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ORIGINAL REPORT

Everolimus for Previously Treated Advanced Gastric Cancer: Results of the Randomized, Double-Blind, Phase III GRANITE-1 Study

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ABSTRACT

Purpose
The oral mammalian target of rapamycin inhibitor everolimus demonstrated promising efficacy in a phase II study of pretreated advanced gastric cancer. This international, double-blind, phase III study compared everolimus efficacy and safety with that of best supportive care (BSC) in previously treated advanced gastric cancer.

Patients and Methods
Patients with advanced gastric cancer that progressed after one or two lines of systemic chemotherapy were randomly assigned to everolimus 10 mg/d (assignment schedule: 2:1) or matching placebo, both given with BSC. Randomization was stratified by previous chemotherapy lines (one *v* two) and region (Asia *v* rest of the world [ROW]). Treatment continued until disease progression or intolerable toxicity. Primary end point was overall survival (OS). Secondary end points included progression-free survival (PFS), overall response rate, and safety.

Results
Six hundred fifty-six patients (median age, 62.0 years; 73.6% male) were enrolled. Median OS was 5.4 months with everolimus and 4.3 months with placebo (hazard ratio, 0.90; 95% CI, 0.75 to 1.08; $P = .124$). Median PFS was 1.7 months and 1.4 months in the everolimus and placebo arms, respectively (hazard ratio, 0.66; 95% CI, 0.56 to 0.78). Common grade 3/4 adverse events included anemia, decreased appetite, and fatigue. The safety profile was similar in patients enrolled in Asia versus ROW.

Conclusion
Compared with BSC, everolimus did not significantly improve overall survival for advanced gastric cancer that progressed after one or two lines of previous systemic chemotherapy. The safety profile observed for everolimus was consistent with that observed for everolimus in other cancers.

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INTRODUCTION

Gastric cancer is the fourth most common malignancy and second leading cause of cancer mortality worldwide, with 989,600 new cases and 738,000 deaths estimated to have occurred in 2008.[1] Although resection may be curative in early-stage disease,[2-4] approximately two thirds of patients present with inoperable or metastatic disease.[5] The exceptions are Japan and Korea, where national screening programs lead to early-stage diagnosis in approximately one half of patients.[6,7] Patients with advanced gastric cancer and distant metastases, who receive systemic treatment with regimens including fluorouracil and related compounds, platinum derivatives, taxanes, or irinotecan, have a 5-year survival rate of less than 5% and median overall survival (OS) less than 12 months.[6,8-10] After failure of first-line therapy, there is little consensus on second- and third-line treatment options, and outcomes are poor[2,8]; in recent phase III trials of second-line chemotherapy for advanced gastric cancer, median OS was only 4.0 to 5.3 months.[11,12] A need exists for effective therapy for patients with advanced gastric cancer whose disease progresses after first-line therapy.

Phosphatidylinositol 3-kinase (PI3K)/Akt and mammalian target of rapamycin (mTOR) are activated in 30% and 60% of human gastric carcinomas, respectively.[13,14] PI3K/Akt/mTOR pathway

dysregulation is also associated with chemotherapy resistance[13] and decreased survival.[15-17] These findings suggest the PI3K/Akt/mTOR pathway is frequently activated in gastric cancer and is directly linked to its progression.

The oral mTOR inhibitor everolimus has demonstrated clinical benefit and a tolerable safety profile in several human cancers and tumor syndromes.[18-22] In preclinical models, everolimus inhibited downstream signaling molecules, cell proliferation, tumor growth and vascularization, and peritoneal metastasis.[14,23-27]

In a phase II study of everolimus 10 mg/d in 53 patients with advanced gastric cancer whose disease progressed after one or two previous chemotherapy lines, the disease control rate was 54.7%, median progression-free survival (PFS) per central radiology review was 2.7 months, and median OS was 10.1 months.[28] The phase III GRANITE-1 (First Gastric Antitumor Trial With Everolimus; Clinical Trial No. NCT00879333) evaluated everolimus efficacy and safety in patients with advanced gastric cancer who experienced treatment failure after one or two lines of previous chemotherapy.

PATIENTS AND METHODS

Patients

Eligible patients were at least 18 years old with histologically or cytologically confirmed gastric adenocarcinoma, including that of the gastroesophageal junction, and had documented disease progression after one or two previous systemic chemotherapy lines for advanced disease. Additional inclusion criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2[29] and adequate organ and hematologic function. Exclusion criteria included enteral feeding, malignant ascites requiring drainage, and chronic treatment with immunosuppressive agents.

All patients provided written informed consent before enrollment. The appropriate ethics committees at each participating center approved the protocol. The study was conducted in accordance with the protocol, good clinical practice principles, the Declaration of Helsinki, and all applicable local regulations. A steering committee supervised the conduct of the study. An independent data monitoring committee performed semiannual safety reviews and reviewed interim efficacy results.

Study Design and Assessment

Patients were randomly assigned at a 2:1 schedule to oral everolimus 10 mg/d or matching placebo. All patients received best supportive care (BSC), defined as care in accordance with local institutional practice, excluding anticancer therapy. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal. The protocol provided guidelines for dose interruption or reduction for adverse events (AEs). An initial dose reduction to 5 mg/d and a subsequent reduction to 5 mg every other day were permitted.

Treatment assignment was determined by a centralized interactive web response system that automated the random assignment of patient numbers to randomization numbers. Randomization numbers were linked to the treatment groups, which were in turn linked to medication numbers. The medication randomization list was produced by Novartis Drug Supply Management using a validated system. Randomization was stratified by the number of previous systemic chemotherapy lines (one *v* two) and region of enrollment (Asia [China, Hong Kong, Japan, Korea, Taiwan, and Thailand] *v* the rest of the world [ROW]). Aside from the independent data monitoring committee, all individuals involved in the study were blinded to treatment assignment.

Tumor response was assessed by the local investigator per the Response Evaluation Criteria in Solid Tumors, version 1.0,[30] every 6 weeks until disease progression; complete (CR) or partial response (PR) required confirmation at least 4 weeks after initial observation. To determine the minimum and maximum concentrations of everolimus in whole blood (C_{min} and C_{max}, respectively), venous blood samples were collected predose and 1 and 2 hours postdose on day 1 of week 5. Hematology, biochemistry, and vital signs were assessed at baseline and at each visit. AEs were monitored continuously and assessed using the Common Terminology Criteria for Adverse Events, version 3.0.[31]

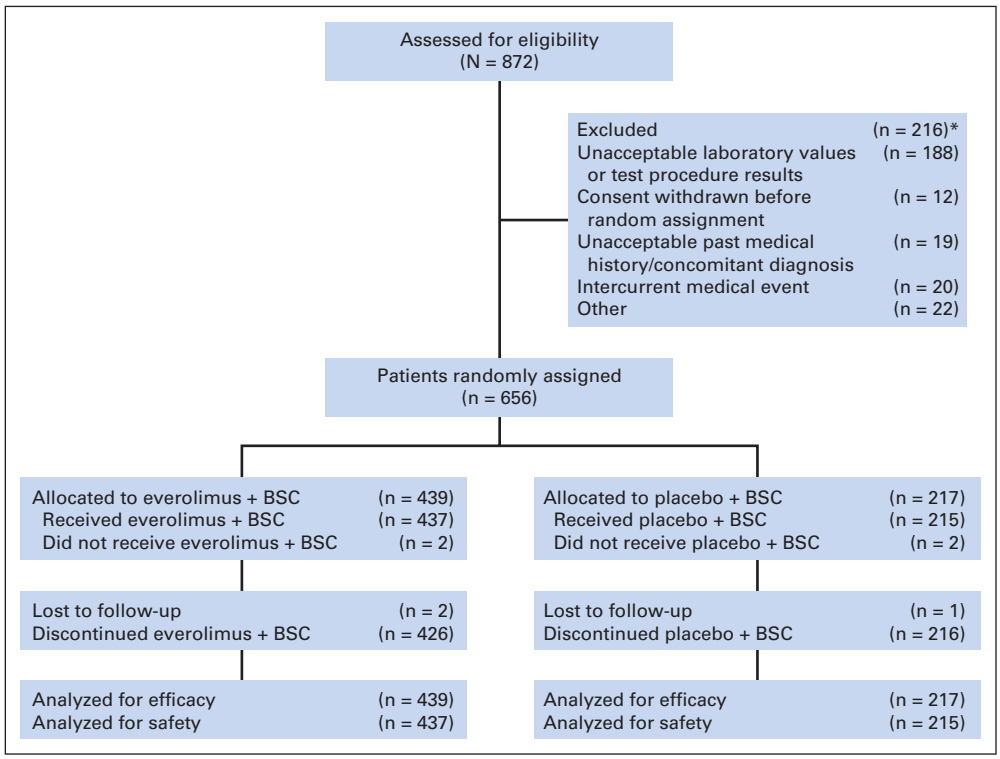

Fig 1. CONSORT diagram. (*) Patients could be excluded for more than one reason. BSC, best supportive care.

Statistical Analysis

All randomly assigned patients were assessed for efficacy; following the intent-to-treat principle, patients were analyzed per the treatment and stratum to which they were assigned on randomization. Safety was assessed in all patients who received at least one dose of study drug and had at least one postbaseline assessment.

Primary end point was OS, defined as the time from randomization to the time of death (any cause). Secondary end points included PFS, defined as the time from randomization to first documented disease progression or death (any cause); overall response rate (ORR); time to definitive deterioration of ECOG PS; time to definitive 5% deterioration in the global health status/quality of life (QoL) and physical, social, and emotional functioning scales of the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire; pharmacokinetics; and safety. (See Appendix [online-only] for information on how missing values were handled.)

Between-arm comparisons of OS and PFS were performed using log-rank tests stratified by the two randomization stratification factors at a one-sided cumulative 2.5% significance level. OS analyses were repeated in several patient subgroups (Appendix); no interaction test was performed. Comparisons of time to definitive deterioration in ECOG PS and time to definitive 5% deterioration in QoL were performed using log-rank tests stratified by the two randomization stratification factors at a two-sided 5% significance level. No other adjustments were performed. A hierarchical testing strategy was implemented such that formal significance for PFS could be declared only if the between-group difference in OS was significant. Subsequent levels of the hierarchy were deterioration in ECOG PS; deterioration in the QLQ-C30 global health status/QoL scale; and deterioration in the QLQ-C30 physical, social, and emotional functioning scales (successively compared). No statistical comparisons were performed for ORR or for pharmacokinetic or safety parameters. For all time-to-event end points, median values were estimated using the Kaplan-Meier method. Hazard ratios (HRs) and 95% CIs were derived from Cox proportional hazards models stratified by the two randomization stratification factors. Exact 95% CIs for ORR were calculated using the Clopper-Pearson method.

The study was designed to detect an improvement in median OS from 4.0 months with placebo to 5.4 months with everolimus (HR, 0.74). Considering the two-look Lan-DeMets group sequential design with an O'Brien-Fleming–type boundary,[32] 526 deaths were required at final analysis (90% power, stratified log-rank test, one-sided cumulative 2.5% significance). Assuming a 24-month recruitment period, 5% loss to follow-up, and 2:1 randomization in favor of everolimus, it was estimated that 633 patients would need to be enrolled. (See Appendix, online only, for results of interim analysis.)

RESULTS

Patient Disposition and Characteristics

From July 2009 to November 2010, 656 patients from 137 centers in 23 countries were enrolled and received everolimus plus BSC (n = 439) or placebo plus BSC (n = 217; Fig 1). As of the analysis cutoff date (September 5, 2011), 11 patients (2.5%) in the everolimus arm and no patients in the placebo arm were still receiving study treatment. The most common reason for treatment discontinuation was disease progression (66.5% in the everolimus arm and 77.9% in the placebo arm). A higher percentage of patients discontinued everolimus because of AEs (21.4% *v* 15.7% with placebo) or consent withdrawal (4.6% *v* 3.2%). Median follow-up duration (ie, time from randomization date of median patient enrolled to date of data cutoff) was 14.3 months.

Baseline demographics and disease characteristics were generally well balanced between treatment groups, although minor differences were observed (Table 1). Compared with the everolimus arm, more patients in the placebo arm had the proximal stomach tumor location, an ECOG PS of 2, and liver metastases. Overall, 47.7% of patients received one previous line of chemotherapy and 52.3% received two previous lines of chemotherapy (Table 1). The most commonly administered chemotherapy regimens contained fluoropyrimidines (96.0%), platinum derivatives (85.8%), and taxanes (38.4%). Other previous therapy included total (21.8%) and partial (28.4%) gastrectomy and radiotherapy (12.0%) (Table 1).

Table 1. Baseline Patient Demographics and Disease Characteristics of All Randomly Assigned Patients

Characteristic	Everolimus Plus BSC (n = 439) No. of Patients	%	Placebo Plus BSC (n = 217) No. of Patients	%
Age, years				
Median	62		62	
Range	20-86		26-88	
< 65	260	59	129	59
≥ 65	179	41	88	41
Male sex	322	73	161	74
Race				
White	166	38	75	35
Black	3	< 1	1	< 1
Asian	251	57	126	58
Other	19	4	15	7
Region and No. of previous chemotherapy lines				
Asia, 1 line	98	22	48	22
Asia, 2 lines	145	33	72	33
Rest of the world, 1 line	112	26	55	25
Rest of the world, 2 lines	84	19	42	19
Time since initial diagnosis, months				
≤ 12	176	40	93	43
> 12 to ≤ 24	156	36	71	33
> 24	107	24	53	24
Anatomic site of cancer				
Proximal stomach	162	37	94	43
Distal stomach	276	63	123	57
Missing	1	< 1	0	0
Gastroesophageal junction involvement	118	27	69	32
Histologic grade				
Well differentiated	33	8	21	10
Moderately differentiated	137	31	69	32
Poorly differentiated	198	45	89	41
Poorly differentiated/undifferentiated	6	1	4	2
Unknown	65	15	34	16
Measurable disease according to RECIST	379	86	192	88
Metastatic site				
Lung	92	21	37	17
Liver	190	43	109	50
ECOG performance status				
0	144	33	70	32
1	269	61	120	55
2	25	6	27	12
Missing	1	< 1	0	0
Prior gastrectomy				
No	216	49	111	51
Partial	126	29	60	28
Total	97	22	46	21
Prior radiotherapy	54	12	25	12

Abbreviations: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group.

Table 2. Exposure to Study Treatment in the Everolimus Plus Best Supportive Care Treatment Arm in the Safety Population

Characteristic	No. of Patients	Duration of Exposure (weeks)		Mean Dose Intensity (mg/d)
		Median	Range	
Overall population	437	7.1	0.1-79.6	8.9
Gastrectomy				
Yes	224	8.0	0.9-70.7	8.8
No	213	6.7	0.1-79.6	9.1
Sex				
Male	322	7.1	0.4-79.6	8.9
Female	115	7.0	0.1-74.7	8.9
Age, years				
< 65	258	6.9	0.1-79.6	9.1
≥ 65	179	8.0	0.9-58.3	8.6
Race				
Asian	251	8.0	0.1-79.6	8.8
White	164	6.6	0.9-74.7	9.1
Other	22	6.1	0.9-42.4	9.5
Ethnicity				
Chinese	110	6.4	0.1-53.0	9.1
Japanese	74	11.4	1.0-70.7	8.3
Hispanic/Latino	35	7.0	0.9-46.3	9.1
Indian	2	7.4	6.3-8.4	7.8
Mixed	1	6.4	—	10.0
Other	215	7.1	0.6-79.6	9.0
Region				
Asia	243	7.9	0.1-79.6	8.9
ROW	194	6.8	0.9-74.7	9.0

Abbreviation: ROW, rest of world.

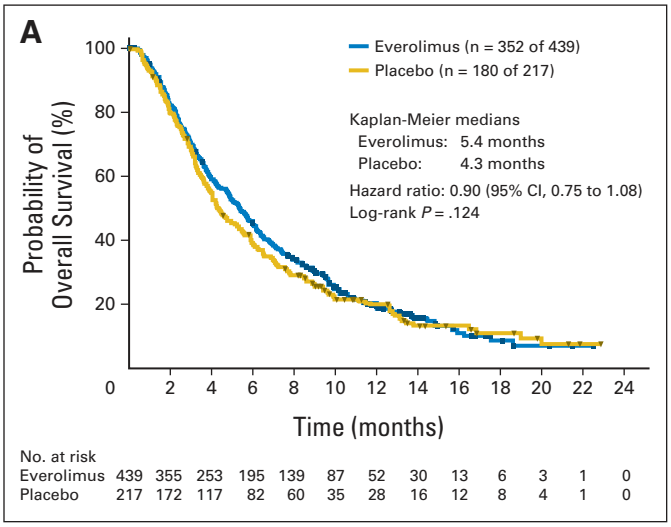

Fig 2. Overall and progression-free survival for all randomly assigned patients. (A) Kaplan-Meier plot of overall survival. (B) Forest plot of overall survival in subgroups. (C) Kaplan-Meier plot of progression-free survival. (D) Longitudinal mean scores of the global health status/quality-of-life scale of the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire. ECOG PS, European Cooperative Oncology Group performance status; GE, gastroesophageal; n, number of patients with event (of the number of patients at risk); ROW, rest of world. Appendix Table A3 (online only) lists details on the events experienced.

Study Drug Exposure

Median duration of study drug exposure was 7.1 weeks for everolimus (range, 0.1 to 79.6 weeks) and 6.4 weeks for placebo (range, 0.4 to 90.9 weeks). Mean duration of exposure was 11.5 weeks (standard deviation [SD], 12.1 weeks) and 8.5 weeks (SD, 8.8 weeks), respectively. Median exposure was slightly longer in patients with versus without gastrectomy, patients at least 65 years old versus those younger than 65 years, Asians versus white patients or patients of other races, Japanese versus other ethnicities, and patients enrolled in Asia versus ROW (Table 2). Dose interruptions or reductions were more common with everolimus (48.5% *v* 16.7% with placebo). The most common reasons for dose interruption or reduction were AEs (34.6% and 11.6% with everolimus and placebo, respectively) and laboratory test abnormalities (14.0% and 0.5%, respectively). The median relative dose intensity was 1.0 for both treatment arms. The mean dose intensity was 8.9 mg/d with everolimus (SD, 1.7 mg/d) and 9.7 mg/d with placebo (SD, 1.0 mg/d).

Median everolimus C_{min} and C_{max} were 13.8 ng/mL and 67.4 ng/mL, respectively, for patients who received everolimus 10 mg/d (Appendix Table A1). There was no apparent difference in steady-state everolimus concentrations between patients enrolled in Asia and ROW or those with and without gastrectomy (Appendix Table A1).

Efficacy

The estimated median OS was 5.4 months with everolimus plus BSC (95% CI, 4.8 to 6.0 months) and 4.3 months with placebo plus BSC (95% CI, 3.8 to 5.5 months; HR for OS, 0.90; 95% CI, 0.75 to 1.08; $P = .124$; Fig 2A). A trend for reduction in the risk of death was observed with everolimus in patients enrolled in ROW (15% reduction in risk) and patients enrolled in ROW with two previous chemotherapy lines (26% reduction in risk; Fig 2B); these trends in ROW seemed to be driven by patients enrolled outside of Europe (Fig 2B). Across the remaining subgroups analyzed, results were consistent with those of the overall population (Fig 2B). The percentage of patients who started other antineoplastic therapy after study treatment discontinuation was slightly higher with placebo (45.2% *v* 39.2% with everolimus; Appendix Table A2).

Estimated median PFS was 1.7 months with everolimus (95% CI, 1.5 to 1.9 months) and 1.4 months with placebo (95% CI, 1.4 to 1.5 months). Although everolimus reduced the risk of disease progression or death compared with placebo (HR, 0.66; 95% CI, 0.56 to 0.78; $P < .001$; Fig 2C), formal statistical significance could not be declared per the hierarchical testing strategy. The estimated percentage of patients progression free at 6 months was approximately three times greater with everolimus (12.0%; 95% CI, 9.0% to 15.4%; *v* 4.3%; 95% CI, 2.1% to 7.7%).

Among patients with measurable disease at baseline, one patient in the everolimus arm experienced a CR, versus no patients in the placebo arm (Table 3). The ORR (percentage of patients with CR or PR) was 4.5% with everolimus (95% CI, 2.6% to 7.1%) and 2.1% with placebo (95% CI, 0.6% to 5.3%). The disease control rate (percentage of patients with CR, PR, or stable disease) was approximately two-fold higher with everolimus (everolimus: 43.3%; 95% CI, 38.2% to 48.4%; *v* placebo: 22.0%; 95% CI, 16.3% to 28.5%). Tumor shrinkage was observed in approximately three times as many patients treated with everolimus (37.8% *v* 12.3% with placebo).

Time to deterioration of ECOG PS did not differ significantly between treatment arms (median time to deterioration, 2.3 months for everolimus *v* 2.2 months for placebo; HR, 0.96; 95% CI, 0.76 to

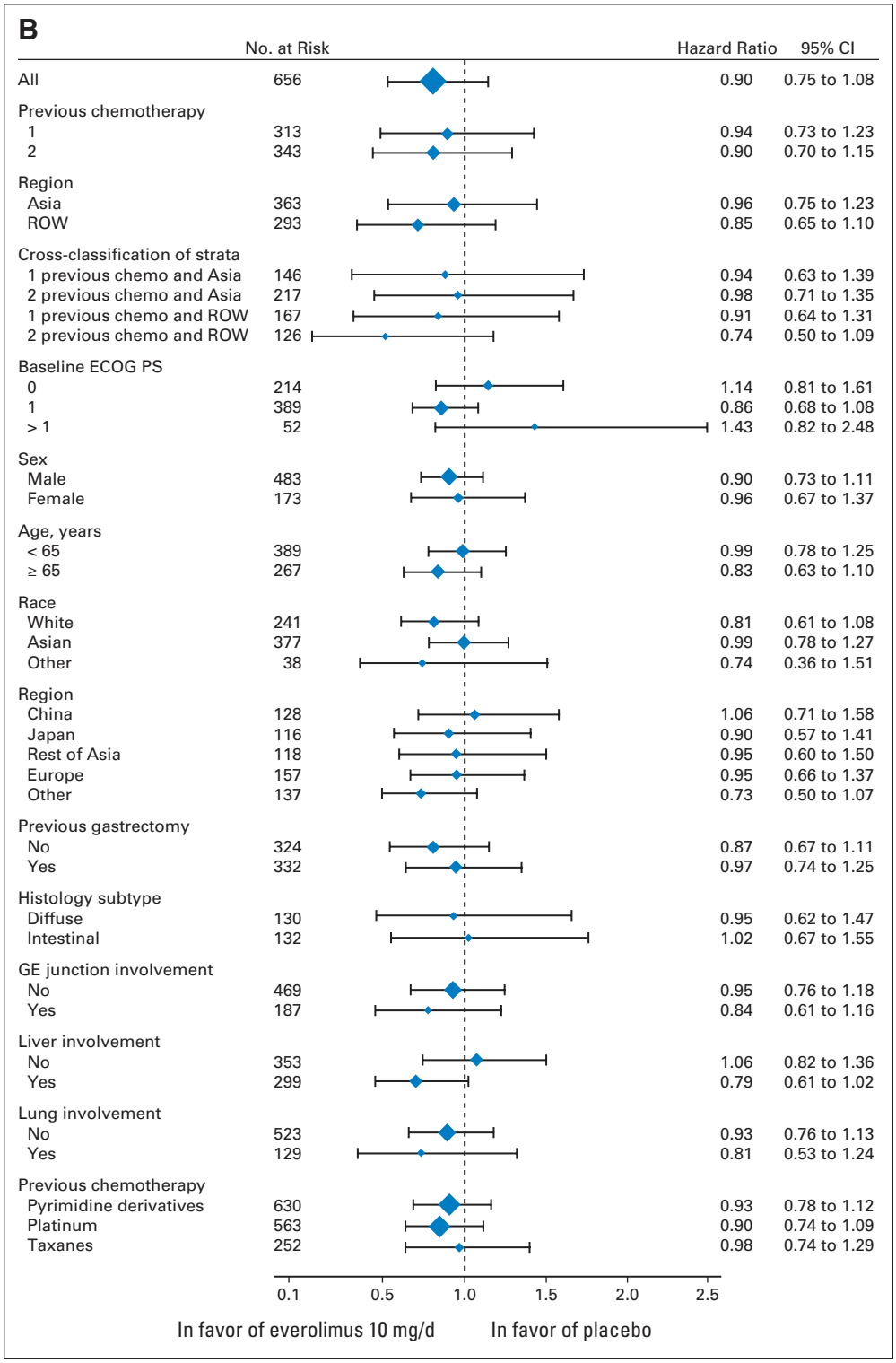

Fig 2. (Continued).

1.20; $P = .693$). A trend for a slightly longer time to ≥ 5% deterioration in global QoL was observed for everolimus (median time to ≥ 5% deterioration, 1.51 months *v* 1.45 months; HR, 0.84; 95% CI, 0.69 to 1.03; $P = .094$). Over time and versus placebo, everolimus recipients had higher mean scores for the global health status/QoL scale of the QLQ-C30 questionnaire (Fig 2D).

Safety

Almost all patients experienced at least one AE (99.1% in the everolimus arm and 96.7% in the placebo arm). The most common AEs (any grade) reported with everolimus were decreased appetite, stomatitis, fatigue, and nausea (Table 4). AEs that occurred in at least 10% of everolimus recipients were decreased appetite,

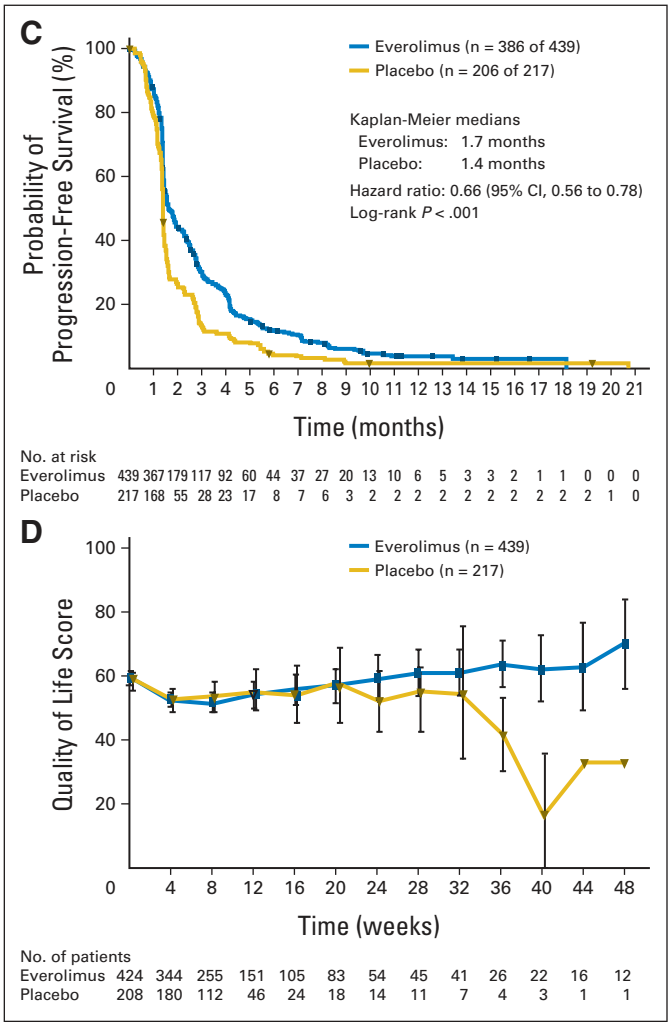

Fig 2. (Continued).

stomatitis, thrombocytopenia, rash, diarrhea, and decreased weight. The most common grade 3/4 AEs with everolimus were anemia, decreased appetite, and fatigue (Table 4). The proportion of patients who experienced grade 3/4 AEs was similar in all patient subgroups assessed (Table 5). All-grade and grade 3/4 pneumonitis were relatively uncommon, with incidences in the everolimus arm of 3.0% (n = 13) and 0.7% (n = 3), respectively. Pneumonitis was not observed in the placebo arm.

AEs leading to study drug discontinuation occurred in 21.5% of everolimus and 15.8% of placebo recipients; those leading to dose adjustments/interruptions occurred in 55.4% of everolimus and 21.4% of placebo recipeints. The most common AEs leading to study drug discontinuation (everolimus *v* placebo) were fatigue (2.1% *v* 1.4%), gastrointestinal hemorrhage (1.4% *v* 0.9%), and abdominal pain (1.1% *v* 0.5%). The AEs most commonly leading to dose adjustment or interruption were thrombocytopenia (everolimus: 10.3% *v* placebo: 0.5%), stomatitis (everolimus: 7.8% *v* placebo: 0.5%), and neutropenia (everolimus: 6.6% *v* placebo: 0%). Three patients in the everolimus arm died and their deaths were suspected to be a result of study treatment (n = 1 each for sudden death, grade 3 pneumonitis, and grade 4 gastrointestinal hemorrhage). In the placebo arm, two patients died and their deaths were suspected to be a result of study treatment (n = 1 each for multiorgan failure and cerebrovascular accident).

Table 3. Best Overall Tumor Response According to RECIST for Patients With Measurable Disease

Response	Everolimus Plus BSC (n = 379) No. of Patients	%	Placebo Plus BSC (n = 191) No. of Patients	%
Best overall response				
CR	1	< 1	0	0
PR	16	4	4	2
SD	147	39	38	20
PD	157	41	119	62
Unknown*	58	15	30	16
ORR (CR and PR)	17	4	4	2
DCR (CR, PR, and SD)	164	43	42	22

Abbreviations: BSC, best supportive care; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*Tumor response data not available.

DISCUSSION

GRANITE-1 did not demonstrate a significant survival benefit for everolimus versus BSC in patients with advanced gastric cancer whose

Table 4. Adverse Events Irrespective of Relationship to Study Treatment With ≥ 10% Incidence in the Everolimus Plus BSC Treatment Arm in the Safety Population

Adverse Event	Everolimus Plus BSC (n = 437) Any Grade No. of Patients	%	Everolimus Plus BSC (n = 437) Grade 3/4 No. of Patients	%	Placebo Plus BSC (n = 215) Any Grade No. of Patients	%	Placebo Plus BSC (n = 215) Grade 3/4 No. of Patients	%
Decreased appetite	208	48	48	11	78	36	12	6
Stomatitis	174	40	20	5	23	11	0	0
Fatigue	150	34	34	8	65	30	11	5
Nausea	132	30	16	4	69	32	8	4
Diarrhea	115	26	15	3	33	15	2	1
Anemia	114	26	70	16	42	20	27	13
Abdominal pain	107	24	21	5	57	27	13	6
Vomiting	107	24	13	3	62	29	9	4
Constipation	91	21	3	< 1	42	20	3	1
Rash	87	20	1	< 1	19	9	0	0
Weight decreased	86	20	11	3	19	9	0	0
Pyrexia	81	19	3	< 1	24	11	2	1
Thrombocytopenia	80	18	22	5	5	2	3	1
Asthenia	70	16	20	5	22	10	9	4
Dyspnea	61	14	18	4	23	11	9	4
Upper abdominal pain	53	12	6	1	27	13	2	1
Peripheral edema	53	12	1	< 1	23	11	2	1
Hypokalemia	52	12	26	6	9	4	2	1
Insomnia	51	12	2	< 1	22	10	0	0
Cough	50	11	1	< 1	17	8	0	0
Back pain	48	11	10	2	16	7	2	1
Neutropenia	47	11	17	4	6	3	1	< 1
Pruritus	47	11	0	0	9	4	0	0

NOTE. All data are sorted by descending frequency in the everolimus plus BSC treatment group.
Abbreviation: BSC, best supportive care.

Table 5. Incidence of Grade 3/4 Adverse Events by Patient Subgroup in the Safety Population

	Everolimus Plus BSC		Placebo Plus BSC	
Patient Subgroup	No. of Patients	%	No. of Patients	%
Overall population	437	71	215	53
Gastrectomy				
Yes	224	70	107	48
No	213	72	108	59
Sex				
Male	322	69	161	55
Female	115	76	54	48
Age, years				
< 65	258	71	128	54
≥ 65	179	71	87	53
Race				
Asian	251	67	125	44
White	164	77	74	64
Other	22	77	16	81
Ethnicity				
Chinese	110	62	56	48
Japanese	74	70	41	39
Hispanic/Latino	35	74	15	60
Indian	2	50	0	0
Mixed	1	0	3	67
Other	215	76	100	61
Region				
Asia	243	65	119	45
ROW	194	78	96	65

Abbreviations: BSC, best supportive care; ROW, rest of world.

disease progressed on one or two lines of previous systemic chemotherapy. The lack of significant benefit for everolimus may be partially attributable to the slightly higher percentage of placebo recipients who initiated antineoplastic therapy after study drug discontinuation (45.2% *v* 39.2% for everolimus). OS results were consistent across subgroups, although a trend toward a reduced risk of death with everolimus was noted for patients enrolled in ROW (15% reduction in risk) and patients enrolled in ROW who received two previous systemic chemotherapy lines (26% reduction in risk). These trends, which may be a result of chance alone, were mostly driven by patients enrolled outside Europe. A 34% reduction in the risk of disease progression or death with everolimus was observed. Notably, the estimated percentage of patients remaining progression free at 6 months was higher with everolimus (12.0% *v* 4.3%), as were the disease control rate (43.3% *v* 22.0%) and the tumor shrinkage rate (37.8% *v* 12.3%). These results suggest everolimus has activity in this heavily pretreated population.

Identification of specific biomarkers for various patient subpopulations with advanced gastric cancer may help define those patients who would receive the most benefit from everolimus treatment. Despite extensive efforts, including those of a phase II study of everolimus in gastric cancer,[33] identification of gastric cancer biomarkers predictive of benefit from everolimus has been elusive. Results of ongoing biomarker analyses of GRANITE-1 are eagerly awaited.

Advanced gastric cancer, particularly that which progresses after systemic chemotherapy, is associated with a poor prognosis. The fact that 96.7% of placebo recipients in our study experienced at least one AE highlights the large number of comorbidities and overall high level of underlying risk in patients with heavily pretreated advanced gastric cancer. Although cross-study comparisons should be performed with caution, it is interesting that the median OS reported for everolimus in our trial (5.4 months) is similar to, or even longer than, that reported for second-line chemotherapy in two recent phase III studies, whereas the median OS reported for placebo in our study (4.3 months) is similar to, or even longer than, that reported for the control arms.[11,12] In a study of irinotecan versus BSC in 40 patients with advanced gastric cancer previously treated with only one line of systemic chemotherapy, irinotecan significantly reduced the risk of death (HR, 0.48; 95% CI, 0.25 to 0.92; $P = .012$).[11] Median OS was 4.0 months with irinotecan and 2.4 months with BSC; the disease control rate was 53% with irinotecan but was not reported for BSC. In the second study, 202 patients with advanced gastric cancer previously treated with one chemotherapy regimen that included both a fluoropyrimidine and platinum derivative or two chemotherapy regimens, of which one contained a fluoropyrimidine derivative and the other a platinum derivative, were randomly assigned to receive chemotherapy (docetaxel or irinotecan) or BSC.[12] Results of this study showed that second-line chemotherapy significantly reduced the risk of death (HR, 0.66; 95% CI, 0.49 to 0.89; $P = .007$). Median OS was 5.3 months with second-line chemotherapy versus 3.8 months with BSC. These results highlight the need to standardize chemotherapy regimens when designing clinical trials following first-line therapy. Notably, the use of post–first-line chemotherapy and types of regimens used differ owing to between-country differences in approved/preferred agents and reimbursement systems.

The everolimus AE profile observed in our study was generally consistent with that previously observed for everolimus in cancer, with no new safety signals identified.[18-20,28] Although stomatitis and pneumonitis, AEs commonly associated with everolimus, were observed in 39.8% and 3.0% of patients, respectively, they led to treatment discontinuation in only three patients (n = 2 for stomatitis, n = 1 for pneumonitis). The median duration of everolimus exposure was longer in patients with versus without gastrectomy, patients age at least 65 years versus those younger than 65 years, Asian versus white patients or patients of other races, Japanese versus other ethnicities, and patients enrolled in Asia versus ROW. AE incidence was mostly similar across patient subgroups.

In conclusion, the phase III GRANITE-1 study did not meet its primary objective of demonstrating a significant survival benefit for everolimus compared with BSC in patients with advanced gastric cancer whose disease progressed after one or two lines of previous systemic chemotherapy. The everolimus AE profile was consistent with that observed for everolimus in other cancers.

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Appendix

Supportive methodology: Handling of missing values. For the primary end point of overall survival, if a patient was not known to have died, survival was censored at the date of last contact. For the secondary end point of progression-free survival (PFS), if a patient was not known to have died or experienced disease progression at the date of the analysis cutoff or when he/she received further antineoplastic therapy, PFS was censored at the time of the last adequate tumor assessment before the analysis cutoff date or the date of the start of new antineoplastic therapy, whichever occurred first. If a PFS event was observed after at least two missing tumor assessments, then the date of progression was censored at the date of the last adequate tumor assessment. If a PFS event occurred after a single missing tumor assessment, the actual date of disease progression was used. For the secondary end points of time to definitive deterioration of Eastern Cooperative Oncology Group (ECOG) performance status and time to definitive 5% deterioration in the global health status/quality of life scale of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, if a patient died before definitive deterioration but within 8 weeks (ie, twice the planned period between two assessments), the date of death was considered as the event date; patients who died after more than 8 weeks were censored at the date of their last available assessment. If definitive deterioration was observed after at least two missing assessments, the event was backdated to the first missing assessment before deterioration. For each EORTC QLQ-C30 subscale, the raw scores were standardized as described in the third edition of the EORTC QLQ-C30 manual (Fayers P et al: The EORTC QLQ-C30 Scoring Manuscript [ed 3]. Brussels, Belgium, EORTC, 2001). No specific methodology was applied to handle individual missing answers to specific questions of the EORTC QLQ-C30.

Subgroup analyses. For the primary end point of overall survival, analyses were performed for the following subgroups: number of prior chemotherapy lines (1 or 2), region (Asia or rest of world [ROW]), cross-classification of the number of prior chemotherapy lines and region (one prior regimen plus Asia; two prior regimens plus Asia; one prior regimen plus ROW, or two prior regimens plus ROW), baseline ECOG performance status (0, 1, or ≥ 2), sex (male or female), age (< 65 years or ≥ 65 years), race (white, Asian, or other), specific region (China, Japan, rest of Asia, Europe, or other), prior gastrectomy (yes or no), histology subtype (diffuse or intestinal), gastroesophageal junction involvement (yes or no), liver involvement (yes or no), lung involvement (yes or no), and prior chemotherapy (pyrimidine derivatives, platinum, or taxanes).

Results of the interim analysis. A single interim analysis was performed after approximately 60% of the number of deaths required for final analysis was observed. At the time of the interim analysis, which occurred after 382 deaths were observed, the observed hazard ratio was 0.93 (95% CI, 0.75 to 1.16), and the *P* value from the stratified log-rank test was .266. This *P* value was greater than the .008 threshold required to stop the study for outstanding efficacy.

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Table A1. Everolimus Steady-State Blood Concentrations by Actual Dose in the Safety Population

	C_{min} (ng/mL)			C_{max} (ng/mL)		
Population	No. of Patients	Median	Range	No. of Patients	Median	Range
Everolimus, 10 mg/d						
Overall	201	13.8	0-81.8	218	67.5	15.3-282.0
Asia	127	15.1	0-54.9	132	69.4	18.3-167.0
ROW	74	11.4	2.2-81.8	86	63.7	15.3-282.0
With gastrectomy	118	13.8	0-81.8	125	72.9	19.9-282.0
Without gastrectomy	83	13.2	2.6-60.3	93	53.8	15.3-157.0
Everolimus, 5 mg/d						
Overall	18	9.3	2.1-24.3	16	34.7	6.3-98.9
Asia	11	9.8	2.1-21.2	10	29.1	6.3-81.0
ROW	7	6.3	4.0-24.3	6	34.7	12.3-98.9
With gastrectomy	10	9.0	4.9-24.3	9	41.9	14.8-81.0
Without gastrectomy	8	10.0	2.1-17.2	7	12.3	6.3-98.9

Abbreviations: C_{max}, maximum concentration in whole blood; C_{min}, minimum concentration in whole blood; ROW, rest of world.

Table A2. Antineoplastic Therapies Since Discontinuation of Study Treatment in the Full Analysis Set

	Everolimus Plus BSC (n = 439)		Placebo Plus BSC (n = 217)	
Type of Therapy	No. of Patients	%	No. of Patients	%
Any	172	39.2	98	45.2
Type of therapy*				
Chemotherapy	155	35.3	89	41.0
Immunotherapy	1	0.2	0	0
Radiation therapy	13	3.0	6	2.8
Surgery	0	0	1	0.5
Targeted therapy	5	1.1	1	0.5
Other	3	0.7†	4	1.8‡

Abbreviation: BSC, best supportive care.
*Patients could receive > 1 type of therapy.
†Includes Chinese traditional medicine (n = 2) and Java Brucea fruit fat injection (n = 1).
‡Includes Chinese traditional medicine (n = 1), antineoplastic agents (n = 1), fluorouracil (n = 1), and PDK1 inhibitor (n = 1).

Table A3. Analysis of Survival in the Full Analysis Set

	Everolimus Plus BSC (n = 439)		Placebo Plus BSC (n = 217)				
Survival	No. of Patients	%	No. of Patients	%	Hazard Ratio	95% CI	*P*
Overall survival							.1244
Deaths	352	80.2	180	82.9	0.90	0.75 to 1.08	
Censored	87	19.8	37	17.1	—		
PFS							
Total events	386	87.9	206	94.9	0.66	0.56 to 0.78	< .001
Progression	315	71.8	174	80.2	—		
Deaths	71	16.2	32	14.7	—		
Censored	53	12.1	11	5.1	—		

Abbreviations: BSC, best supportive care; PFS, progression-free survival.