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ORIGINAL REPORT

Report of a Multicenter Phase II Trial Testing a Combination of Biweekly Bevacizumab and Daily Erlotinib in Patients With Unresectable Biliary Cancer: A Phase II Consortium Study

Sam J. Lubner, Michelle R. Mahoney, Jill L. Kolesar, Noelle K. LoConte, George P. Kim, Henry C. Pitot, Philip A. Philip, Joel Picus, Wei-Peng Yong, Lisa Horvath, Guy Van Hazel, Charles E. Erlichman, and Kyle D. Holen

From the University of Wisconsin, Madison, WI; Mayo Clinic, Rochester, MN; Mayo Clinic Jacksonville, Jacksonville, FL; Karmanos Cancer Institute, Detroit, MI; Washington University, St. Louis, MO; National University Hospital, Singapore; Royal Prince Alfred Hospital, Sydney; and Sir Charles Gairdner Hospital, Perth, Australia.

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Corresponding author: Sam Lubner, MD, K6/518 CSC, University of Wisconsin Hospital-Carbone Cancer Center, 600 Highland Ave, Madison, WI 53792; e-mail: sjlubner@medicine.wisc.edu.

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ABSTRACT

Purpose
Biliary cancers overexpress epidermal growth factor receptor (EGFR), and angiogenesis has been correlated with poor outcome. Erlotinib, an EGFR tyrosine kinase inhibitor, and bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor have each been shown to have activity in biliary cancer. The primary objective of this study was to evaluate the response rate by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary end points included overall survival (OS), time to progression (TTP), VEGF levels, and molecular studies of EGFR and k-ras.

Patients and Methods
Eligible patients had advanced cholangiocarcinoma or gallbladder cancer. Patients were treated with bevacizumab 5 mg/kg intravenously on days 1 and 15 and erlotinib 150 mg by mouth daily on days 1 through 28. Responses were evaluated by RECIST. VEGF levels were collected, and samples were analyzed for EGFR mutation by polymerase chain reaction.

Results
Fifty-three eligible patients were enrolled at eight sites. Of 49 evaluable patients, six (12%; 95% CI, 6% to 27%) had a confirmed partial response. Stable disease was documented in another 25 patients (51%). Rash was the most common grade 3 toxicity. Four patients had grade 4 toxicities. Median OS was 9.9 months, and TTP was 4.4 months. Low repeats (< 16) in EGFR intron 1 polymorphism and G>G k-ras Q38 genotype (wild type) were associated with improved outcomes.

Conclusion
Combination chemotherapy with bevacizumab and erlotinib showed clinical activity with infrequent grade 3 and 4 adverse effects in patients with advanced biliary cancers. On the basis of preliminary molecular analysis, presence of a k-ras mutation may alter erlotinib efficacy. The combination of bevacizumab and erlotinib may be a therapeutic alternative in patients with advanced biliary cancer.

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INTRODUCTION

Biliary tract carcinoma is a rare but highly lethal malignancy. Estimated incidence of bile duct and gallbladder cancer approached 10,000 cases in 2009, with nearly 3,400 estimated deaths.[1] Median age at presentation is 65 years. Risk factors for gallbladder cancer include gallstones, choledochal cysts, porcelain gallbladder, and adenomatous gallbladder polyps, along with obesity and female sex. For bile duct cancer, cholelithiasis, choledochal cysts, primary sclerosing cholangitis, ulcerative colitis, and parasitic infections (*Clonorchis sinensis*, *Opisthorcis viverrini*) are the most often cited risk factors.[2,3]

Only one fourth to one third of patients are eligible for potentially curative surgery; even among patients treated surgically, relapse rates are high. If not resectable, median survival for biliary cancer is approximately 6 months.[2,4]

Data regarding chemotherapy are disappointing, but new combinations show promise. ABC-02, a randomized phase III study recently published by Valle et al,[5] enrolled more than 300 patients and compared gemcitabine plus cisplatin with gemcitabine alone. The median overall survival (OS) and progression-free survival (PFS) were greater for gemcitabine plus cisplatin than for gemcitabine alone without significantly increased toxicity (OS: 11.7 *v* 8.2 months; log-rank $P = .002$; PFS: 8.5 *v* 6.5

months; log-rank $P = .003$).[5] This drug combination set a new international standard of care for advanced biliary tract cancers.

Phase II trials showed activity among chemotherapeutic agents including gemcitabine, platinum analogs, and capecitabine.[6,7] A phase II study by Knox et al[8] demonstrated a response rate of 31% with gemcitabine plus capecitabine, and an additional 42% of patients had stable disease (SD). Other phase II studies explored the activity of biologic agents. Philip et al[9] suggested a benefit from the oral epidermal growth factor receptor (EGFR) inhibitor erlotinib (Tarceva, OSI-774; OSI Pharmaceuticals, Melville, NY), with 8% of patients (3 of 36) demonstrating a partial response (PR), 25% of patients (7 of 36) with no progression at 6 months, and minimal therapy-related toxicity. Vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin; Genentech, South San Francisco, CA) demonstrated efficacy in a number of other solid tumors, including colorectal cancer, renal cell cancer, non–small-cell lung cancer, and metastatic breast cancer.[10-13] VEGF has been identified as overexpressed in biliary tract cancers and has been suggested as a potential prognostic marker and therapeutic target.[14,15] The combination of bevacizumab and erlotinib has been studied in phase I and II trials in metastatic breast, lung, and hepatocellular cancers; no pharmacokinetic interaction between the two agents was demonstrated.[16-19] In colorectal malignancies, the addition of anti-EGFR therapy with cetuximab to bevacizumab worsened outcomes of PFS and quality of life.[20] In vitro and murine models have shown that EGFR agents downregulate VEGF production; the combination of bevacizumab and erlotinib may be synergistic in this regard.[21-24]

This study reports the results of a multi-institution phase II trial of bevacizumab and erlotinib combination therapy for patients with advanced biliary cancers. The objectives were to determine response rate, time to progression (TTP), OS, and safety of this novel combination. Correlative analysis was performed to examine the effect of bevacizumab on VEGF levels and evaluate EGFR mutations/polymorphisms as predictors of response. Descriptive analysis of the correlates relative to antitumor effect was also explored.

PATIENTS AND METHODS

Patients were eligible if they had histologically or cytologically confirmed cholangiocarcinoma or gallbladder carcinoma, either surgically unresectable or metastatic at time of diagnosis. Disease had to be measurable by computed tomography scan ($\geq$ 1.0 cm by spiral computed tomography, $\geq$ 2.0 cm by conventional techniques), as assessed by Response Evaluation Criteria in Solid Tumors (RECIST).[25] No prior chemotherapy for advanced disease was allowed, but adjuvant/neoadjuvant therapy was allowed. Additional inclusion criteria included age $\geq$ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2, estimated life expectancy of $\geq$ 3 months, absolute neutrophil count $\geq$ 1,500/μL, platelets $\geq$ 75,000/μL, total bilirubin $<$ 2$\times$ upper limit of normal (ULN), serum AST $\leq$ 2.5$\times$ ULN, serum ALT $\leq$ 2.5$\times$ ULN, serum creatinine $\leq$ 2 mg/dL, serum albumin $\geq$ 2.5 g/dL, alkaline phosphatase $\leq$ 5$\times$ ULN, and 24-hour urine protein $<$ 1,000 mg/24 hours if spot urine protein/creatinine ratio was abnormal. Use of anticoagulants for other conditions was allowed, provided the dose of anticoagulants was stable and the coagulation parameters were within acceptable limits. Written informed consent was obtained from each patient. The protocol and informed consent were reviewed by the Phase II Consortium and the institutional review board at each registering institution.

Exclusion criteria included ampulla of Vater tumors, prior chemotherapy or radiotherapy for biliary cancer, chemotherapy/radiotherapy within 4 weeks of enrollment (6 weeks for mitomycin or nitrosoureas), known sensitivity to investigated agents or components, nonhealing wounds, impairment of GI function that would alter the absorption of erlotinib, significant GI bleeding $\leq$ 3 months before registration, GI fistula/perforation in the previous $\leq$ 28 days, recent invasive procedure, history of other malignancy, evidence of CNS diseases/tumors, corneal abnormalities, and clinically significant cardiovascular disease. HIV patients on antiretroviral therapy, pregnant or breastfeeding women, or patients receiving CYP 3A4 inducers were also excluded.

Treatment Plan

Patients were treated on a 28-day cycle. Bevacizumab was administered intravenously at 5 mg/kg on days 1 and 15. Erlotinib was administered at 150 mg by mouth once daily on days 1 through 28. Treatment was continued until disease progression, unacceptable adverse events, withdrawal of patient consent, illness preventing additional administration of treatment, or a change in condition rendering the patient unacceptable for additional treatment in the investigator's judgment. Adverse events were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Dose delays were allowed for adverse events in patients taking bevacizumab, but dose reductions were not allowed by the protocol. Doses were held for grade 3 infusion reactions, symptomatic hypertension, urine protein/creatinine ratio $>$ 3.5, or grade 3 hemorrhage. For grades 1 to 3 infusion reactions, premedications were administered with the next dose, and the patient was closely monitored at the next administration. If venous thromboembolism occurred, bevacizumab was stopped until a stable anticoagulation regimen was administered. Bevacizumab was discontinued for any grade 4 adverse event.

Dose interruptions and reductions were allowed for erlotinib. Specifically, for grade 2 skin rashes, the dose was held until the rash resolved to grade 0 to 1; a dose reduction was not automatically mandated for the first grade 2 rash. Recurrent or intolerable grade 2 rashes required dose reduction by one level. Grade 3 rashes required dose reduction by one level, and the dose was held until resolution to grade 0 to 1. The first reduction was to 100 mg/d for adverse events, and a second reduction to 50 mg/d was allowed. If patients experienced additional toxicity at 50 mg/d, therapy was discontinued and the patient was taken off study.

Patients were given pill diaries for erlotinib and asked to bring the pill diary, their bottle, and any unused pills with them to each appointment, with a new diary given with each new cycle of therapy. The patients were instructed to take the medication on an empty stomach, either 1 or 2 hours before a meal. Missed doses were allowed to be taken up to 12 hours late, and patients were instructed not to double dose for missed doses.

Disease Assessment

All eligible patients who initiated treatment and had at least one post-baseline disease assessment were evaluable for the primary end point. Tumor response was assessed using RECIST, with re-evaluation every 8 weeks.[25] Patients were re-evaluated for disease status 4 weeks after initial documentation of complete response (CR) or PR to confirm the assessment. Similarly, SD was reassessed at a minimum interval of 8 weeks. Patients with global deterioration of health status that required discontinuation of treatment without objective evidence of disease progression at that time and that was not related to study treatment or other medical conditions were considered to have progressive disease (PD) due to symptomatic deterioration. For the primary end point of the study, a confirmed tumor response was defined to be either a CR or PR on two consecutive evaluations at least 4 weeks apart during the first six cycles of treatment.

Duration of response was calculated from the first date of a patient's objective status of either CR or PR to the date of PD (or last tumor assessment). Duration of SD was calculated from the date of registration to the date of PD (or last tumor assessment if no PD) for patients having achieved a best response of SD. Patients were censored for progression (survival) at their date of last assessment (last contact) if no progression (death) occurred. Time to PD was calculated from the date of registration to the date of PD. Survival or time to death was calculated from the date of registration to the date of death. All

Table 1. Baseline Characteristics of Eligible Patients (N = 53)

Characteristic	Frequency No.	Frequency %
Age, years		
Median	63	
Range	31-87	
Male sex	23	43
ECOG performance status		
0	26	49
1	26	49
2	1	2
Primary tumor site		
Intrahepatic cholangiocarcinoma	35	66
Extrahepatic cholangiocarcinoma	8	15
Gallbladder	10	19
Differentiation		
Well	4	8
Moderate	16	31
Poor	8	15
Unknown	25	47
Previous radiotherapy	6	11
Site of previous radiotherapy*		
Anterior	1	17
Gallbladder	2	33
Abdomen	1	17
Abdomen and liver	1	17
Spine	1	17
Previous systemic adjuvant cancer therapy	5	9
Type of previous systemic therapy*		
Gemcitabine	1	20
Fluorouracil	2	40
Fluorouracil plus gemcitabine	1	20
Capecitabine	1	20
Any previous cancer	5	9
Type of previous cancer		
Melanoma	1	20
Cervical	1	20
Nose	1	20
Uterine	1	20
Prostate	1	20
Registration location		
University of Wisconsin (Madison, WI)	29	55
Mayo Clinic (Jacksonville, FL)	6	11
Mayo Clinic (Rochester, MN)	4	8
Washington University (St. Louis, MO)	4	8
Wayne State University (Detroit, MI)	4	8
National University Hospital (Singapore)	4	8
Royal Prince Alfred Hospital (Sydney , Australia)	1	2
Sir Charles Gairdner Hospital (Perth, Australia)	1	2
Race/ethnicity		
White	48	91
Asian	5	9
Status of primary tumor		
Resected with no residual	5	9
Resected with known residual	8	15
Unresected	38	72
Recurrent	2	4
Distant metastases		
Median	1	
Range	0-2	
Sites of extrahepatic metastases*		
Liver	13	25
Pleura and diaphragm	1	2
Nodal, peritoneum, duodenum, and gallbladder	1	2
Liver and peritoneum	2	4
Nodal	3	6
Nodal and liver	5	9
Nodal and bone	1	2
Bone and liver	1	2
Lung	1	2

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Patients are reflected once in each classification.

patients were followed for a maximum of death or 3 years after registration, whichever was earlier.

Molecular Analyses

Laboratory measures included the presence of EGFR mutations in tumor tissue and measurement of VEGF serum levels. Analyses were performed on all evaluable samples. For analysis of the EGFR mutation, cells were prepared by laser capture microdissection and polymerase chain reaction size exclusion or pyrosequencing. Deletions in exon 1 (EGFR variant vIII) 2235 to 2249, 2240 to 2251, and 2240 to 2257 were analyzed by amplifying the exon containing the deletion and running the polymerase chain reaction product by capillary electrophoresis. VEGF levels were measured by a commercially available sandwich immunoassay (Quantikine human VEGF; R&D Systems, Minneapolis, MN).

Statistical Design

A two-stage Fleming phase II design, with no suspension for interim analysis, was used to test whether there was sufficient evidence to determine that the proportion of confirmed tumor responses was at least 25% (ie, warranted additional study) versus 10% (ie, clinically inactive).[26] Eligible patients were considered evaluable for the primary end point if they had at least one postbaseline disease assessment. Patients having died or progressed before their first postbaseline assessment were still considered evaluable for the primary end point. Three confirmed responses in the initial 21 evaluable patients warranted the expansion of enrollment to 50 patients. Nine confirmed responses among 50 evaluable patients was considered sufficient evidence of promising activity to recommend additional testing of this regimen. This design yielded 85% power at 0.04 level of significance to detect a true response rate of 25%. CIs were calculated using the method of Duffy and Santner.[27] Unless otherwise specified, analyses were conducted per protocol.

Summary statistics and frequency tables were used to summarize baseline patient characteristics and adverse event rates. Adverse events were reported as a maximum severity per patient and type across all cycles of treatment. All attributions collected for adverse events were reported unless otherwise noted. The Kaplan-Meier method was used to estimate the distributions of TTP and time to death. All analyses were conducted using SAS version 9.0 (SAS Institute, Cary, NC).[28] Cox proportional hazard models were used to evaluate associations with tumor progression and survival.[29] Nonparametric tests were used when the underlying distributional assumptions were not satisfied. Laboratory measures were correlated with clinical and study end points using frequency tables, logistic regression, and Cox proportional hazards modeling. Two-sided P values were reported, and $P < .05$ was considered statistically significant.

RESULTS

Patient Characteristics

Fifty-six patients were enrolled between August 2006 and April 2008 at eight sites in the Phase II Consortium. The data are reported as of November 2009. Three patients were ineligible after starting treatment (brain metastases, alteration in pathologic diagnosis, colitis) and were included in the toxicity analysis but not the primary end point analysis. Median age was 63 years (range, 31 to 87 years). A majority of patients were female (30 patients, 57%) and white (48 patients, 91%). At study entry, 52 patients (98%) had a performance status of 0 or 1, 43 patients (81%) had cholangiocarcinoma, and 10 patients (19%) had gallbladder cancer. Metastatic disease was seen in 58% of patients, with the liver being the most common site of metastasis (13 patients; Table 1).

Efficacy and Patient Outcome

Fifty-three patients completed a total of 327 cycles of treatment (median, 4 cycles; range, 1 to 33 cycles). The primary end point was confirmed tumor response. Forty-nine patients were evaluable for assessing response. Nine patients achieved a best response of PR while six patients (12%; 95% CI, 6% to 27%; five at University of Wisconsin Carbone Cancer Center, one at Mayo Clinic [Rochester, MN]) had prolonged responses confirmed 4 weeks after their initial response was observed. Each PR was reviewed and confirmed by an independent investigator. Twenty-five and 15 patients achieved a best response of SD and PD, respectively. Among the six patients with confirmed PRs, median duration of response was 8.4 months (95% CI, 6.0 to 11.7 months). At the time of data cutoff, three patients remained on study medication, having received 18, 29, and 33 cycles of therapy. Eighty-seven percent of patients progressed with a median time to disease progression of 4.4 months (95% CI, 3.0 to 7.8 months). Median OS was 9.9 months (95% CI, 7.2 to 13.6 months; Table 2, Fig 1).

Table 2. Patient Outcomes (N = 53)

Outcome	Estimate			
	No.	%	Range	95% CI
Best objective response				
Evaluable*	49	100		
Too early/not evaluable	4			
CR	0			
PR	9	18		
Stable disease	25	51		
Disease progression	15	31		
Confirmed CR/PR	6			
Time to progression, months				
Median†	4.4			3.0 to 7.8
Progressions	46			
Progression-free, months				
3		62	50-76	
6		43	32-59	
12		21	12-36	
18		10	4-245	
24		6	3-21	
Survival, months				
Median†	9.9			7.2 to 13.6
Deaths	44			
Alive, months				
3		87	78-96	
6		70	59-83	
12		40	28-55	
18		19	10-35	
24		16	8-32	
Time to treatment failure, months				
Median†	3.6			2.8 to 4.8
Failures	50			
On study, months				
3		59	47-73	
6		32	22-48	
12		11	5-24	
18		6	2-17	
24		6	2-17	

Abbreviations: CR, complete response; PR, partial response.
*Eligible patients having begun treatment and having at least one post-baseline disease assessment.
†Kaplan-Meier method.

Adverse Events

Grade 4 adverse events which were at least possibly related to study treatment were experienced by four patients (8%), including cerebral ischemia and thrombosis (two patients each). Fourteen patients (27%) experienced grade 3 adverse events considered at least possibly related, including rash/desquamation (three), anorexia (three), fatigue (three), hyponatremia (three), nausea (three), ALT (one), bilirubin (one), diarrhea (one), dizziness (one), hypertension (one), nail changes (one), prothrombin time (one), and alkaline phosphatase (one). Details on toxicity are provided in Table 3. The most common of these events included (number of patients experiencing grade 1, 2, or 3): rash/desquamation (16, 21, three), diarrhea (15, six, one), fatigue (18, six, two), nausea (seven, four, two), anorexia (six, five, two), and oral mucositis (10, two, zero).

Two patients (4%) died during treatment of causes felt to be unrelated to study treatment. A 79-year-old male died suddenly on day 21 of the first cycle, experiencing grade 4 cerebral ischemia (possibly related) and grade 1 blood bilirubin increase (possibly related). Bevacizumab was held on day 15. This death was considered unlikely to be related to study treatment. A 69-year-old male died within 30 days of initiating treatment, possibly due to disease progression. Adverse events before death included unrelated grade 3 anorexia, dyspnea, epigastric and back pain, and nausea; treatment-related grade 2 rash/desquamation combined; and unrelated grade 1 vomiting. This patient received full doses of both study agents during treatment.

Correlative Data

Evaluable tissue was submitted from 26 patients, four of whom had a confirmed response. Characteristics of this subset were comparable to the larger study population in terms of age, sex, performance status, and enrolling site. Fewer patients had gallbladder tumors (8% *v* 19%) or poorly differentiated tumors (4% *v* 15%) in the subset with available tissue (Appendix Table A1, online only).

Mutation on EGFR vIII, ≤ 16 C>A repeats for the EGFR intron 1 polymorphism, a G>G genotype measured by EGFR-Q787 single nucleotide polymorphisms, and wild-type (ie, nonmutant) KRAS measured by 38G primer I were hypothesized to be positively correlated with patient outcome (ie, confirmed response, tumor progression, and survival). Although only four patients experienced a confirmed response in this group and the results were not statistically significant, the data appeared to be in the direction of our hypotheses

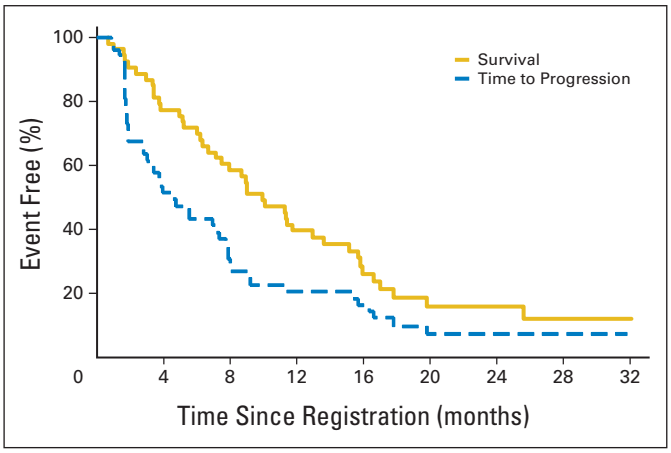

Fig 1. Time to progression and overall survival.

(Appendix Tables A2 and A3, online only), albeit with a limited sample size. VEGF expression did not change significantly from baseline between the responding and nonresponding patients (Appendix Table A2 and Appendix Fig A1, online only).

Desirable results (responders *v* nonresponders) were most often observed in patients having low repeats (≤ 16) for the EGFR intron 1 polymorphism (75% *v* 55%) or G>G K-ras Q38 genotype (100% *v* 82%). In univariate models, EGFR-Q787 genotype of G>G trended toward lower hazard rates for TTP (hazard ratio [HR], 0.7; 95% CI, 0.3 to 2.0; $P = .56$) and survival (HR, 0.6; 95% CI, 0.2 to 1.7; $P = .34$), although it was not statistically significant. VEGF 38Q genotype of G>G (ie, nonmutant) may be associated with a lower hazard rate for TTP (HR, 0.4; 95% CI, 0.1 to 1.4; $P = .13$). Conversely, EGFR vIII mutation is suggestive of worsened TTP (HR, 2.0; 95% CI, 0.6 to 7.1; $P = .27$) and survival (HR, 1.7; 95% CI, 0.5 to 6.1; $P = .39$; Appendix Table A3).

DISCUSSION

The combination of bevacizumab and erlotinib produced nine PRs in patients with biliary tract cancers, six of which were sustained (12%; 95% CI, 6% to 27%). When compared with that in other published trials of combination chemotherapy, the confirmed PR plus SD rate of 64% (31 of 49) is comparable with that for gemcitabine plus capecitabine, gemcitabine plus oxaliplatin, and gemcitabine plus cisplatin.[5,7-9,30] In responders, the duration of best response for an average of 7.6 months is similarly comparable to that in other published trials. TTP and OS are also consistent with previously published data as summarized in Appendix Table A4 (online only).

From the safety analysis, the majority of adverse effects were grade 1 or 2. While there were two deaths on study and four patients with grade 4 toxicity, the regimen was not associated with prolonged neutropenia or GI adverse effects. The results of this trial suggest that a biologic-only combination of bevacizumab and erlotinib has activity in biliary tract cancers and demonstrates a different adverse event profile that merits additional exploration.

The molecular analyses performed in this study suggest that patients whose tumors have mutations in EGFR vIII, or have non–wild-type k-ras may be less likely to respond to erlotinib therapy. These findings are consistent with trials in lung cancer and colon cancer relative to k-ras mutants and EGFR-based biologic therapy.[31,32] Similar trials have been published in abstract form in biliary tract cancer relative to the use of cetuximab, but they did not demonstrate any difference between PFS/OS or response to cetuximab.[33] Additional exploration into the EGFR pathway as a potential therapeutic

Table 3. Maximum Severity of Adverse Events (N = 53)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Thrombocytopenia	5	2	0	0
Leukopenia	2	2	0	0
Neutropenia	0	1	0	0
Hepatic				
ALT	3	2	1	0
AST	5	3	0	0
Bilirubin	4	1	2	0
Infection/febrile neutropenia				
Nail bed infection	0	1	0	0
Urinary tract infection	0	1	0	0
Infection	1	0	0	0
Metabolic/laboratory				
Hyponatremia	1	0	2	0
Alkaline phosphatase	1	1	1	0
Neurologic				
Ischemia-cerebral	0	0	0	2
Dizziness	0	0	1	0
Ocular/visual				
Conjunctivitis	0	1	0	0
Dry eye	0	2	0	0
Pain				
Abdominal	1	2	0	0
Chest	0	1	0	0
Stomach	0	1	0	0
Pulmonary				
Cough	0	1	0	0
Voice change	0	1	0	0
Pneumothorax	0	1	0	0
Proteinuria	4	1	0	0
Cardiovascular				
Hypertension	6	3	1	0
Thrombosis	0	0	0	2
Coagulation				
Prothrombin time	0	0	1	0
Constitutional symptoms				
Fatigue	18	6	2	0
Weight loss	3	4	0	0
Dermatology/skin				
Acne, not otherwise specified	3	6	0	0
Alopecia	4	2	0	0
Rash/desquamation	16	21	3	0
Dry skin	8	7	0	0
Nail changes	4	1	1	0
GI				
Anorexia	6	5	2	0
Constipation	5	2	0	0
Dehydration	1	1	0	0
Diarrhea	15	6	1	0
Nausea	7	4	2	0
Stomatitis/pharyngitis	10	2	0	0
Vomiting	5	2	0	0

NOTE. Adverse event grade according to National Cancer Institute Common Terminology Criteria for Adverse Events v.3. Events reported are considered at least possibly related to study treatment.

target is warranted, particularly in patients with intron 1 polymorphism and Q787 genotype.

Shortcomings of this combination (bevacizumab and erlotinib) include a lack of demonstrable improvement in OS compared with that of historical controls, a problem plaguing many trials in biliary tract cancers. The trial included both cholangiocarcinoma and gallbladder cancer; historically, gallbladder cancers have had poorer prognoses, potentially underestimating disease-free survival.[34] The relatively few gallbladder cases in the trial may mitigate that estimation. Additionally, this combination is associated with significant cost. On the basis of prior cost analyses in other tumor types and on pricing effective October 2009, this regimen would cost nearly $10,000/month (estimating ≈$5,000/month for bevacizumab and $4,500 for erlotinib).[35,36] We did not perform a cost analysis on this trial, but the expense of this combination could be explored relative to the cost of combinations of gemcitabine plus platinum.

In conclusion, the biologic-only combination of bevacizumab and erlotinib has demonstrable activity in advanced biliary tract cancers with few grade 3 or 4 adverse events. Given the demonstrated efficacy and safety profile, we believe that this combination could be additionally explored in future trials as a combination with gemcitabine plus cisplatin, an alternative first-line regimen or a salvage regimen after progression on standard cytotoxic therapy.

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.

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AUTHOR CONTRIBUTIONS

Conception and design: Charles E. Erlichman, Kyle D. Holen
Financial support: Charles E. Erlichman
Administrative support: Charles E. Erlichman
Provision of study materials or patients: Noelle K. LoConte, George P. Kim, Henry C. Pitot, Philip A. Philip, Joel Picus, Wei-Peng Yong, Lisa Horvath, Guy Van Hazel, Kyle D. Holen
Collection and assembly of data: Michelle R. Mahoney, Jill L. Kolesar, Kyle D. Holen
Data analysis and interpretation: Sam J. Lubner, Michelle R. Mahoney, Jill L. Kolesar, Kyle D. Holen
Manuscript writing: Sam J. Lubner, Michelle R. Mahoney, Kyle D. Holen
Final approval of manuscript: Sam J. Lubner, Michelle R. Mahoney, Jill L. Kolesar, Noelle K. LoConte, George P. Kim, Henry C. Pitot, Philip A. Philip, Joel Picus, Wei-Peng Yong, Lisa Horvath, Guy Van Hazel, Charles E. Erlichman, Kyle D. Holen

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