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ORIGINAL REPORT

Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study

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ABSTRACT

Purpose
The Avastin in Gastric Cancer (AVAGAST) trial was a multinational, randomized, placebo-controlled trial designed to evaluate the efficacy of adding bevacizumab to capecitabine-cisplatin in the first-line treatment of advanced gastric cancer.

Patients and Methods
Patients received bevacizumab 7.5 mg/kg or placebo followed by cisplatin 80 mg/m^2 on day 1 plus capecitabine 1,000 mg/m^2 twice daily for 14 days every 3 weeks. Fluorouracil was permitted in patients unable to take oral medications. Cisplatin was given for six cycles; capecitabine and bevacizumab were administered until disease progression or unacceptable toxicity. The primary end point was overall survival (OS). Log-rank test was used to test the OS difference.

Results
In all, 774 patients were enrolled; 387 were assigned to each treatment group (intention-to-treat population), and 517 deaths were observed. Median OS was 12.1 months with bevacizumab plus fluoropyrimidine-cisplatin and 10.1 months with placebo plus fluoropyrimidine-cisplatin (hazard ratio 0.87; 95% CI, 0.73 to 1.03; $P = .1002$). Both median progression-free survival (6.7 *v* 5.3 months; hazard ratio, 0.80; 95% CI, 0.68 to 0.93; $P = .0037$) and overall response rate (46.0% *v* 37.4%; $P = .0315$) were significantly improved with bevacizumab versus placebo. Preplanned subgroup analyses revealed regional differences in efficacy outcomes. The most common grade 3 to 5 adverse events were neutropenia (35%, bevacizumab plus fluoropyrimidine-cisplatin; 37%, placebo plus fluoropyrimidine-cisplatin), anemia (10% *v* 14%), and decreased appetite (8% *v* 11%). No new bevacizumab-related safety signals were identified.

Conclusion
Although AVAGAST did not reach its primary objective, adding bevacizumab to chemotherapy was associated with significant increases in progression-free survival and overall response rate in the first-line treatment of advanced gastric cancer.

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INTRODUCTION

Gastric cancer is a common malignancy and is associated with a high mortality rate. It is the fourth most prevalent cancer diagnosed in men worldwide (fifth in women), and the third most common cause of cancer-related deaths in men (fifth in women).[1] In the West, most patients with gastric adenocarcinoma present with advanced or metastatic disease, whereas in several Asian countries (eg, Korea and Japan), gastric cancer is usually identified early when cure rates remain high.[2] Other regional differences in gastric cancer are readily identifiable. For example, proximal gastric cancers are more prevalent in Europe and the Americas than in Asia.[3] Conversely, intestinal gastric cancer, characterized by chronic *Helicobacter pylori* infection, is more prevalent in high-incidence areas such as Japan, Korea, and Eastern Europe.[4] Although gastric cancer may be considered a heterogeneous disease with potential implications for disease biology,[5] patients are generally grouped together and treated irrespective of these differences. Prognosis is poor for most patients; only marginal improvements in patient outcomes have been achieved with chemotherapy despite extensive phase III testing.[6-8]

Targeted therapy may offer new possibilities for the treatment of gastric cancer, as illustrated by the Study of Herceptin (Trastuzumab) in Combination With Chemotherapy Compared

With Chemotherapy Alone in Patients With HER2-Positive Advanced Gastric Cancer (ToGA study),[9] which demonstrated a substantial increase in overall survival (OS) in HER2-positive patients with metastatic gastric cancer treated with trastuzumab plus chemotherapy versus chemotherapy alone.

Angiogenesis is recognized as an important aspect of tumorigenesis. Vascular endothelial growth factor A (VEGF-A) is a key mediator of physiologic and pathologic angiogenesis.[10] Activities of VEGF-A are mediated by two tyrosine kinase receptors, VEGFR-1 and VEGFR-2. Preclinical studies show that bevacizumab (Avastin, Genentech/Roche, San Francisco, CA/Basel, Switzerland), a monoclonal antibody targeting VEGF-A, results in tumor growth inhibition when given as monotherapy or in combination with cytotoxic agents.[11] Clinical trials have further demonstrated that bevacizumab in combination with chemotherapy has efficacy in several malignancies, including colon cancer,[12] breast cancer,[13] lung cancer,[14] and glioblastoma.[15] In patients with gastric cancer, VEGF expression has been linked to tumor aggressiveness[16] and poor prognosis.[17-19] Shah et al[20] showed that bevacizumab plus platinum-containing chemotherapy had promising efficacy in patients with metastatic gastric/gastroesophageal junction adenocarcinoma (median time to progression, 8.3 months; median OS, 12.3 months).

On the basis of the broad activity of antiangiogenic inhibition in epithelial malignancies and compelling results in metastatic gastric cancer, the Avastin in Gastric Cancer (AVAGAST) study was initiated. It was designed to demonstrate the benefit of bevacizumab in gastric cancer when added to a first-line chemotherapy doublet (cisplatin and capecitabine or fluorouracil [FU]). Capecitabine or FU was included in AVAGAST on the basis of the results of a randomized phase III study in which capecitabine-cisplatin and FU-cisplatin showed equal efficacy without any substantial change in safety profile.[21] This article reports the primary efficacy and safety analyses from AVAGAST. An additional objective was the mandatory sampling of tumor tissue and blood for analysis of predefined and exploratory biomarkers (presented elsewhere).[22]

PATIENTS AND METHODS

Study Design

AVAGAST was a prospective, random-assignment, double-blind, placebo-controlled phase III clinical trial. The protocol was approved at each participating site by an independent ethics committee or institutional review board (ClinicalTrials.gov identifier: NCT00548548). The trial was carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry.

Patients were assigned (1:1 ratio) to treatment by using permuted-block randomization (see Appendix, online only), with geographic region (Asia-Pacific/Europe/Pan-America), fluoropyrimidine (capecitabine/FU), and disease status (metastatic/locally advanced) as stratification factors.

Patients

Patients age ≥ 18 years with previously untreated, histologically confirmed, unresectable locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and life expectancy of ≥ 3 months were eligible. Measurable and nonmeasurable disease was allowed, but disease had to be evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.0.[23] (Neo)adjuvant chemotherapy was permitted if completed ≥ 6 months before random assignment. Surgery or radiotherapy was permitted if completed ≥ 28 days before random assignment. Prior platinum or antiangiogenic therapy was not allowed. Patients were required to have adequate bone marrow, hepatic, and renal function (including proteinuria of ≤ 1 g/24 hours).

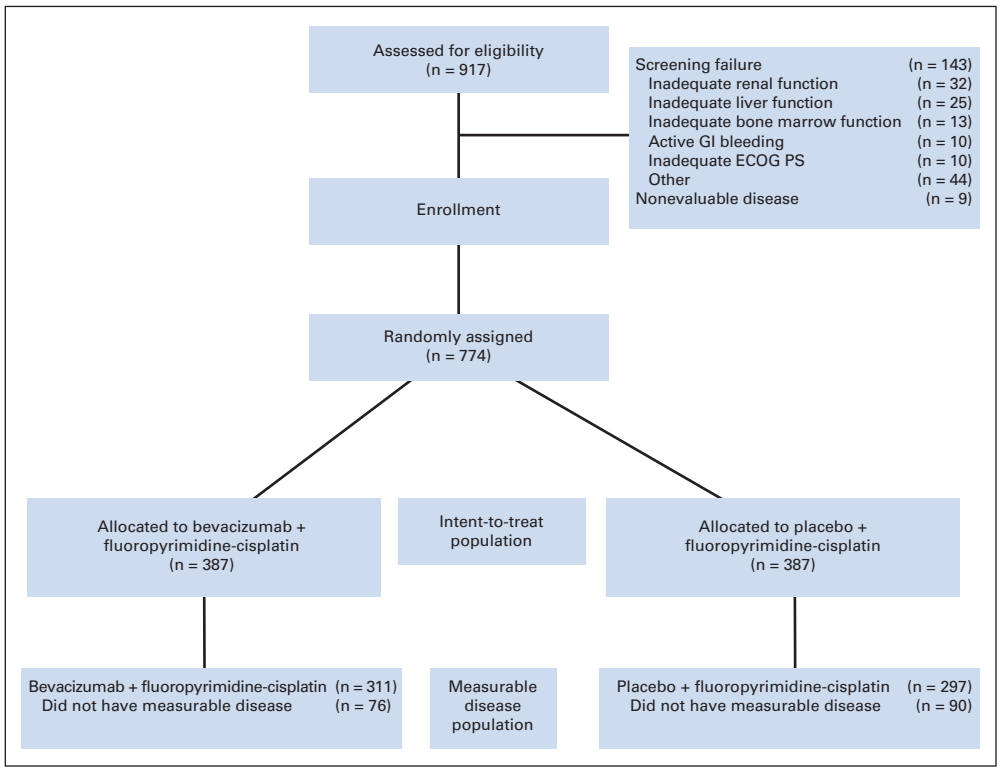

Fig 1. CONSORT diagram. ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Treatment

Bevacizumab or placebo (bevacizumab vehicle) 7.5 mg/kg was administered on day 1 as a 30-minute infusion (infusion rate, 0.25 mg/kg/min) every 3 weeks. In the absence of infusion-related reactions, subsequent infusions were delivered over 15 minutes (infusion rate, 0.5 mg/kg/min). Following bevacizumab or placebo, cisplatin 80 mg/m^2 was given on day 1 as a 2-hour intravenous infusion with standard premedication and hydration, followed by oral capecitabine 1,000 mg/m^2 twice daily for 14 days every 3 weeks. Cisplatin was given for six cycles; capecitabine and bevacizumab were administered until disease progression or unacceptable toxicity. If any study drugs were discontinued, patients could continue with the remaining drugs. For patients unable to take oral medications, FU 800 mg/m^2/d was administered as a continuous intravenous infusion on days 1 to 5 every 3 weeks instead of capecitabine. Switching from capecitabine to FU during the study was not permitted. In the presence of toxicity, the bevacizumab dose was not modified or reduced, whereas dose modifications for fluoropyrimidines and cisplatin were performed per the study protocol.

Assessments

Medical history, chest x-ray, and ECG were performed within 21 days before random assignment. Assessments of vital signs, ECOG performance status, creatinine clearance, and a routine blood analysis were performed within 7 days of random assignment. Baseline samples from the primary or recurrent tumor were collected for biomarker analysis. During treatment, physical examination, hematology, biochemistry, and urinalysis were repeated at the beginning of each cycle.

Tumor assessments (computed tomography scan of chest, abdomen, and pelvis or computed tomography scan of chest and magnetic resonance imaging scan of abdomen and pelvis) were performed within 21 days before random assignment and were repeated every 6 weeks for the first year after random assignment and every 12 weeks thereafter until disease progression. The same radiologic method used to document disease at baseline was used at subsequent assessments. RECIST guidelines were used to define all responses.[23] No independent radiologic review was performed. Survival status was assessed every 3 months after completion of study treatment.

Safety assessments were performed until 28 days after the last exposure to study treatment, followed by an additional 6-month safety follow-up period. Intensity of adverse events was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. An independent data safety monitoring board regularly reviewed study safety and efficacy data.

Statistical Analysis

The intention-to-treat patient population, the primary population for efficacy analysis, included all randomly assigned patients. The safety population included all randomly assigned patients who received at least one dose of study medication. The measurable disease population was used to evaluate response rate only. In the safety analysis, patients were analyzed as treated. The primary study end point was OS, defined as time between random assignment and death irrespective of cause. Secondary end points were progression-free survival (PFS; defined as time between random assignment and first documented disease progression or death), overall response rate, and safety.

AVAGAST was designed as a group sequential study with up to two data looks, with the final analysis planned after approximately 517 deaths had occurred. Per protocol, the preplanned interim analysis (after two thirds of the expected events [ie, 345]) was dropped because, at the time the analysis was due, it was estimated that the final analysis would follow in $\leq$ 6 months. On the basis of a systematic literature review, it was assumed that median OS in the placebo group would be 10 months. The study was powered to test the hypothesis that the addition of bevacizumab would improve median OS to 12.8 months, equivalent to a hazard ratio (HR) of 0.78 between study groups, assuming an exponential distribution for the time-to-death variable. Because no interim analysis was performed, the study became a fixed-sample study. To detect an HR of 0.78, 509 deaths were necessary to ensure 80% power for a two-sided log-rank test at a significance level of 0.05.

Survival functions of time-to-event end points were estimated by using the Kaplan-Meier method, and differences between treatment groups were tested by using an unstratified two-sided log-rank test. OS was also tested by using a stratified log-rank test as a preplanned supporting analysis. Preplanned analyses of OS that used Cox's proportional hazards models were conducted with the stratification variables and other relevant covariates (ECOG performance status, prior neoadjuvant chemotherapy, sex, age, presence of baseline bone metastases, number of baseline metastatic sites, prior gastrectomy, liver metastases, and gastric cancer type). Exploratory subgroup analyses of OS and analyses by region were also performed.

RESULTS

Patients

From September 2007 to December 2008, 774 patients (387 in each group) were enrolled and underwent random assignment at 93 centers in 17 countries (intention-to-treat population; Fig 1, CONSORT diagram). Almost half (49%; n = 376) the patients were enrolled from the Asia-Pacific region (90% from Japan and Korea); the remainder were enrolled in Europe (32%; n = 249) and Pan-America (19%; n = 149), mainly Eastern Europe and Latin America, respectively. Both study groups were well balanced in terms of baseline characteristics (Table 1).

Table 1. Baseline Characteristics (intention-to-treat population)

Variable	Fluoropyrimidine-Cisplatin + Bevacizumab (n = 387) No.	%	Fluoropyrimidine-Cisplatin + Placebo (n = 387) No.	%
Sex				
Male	257	66	258	67
Female	130	34	129	33
Age, years				
Median	58		59	
Range	22-81		22-82	
ECOG performance status				
0-1	365	94	367	95
$\geq$ 2	22	6	20	5
Geographic region				
Asia-Pacific	188	49	188	49
Europe	125	32	124	32
Pan-America	74	19	75	19
Fluoropyrimidine treatment				
Capecitabine	364	94	365	94
Fluorouracil	23	6	22	6
Primary tumor site				
Stomach	333	86	338	87
Gastroesophageal junction	54	14	49	13
Measurable disease	311	80	297	77
Extent of disease				
Metastatic	367	95	378	98
Locally advanced	20	5	9	2
Liver metastases	130	34	126	33
Previous treatment				
Neoadjuvant therapy	30	8	30	8
Gastrectomy	110	28	107	28

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Unadjusted Analysis of Efficacy (intention-to-treat population)

Variable	Fluoropyrimidine-Cisplatin + Bevacizumab (n = 387) No.	%	95% CI	Fluoropyrimidine-Cisplatin + Placebo (n = 387) No.	%	95% CI	HR for Difference*	95% CI	P†
Overall survival									
Deaths	252	65.1		265	68.5		0.87	0.73 to 1.03	.1002
Median overall survival, months	12.1		11.1 to 13.8	10.1		9.0 to 11.3			
1-year survival		50.2	45.1 to 55.3		42.3	37.2 to 47.3	7.9	0.8 to 15.1	.0301
Progression-free survival									
Progression events	324	83.7		339	87.6		0.80	0.68 to 0.93	.0037
Median progression-free survival, months	6.7		5.9 to 7.1	5.3		4.4 to 5.6			
Response	311			297					
Overall response rate	143	46.0	40.3 to 51.7	111	37.4	31.9 to 43.1	8.61	0.6 to 16.6	.0315
Complete response	5	1.6		3	1.0				
Partial response	138	44.4		108	36.4				
Stable disease	93	29.9		90	30.3				

Abbreviation: HR, hazard ratio.
*The ratios listed are hazard ratios, except for 1-year survival and overall response rates for which the differences are shown.
†*P* values were calculated by using the log-rank test, except for overall response rate (χ^2 test) and 1-year survival (approximate Z-test).

Treatment

Mean treatment duration was 6.8 (± 5.1) months in the bevacizumab plus fluoropyrimidine-cisplatin group and 5.8 (± 4.9) months in the placebo plus fluoropyrimidine-cisplatin group (Appendix Table A1, online only). Median dose intensities (ie, actual dose administered divided by planned dose) were more than 80% for bevacizumab and capecitabine-FU or placebo and capecitabine-FU, and 79% and 71% for cisplatin in the bevacizumab and placebo groups, respectively. The use of second-line therapy was balanced between study groups (41%, bevacizumab group; 45%, placebo group) but not between regions (66%, Asia-Pacific; 31%, Europe; 21%, Pan-America). The most commonly used agents included irinotecan (19%), paclitaxel (16%), FU (16%), and docetaxel (12%), which were equally distributed between study groups (Appendix Table A2, online only). Second-line bevacizumab was given to one patient (< 1%) in each treatment group.

Efficacy

The cutoff date for this analysis was November 30, 2009, after 517 deaths had occurred. Median follow-up was 11.4 months in the bevacizumab group and 9.4 months in the placebo group. Median OS, the primary study end point, was 12.1 months (95% CI, 11.1 to 13.8 months) in the bevacizumab group and 10.1 months (95% CI, 9.0 to 11.3 months) in the placebo group (Table 2). The estimated HR was 0.87 (95% CI, 0.73 to 1.03), indicating a 13% reduction in the risk of death ($P = .1002$; Figure 2A. A similar outcome was observed when the analysis was adjusted for stratification variables (ie, region, disease status, and fluoropyrimidine; HR, 0.87; 95% CI, 0.73 to 1.04; $P = .1300$) or all preplanned covariates (HR, 0.84; 95% CI, 0.70 to 1.00; $P = .0563$). The estimated 1-year OS rate was improved significantly with bevacizumab (50.2% *v* 42.3% in the placebo group; $P = .0301$).

PFS was prolonged significantly in the bevacizumab group compared with the placebo group (HR, 0.80; 95% CI, 0.68 to 0.93; $P = .0037$; Figure 2B). Median PFS was 6.7 months (95% CI, 5.9 to 7.1 months) in the bevacizumab group and 5.3 months (95% CI, 4.4 to 5.6 months) in the placebo group. Overall response rate was improved significantly with the addition of bevacizumab (46.0% *v* 37.4% in the placebo group; $P = .0315$).

Safety

The safety population comprised 767 patients (n = 386, bevacizumab group; n = 381, placebo group). The overall incidence of grade 3 to 5 adverse events was 76% in the bevacizumab group and 77% in the placebo group (Table 3); 66% and 64%, respectively, were judged to be treatment-related. The most common adverse events were neutropenia, anemia, decreased appetite, and nausea. The addition of bevacizumab appeared to cause no clinically relevant increase in chemotherapy-related toxicity, with the possible exceptions of diarrhea (8% *v* 4% in the placebo group) and hand-foot syndrome (6% *v* 3%). The overall incidence of predefined grade 3 to 5 events potentially related to bevacizumab was 20% in the bevacizumab group versus 15% in the placebo group (Table 3); the difference between groups was mainly attributable to a higher incidence of hypertension in the bevacizumab group (6% *v* < 1% in the placebo group). Grade 3 to 5 venous thromboembolic events were more common in the placebo group (9% *v* 6% in the bevacizumab group). Grade 3 to 4 bleeding was documented in 4% of patients in both groups. GI perforation occurred in nine (2.3%) and two (0.5%) patients in the bevacizumab and placebo groups, respectively, which is similar to the incidence found in colorectal cancer. All other events of special interest to bevacizumab were rare. No new bevacizumab-related safety signals were identified. Infusion-related adverse reactions were documented in five patients (1%); all events occurred in the bevacizumab group and were grade 1 to 2 (hypersensitivity, n = 2; headache, dysphonia, hypotension, n = 1 each).

Adverse events or laboratory abnormalities led to withdrawal from a component of study treatment in 81 patients (21%) in the bevacizumab group versus 71 patients (19%) in the placebo group.

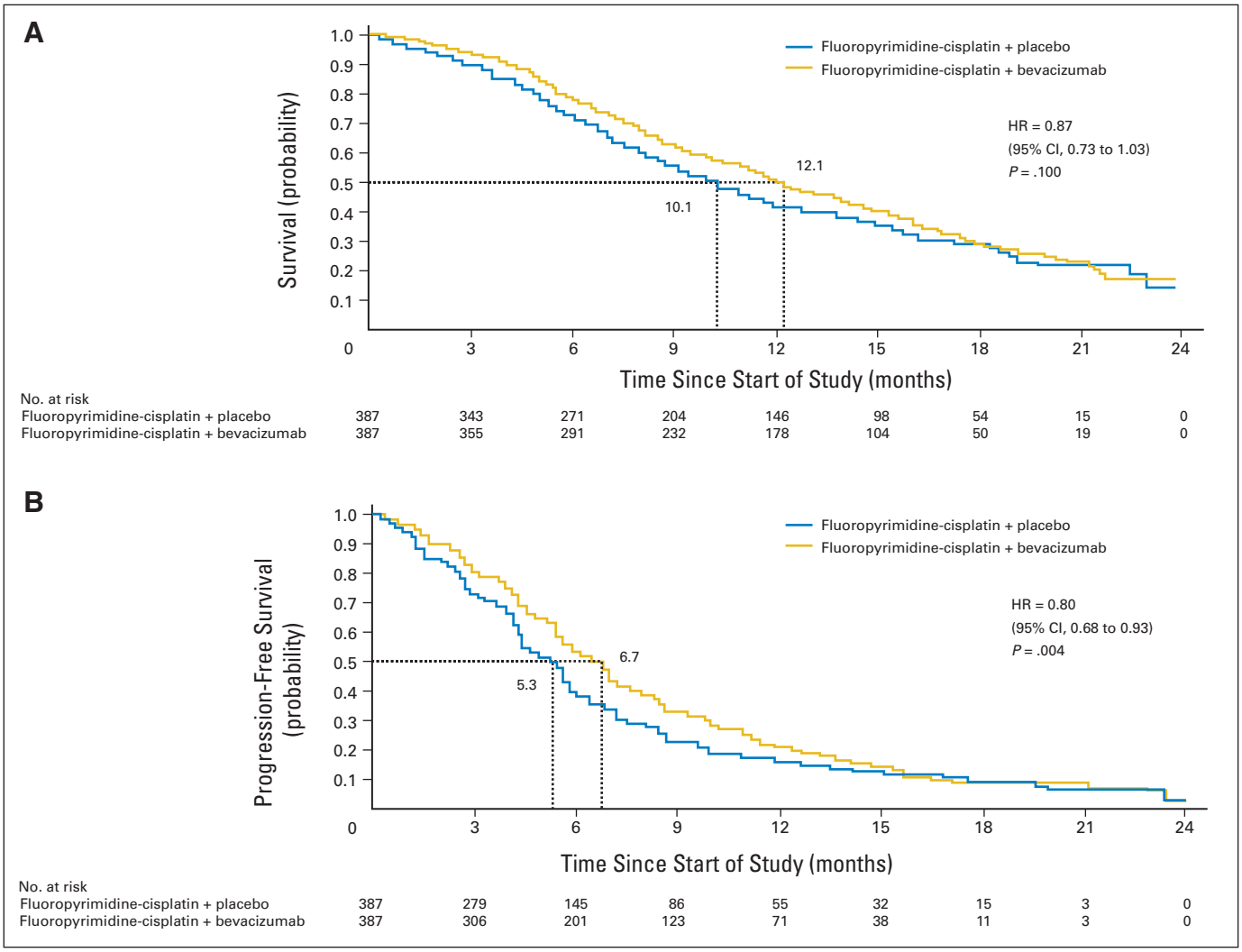

Fig 2. Kaplan-Meier estimates of overall survival (A) and progression-free survival (B) in the intention-to-treat population. HR, hazard ratio.

Seven (2%) and 12 (3%) deaths (all considered related to treatment) occurred in the bevacizumab and placebo groups, respectively. Sixty-day mortality rates were 3% and 6% in the bevacizumab and placebo groups, respectively.

Subgroup Analysis

Preplanned subgroup analyses of OS were consistent with the overall estimate in most patient subgroups (ie, point estimates < 1 and CI included 1; Figure 3). Subgroups in which the 95% CI upper limits were less than 1 were patients recruited at Pan-American centers, patients with locally advanced disease, and patients with nonmeasurable disease.

On the basis of differences in patient outcome according to region, an exploratory analysis of baseline patient characteristics according to region was performed (Table 4). Differences of more than 10% were observed between regions in the proportions of patients with gastroesophageal junction tumors, measurable lesions, liver metastases, and tumor histology. (For details on quality of life, see Appendix).

DISCUSSION

To the best of our knowledge, AVAGAST is the first phase III evaluation of an antiangiogenic agent with chemotherapy in advanced gastric cancer. The primary objective was to improve median OS from an estimated 10.0 months with chemotherapy alone to 12.8 months with the addition of bevacizumab to chemotherapy, for an estimated reduction in the risk of death by 22% (HR, 0.78). We observed that adding bevacizumab to fluoropyrimidine-cisplatin in the first-line treatment of advanced gastric cancer was associated with a risk reduction of death by 13% (HR, 0.87; $P = .1002$) in the overall study population, improving OS from 10.1 months in the placebo group to 12.1 months. However, other efficacy measures showed clear activity with bevacizumab and chemotherapy versus chemotherapy alone, including PFS (6.7 *v* 5.3 months; HR, 0.80; $P = .0037$), response rate (46.0% *v* 37.4%; $P = .0315$), and 1-year survival (50% *v* 42%; $P = .0301$).

Although there are several standard three-drug regimens for the first-line treatment of advanced gastric cancer,[24,25] toxicity and convenience limit the routine use of these combinations for most patients with advanced disease.[7] The capecitabine-cisplatin doublet was reported to be noninferior to cisplatin and infusional FU[21] and is an acceptable standard first-line doublet regimen, as demonstrated in recent and ongoing phase III registration studies.[9,26] Patients randomly assigned to the control arm of the AVAGAST study

Table 3. Most Common Grade 3 to 5 Adverse Events and Adverse Events of Special Interest to Bevacizumab (related and unrelated events; safety population)

	Fluoropyrimidine-Cisplatin +			
	Bevacizumab (n = 386)		Placebo (n = 381)	
MedDRA Term	No.	%	No.	%
Any adverse events	293	76	293	77
Neutropenia	136	35	140	37
Febrile neutropenia	18	5	16	4
Anemia	40	10	53	14
Decreased appetite	32	8	41	11
Nausea	27	7	39	10
Vomiting	24	6	34	9
Diarrhea	32	8	17	4
Hypokalemia	13	3	21	6
Hand-foot syndrome	25	6	13	3
Pulmonary embolism	12	3	18	5
Bevacizumab special adverse events				
Any special adverse event	76	20	56	15
Venous thromboembolic event	25	6	36	9
Arterial thromboembolic event	5	1	8	2
Hypertension	24	6	2	< 1
Hemorrhage	9	2	9	2
GI perforation	9	2	1	< 1
Congestive heart failure	2	< 1	1	< 1
Proteinura	2	< 1	0	0
Wound complications	2	< 1	0	0
Reversible posterior leukoencephalopathy syndrome	1	< 1	0	0
Fistula/abscess	0	0	0	0

Abbreviation: MedDRA, Medical Dictionary for Regulatory Affairs, version 12.1.

survived as expected (median OS, 10.0 months), consistent with the capecitabine-cisplatin arms of previous studies.[9,21]

Preplanned subgroup analyses in AVAGAST suggest regional differences in the efficacy of antiangiogenic therapy. Patients enrolled in North America and Latin America appeared to have a survival benefit with the addition of bevacizumab (median, 11.5 *v* 6.8 months for placebo-chemotherapy; HR, 0.63; 95% CI, 0.43 to 0.94), whereas patients enrolled in Asia (90% from Japan and

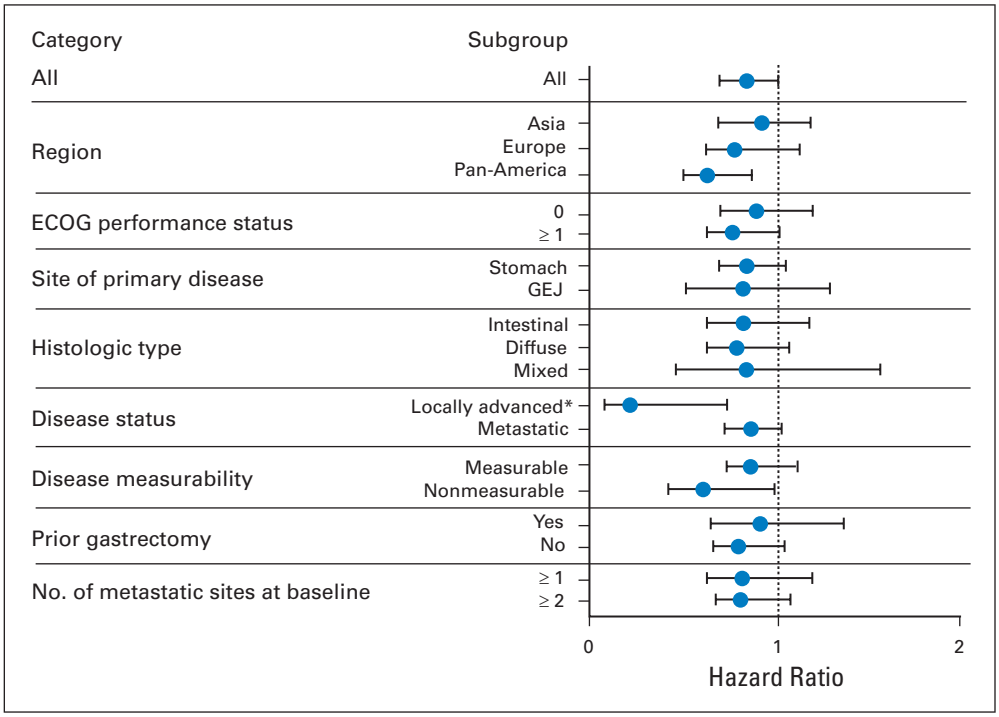

Fig 3. Subgroup analysis of overall survival in the intent-to-treat population. (*) Twenty-nine patients with locally advanced disease only. ECOG, Eastern Cooperative Oncology Group; GEJ, gastroesophageal junction.

Table 4. Baseline Characteristics and Efficacy by Region (intention-to-treat population)

Characteristic	Asia							Europe							Pan-America						
	Fluoropyrimidine-Cisplatin +							Fluoropyrimidine-Cisplatin +							Fluoropyrimidine-Cisplatin +						
	Bevacizumab (n = 188)		Placebo (n = 188)					Bevacizumab (n = 125)		Placebo (n = 124)					Bevacizumab (n = 74)		Placebo (n = 75)				
	No.	%	No.	%	HR	OR	95% CI	No.	%	No.	%	HR	OR	95% CI	No.	%	No.	%	HR	OR	95% CI
Sex																					
Male	68		67					66		67					64		65				
Female	32		33					34		33					36		35				
Age, years																					
Median	58.5		59.0					59.0		59.0					53.5		56.0				
Range	27-78		27-78					31-81		28-80					22-77		22-82				
ECOG performance status																					
0-1	98		95					89		93					95		97				
≥ 2	2		5					11		7					5		3				
Primary tumor site																					
Stomach	93		95					77		78					85		83				
Gastroesophageal junction	7		5					23		22					15		17				
Measurable disease	76		70					87		89					81		73				
Tumor histology (Lauren's classification)																					
Intestinal	36		27					49		50					35		31				
Diffuse	53		61					31		38					50		59				
Mixed	7		5					11		10					11		7				
Missing	4		7					9		2					4		4				
Liver metastases	29		26					35		38					42		41				
Prior gastrectomy	32		31					22		25					31		23				
Poststudy therapies																					
Patients with at least one treatment	59		67					24		29					24		15				
Efficacy																					
Median overall survival, months	13.9		12.1		0.97		0.75 to 1.25	11.1		8.6		0.85		0.63 to 1.14	11.5		6.8		0.63		0.43 to 0.94
Median progression-free survival, months	6.7		5.6		0.92		0.74 to 1.14	6.9		4.4		0.71		0.54 to 0.93	5.9		4.4		0.65		0.46 to 0.93
Response rate	142		132					109		110					60		55				
Overall response rate	47.9		45.5			1.10	0.69 to 1.77	41.3		28.2			1.79	1.02 to 3.15	50.0		36.4			1.75	0.83 to 3.69

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OR, odds ratio.

Korea) appeared to have no benefit (HR, 0.97; 95% CI, 0.75 to 1.25), and European patients had intermediate results (HR, 0.85; 95% CI, 0.63 to 1.14). Differences in median OS in the comparator arm, broken down by region, were also observed (median OS, 12.1 months, Asia; 8.6 months, Europe; 6.8 months, Pan-America). These estimates are robust because 60% to 70% of patients from each region had died at the time of analysis.

Although gastric cancer is a global disease, it is not uniform. There are differences in the presentation and management of gastric cancer patients in different countries and regions. Specifically, as observed in AVAGAST, Asian patients with advanced gastric cancer more commonly receive second and further lines of therapy, more frequently have a prior history of gastrectomy, present with a higher proportion of nonmeasurable disease, and have liver metastases or proximal or gastroesophageal junction tumors less frequently. There are imbalances in the histologic tumor types across the geographic regions and between the treatment arms within the respective regions. Differences in independent prognostic factors and use of subsequent therapies may explain the different OS results between geographic regions. However, whether differences in the spectrum of gastric cancer between regions and/or different treatment practices are responsible for the regional differences for PFS in AVAGAST remains an unanswered question. An additional question is whether bevacizumab dose influences efficacy, because previous phase II studies of bevacizumab in gastric cancer incorporated a higher dose (10 or 15 mg/kg)[20,27,28] than AVAGAST (7.5 mg/kg). Further investigations are needed to answer these questions.

AVAGAST showed that adding bevacizumab to fluoropyrimidine-cisplatin did not substantially alter the safety profile of the chemotherapy backbone. Sixty-day mortality was less in the bevacizumab group (3% *v* 6% with placebo) and compares well with results from other pivotal trials in metastatic cancer of the gastric tract.[16,29] The safety profile of bevacizumab in this study was also consistent with that of previous trials in patients with other solid tumors. No new safety signals were observed. The incidence of GI perforation with

bevacizumab in AVAGAST was low (2%) and in keeping with incidences observed with bevacizumab in other cancers (0% to 2.5%)[16-19,29,30] and with chemotherapy.[31] In this study, we did not observe an increase in other bevacizumab-related toxicities, in particular venous or arterial thromboembolic events or bleeding. We also confirm the safety of a shorter bevacizumab infusion time (ie, 30 minutes and then 15 minutes for subsequent doses).[32]

Overall, these findings are indicative of clinical activity of bevacizumab plus chemotherapy as first-line therapy in advanced gastric cancer. Several lessons have been learned. It is possible that improved (and significant) bevacizumab efficacy may be achieved by refining the selection of the patient population. The ongoing biomarker analyses from this study may also help identify a subgroup of patients that preferentially benefit from the addition of an antiangiogenic agent.

In conclusion, although this trial did not reach its primary objective, the addition of bevacizumab to chemotherapy was associated with significant increases in PFS and overall response rate in the first-line treatment of advanced gastric cancer. Regional analysis indicated increased benefit in the European and Pan-American regions. Further analysis, particularly with data from the AVAGAST biomarker program, may lead to a better understanding of the study outcome, which patient subgroups will benefit from bevacizumab treatment, and how best to design future trials with bevacizumab in metastatic gastric cancer.

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