

## Phase II Trial of Cisplatin, Gemcitabine, and Bevacizumab As First-Line Therapy for Metastatic Urothelial Carcinoma: Hoosier Oncology Group GU 04-75

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Submitted July 17, 2010; accepted February 3, 2011; published online ahead of print at [www.jco.org](http://www.jco.org) on March 21, 2011.

Supported by investigator-initiated funds from Genentech, South San Francisco, CA.

Presented in part at the 45th Annual Meeting of the American Society of Clinical Oncology, May 29-June 2, 2009, Orlando, FL; and 46th Annual Meeting of the American Society of Clinical Oncology, June 4-8, 2010, Chicago, IL.

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](http://JCO.org).

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0732-183X/11/2912-1525/\$20.00

DOI: 10.1200/JCO.2010.31.6067

### A B S T R A C T

#### Purpose

Novel approaches are needed for patients with metastatic urothelial cancer (UC). This trial assessed the efficacy and toxicity of bevacizumab in combination with cisplatin and gemcitabine (CGB) as first-line treatment for patients with metastatic UC.

#### Patients and Methods

Chemotherapy-naïve patients with metastatic or unresectable UC received cisplatin 70 mg/m<sup>2</sup> on day 1, gemcitabine 1,000 to 1,250 mg/m<sup>2</sup> on days 1 and 8, and bevacizumab 15 mg/kg on day 1, every 21 days.

#### Results

Forty-three patients with performance status of 0 (n = 26) or 1 (n = 17) and median age of 66 years were evaluable for toxicity and response. Grade 3 to 4 hematologic toxicity included neutropenia (35%), thrombocytopenia (12%), anemia (12%), and neutropenic fever (2%). Grade 3 to 5 nonhematologic toxicity included deep vein thrombosis/pulmonary embolism (21%), hemorrhage (7%), cardiac (7%), hypertension (5%), and proteinuria (2%). Three treatment-related deaths (CNS hemorrhage, sudden cardiac death, and aortic dissection) were observed. Best response by Response Evaluation Criteria in Solid Tumors was complete response in eight patients (19%) and partial response in 23 patients (53%), for an overall response rate of 72%. Stable disease lasting ≥ 12 weeks occurred in four patients (9%), and progressive disease occurred in six patients (14%). With a median follow-up of 27.2 months (range, 3.5 to 40.9 months), median progression-free survival (PFS) was 8.2 months (95% CI, 6.8 to 10.3 months) with a median overall survival (OS) time of 19.1 months (95% CI, 12.4 to 22.7 months). The study-defined goal of 50% improvement in PFS was not met.

#### Conclusion

CGB demonstrates promising OS and antiangiogenic treatment-related toxicities in the phase II setting of metastatic UC. The full risk/benefit profile of CGB in patients with metastatic UC will be determined by an ongoing phase III intergroup trial.

*J Clin Oncol* 29:1525-1530. © 2011 by American Society of Clinical Oncology

### INTRODUCTION

Bladder urothelial carcinoma (UC) is the fifth most commonly diagnosed cancer in the United States and accounts for 14,000 deaths annually.<sup>1</sup> For patients with metastatic UC, first-line chemotherapy with cisplatin and gemcitabine (CG) is considered a standard of care.<sup>2,3</sup> Despite treatment, most patients with metastatic disease die from their cancer. Therefore, novel first-line regimens remain a high priority.

The critical role of angiogenesis in migration, proliferation, and metastasis of malignant tumors is well established.<sup>4-8</sup> Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis. In UC,

investigators have demonstrated associations between tumor VEGF expression and prognosis, improved tumor control with platinum-based chemotherapy plus antiangiogenic therapy in pre-clinical models, and signals of clinical benefit in single-agent human UC trials.<sup>9-15</sup> Bevacizumab, a recombinant monoclonal antibody for circulating VEGF-A, has demonstrated significant improvement in clinical outcomes across multiple tumor types in combination with chemotherapy.<sup>16-23</sup> With this background, the Hoosier Oncology Group assessed the efficacy and toxicity of bevacizumab in combination with CG (CGB) as first-line therapy for patients with metastatic UC.

## PATIENTS AND METHODS

**Patients**

Institutional review board approval was obtained from all participating centers. All patients provided written informed consent. Eligibility criteria included the following: age  $\geq 18$  years; metastatic or unresectable predominantly urothelial cell carcinoma of the urethra, bladder, or upper urinary tract; measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST); and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Patients were required to have adequate bone marrow function (absolute neutrophil count [ANC]  $\geq 1,500/\mu\text{L}$ , platelet count  $\geq 100,000/\mu\text{L}$ , and hemoglobin  $\geq 8$  g/dL with transfusion or erythropoietic growth factor support), coagulation parameters (international normalized ratio [INR]  $< 1.5$ ), renal function (creatinine  $< 1.5$  mg/dL and urine protein-to-creatinine ratio  $< 1.0$ ), and hepatic function (bilirubin  $< 1.5$  mg/dL and ALT  $< 5\times$  upper limit of normal for patients with liver metastases or ALT  $< 2.5\times$  upper limit of normal for patients without liver metastases). Exclusion criteria included neoadjuvant or adjuvant chemotherapy within 1 year before study registration, therapeutic-dose anticoagulation, prior venous thromboembolism (deep vein thrombosis [DVT]/pulmonary embolism [PE]), any CNS metastases, or clinical contraindications to bevacizumab use.

**Treatment**

Patients received intravenous cisplatin 70 mg/m<sup>2</sup> over 60 minutes on day 1, gemcitabine 1,250 mg/m<sup>2</sup> over 30 minutes on days 1 and 8, and bevacizumab 15 mg/kg over 30 minutes (90 minutes for cycle 1 only) on day 1 of each 21-day treatment cycle. After DVT/PE events were observed in seven of the first 17 patients, the gemcitabine dosing was reduced to 1,000 mg/m<sup>2</sup> on days 1 and 8 for all on-study and subsequent patients. Cisplatin and gemcitabine continued for a maximum of eight cycles; bevacizumab continued for a maximum of 12 months.

Subsequent cycles required an ANC  $\geq 1,500/\mu\text{L}$ , platelet count  $\geq 100,000/\mu\text{L}$ , and creatinine less than 2 mg/dL. For myelosuppression-related treatment delays  $\geq 7$  days, gemcitabine dose was reduced to 750 mg/m<sup>2</sup> with maintenance of full-dose cisplatin and bevacizumab. If the day 8 ANC was less than 750/ $\mu\text{L}$ , the gemcitabine dose was held and not made up. If creatinine failed to resolve to less than 2 mg/dL with hydration, cisplatin was held for all subsequent cycles with the gemcitabine dose reduced to 750 mg/m<sup>2</sup> but with full-dose bevacizumab. All treatment was withheld until resolution and gemcitabine dose was reduced to 750 mg/m<sup>2</sup> for all subsequent cycles in the event of clinically significant toxicity, defined as follows: febrile grade 4 neutropenia, grade 4 neutropenia for more than 5 days, any platelet count less than 25,000/ $\mu\text{L}$ , grade 4 emesis despite maximum supportive care, grade 3 or 4 neurotoxicity, or other unresolving grade 3 toxicities. Patients requiring two dose reductions were removed from study.

Blood product transfusions, antibiotics, antidiarrheals, antiemetics, and analgesics were permitted. Granulocyte and granulocyte-macrophage colony-stimulating factor use was permitted for grade 4 neutropenia lasting more than 5 days or neutropenic fevers with ANC less than 1,000/ $\mu\text{L}$ . Pegfilgrastim use was not permitted. Patients experiencing grade 3 or asymptomatic grade 4 venous thrombosis were allowed to remain on study with ongoing bevacizumab and full-dose anticoagulation with low molecular weight heparin or warfarin provided that an in-range INR (2.0 to 3.0) was documented, no grade 3 or 4 hemorrhage was present, and no tumor involving major blood vessels was documented.

**Patient and Disease Evaluations**

Baseline computed tomography (CT) scan of the abdomen and pelvis, chest x-ray or chest CT, and tumor measurements were recorded within 28 days of registration. History and physical examination, ECOG PS, toxicity grading per National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), WBC count, hemoglobin, platelet count, cell differential, blood urea nitrogen, total bilirubin, alkaline phosphatase, albumin, ALT, creatinine, INR, and urine protein-to-creatinine ratio were collected within 14 days before registration. All parameters except INR and urine protein-to-creatinine ratio were repeated on day 1 of each subsequent cycle of

therapy. CBC count and toxicity assessment were repeated on day 8 of each cycle. Urine protein-to-creatinine ratio was repeated on day 1 of every other cycle.

CT scan of the abdomen/pelvis, chest x-ray or chest CT, and tumor measurements were repeated every other cycle (every 6 weeks). All documented response evaluations were repeated at least 4 weeks after initial response for confirmation. After completion of therapy, radiographic assessments were repeated every 2 months until disease progression. After progression, patients were observed for overall survival (OS) every 4 months for life.

Tumor responses and progression-free survival (PFS) were assessed by investigators according to RECIST criteria. OS was defined as the time from registration until death as a result of any cause. Stable disease was defined as tumors that did not fulfill RECIST criteria for response (complete or partial) or progression for a duration of at least 12 weeks. Modified Bajorin risk groups were defined as follows: PS 0 and no visceral metastases (low risk); PS 1 and no visceral metastases or PS 0 and visceral metastases (intermediate risk); and PS 1 and visceral metastases (high risk).<sup>24</sup>

**Statistical Considerations**

All patients who received at least one dose of study therapy were considered evaluable and were included in study efficacy analyses. The primary end point was PFS. The study was designed to detect a 50% increase in median PFS from an expected 7.5 months ( $H_0$ ) with traditional CG therapy to an improved PFS of 11.25 months ( $H_a$ ) with the CGB regimen.<sup>2,3</sup> With a one-sided type I error rate of 10%, a sample size of 40 patients provided an 86% power to detect this difference between  $H_0$  and  $H_a$ . Assuming 10% of patients would be lost to follow-up, a sample size of 45 patients was required. PFS and OS analyses were performed using the Kaplan-Meier method.<sup>25</sup> Exact binomial CIs for response and toxicity were reported.<sup>26</sup>

Unplanned analyses were performed to assess associations between patient characteristics (age, sex, body mass index [BMI], ECOG PS, presence of visceral metastases, modified Bajorin risk group, presence of pelvic/abdominal metastases, creatinine, platelets, hemoglobin, WBC count, history of prior cystectomy, gemcitabine dose, and administration of second-line chemotherapy) and OS (univariate log-rank test and multivariable Cox proportional hazards analysis) and univariate toxicity rates (Fisher's exact test). Continuous variables were split at the median value. All variables significant at the  $P = .10$  level on univariate analysis were included in the multivariable model. Backward elimination was used to determine the final model ( $\alpha = .10$ ).

Stopping rules based on 90% CI limits for clinically significant toxicity event rates were instituted from the beginning of the study. The 90% CIs for clinically significant toxicity were assessed after every 10 patients were enrolled. The trial would stop if the lower 90% CI exceeded 30% at any point in the study. After seven DVT/PE events were observed in the first 17 patients, an additional stopping rule based on the 90% CIs for DVT/PE rate with the lowered gemcitabine dosing was added for subsequent patients such that the trial would stop if the lower 90% CI exceeded 10% for subsequent patients enrolled (patients 18 through 45).

## RESULTS

**Patients**

From January 2006 through December 2008, 45 patients were enrolled. Two patients were registered but deemed ineligible (decline in performance status,  $n = 1$ ; minor surgical procedure within 7 days,  $n = 1$ ) before receiving study therapy. Forty-three patients were evaluable for toxicity and response analyses. The median age was 66 years, 77% of patients were male, 70% of patients had visceral metastases, and 40% of patients had not undergone cystectomy. Baseline characteristics are listed in Table 1.

**Table 1.** Baseline Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients	%
<b>Age, years</b>		
Median	66	
Range	41-78	
<b>Body mass index, kg/m<sup>2</sup></b>		
Median	27.7	
Range	19.1-44.0	
<b>Creatinine, mg/dL</b>		
Median	1.1	
Range	0.6-1.4	
<b>WBC count, /μL</b>		
Median	7,600	
Range	4,100-22,000	
<b>Hemoglobin, g/dL</b>		
Median	13.0	
Range	9.1-15.6	
<b>Platelet count, /μL</b>		
Median	291,000	
Range	139,000-770,000	
<b>No. of metastatic sites</b>		
Median	2	
Range	0-6	
<b>Sex</b>		
Male	33	76.7
Female	10	23.3
<b>Prior cystectomy</b>		
	17	39.5
<b>ECOG PS</b>		
0	26	60.5
1	17	39.5
<b>Metastatic sites</b>		
Any lymph node	39	90.7
Pelvic/abdominal lymph node	27	62.8
Any visceral metastases	30	69.8
Lung	18	41.9
Bone	11	25.6
<b>Modified Bajorin risk group</b>		
Good risk	8	18.6
Intermediate risk	23	53.5
Poor risk	12	27.9

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

**Toxicity**

Treatment-associated toxicity was common. Three treatment-related deaths occurred (one episode each of aortic dissection, sudden cardiac death, and CNS hemorrhage). Treatment-related grade 3 to 4 hematologic toxicities included anemia (12%), thrombocytopenia (12%), neutropenia (35%), and febrile neutropenia (2%). Bevacizumab-related nonhematologic grade 3 to 5 toxicities included DVT/PE (21%), hemorrhage (7%), cardiac toxicity (7%; sudden cardiac death, n = 1; reversible decline in left ventricular systolic function, n = 2), hypertension (5%), proteinuria (2%), vascular events (2%; aortic dissection), and renal failure (2%). After modification of the gemcitabine regimen, DVT/PE events were observed in only two of 25 patients (8% after dose reduction v 41% before dose reduction; Fisher's exact test, P = .023). Table 2 lists the treatment-related toxicity. Neither the clinically significant toxicity rate (42%; 90% CI, 29% to 56%) nor the postamendment DVT/PE toxicity rate (8%; 90% CI, 1% to 23%) exceeded the prespecified stopping limits.

On unplanned univariate analysis, patient characteristics associated with higher rates of grade 3 to 5 toxicity included the following: ≤ two metastatic sites (P = .019); platelets ≤ 291,000/μL (P = .034); gemcitabine dose 1,000 mg/m<sup>2</sup> (P = .067); absence of modified Bajorin poor-risk features (P = .111); BMI greater than 27.7 kg/m<sup>2</sup> (P = .130); and PS 0 (P = .158). In multivariable logistic regression analysis, only ≤ two metastatic sites (odds ratio [OR], 21.51; P = .010) and gemcitabine dose 1,000 mg/m<sup>2</sup> (OR, 15.22; P = .022) remained significant. Similarly, features associated with higher rates of DVT/PE included age ≤ 66 years (P = .021), gemcitabine dose 1,250 mg/m<sup>2</sup> (P = .023), prior cystectomy (P = .122), and ≤ two metastatic sites (P = .129). In multivariable logistic regression analysis, only age ≤ 66 years (OR, 19.13; P = .016) and gemcitabine dose 1,250 mg/m<sup>2</sup> (OR, 12.37; P = .013) remained significant.

**Chemotherapy Administration**

Patients received a median of six cycles of chemotherapy (range, two to eight cycles). Mean total doses of cisplatin, gemcitabine, and bevacizumab were 679, 19,992, and 6,472 mg, respectively. These totals represent planned dose-intensities of 65% (cisplatin, eight cycles planned), 60% (gemcitabine, eight cycles planned), and 46% (bevacizumab, 12 months planned). Fourteen patients (32.6%) completed eight cycles of chemotherapy. Only two patients received 12 months of bevacizumab treatment, both of whom experienced DVT/PE. Dose modifications as a result of toxicity were common, with 30 patients (69.8%) experiencing at least one dose adjustment on study. Nineteen patients (44.2%) discontinued at least one component of the CGB regimen as a result of toxicity. In particular, six patients (14.0%) discontinued bevacizumab as a result of known bevacizumab-related toxicities (DVT/PE, n = 5; proteinuria, n = 1). Four patients with DVT/PE remained on bevacizumab after therapeutic anticoagulation was achieved.

**Response and Survival**

Best RECIST response included eight patients (19%; 95% CI, 8% to 33%) with complete response and 23 patients (53%; 95% CI, 38% to 69%) with partial response, for an overall response rate of 72% (95% CI, 56% to 85%). Stable disease for ≥ 12 weeks was observed in four patients (9%; 95% CI, 3% to 22%), and progressive disease before 12 weeks occurred in six patients (14%; 95% CI, 5% to 28%). Two patients had clinically stable disease for ≥ 12 weeks that was radiographically unconfirmed. Three patients who completed eight cycles of CGB and continued on bevacizumab monotherapy converted from stable disease to partial response or complete response. Three patients with clinical complete response underwent cystectomy with observed pathologic stages of pTisN0, pT1N2, and pT3N0.

After a median follow-up time of 27.2 months (range, 3.5 to 40.9 months), the median PFS time was 8.2 months (95% CI, 6.8 to 10.3 months; Fig 1A). Among patients with good, intermediate, and poor modified Bajorin risk features, PFS was 8.2, 7.6, and 7.8 months, respectively (log-rank P = .776). Statistical significance to reject the null hypothesis for PFS was not achieved. The median OS time was 19.1 months (95% CI, 12.4 to 22.5 months; Fig 1B). Among patients with good, intermediate, and poor modified Bajorin risk features, OS was 27.0, 20.4, and 15.7 months, respectively (log-rank P = .451).

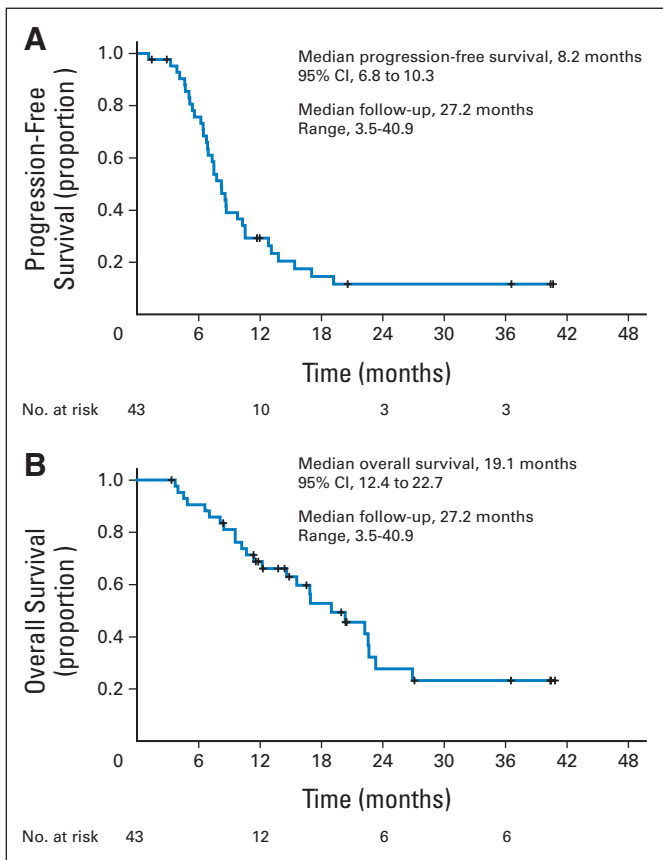
**Table 2.** Treatment-Related Toxicity

Toxicity	Gemcitabine 1,250 mg/m <sup>2</sup> (n = 18)				Gemcitabine 1,000 mg/m <sup>2</sup> (n = 25)				All Patients (N = 43)			
	All Grades		Grades 3-4		All Grades		Grades 3-5		All Grades		Grades 3-5	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
<b>Hematologic toxicity</b>												
Anemia	10	56	2	11	11	44	3	12	21	49	5	12
Thrombocytopenia	5	28	3	17	6	24	2	8	11	26	5	12
Neutropenia	9	50	6	33	13	52	9	36	22	51	15	35
Febrile neutropenia	0	0	0	0	1	4	1	4	1	4	1	4
<b>Nonhematologic toxicity</b>												
DVT/PE	7	39	7	39	2	8	2	8	9	21	9	21
HTN	3	17	1	6	6	24	1	4	9	21	2	5
Proteinuria	3	17	1	6	4	16	0	0	7	16	1	2
Hemorrhage	7	39	0	0	9	36	3	12*	16	37	3	7
Renal failure	6	33	0	0	6	24	1	4	12	28	1	2
Cardiac	3	17	1	6	10	40	3	12*	13	30	4	9
Vascular	0	0	0	0	1	4	1	4*	1	2	1	2

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; HTN, hypertension.  
 \*Three treatment-related deaths occurred (CNS hemorrhage, n = 1; sudden cardiac death, n = 1; aortic dissection, n = 1).

On unplanned univariate analysis, patient characteristics associated with shorter OS included creatinine greater than 1.1 mg/dL ( $P = .012$ ), greater than two metastatic sites ( $P = .037$ ), presence of visceral metastases ( $P = .082$ ), hemoglobin greater than 13 g/dL

( $P = .142$ ), and BMI greater than 27.7 kg/m<sup>2</sup> ( $P = .246$ ). In multivariable Cox proportional hazards analysis, only creatinine greater than 1.1 mg/dL (hazard ratio [HR], 3.43;  $P = .010$ ) and hemoglobin greater than 13 g/dL (HR, 2.33;  $P = .049$ ) remained significant, with a trend toward significance in patients with greater than two metastatic sites (HR, 2.02;  $P = .104$ ).



**Fig 1.** (A) Progression-free survival (PFS). (B) Overall survival (OS).

## DISCUSSION

Among nonhematologic malignancies, UC is a chemotherapy-sensitive malignancy, with treatment regimens producing tumor responses in  $\geq 50\%$  of patients.<sup>2,27,28</sup> Dose-dense and triplet combination chemotherapy regimens have not significantly improved the clinical efficacy established a decade ago by the CG regimen.<sup>29-32</sup> This suggests that a ceiling has been reached on advancements through cytotoxic therapy approaches. On the basis of strong preclinical rationale implicating VEGF as a critical mediator of UC progression and the proven benefit of antiangiogenic therapy in multiple malignancies, we conducted a phase II study to evaluate the activity and safety of CGB in the first-line treatment of metastatic UC.

We observed significant antitumor efficacy, with 72% of patients demonstrating tumor response and a 19% complete response rate. These results compare favorably to the 49% response rate and 12% complete response rate reported in the phase III first-line CG trial conducted in a similar population with metastatic UC.<sup>2,3</sup> However, caution is warranted in comparing response rates between studies because multiple unaccounted confounding factors between populations can significantly affect study outcomes.

The observed PFS time of 8.2 months (95% CI, 6.8 to 10.3 months) did not satisfy requirements to reject the null hypothesis. This PFS result is similar to results from other first-line studies in this population.<sup>2,3,29-32</sup> In contrast, the median OS time of 19.1 months compares favorably with other first-line trial results, which have ranged from 13.8 to 18.3 months.<sup>2,3,29-32</sup> The OS results of our trial are

encouraging compared with historical results, particularly in patients with intermediate (20.4 v 13.4 months, respectively) and poor (15.7 v 9.3 months, respectively) Bajorin risk.<sup>24</sup> Both hemoglobin greater than 13.0 g/dL and creatinine greater than 1.1 mg/dL were significant risk factors for shorter OS. Although never reported in UC, high hemoglobin levels have been associated with shorter OS in multiple malignancies in association with the use of erythropoietin-stimulating agents.<sup>33,34</sup> Similarly, renal insufficiency has been associated with reduced OS across many tumor types.<sup>35</sup>

The use of investigator-reported PFS assessments, rather than independent blinded radiologic assessments, is one possible factor in the discrepancy between the observed PFS and OS results.<sup>36</sup> In smaller phase II studies, greater consideration of independent review of PFS outcomes may be required because of the large relative impact of individual patient outcomes in overall study efficacy interpretation. Another potential factor may be an underappreciation of bevacizumab-mediated antitumor immunologic effects. Investigators have recently demonstrated improved antitumor immune responses as a result of antiangiogenic therapy in preclinical cancer models.<sup>37,38</sup> It is plausible that a bevacizumab-mediated antitumor immunologic effect may have long-lasting benefits beyond treatment with first-line cytotoxic chemotherapy. The disconnect between PFS and OS may also be a result of limitations of the RECIST definition of progression. In patients with large tumor reduction, a 20% growth from maximum tumor reduction fulfilling RECIST progression criteria may still result in a lower bulk of disease than present at study entry. Lastly, in phase II trials, OS improvements may reflect treatment of patients with locally advanced or low-volume metastatic disease rather than true treatment-related effect.<sup>39</sup> In the current study population composed of 70% of patients with visceral metastases, the potential for early-stage disease confounding OS results is low.

The addition of bevacizumab to CG resulted in significant treatment-related toxicity. In particular, an exceedingly high rate of DVT/PE events was observed, necessitating an unplanned protocol-amended dose reduction of gemcitabine from 1,250 to 1,000 mg/m<sup>2</sup>. The decision to reduce the gemcitabine dose was based on several factors including preliminary data in other trials of antiangiogenic agents in combination with CG demonstrating increased serum thrombotic mediators in response to the cytotoxic rather than antiangiogenic agents, a desire to keep the most active agent (cisplatin) at full dose, no clear relationship between bevacizumab dose and DVT/PE rates in prior bevacizumab trials, and no increased DVT/PE rate with high-dose bevacizumab in a parallel phase III trial examining the CGB triplet regimen at two bevacizumab doses (7.5 and 15 mg/kg) in patients with metastatic non-small-cell lung cancer.<sup>17,19,21-23,40-48</sup> After the gemcitabine dose reduction, DVT/PE rates were reduced in our trial ( $P = .023$ ). Neither of the prespecified toxicity stopping rules was met. However, it should be noted that the stopping rules were set to detect extreme rates of toxicity. Furthermore, the effects of other potential mediators of chemotherapy and antiangiogenic therapy toxicity were not evaluated within this study.

With respect to DVT/PE events, prior bevacizumab studies have reported DVT/PE rates ranging from 2% to 14%.<sup>17,19,21-23,40-42,44</sup> A pooled analysis of five randomized trials ( $n = 1,745$ ) of combination chemotherapy and bevacizumab in breast, colon, and lung cancer showed a significantly increased risk of arterial thrombotic events (HR, 2.0;  $P = .03$ ) but not DVT/PE in association with

bevacizumab treatment.<sup>43</sup> Recent data in UC suggest that patients with UC may be at a higher risk of arterial and venous thromboembolic events than previously believed. In a phase II study in patients with metastatic UC treated with carboplatin, gemcitabine, and bevacizumab, investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) reported a DVT/PE rate of 16% with no treatment-related deaths.<sup>49</sup> Interestingly, in a cohort of patients with metastatic UC treated off-protocol without bevacizumab at MSKCC during the same time period, a DVT/PE rate of 17% was observed. With the high DVT/PE rates observed in both ours and the MSKCC study, additional prospective trials with detailed demographic data and tissue collections are required to more fully characterize the true risk rate, risk factors, and mechanisms of vascular toxicity in patients with UC, particularly in studies using antiangiogenic therapies.

In summary, CGB demonstrates promising antitumor activity in the first-line treatment of patients with metastatic UC. Enthusiasm for this regimen is tempered by significant toxicity rates observed in this phase II trial. Further characterization of the true risks and benefits of CGB therapy will be defined in a phase III intergroup study.

#### 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:** Cynthia S. Johnson, Eli Lilly (C)  
**Consultant or Advisory Role:** Walter M. Stadler, Genentech (C); Christopher J. Sweeney, Roche (C) **Stock Ownership:** Cynthia S. Johnson, Eli Lilly **Honoraria:** David Waterhouse, Eli Lilly **Research Funding:** Walter M. Stadler, Genentech, Eli Lilly **Expert Testimony:** None **Other Remuneration:** None

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