VOLUME 28 · NUMBER 30 · OCTOBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Randomized Trial Assessing Rofecoxib in the Adjuvant Setting of Colorectal Cancer: Final Results of the VICTOR Trial

Rachel S. Midgley, Christopher C. McConkey, Elaine C. Johnstone, Janet A. Dunn, Justine L. Smith, Simon A. Grumett, Patrick Julier, Claire Iveson, Yoko Yanagisawa, Bryan Warren, Michael J. Langman, and David J. Kerr

See accompanying editorial on page 4546

From the University of Oxford; Oxford Radcliffe Hospitals Trust, Oxford; University of Warwick, Coventry; and Cancer Research UK Institute for Cancer Studies, University of Birmingham, Birmingham, United Kingdom.

Submitted April 1, 2010; accepted July 12, 2010; published online ahead of print at www.jco.org on September 13, 2010.

Written on behalf of the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) Trial Group.

Supported by the University of Oxford and enabled by an educational study grant from Merck (Whitehouse Station, NJ). R.S.M. was supported by the United Kingdom Department of Health/Higher Education Funding Council for England in the form of a personal fellowship and by the Oxford Biomedical Research Centre.

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

Clinical Trials repository link available on JCO.org.

Corresponding author: Rachel S. Midgley, MD, PhD, Department of Clinical Pharmacology, University of Oxford, Old Road Campus Research Bldg, Churchill Hospital Site, Headington, Oxford, OX3 7DQ, United Kingdom; e-mail: rachel.midgley@clinpharm.ox.ac.uk.

0732-183X/10/2830-4575/$20.00

DOI: 10.1200/JCO.2010.29.6244

ABSTRACT

Purpose
Laboratory and case-control studies suggest a pivotal role for the cyclooxygenase-2 (COX-2) pathway in colorectal carcinogenesis. The purpose of this study was to test whether the COX-2 inhibitor rofecoxib could reduce recurrence and improve survival when administered in the adjuvant setting of colorectal cancer (CRC).

Patients and Methods
Patients who had undergone potentially curative surgery and completion of adjuvant therapy for stage II and III CRC were randomly assigned to receive rofecoxib (20 mg daily) or placebo. The primary end point was overall survival (OS). Where formalin-fixed paraffin-embedded tumor tissue samples were available, COX-2 expression was evaluated by immunohistochemistry and correlated with clinical outcome.

Results
Two thousand four hundred thirty-four patients were entered onto the study. The trial was terminated early because of the worldwide withdrawal of rofecoxib. At this point, 1,167 patients had received rofecoxib and 1,160 patients had received placebo for median treatment durations of 7.4 and 8.2 months, respectively. For the rofecoxib and placebo arms, median follow-up times were 4.84 and 4.85 years, with 241 and 246 deaths and 297 and 329 recurrences, respectively. No difference was demonstrated in OS (hazard ratio [HR] = 0.97; 95% CI, 0.81 to 1.16; $P = .75$) or recurrence (HR = 0.89; 95% CI, 0.76 to 1.04; $P = .15$) comparing the two groups. Tumor COX-2 expression by immunohistochemistry was assessed for 871 patients, but neither prognostic nor predictive effects were observed.

Conclusion
In this study of abbreviated therapy in the adjuvant setting of CRC, rofecoxib did not improve OS or protect from recurrence in unselected patients. In addition, COX-2 expression did not correlate with prognosis overall or predict effectiveness of COX-2 inhibitors.

J Clin Oncol 28:4575-4580. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Approximately half of all patients undergoing potentially curative surgery for colorectal cancer (CRC) ultimately experience relapse and die of metastatic disease. This has led to the introduction of adjuvant chemotherapy,[1] the absolute overall survival (OS) benefits of which are stage dependent and relatively small (4% to 10% improvement in 5-year OS).[2-4]

Cyclooxygenase-2 (COX-2) plays an important role in colorectal carcinogenesis during the transition from adenoma to carcinoma and in invasion, angiogenesis, and metastasis.[5-7] Immunohistochemical analysis of CRC tissue suggests that 70% of tumors express COX-2; this increases with stage progression and correlates with coexpression of the progression factors matrix metalloproteinase-2 and vascular endothelial growth factor.[8,9] Haile et al[10] demonstrated that nonsteroidal anti-inflammatory drug–induced reduction in polyp recurrence was greater in adenomas with high levels of COX-2 expression. Similarly, Chan et al[11] found that aspirin use significantly reduced CRC risk in tumors overexpressing COX-2 (relative risk = 0.64; 95% CI, 0.52 to 0.78) but not in cancers with weak or absent

COX-2 expression (relative risk = 0.96; 95% CI, 0.73 to 1.26). We hypothesized that rofecoxib[12-18] would provide a safe approach to blocking COX-2 and reduce the rate of tumor recurrence in patients who had undergone potentially curative surgery for CRC and that the level of tissue expression of the COX-2 enzyme in the tumor might modulate this effect. We have previously reported cardiovascular safety data from the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) trial[19] and now present efficacy analyses with comparisons of OS and disease-free survival (DFS) for rofecoxib versus placebo.

PATIENTS AND METHODS

Patients

Inclusion criteria included the following: histologically proven stage II and III CRC in patients who had complete resection of the primary tumor; WHO performance status of 0 or 1; and hematologic, liver, and renal function within the normal range. All patients had completed therapy (surgery ± radiotherapy ± chemotherapy) 12 or fewer weeks previously and had given written informed consent. Patients with peptic ulceration or GI bleeding in the past year; receiving long-term nonsteroidal anti-inflammatory drug therapy (except low-dose aspirin, ≤ 100 mg/d); younger than age 18 years; or with a history of cancer (other than treated in situ cervical carcinoma, basal cell carcinoma, or squamous cell carcinoma), inflammatory bowel disease, or severe congestive heart failure; women who were pregnant or lactating; and premenopausal women not using contraception were excluded. Patients who had stable angina, a myocardial infarction, or transient ischemic attack more than 6 months earlier were eligible.

Trial Design

Patients were randomly assigned in a double-blind fashion to rofecoxib or placebo by the VICTOR Trial Office, which supplied drugs to 151 hospitals in the United Kingdom every 6 months. Balance of prognostic variables was ensured by a sequential allocation procedure (minimization) using stage (II or III), disease site (colon, rectum, or rectosigmoid), age (< 50, 50 to 59, 60 to 69, or 70+ years), prior adjuvant chemotherapy, and radiotherapy.[20]

Protocol Modifications

Data collection forms were amended in January 2004 to solicit baseline data on cardiovascular risk factors for all patients. After withdrawal of rofecoxib in September 2004, all investigators and patients were informed, study treatment was stopped, and follow-up was continued at 3, 6, 12, 18, and 24 months after random assignment and annually thereafter. Patients received a colonoscopy between 1 and 2 years after primary surgery and every 3 years thereafter, a computed tomography scan 1 year after surgery, and clinical examination and routine blood tests at outpatient visits. All recurrences were confirmed by computed tomography or magnetic resonance imaging scan, and patients were flagged for survival with the United Kingdom's Office of National Statistics. Adverse event data were recorded systematically throughout the study and were reviewed by the trials team (R.S.M., D.J.K., and M.J.L.) to clarify diagnoses.

Assessment of COX-2 Expression

An a priori hypothesis was generated that COX-2 expression would correlate with response to rofecoxib. Immunohistochemical staining of tumors was performed for 871 patients on tissue microarrays that contained triplicate cores for each tumor specimen, using a rabbit polyclonal COX-2 antibody (1:1,000 dilution; Abcam, Cambridge, United Kingdom). COX-2 expression was evaluated independently by two researchers and was graded using a standardized grading system as absent (score = 0), weak staining (score = 1), moderate staining (score = 2), or strong staining (score = 3); the same criteria were used in the study by Chan et al.[11] The staining category of absent was used if COX-2 expression in the tumor was the same level of intensity as in the adjacent normal epithelium, with weak, moderate, and strong staining indicating increasing degrees of overexpression. The study pathologists in this case considered those tissues that were strongly stained (score = 3) to be sufficiently distinct from the other categories to warrant separate categorization in the statistical analyses. Patients used in this biomarker study were similar to the main trial population with respect to age, sex, stage, site, and treatment.

Statistical Considerations

The original study aimed to recruit 7,000 patients and was powered to detect a reduction in risk of death between treatments for stage II and III separately (hazard ratio [HR] = 0.80, with type I error of 0.05) at more than 85% power (two-sided test), assuming 60% of patients had stage III disease The modified statistical plan, after premature closure with 2,434 patients, aimed to detect a reduction in risk of death of HR = 0.75 with 87% power and type I error of 0.05. OS, the primary end point, was measured from random assignment to death from any cause. Secondary end points include DFS, which was measured from random assignment to recurrence or death from any cause, and recurrence-free survival (RFS), which was measured from random assignment to recurrence and/or CRC death.

Kaplan-Meier curves and log-rank analysis were used for comparisons of OS, DFS, and RFS. Subgroups were examined using HR plots, and HR CIs were calculated from log-rank statistics and variances.[21] Cox proportional hazards models were used to estimate the treatment effect adjusted by prognostic factors. All reported *P* values are two-sided. All HRs are unadjusted unless otherwise specified. Graphical examination showed no clear departure from proportional hazards. For analysis of OS, patients not reported as dead were censored at their last known date alive. For analysis of DFS, patients who were alive and recurrence free were censored at their last known recurrence-free date. For analysis of RFS in first year after random assignment, patients who were alive and recurrence free at 1 year were censored at that time. Numbers of serious adverse events (SAEs) and sites of first recurrence were compared using a normal approximation to the Poisson distribution. All statistical analyses were carried out using the SAS version 9.2 statistical software (SAS Institute, Cary, NC).

Ethics and Indemnity

The protocol was peer reviewed by the Cancer Research Campaign, the Multicenter Research Ethics Committee, and research ethics committees at participating centers.

Role of the Funding Source

The trial was supported by an unrestricted grant from Merck (Whitehouse Station, NJ), which also provided rofecoxib, placebo, and indemnity but otherwise had no input into data accrual, analysis, or manuscript preparation.

RESULTS

Between April 2002 and September 2004, 2,434 patients were recruited at 151 hospitals in the United Kingdom. The intent-to-treat population used for outcome analysis comprised 1,217 patients randomly assigned to rofecoxib and 1,217 patients assigned to placebo. Fifty patients randomly assigned to rofecoxib and 57 patients randomly assigned to placebo had not yet started treatment when the drug was withdrawn. Therefore, the treated population comprised 1,167 rofecoxib-treated patients and 1,160 placebo-treated patients (Fig 1).

Study treatment assignment was balanced based on sex, disease site, stage, age and prior adjuvant treatment (Table 1). The median time on treatment was 7.4 months (interquartile range, 3.1 to 14.0 months) and 8.2 months (interquartile range, 3.7 to 14.9 months) for

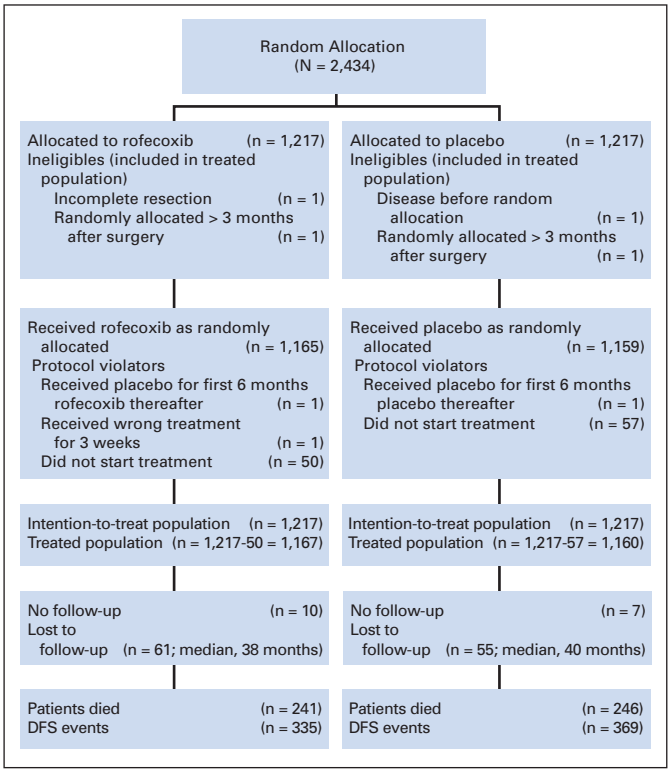

Fig 1. CONSORT diagram. DFS, disease-free survival.

Table 1. Baseline Demographics and Clinical Characteristics of Randomly Assigned Patients

Demographic or Clinical Characteristic	Rofecoxib (n = 1,217) No. of Patients	%	Placebo (n = 1,217) No. of Patients	%
Minimization variables				
Disease site				
Colon	790	64.9	802	65.9
Rectum	329	27.0	332	27.3
Junction	98	8.1	83	6.8
Stage				
II	579	47.6	580	47.7
III	638	52.4	637	52.3
Age, years				
< 50	91	7.5	90	7.4
50-59	294	24.2	296	24.3
60-69	470	38.6	470	38.6
70+	362	29.7	361	29.7
Chemotherapy				
Bolus FU	671	55.1	677	55.6
Infusional or oral FU	110	9.0	107	8.8
New agent with or without FU	8	0.7	7	0.6
No chemotherapy	428	35.2	426	35.0
Other entry characteristics				
Sex				
Male	781	64.2	779	64.0
Female	436	35.8	438	36.0
Race				
White	1,193	98.0	1,193	98.0
Other	14	1.2	16	1.3
Not known	10	0.8	8	0.7
Radiotherapy				
Preoperative	122	10.0	132	10.8
Postoperative	21	1.7	24	2.0
None	1,074	88.2	1,061	87.2
Long-term low-dose aspirin use at random assignment	106	8.7	84	6.9
Smokers	151	12.4	136	11.2

Abbreviation: FU, fluorouracil.

rofecoxib and placebo, respectively, with 33% of patients having completed at least 12 months of treatment. Eighteen patients randomly assigned to 2 years of rofecoxib and 23 patients randomly assigned to 2 years of placebo were reported as having completed their study treatment. Eight hundred six patients were still on rofecoxib and 862 patients were still on placebo when rofecoxib was withdrawn. The difference in the duration of treatment was related to a higher proportion of early discontinuations in the rofecoxib arm for adverse effects. The most common medical reasons for early drug withdrawal were GI pain or heartburn (15 patients on rofecoxib and five patients on placebo), analgesia required for arthritis (four on rofecoxib and 15 on placebo), hypertension (seven on rofecoxib and one on placebo), renal impairment (seven on rofecoxib and one on placebo), diarrhea (four on rofecoxib and four on placebo), and heart failure (two on rofecoxib).

Safety (Treated Population)

SAEs were collected for each patient from enrollment until the SAE data lock of November 2007 (Table 2). Cardiovascular thrombotic events have been reported in detail elsewhere.[19] GI SAEs included indigestion/gastroduodenal ulceration, diarrhea, constipation, and obstruction as a result of probable adhesions, all of which were reported in less than 1% of patients with no significant difference in frequency comparing rofecoxib and placebo.

OS

Median follow-up time was 58.1 months (interquartile range, 48.1 to 62.0 months) for the rofecoxib group and 58.2 months (interquartile range, 47.8 to 61.9 months) for the placebo group. Over the study period, there were 241 deaths in the rofecoxib group and 246 in the placebo group. The HR for dying from any cause with rofecoxib compared with placebo was 0.97 (95% CI, 0.81 to 1.16; $P = .75$). The HR for CRC-specific mortality was 0.98 (95% CI, 0.81 to 1.19; $P = .82$). The 3-year Kaplan-Meier OS rates were 87.7% (95% CI, 85.7% to 89.4%) for the rofecoxib group and 86.9% (95% CI, 84.8% to 88.7%) for the placebo group (Fig 2), with little evidence of variation according to known prognostic factors (stage, age, radiotherapy, and sex; Appendix Fig A1, online only).

DFS and RFS

There were 335 DFS events in the rofecoxib group and 369 in the placebo group. The HR for disease recurrence or death from any cause with rofecoxib compared with placebo was 0.89 (95% CI, 0.77 to 1.04; $P = .14$). In absolute terms, the 3-year DFS rates were 75.6% (95% CI, 73.0% to 78.0%) for the rofecoxib group and 73.4% (95% CI, 70.7% to 75.9%) for the placebo group. The HR for RFS with rofecoxib compared with placebo was 0.89 (95% CI, 0.76 to 1.04; $P = .15$). There were 297 recurrences in the rofecoxib group and 329 in the placebo

Table 2. Safety Data: Comparison of Rofecoxib With Placebo

Adverse Event	Placebo (No. of events/ No. of patients)	Rofecoxib (No. of events/No. of patients)	*P* (difference for rofecoxib *v* placebo)*	Total No. of Events
GI system				
Indigestion/ gastroduodenal ulceration	2	0		2
Diarrhea	1	1		2
Constipation	2	1		3
Bowel obstruction	10	7		17
GI bleed (nonulcer)	1	5		6
Other GI	9	14		23
GI subtotal	25/25	28/28	.68	53
Respiratory system				
SOB (cause unknown)	0	1	.32	1
Neuropsychiatric				
Depression/anxiety	0	1		1
Neuralgia	1	0		1
Polymyositis	0	1		1
Epilepsy/other	2	2		4
Neuropsychiatric subtotal	3/3	4/4	.71	7
Infection				
Range of sites	3/3	10/10	.05	13
Other miscellaneous				
Trauma, incidental operations, other comorbidities	9/9	13/13	.39	22
New other cancer	8/8	5/5	.41	13
Cardiovascular system, event subtotal†	24/20	36/36	.12	60
Total adverse events	72/65	97/92	.05	169

Abbreviation: SOB, shortness of breath.
*P values in table compare number of events between arms.
†More details on the cardiovascular events are provided in Kerr et al.[19]

group, of which 110 and 141, respectively, were in the first year ($P = .044$; Fig 3; Appendix Fig A2, online only). Sites of recurrence were reported for 98% of patients on first recurrence. The total number of sites (each patient may have > one) was 433 in the rofecoxib group and 502 in the placebo group ($P = .02$). The slight excess was not restricted to any particular site.

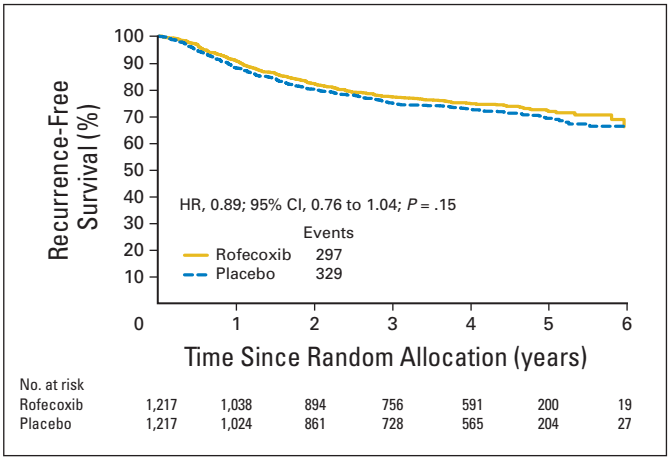

Fig 3. Kaplan-Meier curves of recurrence-free survival comparing rofecoxib versus placebo. HR, hazard ratio.

COX-2 Expression

Little evidence was found to suggest that the degree of COX-2 expression is associated with prognosis (low [score of 0 or 1] *v* moderate [score of 2] *v* high [score of 3]; HR for RFS = 0.93; 95% CI, 0.78 to 1.12; $P = .45$; Fig 4). Although the RFS curves (Fig 5) comparing low-moderate COX-2 expressors (score of 0 to 2) versus high COX-2 expressors (score of 3) and the effect of rofecoxib treatment hint at a disproportionately beneficial effect of rofecoxib versus placebo in patients whose tumors had high expression of COX-2, statistically there is no treatment interaction (HR = 0.75; 95% CI, 0.37 to 1.52; $P = .42$) comparing these groups. However, possibility of statistical significance is hampered by the small number of events in this adjusted analysis (adjusted by stage, age, and radiotherapy group).

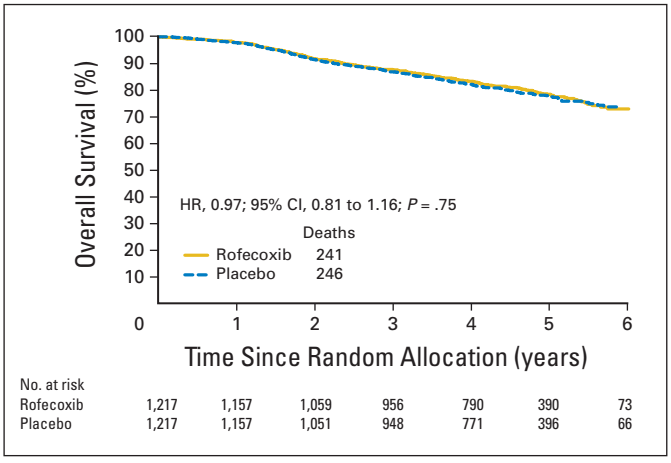

Fig 2. Kaplan-Meier curves of overall survival comparing rofecoxib versus placebo. HR, hazard ratio.

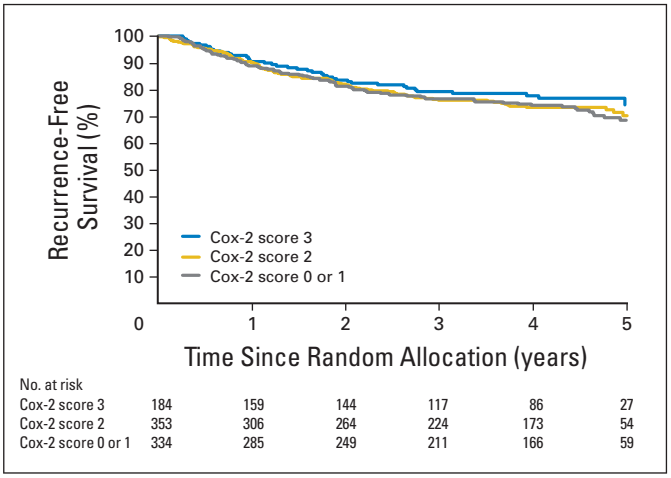

Fig 4. Kaplan-Meier curves of recurrence-free survival comparing the different patient groups according to cyclooxygenase-2 (COX-2) expression by immunohistoochemistry.

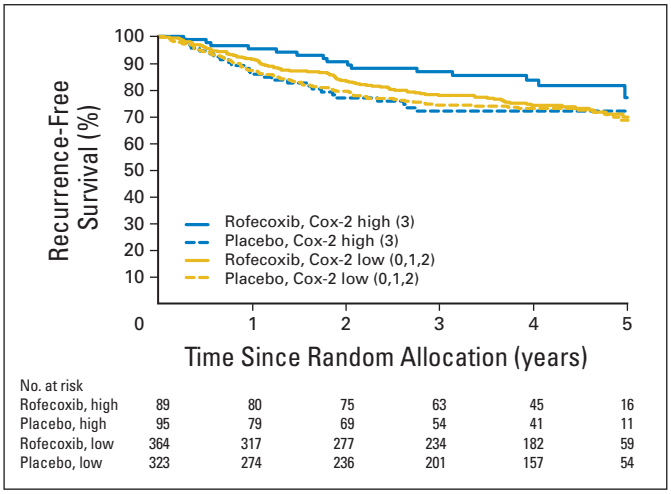

Fig 5. Kaplan-Meier curves of recurrence-free survival comparing rofecoxib versus placebo in different cyclooxygenase-2 (COX-2) expression groups.

DISCUSSION

We reasoned that blockade of COX-2 by rofecoxib would induce the following downstream events: direct inhibition of growth of residual micrometastases, prevention of angiogenesis, and reduction in tumoral expression of matrix metalloproteinases. Given the relative GI safety of rofecoxib,[14] we initially reasoned that a small (3%) absolute improvement in 5-year survival, if proven, would be sufficient to warrant use of this agent in the adjuvant setting. Results show no overall benefit for rofecoxib, with no improvements in DFS or OS. Although the trial recruited 2,434 patients, four potential reasons why a statistically significant benefit was not established are as follows: the drug is inactive; there were too few patients to demonstrate a clinically relevant but small effect; the duration of effective COX-2 inhibition may have been insufficient to alter the malignant phenotype; or there was inadequate representation of a COX-2–sensitive subpopulation. Data from the aspirin CRC prevention studies suggest a dose and duration effect for cancer risk reduction,[22] and the positive adenoma prevention studies with COX-2 inhibitors exposed patients to 16 to 36 months of drug treatment.[12,15,17] The premature closure of this trial and abbreviated duration of treatment may have attenuated therapeutic benefit. From previous adjuvant studies, it has been established that the greatest number of CRC recurrences occur in the first year after surgery[23] and the majority of adjuvant chemotherapy benefits are accrued then, with little demonstrable therapeutic effect in subsequent years.[2] In this study, there was a significant trend toward prevention of recurrence by rofecoxib in the first year (110 *v* 141 recurrences in the first year for rofecoxib and placebo, respectively; $P = .044$), which could indicate that more prolonged exposure to rofecoxib would be beneficial.

There are prior data suggesting that tumoral expression of COX-2 is a poor prognostic feature,[24-26] although this was not observed in the current study. Edelman et al[24] demonstrated a survival benefit for a subgroup of patients with advanced non–small-cell lung cancer with increased COX-2 expression who received celecoxib, suggesting that COX-associated biomarkers might be used to select patients who could enjoy therapeutic benefit. However, in our study, despite the RFS curves hinting at a similar effect, statistically there was no evidence of a treatment interaction for rofecoxib relative to COX-2 expression.

In general, rofecoxib was well tolerated apart from the enhanced cardiovascular adverse event profile (1% to 2% of treated patients),[13,16,27,28] which could likely be avoided by better patient selection. The present study was compromised by the worldwide withdrawal of rofecoxib and, therefore, significant reduction in the duration of exposure for patients who were randomly assigned. However, there is still significant interest in the potential role of COX-2 inhibition in cancer secondary prevention, and a further trial of this family of drugs with careful patient selection, maintenance of exposure, and a careful parallel assessment of biomarkers is worthy of consideration. Indeed, a Cancer and Leukemia Group B/Southwest Oncology Group phase III trial that is about to open will test celecoxib in a 2 × 2 factorial fashion with infusional fluorouracil, leucovorin, and oxaliplatin (3 months *v* 6 months of therapy) in the adjuvant setting of CRC. It will be extremely interesting to see whether the size of this study will allow confirmation of the provocative findings we describe here.

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:** Michael J. Langman, Merck (C), Procter & Gamble (C), Bayer Pharmaceuticals (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** David J. Kerr, Merck - educational grant to support VICTOR trials **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Rachel S. Midgley, Christopher C. McConkey, Janet A. Dunn, Simon A. Grumett, Michael J. Langman, David J. Kerr
Administrative support: Justine L. Smith, Patrick Julier, Claire Iveson
Provision of study materials or patients: Rachel S. Midgley, Elaine C. Johnstone, Simon A. Grumett, David J. Kerr
Collection and assembly of data: Rachel S. Midgley, Christopher C. McConkey, Justine L. Smith, Patrick Julier, Claire Iveson, Yoko Yanagisawa, Bryan Warren
Data analysis and interpretation: Rachel S. Midgley, Christopher C. McConkey, Elaine C. Johnstone, Janet A. Dunn, Simon A. Grumett, Bryan Warren, Michael J. Langman, David J. Kerr
Manuscript writing: Rachel S. Midgley, Christopher C. McConkey, Elaine C. Johnstone, Janet A. Dunn, Justine L. Smith, Simon A. Grumett, Patrick Julier, Claire Iveson, Yoko Yanagisawa, Bryan Warren, Michael J. Langman, David J. Kerr
Final approval of manuscript: Rachel S. Midgley, Christopher C. McConkey, Elaine C. Johnstone, Janet A. Dunn, Justine L. Smith, Simon A. Grumett, Patrick Julier, Claire Iveson, Yoko Yanagisawa, Bryan Warren, Michael J. Langman, David J. Kerr

REFERENCES

1. Midgley R, Kerr D: Towards post-genomic investigation of colorectal cancer. Lancet 355:669-670, 2000

2. Gray R, Barnwell J, McConkey C, et al: Adjuvant chemotherapy versus observation in patients with colorectal cancer: A randomised study. Lancet 370:2020-2029, 2007

3. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: A randomised trial—QUASAR Collaborative Group. Lancet 355:1588-1596, 2000

4. Sargent DJ, Wieand HS, Haller DG, et al: Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: Individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 23:8664-8670, 2005

5. Fenwick SW, Toogood GJ, Lodge JP, et al: The effect of the selective cyclooxygenase-2 inhibitor rofecoxib on human colorectal cancer liver metastases. Gastroenterology 125:716-729, 2003

6. Oshima M, Murai N, Kargman S, et al: Chemoprevention of intestinal polyposis in the Apcdelta716 mouse by rofecoxib, a specific cyclooxygenase-2 inhibitor. Cancer Res 61:1733-1740, 2001

7. Sheehan KM, Sheahan K, O'Donoghue DP, et al: The relationship between cyclooxygenase-2 expression and colorectal cancer. JAMA 282:1254-1257, 1999

8. Soumaoro LT, Uetake H, Higuchi T, et al: Cyclooxygenase-2 expression: A significant prognostic indicator for patients with colorectal cancer. Clin Cancer Res 10:8465-8471, 2004

9. Xiong B, Sun TJ, Hu WD, et al: Expression of cyclooxygenase-2 in colorectal cancer and its clinical significance. World J Gastroenterol 11:1105-1108, 2005

10. Haile RW, Yochim JM, Cortessis VK, et al: A molecular/epidemiologic analysis of expression of cyclooxygenases 1 and 2, use of nonsteroidal anti-inflammatory drugs, and risk of colorectal adenoma. Clin Colorectal Cancer 4:390-395, 2005

11. Chan AT, Ogino S, Fuchs CS: Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 356:2131-2142, 2007

12. Arber N, Eagle CJ, Spicak J, et al: Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 355:885-895, 2006

13. Baigent C, Patrono C: Selective cyclooxygenase 2 inhibitors, aspirin, and cardiovascular disease: A reappraisal. Arthritis Rheum 48:12-20, 2003

14. Baron JA, Cole BF, Sandler RS, et al: A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 348:891-899, 2003

15. Bertagnolli MM, Eagle CJ, Zauber AG, et al: Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 355:873-884, 2006

16. Bresalier RS, Sandler RS, Quan H, et al: Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 352:1092-1102, 2005

17. Hallak A, Alon-Baron L, Shamir R, et al: Rofecoxib reduces polyp recurrence in familial polyposis. Dig Dis Sci 48:1998-2002, 2003

18. Langman MJ, Jensen DM, Watson DJ, et al: Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 282:1929-1933, 1999

19. Kerr DJ, Dunn JA, Langman MJ, et al: Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. N Engl J Med 357:360-369, 2007

20. Altman DG: Practical Statistics for Medical Research. London, United Kingdom, Chapman and Hall, 1991, pp 443-445

21. Mahesh K, Parmar B, Machin D: Survival Analysis: A Practical Approach. New York, NY, John Wiley & Sons, 2005

22. Flossmann E, Rothwell PM: Effect of aspirin on long-term risk of colorectal cancer: Consistent evidence from randomised and observational studies. Lancet 369:1603-1613, 2007

23. O'Connell MJ, Campbell ME, Goldberg RM, et al: Survival following recurrence in stage II and III colon cancer: Findings from the ACCENT data set. J Clin Oncol 26:2336-2341, 2008

24. Edelman MJ, Watson D, Wang X, et al: Eicosanoid modulation in advanced lung cancer: Cyclooxygenase-2 expression is a positive predictive factor for celecoxib + chemotherapy—Cancer and Leukemia Group B Trial 30203. J Clin Oncol 26:848-855, 2008

25. Khor LY, Bae K, Pollack A, et al: COX-2 expression predicts prostate-cancer outcome: Analysis of data from the RTOG 92-02 trial. Lancet Oncol 8:912-920, 2007

26. Pantaleo MA, Astolfi A, Nannini M, et al: Gene expression profiling of liver metastases from colorectal cancer as potential basis for treatment choice. Br J Cancer 99:1729-1734, 2008

27. Kearney PM, Baigent C, Godwin J, et al: Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 332:1302-1308, 2006

28. Solomon SD, McMurray JJ, Pfeffer MA, et al: Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 352:1071-1080, 2005

