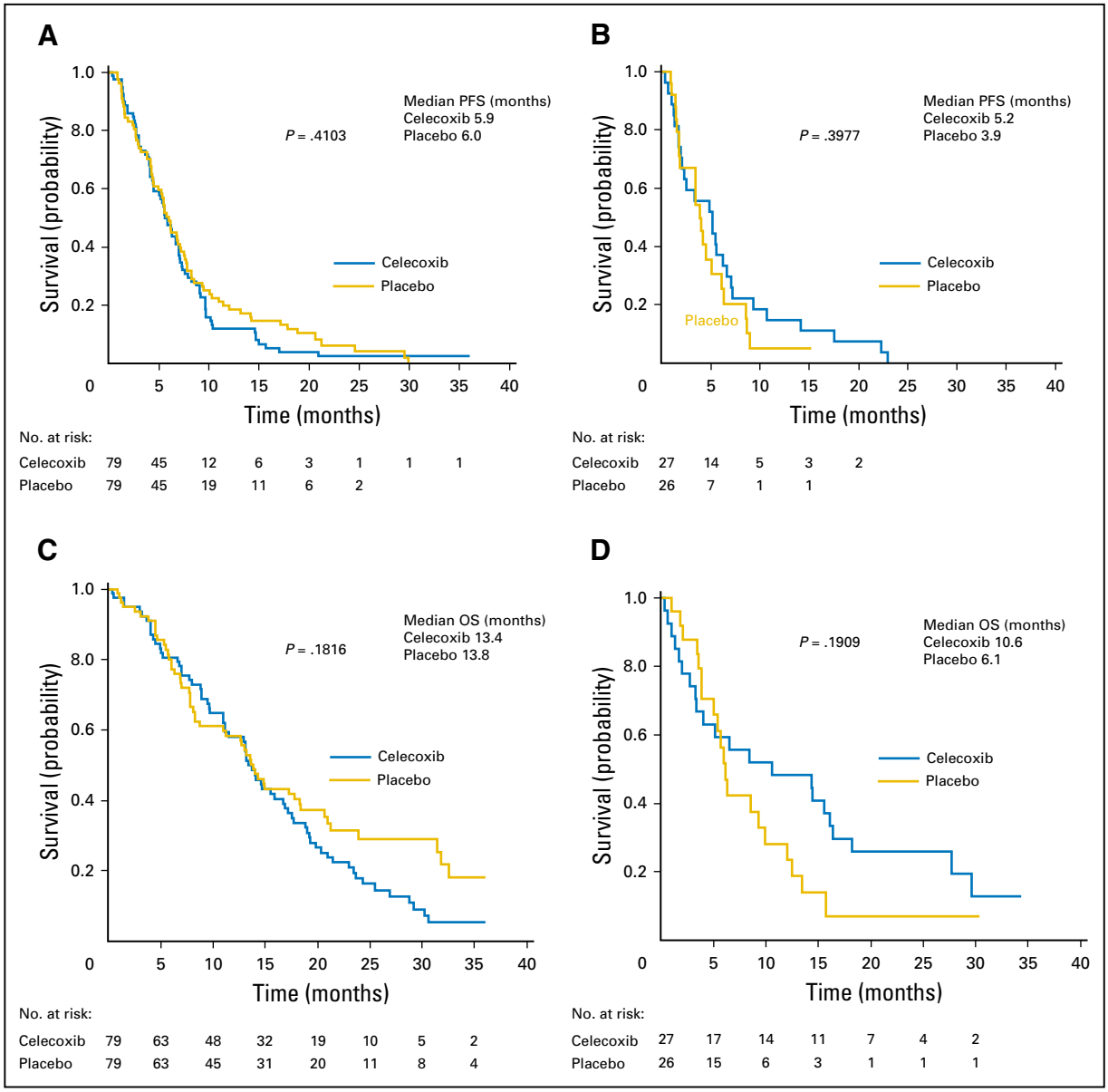

Fig 4. High metabolite of prostaglandin E2 (PGE-M) value (≥ quartile 3 [Q3]) as possible predictive marker for celecoxib over placebo. Arm effect on (A, B) progression-free (PFS) and (C, D) overall survival (OS) in pretreatment PGE-M (A, C) < Q3 and (B, D) ≥ Q3.

differences observed in PFS or OS by histology (Appendix Table A1, online only). We did not confirm that increasing baseline COX-2 expression, either dichotomized (COX-2 ≥ 4 *v* 2 < COX-2 < 4) or as a continuous variable, was an adverse prognostic factor in the control arm (PFS: $P = .523$ and .798, respectively; OS: $P = .797$ and .956, respectively). There were substantial differences in the distribution of COX-2 expression between C30801 and C30203 (Appendix Table A2, online only). The addition of celecoxib did not result in an increase in toxicity (Appendix Table A3, online only). Celecoxib dose delivery is summarized in Appendix Table A4 (online only). A sensitivity analysis did not demonstrate an advantage for celecoxib in patients who received at least four cycles of treatment (Appendix Table A5, online only).

Urinary PGE-M was evaluated at baseline and on day 8 of the first cycle (arm A, n = 106; arm B, n = 105). Correlation and agreement were poor between urinary PGE-M and COX-2 staining by IHC. Pearson's correlation coefficient was 0.089 ($P = .2$) for baseline PGE-M and 0.04 ($P = .62$) for day-8 PGE-M. The absolute agreement measured by intraclass correlation and the additive agreement measured by concordance correlation coefficient were also low for COX-2 and baseline PGE-M (0.0916 and 0.0892, respectively).[16]

Patients were evenly divided into four groups (quartiles) based on the quantity of urinary PGE-M at baseline (Q1, 10.09; Q2, 15.38; and Q3, 27.86). These groups were found to be prognostic for PFS and OS in the placebo arm (Figs 3A and 3B). Day-8 levels were not prognostic. The negative prognostic effect of elevated urinary PGE-M was not seen in patients who received celecoxib, implying that celecoxib can prevent the adverse effects of an activated COX-2 pathway (Fig 3C). For example, patients receiving placebo who had baseline urinary PGE-M that was above the third quartile had substantially

inferior OS compared with those in the lower quartiles ($P < .001$; Fig 3B), whereas there was no difference in survival for patients who received celecoxib ($P = .93$; Fig 3D). We explored whether baseline urinary PGE-M level could serve as a predictive marker for benefit from celecoxib (Fig 4). In terms of both PFS and OS, patients treated with celecoxib who presented with high levels (ie, third quartile) of baseline urinary PGE-M had numerically superior outcomes, but these results did not achieve statistical significance ($P = .4$ and .19, respectively; Figs 4B and 4D). The interaction between treatment effect (celecoxib *v* placebo) and baseline urinary PGE-M level (≥ Q3 *v* < Q3) from multivariable Cox regression analysis was significant for OS ($P = .02$) but not for PFS ($P = .22$). The significant interaction held for OS ($P = .044$) after adjusting for histology/chemotherapy ($P < .001$), which was the only additional variable selected in the final model from all prognostic factors listed in Table 1.

DISCUSSION

CALGB 30801 (Alliance) was the first biomarker-driven trial in NSCLC to our knowledge conducted in the United States. The National Cancer Institute Cooperative Group Program demonstrated the feasibility of performing this type of study. Unfortunately, the results failed to confirm that COX-2 inhibition in addition to standard chemotherapy treatment for patients who were selected by COX-2 expression could improve outcomes. It is possible that COX-2 is not an important target in advanced NSCLC. For the reasons stated previously, this seems unlikely, because there is a wealth of evidence that the COX-2 pathway is involved in the promotion, perpetuation, and spread of multiple malignancies. Furthermore, there is emerging evidence that COX-2–dependent mechanisms are involved in immune evasion, an area of importance given the validation of immune checkpoint inhibitors for advanced NSCLC.[17]

It is more likely that IHC for patient selection was not appropriate. Tissue specimens are often obtained at an earlier time in a patient's illness and may not reflect tumor heterogeneity. Additionally, antibodies may shift in specificity and may detect multiple isoforms and epitopes.[18]

An alternative approach to evaluating the role of COX-2 is to measure urinary PGE-M, which allows a real-time assessment of this pathway. We found that baseline urinary PGE-M was a negative prognostic and possibly a predictive marker in advanced NSCLC. In contrast, Csiki et al[8] found that suppression of urinary PGE-M was predictive but that baseline values were not.

Another problem with COX-2 inhibition is that the metabolites signal through at least four receptors, prostaglandin E2 receptor 1 (EP1) to EP4, with distinct and sometimes antagonistic effects.[19] Overexpression of EP4 is associated with inferior outcomes in lung cancer.[20] Agents targeting EP4 are in clinical development.

C30801 failed to demonstrate the value of COX-2 inhibition in patients with advanced NSCLC selected for elevated COX-2 by IHC. However, the finding that the adverse effects of an activated COX-2 pathway (indicated by an elevated urinary PGE-M level) are abrogated by celecoxib indicates that there is a population of patients who may benefit from this approach.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Appendix

Table A1. Survival by Histology and Chemotherapy Regimen

Survival	Celecoxib	Placebo	*P** Unstratified	*P** Stratified†
PFS				
All patients with COX-2 ≥ 4 (n = 224)				
No. of patients	115	109		
Observed events	108	98		
Median PFS, months (95% CI)	5.16 (4.40 to 5.91)	5.45 (4.27 to 6.80)	.7502	.6415
HR celecoxib/placebo (95% CI)‡	1.046 (0.794 to 1.377)			
Patients with nonsquamous histology and COX-2 ≥ 4 (n = 173)				
No. of patients	89	84		
Observed events	83	77		
Median PFS, months (95% CI)	5.52 (4.44 to 7.00)	6.11 (4.70 to7.72)	.9832	.5994
HR celecoxib/placebo (95% CI)‡	0.997 (0.729 to 1.363)			
Patients with squamous histology and COX-2 ≥ 4 (n = 51)				
No. of patients	26	25		
Observed events	25	21		
Median PFS, months (95% CI)	3.19 (1.91 to 5.68)	3.91 (1.61 to 5.26)	.4887	.9890
HR celecoxib/placebo (95% CI)‡	1.230 (0.684 to 2.213)			
OS				
All patients with COX-2 ≥ 4 (n = 224)				
No. of patients	115	109		
Observed events	96	82		
Median PFS, months (95% CI)	11.10 (9.17 to 14.36)	12.68 (8.74 to 14.32)	.4414	.4272
HR celecoxib/placebo (95% CI)‡	1.123 (0.835 to 1.511)			
Patients with nonsquamous histology and COX-2 ≥ 4 (n = 173)				
No. of patients	89	84		
Observed events	72	61		
Median PFS, months (95% CI)	14.36 (10.58 to 16.72)	13.63 (11.24 to 20.7)	.4231	.3011
HR celecoxib/placebo (95% CI)‡	1.151 (0.816 to 1.623)			
Patients with squamous histology and COX-2 ≥ 4 (n = 51)				
No. of patients	26	25		
Observed events	24	21		
Median PFS, months (95% CI)	7.00 (4.04 to 9.72)	5.39 (3.91 to 6.97)	.7583	.8029
HR celecoxib/placebo (95% CI)‡	0.911 (0.501 to 1.655)			

Abbreviations: COX-2, cyclooxygenase-2; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Log-rank test.
†Strata included: sex (male *v* female), histology (squamous *v* nonsquamous), stage (IIIB *v* IV), smoking status (yes *v* no), and COX-2 (< 4 *v* ≥ 4).
‡HRs were from single-variable model.

Table A2. Comparison of Distribution of COX-2 Expression Between C30203 and C30801

	No. (%)	
COX-2	C30203	C30801
0 ≤x and ≤ 2	33 (39.76)	46 (9.83)
2 < and < 4	18 (21.69)	129 (27.56)
≥ 4	32 (38.55)	293 (62.61)
Total	83	468

Abbreviation: COX-2, cyclooxygenase-2.

Table A3. Grade ≥ 3 AEs: Maximum Grade per Patient per Event at Least Possibly Related to Treatment

	Grade					
	3 (severe)		4 (life threatening)		5 (lethal)	
AEs Observed in Patients in Arms A (n = 145) and B (n = 148)	No.	%	No.	%	No.	%
Hematologic						
Blood/bone marrow						
Anemia						
A	41	28	3	2	0	0
B	33	23	1	1	0	0
Blood and lymphatic system disorder–otherwise specified						
A	1	1	0	0	0	0
B	1	1	0	0	0	0
CD4 lymphocytes decreased						
A	2	1	0	0	0	0
B	0	0	0	0	0	0
Febrile neutropenia						
A	4	3	2	1	0	0
B	2	1	1	1	0	0
Hemoglobin increased						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Leukocytosis						
A	1	1	0	0	0	0
B	1	1	0	0	0	0
Lymphocyte count decreased						
A	8	6	2	1	0	0
B	11	8	1	1	0	0
Lymphocyte count increased						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Neutrophil count decreased						
A	24	17	15	10	0	0
B	22	15	13	9	0	0
Platelet count decreased						
A	20	14	22	15	0	0
B	16	11	20	14	0	0
WBC decreased						
A	10	7	3	2	0	0
B	13	9	3	2	0	0
Nonhematologic						
Cardiac disorders						
Cardiac arrest						
A	0	0	0	0	0	0
B	0	0	1	1	0	0
Myocardial infarction						
A	0	0	0	0	0	0
B	0	0	0	0	1	1

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Table A3. Grade ≥ 3 AEs: Maximum Grade per Patient per Event at Least Possibly Related to Treatment (continued)

	Grade					
	3 (severe)		4 (life threatening)		5 (lethal)	
AEs Observed in Patients in Arms A (n = 145) and B (n = 148)	No.	%	No.	%	No.	%
Ear and labyrinth disorders						
Hearing impaired						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
GI disorders						
Abdominal pain						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Colitis						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Constipation						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Diarrhea						
A	3	2	0	0	0	0
B	0	0	0	0	0	0
Duodenal hemorrhage						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Duodenal perforation						
A	0	0	1	1	0	0
B	0	0	0	0	0	0
GI pain						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Ileus						
A	0	0	1	1	0	0
B	0	0	0	0	0	0
Jejunal hemorrhage						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Lower GI hemorrhage						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Mucositis oral						
A	3	2	0	0	0	0
B	1	1	0	0	0	0
Nausea						
A	0	0	0	0	0	0
B	3	2	0	0	0	0
Oral pain						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Rectal hemorrhage						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Upper GI hemorrhage						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Vomiting						
A	2	1	0	0	0	0
B	0	0	0	0	0	0
General disorders and administration site conditions						
Death NOS						
A	0	0	0	0	1	1
B	0	0	0	0	2	1
Fatigue						
A	11	8	1	1	0	0
B	10	7	0	0	0	0

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Table A3. Grade ≥ 3 AEs: Maximum Grade per Patient per Event at Least Possibly Related to Treatment (continued)

AEs Observed in Patients in Arms A (n = 145) and B (n = 148)	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %
Hepatobiliary disorders						
Cholecystitis						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Immune system disorders						
Allergic reaction						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Infections and infestations						
Esophageal infection						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Infections and infestations–otherwise specified						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Lung infection						
A	7	5	0	0	0	0
B	1	1	0	0	1	1
Mucosal infection						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Sepsis						
A	0	0	1	1	3	2
B	0	0	1	1	0	0
Skin infection						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Urinary tract infection						
A	1	1	0	0	0	0
B	1	1	0	0	0	0
Investigations						
ALT increased						
A	3	2	0	0	0	0
B	0	0	0	0	0	0
Alkaline phosphatase increased						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
AST increased						
A	3	2	0	0	0	0
B	0	0	0	0	0	0
Blood bilirubin increased						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
INR increased						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Investigations–otherwise specified						
A	0	0	1	1	0	0
B	1	1	0	0	0	0
Weight loss						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Metabolic and nutrition disorders						
Anorexia						
A	3	2	0	0	0	0
B	2	1	0	0	0	0
Dehydration						
A	5	3	0	0	0	0
B	4	3	0	0	1	1
Hypercalcemia						
A	0	0	0	0	0	0
B	1	1	0	0	0	0

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Table A3. Grade ≥ 3 AEs: Maximum Grade per Patient per Event at Least Possibly Related to Treatment (continued)

AEs Observed in Patients in Arms A (n = 145) and B (n = 148)	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %
Hyperglycemia						
A	0	0	0	0	0	0
B	4	3	0	0	0	0
Hyperkalemia						
A	1	1	0	0	0	0
B	1	1	0	0	0	0
Hypoalbuminemia						
A	2	1	0	0	0	0
B	1	1	0	0	0	0
Hypocalcemia						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Hypokalemia						
A	1	1	0	0	0	0
B	3	2	1	1	0	0
Hyponatremia						
A	7	5	0	0	0	0
B	4	3	0	0	0	0
Hypophosphatemia						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal and connective tissue–otherwise specified						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Myalgia						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Myositis						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Nervous system disorders						
Ischemia cerebrovascular						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Peripheral motor neuropathy						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Stroke						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Renal and urinary disorders						
Acute kidney injury						
A	2	1	0	0	0	0
B	0	0	0	0	0	0
Chronic kidney disease						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders						
Aspiration						
A	2	1	0	0	0	0
B	0	0	0	0	0	0
Dyspnea						
A	1	1	0	0	0	0
B	1	1	0	0	1	1
Epistaxis						
A	0	0	0	0	0	0
B	1	1	0	0	0	0
Hypoxia						
A	0	0	0	0	0	0
B	1	1	0	0	0	0

(continued on following page)

Table A3. Grade ≥ 3 AEs: Maximum Grade per Patient per Event at Least Possibly Related to Treatment (continued)

AEs Observed in Patients in Arms A (n = 145) and B (n = 148)	Grade 3 (severe) No.	Grade 3 (severe) %	Grade 4 (life threatening) No.	Grade 4 (life threatening) %	Grade 5 (lethal) No.	Grade 5 (lethal) %
Pleural effusion						
A	0	0	0	0	1	1
B	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal–otherwise specified						
A	1	1	0	0	0	0
B	0	0	0	0	0	0
Respiratory failure						
A	0	0	1	1	1	1
B	0	0	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash maculopapular						
A	7	5	0	0	0	0
B	0	0	0	0	0	0
Vascular disorders						
Hypotension						
A	0	0	0	0	0	0
B	2	1	0	0	0	0
Thromboembolic event						
A	1	1	1	1	0	0
B	2	1	0	0	0	0
Visceral arterial ischemia						
A	0	0	0	0	1	1
B	0	0	0	0	0	0

Abbreviations: AE, adverse event; NOS, not otherwise specified.

Table A4. No. of Treatment Cycles of Study Drug Patients Received

Cycles Received*	No. (%) Celecoxib (n = 154)	No. (%) Placebo (n = 158)	No. (%) Total (n = 312)
0	9 (5.8)	19 (12.0)	28 (9.0)
1	25 (16.2)	10 (6.3)	35 (11.2)
2	29 (18.8)	32 (20.3)	61 (19.6)
3	8 (5.2)	4 (2.5)	12 (3.8)
4	13 (8.4)	19 (12.0)	32 (10.3)
5	4 (2.6)	6 (3.8)	10 (3.2)
6	19 (12.3)	22 (13.9)	41 (13.1)
7	5 (3.2)	8 (5.1)	13 (4.2)
8	8 (5.2)	9 (5.7)	17 (5.4)
9	3 (1.9)	4 (2.5)	7 (2.2)
10	12 (7.8)	8 (5.1)	20 (6.4)
99	19 (12.3)	17 (10.8)	36 (11.5)

*There were 136 patients who received fewer than four cycles of protocol drug; 176 patients received four or more cycles of protocol drug.

Table A5. Sensitivity Analyses Evaluating Patients Who Received Four or More Cycles of Treatment

Survival	Celecoxib	Placebo	*P**	
			Unstratified	Stratified†
PFS				
All patients with COX-2 ≥ 2 (n = 176)				
No. of patients	83	93		
Observed events	79	85		
Median PFS, months (95% CI)	6.60 (5.68 to 7.13)	6.87 (5.55 to 8.25)	.3905	.2300
HR celecoxib/placebo (95% CI)‡	1.144 (0.841 to 1.557)			
Patients with COX-2 ≥ 4 (n = 125)				
No. of patients	62	63		
Observed events	58	57		
Median PFS, months (95% CI)	6.65 (5.55 to 7.36)	7.72 (6.08 to 8.97)	.3294	.1384
HR celecoxib/placebo (95% CI)‡	1.200 (0.831 to 1.733)			
OS				
All patients with COX-2 ≥ 2 (n = 176)				
No. of patients	83	93		
Observed events	70	62		
Median PFS, months (95% CI)	11.37 (9.46 to 14.06)	18.2 (13.5 to 21.0)	.0816	.2333
HR celecoxib/placebo (95% CI)‡	1.358(0.961 to 1.919)			
Patients with COX-2 ≥ 4 (n = 125)				
No. of patients	62	63		
Observed events	51	43		
Median PFS, months (95% CI)	15.73 (11.5 to 18.96)	19.45 (13.14 to 27.76)	.2093	.1588
HR celecoxib/placebo (95% CI)‡	1.30(0.863 to 1.958)			

Abbreviations: COX-2, cyclooxygenase-2; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Log-rank test.
†Stratification factors included: histology (squamous *v* nonsquamous), stage (IIIB *v* IV), smoking status (yes *v* no), and COX-2 (< 4 *v* ≥ 4).
‡HRs were from single-variable model.