Phase II Study of Modified Docetaxel, Cisplatin, and Fluorouracil With Bevacizumab in Patients With Metastatic Gastroesophageal Adenocarcinoma

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ABSTRACT

Purpose

To evaluate the safety and efficacy of a modified administration schedule of docetaxel, cisplatin, and fluorouracil (mDCF) with bevacizumab in patients with advanced gastroesophageal malignancies.

Patients and Methods

Previously untreated patients with metastatic gastroesophageal adenocarcinoma received bevacizumab 10 mg/kg, docetaxel 40 mg/m², fluorouracil 400 mg/m², leucovorin 400 mg/m² on day 1, fluorouracil 1,000 mg/m²/d × 2 days intravenous continuous infusion beginning on day 1, and cisplatin 40 mg/m² on day 3. The primary objective was to improve 6-month progression-free survival (PFS) from 43% (historical DCF control) to 63% with the addition of bevacizumab. The target accrual was 44 patients to have 10% type I and II error rates.

Results

In total, 44 eligible patients with cancer were enrolled from October 2006 to October 2008: 22 gastric, 20 gastroesophageal junction (GEJ), and two esophagus. In 39 patients with measurable disease, the confirmed response rate was 67% (95% CI, 50% to 81%). Six-month PFS was 79% (95% CI, 63% to 88%), and median PFS was 12 months (95% CI, 8.8 to 18.2 months). With 26-month follow-up, median overall survival (OS) was 16.8 months (95% CI, 12.1 to 26.1 months), and 2-year survival was 37%. Treatment-related grade 3 to 4 toxicity was as follows: neutropenia without fever (50%), fatigue (25%), venous thromboembolism (39%), and nausea, vomiting, mucositis, neuropathy, and febrile neutropenia less than 10% each. In subset analysis, diffuse gastric cancer had significantly worse PFS and OS, and the response rate in proximal/GEJ tumors was 85% (95% CI, 62% to 97%).

Conclusion

mDCF with bevacizumab appears tolerable and has notable patient outcomes in patients with advanced gastroesophageal adenocarcinoma. Six-month PFS was 79%, surpassing our predefined efficacy end point, and median and 2-year OS were 16.8 months and 37%, respectively.

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INTRODUCTION

Cancers of the stomach and esophagus are highly aggressive malignancies with significant mortality rates. Together, their global incidence is approximately 1.4 million new cases, and they are jointly responsible for 1.1 million deaths annually.¹ Cisplatin/fluoropyrimidines-based therapy is considered standard of care for much of the world, and some patients may also tolerate the addition of epirubicin^{2,3} or docetaxel⁴ with additional benefit.^{3,5,6} Despite optimal treatment, median survival for advanced disease remains less than 1 year.^{2-4,7} Human epidermal growth factor receptor 2 (*HER2-neu*) is a

new validated target in gastric and gastroesophageal junction (GEJ) cancers.⁸ Unfortunately, amplification and/or overexpression of this oncogene occurs in less than 25% of patients with cancers of the stomach, GEJ, or distal esophagus.⁹ Therefore, treatment options for the majority of patients with gastroesophageal malignancies will be limited to cytotoxic therapy alone. New therapies are needed for these diseases.

Inhibition of vascular endothelial growth factor by bevacizumab has had a positive impact on patient outcomes in several malignancies and has received regulatory approval for colorectal,^{10,11} lung,¹² and renal cell carcinomas^{13,14} and recurrent

glioblastoma.^{15,16} Vascular endothelial growth factor is overexpressed in up to 60% of gastroesophageal cancers, and its overexpression correlates with advanced stage, higher risk of recurrence, and worse survival.¹⁷ In a phase II clinical trial,¹⁸ we demonstrated the safety and efficacy of bevacizumab with irinotecan and cisplatin in gastric and GEJ cancers. In that study, median time to progression (the primary end point) appeared to improve from the historical range of 4.2 to 5.8 months^{19,20} to 8.3 months, and median overall survival (OS) was 12.3 months.¹⁸

Although it is a standard first-line option, the addition of docetaxel to cisplatin/fluorouracil (DCF) as currently administered is associated with significant toxicity²¹ and is prohibitive as a backbone for the addition of new targeted agents. We developed a modified DCF regimen (mDCF) to reduce toxicity in an effort to develop a three-drug chemotherapy regimen for advanced gastroesophageal cancer to which a targeted agent such as bevacizumab could be added. The modifications include (1) shortened de Gramont–like fluorouracil schedule to reduce mucositis and diarrhea,²² (2) reduced bimonthly doses of cisplatin and docetaxel, and (3) administration of docetaxel and cisplatin on separate days because of possible pharmacokinetic interaction between docetaxel and the delayed emesis regimen used for cisplatin (being examined in a separate random assignment phase II study²³). Initial results (see the Abstract) showed fewer hospitalizations and less grade 3 to 4 toxicity with the mDCF regimen while maintaining efficacy with median time to treatment failure of 8.6 months and median survival of 15.1 months.²³

On the basis of the biologic rationale and encouraging clinical results for bevacizumab in the treatment of gastroesophageal cancer and the survival improvement when docetaxel is added to cisplatin/fluorouracil-based chemotherapy, we chose to study the efficacy and tolerability of mDCF with bevacizumab in a phase II clinical trial of metastatic gastroesophageal adenocarcinoma. Our aims were to demonstrate the safety and efficacy of a new three-drug chemotherapy regimen for gastric cancer and to confirm our initial reported findings of the potential benefit of bevacizumab with combination chemotherapy in this disease. Subsequently, in September 2007, a global phase III registration study of cisplatin/capecitabine with or without bevacizumab in advanced gastric cancer was initiated by Roche Pharmaceutical. The primary study results of this phase III study were reported at the 46th Annual Meeting of the American Society of Clinical Oncology (June 4–8, 2010, Chicago IL), failing to demonstrate an improvement in OS when bevacizumab was added to cisplatin/capecitabine.²⁴

PATIENTS AND METHODS

Patient Eligibility

This was a phase II clinical trial performed at Memorial Sloan-Kettering Cancer Center (MSKCC) with institutional review board approval. All patients provided informed consent. Patients were required to be age 18 years or older with pathologically confirmed gastric, GEJ, or distal esophageal adenocarcinoma, previously untreated for metastatic disease. Histologic documentation of metastasis or confirmation on two independent imaging modalities was required. Prior chemotherapy or chemoradiotherapy for locoregional disease was allowed if more than 6 months had elapsed following completion of prior therapy and registration on the clinical trial. Patients could not have received prior cisplatin, docetaxel, bevacizumab, or any biologic antiangiogenic agent. Radiographically evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria²⁵ was required. The primary tumor was not considered radiographically evaluable. Anticoagulation therapy was

allowed. Patients not being given anticoagulation therapy were required to have a prothrombin time (international normalized ratio) ≤ 1.5 and a partial thromboplastin time ≤ 3 seconds above upper limit of normal (ULN). Patients were required to have a Karnofsky performance status of at least 70% and adequate organ function defined as absolute neutrophil count $\geq 1,500/\mu\text{L}$, hemoglobin ≥ 9.0 g/dL, platelet count $\geq 100,000/\mu\text{L}$, serum creatinine ≤ 1.5 mg/dL, urinalysis $< 2+$ proteinuria, urine protein (mg/dL):urine creatinine (mg/dL) ratio < 1.0 , total bilirubin $\leq$ ULN, and AST, ALT, and alkaline phosphatase within the eligible range (per Appendix Table A1, online only). Women of childbearing potential were required to have a negative pregnancy test.

Exclusion criteria typical of cisplatin and bevacizumab therapies included uncontrolled hypertension, current or prior arterial or peripheral vascular disease, high bleeding risk, recent surgery, or appreciable hearing deficit. Patients who had another malignancy within the past 3 years (excluding basal cell carcinoma of the skin, cervical carcinoma in situ, or nonmetastatic prostate cancer) or active brain metastases were also excluded.

Treatment Plan

Patients received outpatient therapy with bevacizumab 10 mg/kg, docetaxel 40 mg/m², fluorouracil 400 mg/m², leucovorin 400 mg/m² on day 1, fluorouracil 1,000 mg/m²/d $\times 2$ days intravenous continuous infusion beginning on day 1, and cisplatin 40 mg/m² on day 3. Treatment was repeated every 2 weeks, with standard premedication and delayed emesis regimens. Prophylactic leukocyte growth factor support was not allowed. A cycle was considered three treatments or 6 weeks.

Evaluation of Study and Dose Attenuation

All adverse events were graded according to the National Cancer Institute Common Toxicity Criteria v3.0. Parameters for treatment include absolute neutrophil count $\geq 1,000/\mu\text{L}$, platelet count $\geq 75,000/\mu\text{L}$, creatinine ≤ 2.0 mg/dL (for creatinine level of 1.8 to 1.9 mg/dL, cisplatin dose attenuation was required), urine protein:urine creatinine ratio ≤ 3.5 , total bilirubin $\leq 2 \times$ ULN (docetaxel held for total bilirubin 1 to 2 $\times$ ULN), and AST, ALT, and alkaline phosphatase per Appendix Table A2 (online only; for docetaxel treatment only). Treatment was also held for grade 3 to 4 non-hematologic toxicity (with the exception of grade 3 electrolyte abnormalities or grade 3 anemia not associated with bleeding).

Individual chemotherapy drugs could be dose-reduced per the dose attenuation table (Appendix Table A3, online only) or held on the basis of individual toxicity. No dose reduction in bevacizumab was allowed. Docetaxel was reduced for febrile neutropenia or grade 3 to 4 neutropenia ≥ 7 days, platelet count $\leq 75,000/\mu\text{L}$, grade 3 to 4 anorexia, or grade ≥ 2 peripheral neuropathy. Cisplatin was reduced for grade 3 to 4 nausea/vomiting (or grade 2 nausea or vomiting for > 5 days), creatinine 1.8 to 1.9 mg/dL (or held for creatinine ≥ 2.0 mg/dL), or grade 3 to 4 ototoxicity. Fluorouracil was reduced for grade 3 to 4 diarrhea or grade ≥ 2 stomatitis. After 6 months of therapy, cisplatin, docetaxel, and/or fluorouracil could be discontinued for cumulative toxicity.

Tumor assessments were performed following the completion of every cycle (ie, 6 weeks) for the first six cycles and then every two cycles thereafter. Confirmatory scans were obtained 6 weeks after documentation of response or stable disease. All radiographs were reviewed by the study radiologist (R.A.L.), and RECIST measurements were recorded by the study radiologist in real time. Patients remained on study until disease progression, patient withdrawal, or unacceptable toxicity.

Biostatistics

The primary end point of this study was to test the hypothesis that the addition of bevacizumab would improve 6-month progression-free survival (PFS) from 43% (on the basis of parent DCF regimen⁴) to 63%. PFS was measured from the start of treatment to the date of either documentation of disease progression per RECIST criteria or death. Patients who withdrew before documented progression were censored at their off-study date. A sensitivity analysis was also performed in which patients who withdrew without disease progression were considered as having progression at their off-study date. With 44 evaluable patients, the study had a 90% power to differentiate between 6-month PFS of 43% and 63% with type I and II error rates of 10%

each (exact single-stage binomial design). The combination was considered promising if 24 or more patients were progression free at 6 months.

Our secondary end points of efficacy were response rate in patients with measurable disease, median PFS, OS, and 2-year survival. In an exploratory analysis, we examined the efficacy of mDCF with bevacizumab in predefined gastric cancer subtypes (proximal, distal/body, and diffuse gastric cancer).²⁶ This included evaluation of response, PFS, and OS according to disease type. Adjustment for multiple comparisons was not performed. PFS and OS curves were estimated by using the Kaplan-Meier method and compared by using the permutation log-rank test.²⁷

Study Monitoring

The study was monitored quarterly by the MSKCC Data and Safety Monitoring Board and the MSKCC Therapeutic Response Review Committee. No discrepancies or deviations were identified throughout the study period.

RESULTS

Patient Characteristics

Between October 2006 and October 2008, 44 eligible patients were enrolled. Patient characteristics are listed in Table 1. The majority of patients were white males with a median age of 57 years and with an equal distribution of proximal and distal gastric tumors. The majority of patients (75%) had more than two sites of metastatic disease, and 89% had their primary tumor unresected.

Safety and Drug Delivery

Tables 2 and 3 describe overall nonhematologic and hematologic toxicity. Grade 3 to 4 GI toxicity, neuropathy, and febrile neutropenia rates were < 10%. No arterial thromboembolic events were observed. All 17 patients with venous thromboembolism (including 10 patients with asymptomatic thromboembolism) received anticoagulation therapy and remained on study. One patient subsequently developed upper GI bleeding after 2 months on anticoagulation therapy requiring indwelling venous catheter filter placement. No patients developed grade 3 to 4 hypertension or grade 2 to 4 proteinuria.

Eighteen hospitalizations attributable to treatment occurred in 16 patients (36%): nausea/vomiting/mucositis (n = 5), dehydration/diarrhea (n = 4), fever/infection (n = 3), fever with neutropenia (n = 3), gastric perforation (n = 1), fluorouracil-related coronary vasospasm (n = 1), and generalized fatigue/weakness (n = 1). The dose intensity over the first 6 months of therapy was greater than 85% for all drugs, and 27% of patients (n = 12) received white cell growth factor support to maintain their treatment schedule every 2 weeks. After 6 months of therapy, patients began to develop cumulative toxicity that necessitated discontinuing one or two cytotoxic drugs (generally cisplatin and/or docetaxel). The primary reason for switching to less intensive or maintenance therapy was grade 2 cumulative toxicity $\geq$ 7 days; cumulative toxicity included myelosuppression, fatigue or weakness, neuropathy, and stomatitis. Fifteen patients received more than 6 months of maintenance fluorouracil/bevacizumab and an additional four patients received more than 3 months of docetaxel/fluorouracil/bevacizumab maintenance therapy. Thirty-seven patients (84%) had a grade 3 to 4 treatment-related adverse event over the duration of the study.

Efficacy

With median follow-up of 26 months, 34 patients (77%) have died. Thirty-three patients were removed from the study for disease

Table 1. Patient Characteristics (n = 44)

Characteristic	No.	%
Age, years		
Median	57	
Range	29-74	
Sex (ratio of males to females)	32:12	
Karnofsky performance status		
Median	80	
Range	70-90	
Race/ethnicity		
White	36	82
Black	3	7
Hispanic	3	7
Asian	2	5
Tumor location		
Esophagus	2	5
Gastroesophageal junction	20	45
Gastric	22	50
Differentiation		
Well differentiated	2	5
Moderate	13	29
Poorly differentiated	28	64
Unknown	1	2
Gastric cancer subtype (n = 42)		
Proximal/gastroesophageal junction, non-diffuse	20	48
Diffuse/signet ring cell	12	29
Distal/intestinal	10	24
Prior therapy		
None	41	93
Fluorouracil/radiation (adjuvant)	2	5
Paclitaxel/carboplatin (preoperative) and fluorouracil/radiation (adjuvant)	1	2
Baseline laboratory values		
Hemoglobin, g/dL		
Median	12.3	
Range	9.2-16.1	
Albumen, g/dL		
Median	3.6	
Range	2.3-4.4	
Platelet count, 1,000/ μ L		
Median	329	
Range	165-881	
Primary tumor unresected	39	89
Measurable disease	39	89
Site of metastatic disease		
Liver	25	57
M1 lymph nodes	33	75
Retroperitoneal		31
Mediastinal/supraclavicular		16
Peritoneum	25	57
Lung	12	27
Bone	10	20
Patients with more than one site of M1 disease	40	91
Patients with more than two sites of M1 disease	33	75

progression, and seven patients withdrew for reasons other than disease progression: one patient each for grade 3 upper GI bleeding (not receiving anticoagulation therapy), partial bowel obstruction requiring surgery (no visible disease identified in peritoneum), gastric perforation, and perianal fistula; one patient with treatment response

Table 2. Cumulative Nonhematologic Toxicity

Toxicity	Grade							
	2		3		4		3 to 4 (total)	
	No.	%	No.	%	No.	%	No.	%
Allergy/hypersensitivity	3	7	2	5	0		2	5
Anorexia	2	5	2	5	0		2	5
Dysgeusia	4	9	0		0		0	
Nausea	9	20	1	2	0		1	2
Vomiting	2	5	2	5	0		2	5
Dehydration	3	7	4	9	0		4	9
Diarrhea	10	23	3	7	0		3	7
Mucositis	10	23	3	7	1	2	4	9
Fatigue	16	36	11	25	0		11	25
Neuropathy	14	32	1	2	0		1	2
Hand-foot syndrome	1	2	2	5	0		2	5
Tinnitus	4	9	0		0		0	
Alopecia	3	7	0		0		0	
Electrolytes								
Hypomagnesemia	14	32	4	9	2	5	6	14
Hypophosphatemia	11	25	14	32	0		14	32
Hypokalemia	0		3	7	0		3	7
Liver function elevations (AST/ALT)	4	9	0		0		0	
Possibly bevacizumab-related adverse events (any frequency)								
Thromboembolism	1	2	7	16	10	23	17	39
Hemorrhage	1	2	1	2	0		1	2
GI fistula	1	2	0		0		0	
GI perforation	0		0		1	2	1	2
Hypertension	1	2	0		0		0	
Proteinuria	0		0		0		0	

NOTE. All grade 2 to 4 adverse events with a frequency of at least 5% possibly, probably, or definitely attributed to treatment.

withdrew to undergo resection of the primary cancer following resolution of metastatic disease; and two patients withdrew while they were responding to treatment for personal reasons. Four patients remain on study as of August 2010.

There were 32 patients alive and progression free at 6 months, surpassing our predefined threshold to consider this combination promising. Kaplan-Meier estimates of 6-month PFS and OS are 79% (95% CI, 63% to 88%) and 91% (95% CI, 78% to 96%). Median PFS and OS were 12 months (95% CI, 8.8 to 18.2 months) and 16.8 months (95% CI, 12.1 to 26 months), respectively (Fig 1). Following the sensitivity analysis in which all patients who withdrew were analyzed as having disease progression at their off-study date, 32 patients remained progression free at 6 months, and 6-month PFS was 73%

(95% CI, 57% to 83%). The overall response rate was 67% (95% CI, 50% to 81%), 31% (95% CI, 17% to 48%) had stable disease, and one patient had disease progression as best response. Two patients had a complete response, and 27 patients (69%) received second-line therapy (13 were given irinotecan-based therapy, five oxaliplatin-based therapy, five docetaxel-based therapy, and four investigational therapy); no patients received second-line trastuzumab or bevacizumab beyond progression.

In an exploratory subgroup analysis, when analyzed according to gastric cancer disease type (proximal, diffuse, or distal/body²⁶), both PFS ($P = .01$) and OS ($P = .009$) were significantly diminished for diffuse-type gastric cancer (Table 4). Figure 2 provides the Kaplan-Meier curve for PFS according to gastric cancer subtype.

Table 3. Cumulative Hematologic Toxicity

Toxicity	Grade							
	2		3		4		3 to 4 (total)	
	No.	%	No.	%	No.	%	No.	%
Hemoglobin	22	50	3	7	1	2	4	9
Thrombocytopenia	10	23	9	21	2	5	11	25
Leucopenia	7	16	24	55	4	9	28	64
Neutropenia (without fever)	8	18	13	30	9	21	22	50
Febrile neutropenia	0		1	2	2	5	3	7

NOTE. All grade 2 to 4 adverse events (excluding lymphopenia) possibly, probably, or definitely attributable to treatment.

Fig 1. Kaplan-Meier curve for progression-free survival (PFS) and overall survival (OS). mo, months.

Fig 2. Kaplan-Meier curve for progression-free survival according to gastric cancer subtype. Tumors are categorized as diffuse gastric cancer (n = 12), distal/body subtype (n = 10), and proximal/gastroesophageal junction (GEJ) tumors (n = 20). Response rate was evaluated in measurable patients only (n = 39); ranges indicated in parentheses.

DISCUSSION

Most patients with gastroesophageal malignancies will receive palliative chemotherapy for recurrent or unresectable/metastatic disease. Although combination therapy is superior to single-agent therapy and three-drug therapy (when tolerable) is associated with improved survival when compared with two-drug therapy²⁸ (reviewed by Power et al⁷), patient survival remains less than 12 months despite optimal treatment.^{2,4,26} In the search to improve patient outcomes with targeted therapy, bevacizumab in combination with chemotherapy has been examined and has demonstrated encouraging activity in previous phase II studies.^{18,29} In this single-arm, phase II study of bevacizumab with mDCF, our observed median PFS of 12 months and median OS of 16.8 months, with 37% of patients enrolled alive at 2 years, is noteworthy. Six-month PFS improved from a historical rate of 43% with parent DCF⁴ to 79% (95% CI, 63% to 88%), thereby surpassing our primary end point.

The mDCF regimen appears to be significantly better tolerated than the parent regimen, with reduced rates of febrile neutropenia and grade 3 to 4 nausea/vomiting, mucositis, and diarrhea compared with parent DCF. We have observed similar findings of improved tolerability of mDCF in a separate random assignment phase II study not containing bevacizumab.²³ When mDCF is administered without bevacizumab, we also observed a noteworthy OS of 15.1 months; however, the time to treatment failure was 8.6 months,²³ seemingly less than in this study in which median PFS was 12 months in a nonrandomized comparison. We did observe a high rate of venous thromboembolism in this study, similar to that in our previous study of chemotherapy with bevacizumab.¹⁸ Gastroesophageal cancers are associated with the highest risk of venous thromboembolism,³⁰ and bevacizumab³¹ and cisplatin³² may increase this risk. In this study, however, all patients with venous thromboembolism continued on

Table 4. PFS and OS for the Total Population and by Disease Type

Response	Total (N = 44)		Proximal/GEJ (n = 20)		Diffuse (n = 12)		Distal/Body (n = 10)	
	No.	%	No.	%	No.	%	No.	%
PFS, months								
Median	12.0		16.3		8.6		14.3	
Range	8.8-18.2		8.9-NR		3.1-12.0		1.8-19.9	
6-month (%)								
Median	79		85		74		79	
Range	63-88		60-95		39-91		38-94	
OS, months								
Median	16.8		22.5		11.8		25	
Range	12.1-26.1		13-34		6.3-17.4		2.4-38	
12-month (%)								
Median	68		80		50		70	
Range	52-80		55-92		21-74		33-89	
24-month (%)								
Median	37		49		20		50	
Range	23-52		26-69		1-31		18-75	

NOTE. There is a significant difference in PFS ($P = .01$) and OS ($P = .009$) based on disease subtype. Abbreviations: PFS, progression-free survival; OS, overall survival; GEJ, gastroesophageal junction; NR, not reached.

protocol therapy following the formation of thrombus while receiving anticoagulation therapy without an increased incidence of bleeding. We did not observe an increase in GI bleeding or perforation/fistula formation with the addition of bevacizumab therapy when considering historical data.

On the basis of all predefined measures of efficacy and safety, we conclude that the addition of bevacizumab to chemotherapy is safe and tolerable and appears to be associated with improved activity. However, the phase III study of cisplatin/capecitabine with or without bevacizumab (AVAGAST)²⁴ in gastric cancer was reported as negative for the primary end point of OS. As many as 60% of positive phase II findings are not validated in phase III trials.^{33,34} However, in view of continued compelling phase II data, “Is bevacizumab with chemotherapy still worth examining in gastroesophageal malignancies?” Although the AVAGAST study did not demonstrate an OS advantage for bevacizumab with chemotherapy, a preplanned subgroup analysis suggests regional differences in efficacy. Specifically, Western patients appeared to have a greater benefit with bevacizumab than Asian patients.²⁴

One potential explanation for the apparent discordant results in the AVAGAST study and this phase II study is that gastric cancer is a heterogeneous disease, with different histology and epidemiology that may be reflected in disease biology.²⁶ Our hypothesis is that biologic differences in gastric cancer subtypes may explain the overall negative results but positive signals in subgroup analysis in the AVAGAST study. A similar finding of variable efficacy on the basis of disease type has been observed in other global phase III studies: Multicenter Phase III Comparison of Cisplatin/S-1 With Cisplatin/Infusional Fluorouracil in Advanced Gastric or Gastroesophageal Adenocarcinoma Study (FLAGS)³⁵ and A Study of Herceptin (Trastuzumab) in Combination With Chemotherapy Compared With Chemotherapy Alone in Patients With HER2-Positive Advanced Gastric Cancer (ToGA).³⁶ The incidence of proximal gastric cancer is more common in the West than in Asia, whereas distal tumors typically associated with chronic *Helicobacter pylori* infection predominate in Asia.³⁷ In an exploratory analysis, we found a significant difference in both PFS and OS among different gastric cancer disease types. Patients with diffuse tumors appear to have the least efficacy when compared with proximal or distal/body intestinal tumors, including significantly diminished PFS and OS compared with the other gastric cancer types and a response rate of 38% versus 85% for proximal nondiffuse gastric cancers. Other differences with the AVAGAST study may be significant as well. Beyond the obvious difference in chemotherapy regimen, patients enrolled on AVAGAST less commonly had liver metastases—33% for AVAGAST—whereas the rate was 57% of enrolled patients in this study. We submit that there are notable differences in the types of gastric cancer patients enrolled that may explain the discordant results between this study and AVAGAST.

The improved response rate and survival observed in patients with proximal/GEJ tumors on this study (response rate, 85%) is noteworthy because tumors of the proximal stomach and GEJ are considered more aggressive, having a worse survival stage-for-stage than tumors from the rest of the stomach.^{38,39} Bevacizumab may overcome the adverse prognostic characteristic of having a proximal/GEJ tumor and improve the outcome in these patients. Another example of a poor prognostic factor that subsequently has improved survival following the addition of a targeted agent is HER2⁴⁰ and trastuzumab⁴¹ in breast cancer. However, unlike the

case for trastuzumab and HER2, it remains unexplained why bevacizumab with mDCF appears so active in proximal/GEJ tumors in this phase II study.

We acknowledge that single-arm phase II results should be considered cautiously because of the limitations of sample size, possible enrollment bias, and patient selection.³⁴ Indeed, these are the most likely reasons that positive data from phase II clinical studies are not confirmed in phase III studies.³⁴ However, our efficacy data, particularly in proximal/GEJ gastric tumors are encouraging and supportive of additional investigation of bevacizumab with chemotherapy, particularly our modified regimen. This regimen (when administered without bevacizumab) was associated with considerable survival (median OS, 15.1 months) in a separate phase II randomized study, although time to treatment failure (a surrogate for PFS) was less compelling (median time to treatment failure, 8.6 months).²³ We submit that gastric cancer is not one disease and bevacizumab may have a greater benefit for some subtypes of gastric cancer over others—a question for which prospective validation is necessary.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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