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Exploratory Analysis of Latin American Patients in Two Randomized, Phase III Studies of Ramucirumab Alone or with Paclitaxel for Advanced Gastric Cancer

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ABSTRACT

Treatment with ramucirumab, a recombinant human immunoglobulin G_1 monoclonal antibody vascular endothelial growth factor-receptor-2 antagonist, in two global phase III randomized trials (REGARD and RAINBOW), demonstrated significant improvements in overall and progression-free survival in patients with previously treated advanced gastric cancer. This analysis aims to identify characteristics of Latin American cohorts from REGARD and RAINBOW. In the REGARD study, patients whose disease had progressed after fluoropyrimidine and/or platinum-containing chemotherapy received ramucirumab (8 mg/kg intravenously every two weeks) or placebo plus best supportive care. In the RAINBOW study, patients received either ramucirumab (8 mg/kg) or placebo on days 1 and 15 plus paclitaxel 80 mg/m^2 on days 1, 8, and 15 (28-day cycle). *Post hoc* analyses of baseline patient characteristics, efficacy, and adverse events in Latin American cohorts were performed. Latin American patients comprised 16.1% (57/355) and 6.6% (44/665) of REGARD and RAINBOW intent-to-treat populations, respectively. Baseline imbalances were observed between treatment arms within the Latin American subpopulations in both trials.

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The survival trends in the Latin American patients appear consistent with the outcomes in the intent-to-treat population with a manageable safety profile. Inferences may be limited due to small sample size; however, according to this retrospective analysis, ramucirumab seems to be an appropriate option for Latin American patients with previously treated advanced gastric cancer. (J CANCEROL. 2015;2:91-8)
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INTRODUCTION

Gastric cancer is a deadly malignancy worldwide[1]. Latin American countries have some of the highest gastric cancer incidences and mortality rates in the world, largely associated with a high prevalence of *Helicobacter pylori* infection[1,2]. Survival rates for advanced gastric cancer are poor, with a median survival of less than one year. Despite recent advances in targeted therapy and understanding of the biology and development of the malignancy, progress in the treatment of gastric cancer has been limited[3]. Currently, platinum- and fluoropyrimidine-based (or containing) regimens are established as first-line treatment for advanced gastric cancer. Treatment options after failure of first-line therapy are limited[4].

Vascular endothelial growth factor (VEGF) and vascular endothelial growth factor-receptor-2 (VEGFR-2) play important roles in tumor angiogenesis[5]. Ramucirumab is a recombinant immunoglobulin G_1 monoclonal antibody antagonist of VEGFR-2 that prevents ligand-binding and receptor-mediated pathway activation in endothelial cells[6]. In second-line treatment of advanced gastric cancer, two phase III studies, REGARD[7] and RAINBOW[8], demonstrated that ramucirumab significantly improved survival when used as a single agent or in combination with paclitaxel after failure of first-line therapy. Ramucirumab has received US Food and Drug Administration and the European Medicines Agency approval for therapeutic use as second-line treatment for gastric cancer either alone or in combination with paclitaxel. We performed subgroup analyses of the REGARD and RAINBOW trials to evaluate the Latin American patients treated with ramucirumab as monotherapy and in combination with paclitaxel.

MATERIALS AND METHODS

The study designs for REGARD (NCT00917384) and RAINBOW (NCT01170663) have been published previously[7,8]. Key inclusion criteria for both trials included confirmed metastatic or locally advanced unresectable gastric or gastroesophageal junction adenocarcinoma; disease progression during first-line therapy or ≤ 4 months after last dose of first-line therapy with any platinum/fluoropyrimidine doublet (with or without anthracycline in RAINBOW) for unresectable or metastatic disease; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; and adequate hepatic, hematologic, coagulation, and renal function. Key exclusion criteria included prior therapy targeting VEGF- or the VEGFR-signaling pathways, significant gastrointestinal bleeding within three months before randomization, and arterial thromboembolic event within six months before randomization.

Procedures

In REGARD, patients were randomized 2:1 to receive either ramucirumab 8 mg/kg intravenously every two weeks or placebo plus best supportive care[7]. In RAINBOW, patients were randomized 1:1 to receive either ramucirumab 8 mg/kg or placebo intravenously on days 1 and 15 plus paclitaxel 80 mg/m^2 on days 1, 8, and 15 (28-day cycle)[8].

Safety analyses included all patients who received at least one dose of any study drug. Safety data were collected during treatment and within 30 days of the last dose and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.02[9].

Statistical methods

For the Latin American cohorts, a log-rank test was used to assess overall survival (OS) and progression-free survival (PFS). The hazard ratios (HR) were estimated with a stratified Cox proportional hazards model. The medians and 95% confidence intervals (CI) of OS and PFS were estimated using the Kaplan-Meier method. A multivariable analysis was performed to examine the effect of treatment on OS and PFS after adjustment for imbalances in baseline factors between the Latin American cohorts and the intent-to-treat (ITT) populations from both trials. Response was evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST), version 1.0[10] (REGARD) or version 1.1[11] (RAINBOW). The proportion of patients achieving an objective response and disease control was compared between treatment arms with the Cochran-Mantel-Haenszel test. We calculated the rate of disease control, defined as the best overall response for complete or partial response or stable disease, for each treatment group. All analyses were done with SAS (version 9.2).

RESULTS

Latin American patients comprised 16.1% (n = 57 of 355) in REGARD and 6.6% (n = 44 of 665) in RAINBOW. The majority of the Latin American patients were from Brazil in both REGARD and RAINBOW, with 38 and 35 patients, respectively. The remaining patients were from Argentina, Chile, Columbia, Guatemala, and Mexico. Most patients were male and their median ages ranged from 54 to 59 years.

Table 1 shows the baseline demographics from the REGARD and RAINBOW ITT as well as the Latin American patients. A total of 37 patients received ramucirumab; 20 patients received placebo in the REGARD Latin American cohort; 23 patients received ramucirumab plus paclitaxel and 21 patients received placebo plus paclitaxel in the RAINBOW Latin American cohort. Baseline patient characteristics were generally balanced between the Latin American cohort and overall study populations; however, there were some notable differences.

In the REGARD study, a higher percentage of Latin American patients had an ECOG PS of 1, regardless of treatment arm, than in the ITT population. Between treatment arms in the Latin American cohort, the ramucirumab arm had more patients aged ≥ 65 years, but a lower percentage of patients with tumor present, peritoneal metastases, and intestinal histology, and patients who had progressed on prior therapy in less than six months.

In the RAINBOW study, a higher percentage of Latin American patients in the ramucirumab arm than in the ramucirumab arm from the ITT population had an ECOG PS of 1. Additionally, the Latin American cohort, in contrast to the overall population, had numerical differences in the percentage of patients with ≥ 10% weight loss in the three months prior to study entry and time to progression on first-line therapy < 6 months (Table 1). In the RAINBOW Latin American cohort, there were numerical differences in the incidence of several negative prognostic factors between the treatment arms including patients aged ≥ 65 years, ECOG PS of 1, ≥ 10% weight loss in the three months prior to study entry, metastatic versus locally advanced disease, and peritoneal metastases (Table 1).

Efficacy

Exploratory efficacy outcomes demonstrated the Latin American cohorts had trends towards similar

Table 1. Baseline patient characteristics

REGARD		**Overall**		**Latin American cohort**	
		RAM + BSC, % n = 238	**PBO + BSC, % n = 117**	**RAM + BSC, % n = 37**	**PBO + BSC, % n = 20**
Gender	Male	71	68	62	65
Age (years)	Median (range)	60 (30-86)	60 (24-87)	59 (42-86)	54 (24-74)
	< 65	66	61	65	75
	≥ 65	34	39	35	25
Ethnicity	Hispanic/Latino	17	16	84	80
	Non-Hispanic/Latino	83	84	16	20
ECOG PS*	0	28	26	19	20
	1	72	73	81	80
Weight loss prior 3 months	≥ 10%	17	17	22	20
	< 10%	83	83	78	80
Histologic subtype	Intestinal	22	30	32	45
	Diffuse	40	38	27	35
Primary tumor	Gastric	75	73	92	90
	GEJ	25	27	8	10
	Present	73	74	68	90
Metastases	0-2	68	61	65	60
	≥ 3	32	39	35	40
	Peritoneal metastases	27	38	24	40
Measureable disease	Yes	92	91	86	85
Progression-free interval on prior therapy	< 6 months	65	71	57	70
	≥ 6 months	34	29	43	30
Prior therapy	First-line	84	88	89	85
	Adjuvant/neoadjuvant	16	12	11	15
RAINBOW		**Overall**		**Latin American cohort**	
		RAM + PAC, % n = 330	**PBO + PAC, % n = 335**	**RAM + PAC, % n = 23**	**PBO + PAC, % n = 21**
Gender	Male	69	73	70	71
Age (years)	Median (range)	61 (25-83)	61 (24-84)	54 (30-72)	57 (33-74)
	< 65	62	63	61	86
	≥ 65	38	37	39	14
Ethnicity	Hispanic/Latino	9	8	87	90
	Non-Hispanic/Latino	91	92	13	10
ECOG PS	0	35	43	22	43
	1	65	57	78	57

(Continue).

Table 1. Baseline patient characteristics *(continued)*

RAINBOW		Overall		Latin American cohort	
		RAM + PAC, % n = 330	PBO + PAC, % n = 335	RAM + PAC, % n = 23	PBO + PAC, % n = 21
Weight loss prior three months	≥ 10%	16	14	35	19
	< 10%	84	85	65	81
Histologic subtype	Intestinal	44	40	48	48
	Diffuse	35	40	39	38
Primary tumor	Gastric	80	79	83	95
	GEJ	20	21	17	5
	Present	63	62	57	71
Metastases	0-2 sites	63	69	74	71
	≥ 3	37	31	26	29
	Peritoneal metastases	49	45	39	24
Measurable disease	Yes	81	81	74	76
Time to progression on first-line therapy	< 6 months	76	76	87	95
	≥ 6 months	24	24	13	5
Extent of disease at study entry	Locally advanced	2	3	4	19
	Metastatic	98	97	96	81
Prior therapy	First-line	100	100	100	100
	Adjuvant/neoadjuvant	17	14	4	0

*One patient randomized to the placebo arm in the overall population had an ECOG PS of 2.
BSC: best supportive care; ECOG PS: Eastern Cooperative Oncology Group performance status; GEJ: gastroesophageal junction; n: number; PAC: paclitaxel; PBO: placebo; RAM: ramucirumab.

outcomes as in the ITT populations from both trials (Table 2).

Median OS in the REGARD Latin American cohort was 5.4 months in the ramucirumab arm and 2.6 months in the placebo arm (HR: 0.506; 95% CI: 0.259-0.998). Median PFS was 2.8 months in the ramucirumab arm and 1.4 months in the placebo arm (HR: 0.429; 95% CI: 0.230-0.800). The hazard ratios for survival were consistent after adjusting for imbalances in baseline factors between the ITT and Latin American populations (OS, HR: 0.496; 95% CI: 0.259-0.949; PFS, HR: 0.403; 95% CI: 0.222-0.733). Disease control rate in the Latin American cohort was higher in the ramucirumab arm (48.6 vs. 25.0%).

In the RAINBOW Latin American cohort, the hazard ratios for OS and PFS were similar to the ITT population, but did not meet statistical significance (OS, HR: 0.797; 95% CI: 0.383-1.660; PFS, HR: 0.725; 95% CI: 0.355-1.482). Results for the survival hazard ratios in the Latin American cohort were similar even after adjusting for imbalances in baseline factors (Table 2).

Safety

Safety outcomes were generally similar across cohorts and treatment arms (Table 3). In REGARD, the Latin American cohort ramucirumab arm had a higher incidence of grade ≥ 3 anemia than in the

Table 2. Efficacy outcomes

REGARD	RAM + BSC	PBO + BSC	HR (95% CI)
ITT	n = 238	n = 117	
– OS, median (95% CI), months	5.2 (4.4-5.7)	3.8 (2.8-4.7)	0.776 (0.603-0.998)
– PFS, median (95% CI), months	2.1 (1.5-2.7)	1.3 (1.3-1.4)	0.483 (0.376-0.620)
– Objective response rate: CR + PR, %	3.4	2.6	
– Disease control rate: CR + PR + SD, %	48.7	23.1	
Latin American cohort	n = 37	n = 20	
– OS, median (95% CI), months	5.4 (2.8-8.8)	2.6 (1.1-4.1)	0.506 (0.259-0.988)
– PFS, median (95% CI), months	2.8 (1.4-4.0)	1.4 (1.0-2.1)	0.429 (0.230-0.800)
– Adjusted OS*			0.496 (0.259-0.949)
– Adjusted PFS*			0.403 (0.222-0.733)
– Objective response rate: CR + PR, %	2.7	0.0	
– Disease control rate: CR + PR + SD, %	48.6	25.0	
RAINBOW	**RAM + PAC**	**PBO + PAC**	**HR (95% CI)**
ITT	n = 330	n = 335	
– OS, median (95% CI), months	9.6 (8.5-10.8)	7.4 (6.3-8.4)	0.807 (0.678-0.962)
– PFS, median (95% CI), months	4.4 (4.2-5.3)	2.9 (2.8-3.0)	0.635 (0.536-0.752)
– Objective response rate: CR + PR, %	27.9	16.1	
– Disease control rate: CR + PR + SD, %	80.0	63.6	
Latin American cohort	n = 23	n = 21	
– OS, median (95% CI), months	7.1 (3.7-16.2)	8.1 (4.2-9.6)	0.797 (0.383-1.660)
– PFS, median (95% CI), months	3.8 (1.5-6.8)	4.2 (2.3-5.7)	0.725 (0.355-1.482)
– Adjusted OS†			0.734 (0.343-1.568)
– Adjusted PFS†			0.639 (0.304-1.342)
– Objective response rate: CR + PR, %	8.7	23.8	
– Disease control rate: CR + PR + SD, %	65.2	71.4	

*Adjusted for ECOG PS (≥ 1 vs. 0); †Adjusted for ECOG PS (1 vs. 0), age (≥ 65 vs. < 65), weight loss over the prior three months (≥ 10 vs. < 10%), time to progression (≥ 6 vs. < 6 months), and metastatic disease (yes vs. no).

BSC: best supportive care; CI: confidence interval; CR: complete response; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; ITT: intent-to-treat; n: number; OS: overall survival; PAC: paclitaxel; PBO: placebo; PFS: progression-free survival; PR: partial response; RAM: ramucirumab; SD: stable disease.

overall population (13.9 vs. 6.4%). In RAINBOW, the Latin American cohort had a higher incidence of abdominal pain, anemia, and vomiting, but a lower incidence of bleeding, hypertension, and grade ≥ 3 neutropenia than in the overall population. Inferences about differences in adverse events between these populations may be limited due to the small sample sizes of the Latin American cohorts.

DISCUSSION

Geographical differences exist in treatment strategies and clinical outcomes, leading to disparities in gastric cancer survival among different races and ethnicities[12]. Results from large, global, randomized phase III trials can assess the attributes of a study subpopulation, describing similarities and differences to the overall study population, to better understand how treatment may be utilized. Limited data describe treatment strategies for Latin American patients with advanced gastric cancer. In the REGARD and RAINBOW studies, baseline characteristics and efficacy and safety outcomes in the Latin American cohorts, although with a few notable exceptions, were similar to the overall study populations. Several negative prognostic factors were more prevalent in the RAINBOW Latin American population. The hazard ratios for survival were consistent with the overall ITT populations in both Latin American cohorts. The most

Table 3. Select treatment-emergent adverse events

REGARD	ITT				Latin American cohort			
	RAM n = 236		PBO n = 115		RAM n = 36		PBO n = 20	
TEAEs (%)*	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3
All TEAEs	94.5	56.8	87.8	58.3	97.2	61.1	90.0	70.0
Fatigue†	35.6	6.4	40.0	9.6	30.6	8.3	35.0	0.0
Neutropenia†	4.7	2.1	0.9	0.0	11.1	5.6	0.0	0.0
Abdominal pain†	28.8	5.9	27.8	2.6	27.8	2.8	35.0	0.0
Decreased appetite	24.2	3.4	22.6	3.5	19.4	0.0	25.0	10.0
Vomiting	19.9	2.5	25.2	4.3	16.7	0.0	25.0	0.0
Constipation	15.3	0.4	22.6	2.6	11.1	0.0	30.0	5.0
Anemia†	14.8	6.4	14.8	7.8	33.3	13.9	25.0	0.0
Dyspnea	9.3	1.7	13.0	6.1	2.8	0.0	15.0	15.0
Hypertension‡	16.1	7.6	7.8	2.6	13.9	8.3	0.0	0.0
Bleeding/Hemorrhage	12.7	3.4	11.3	2.6	13.9	2.8	0.0	0.0
Arterial thrombotic events	1.7	1.3	0.0	0.0	0.0	0.0	0.0	0.0
Venous thrombotic events	3.8	1.3	7.0	4.3	0.0	0.0	10.0	5.0
Proteinuria	3.0	0.4	2.6	0.0	0.0	0.0	0.0	0.0
GI perforation	0.8	0.8	0.9	0.9	0.0	0.0	5.0	5.0
Infusion-related reaction	0.4	0.0	1.7	0.0	2.8	0.0	5.0	0.0
Cardiac failure	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RAINBOW	**ITT**				**Latin American cohort**			
	RAM + PAC n = 327		PBO + PAC n = 329		RAM + PAC n = 23		PBO + PAC n = 20	
TEAEs (%)*	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3	Any Gr	Gr ≥ 3
All TEAEs	99.1	81.7	97.9	62.6	100.0	87.0	100.0	90.0
Fatigue†	56.9	11.9	43.8	5.5	47.8	17.4	35.0	10.0
Neutropenia†	54.4	40.7	31.0	18.8	43.5	21.7	10.0	10.0
Decreased appetite	40.1	3.1	31.9	4.0	30.4	4.3	25.0	5.0
Abdominal pain†	36.1	6.1	29.8	3.3	47.8	8.7	70.0	0.0
Anemia†	34.9	9.2	36.2	10.3	52.2	17.4	50.0	20.0
Vomiting	26.9	3.1	20.7	3.6	39.1	13.0	20.0	5.0
Constipation	21.4	0.0	21.6	0.6	17.4	0.0	5.0	0.0
Dyspnea	12.8	2.4	9.4	0.6	4.3	0.0	20.0	5.0
Bleeding/hemorrhage	41.9	4.3	17.9	2.4	26.1	0.0	15.0	5.0
Hypertension	25.1	14.7	5.8	2.7	8.7	8.7	15.0	15.0
Proteinuria	16.8	1.2	6.1	0.0	13.0	0.0	5.0	0.0
Infusion-related reaction	5.8	0.6	3.6	0.0	4.3	0.0	5.0	0.0
Venous thromboembolic	4.0	2.4	5.5	3.3	0.0	0.0	15.0	10.0
Congestive heart failure	2.4	0.6	1.2	0.6	8.7	4.3	5.0	0.0
Arterial thromboembolic	1.8	0.9	1.5	0.9	0.0	0.0	0.0	0.0
GI perforation	1.2	1.2	0.3	0.0	0.0	0.0	0.0	0.0

*Treatment-emergent adverse events published in both REGARD[7] and RAINBOW[8] trials are shown in addition to neutropenia; †Consolidated adverse event terms are comprised of synonymous MedDRA preferred terms version 15.0; ‡No grade 4 hypertension was observed among ramucirumab-treated patients.

Note: Adverse events of special interest are highlighted in grey.

GI: gastrointestinal; Gr: grade; ITT: intent-to-treat; LA: Latin American; MedDRA: Medical Dictionary for Regulatory Activities; n: number; PAC: paclitaxel; PBO: placebo; RAM: ramucirumab; TEAE: treatment-emergent adverse event.

significant limitation to this study was the small sample sizes of Latin American patients.

CONCLUSIONS

Results from this exploratory analysis of small patient cohorts should be interpreted with caution due to inherent risk of bias, and the limitations to inferences imposed by small sample size. Based on the similarities of the Latin American population to the overall study population, use of ramucirumab as monotherapy or in combination with paclitaxel in Latin American patients with metastatic gastric or gastroesophageal junction adenocarcinoma (as described in the global phase III randomized trials) may provide similar therapeutic benefits.

DECLARATION OF INTEREST

This work was supported by Eli Lilly and Company. The studies were designed under the responsibility of Eli Lilly and Company, in conjunction with the steering committee. Eli Lilly and Company collected and analyzed the data and contributed to the interpretation of the studies. All authors had full access to all of the data in the studies and had final responsibility for the decision to submit for publication.

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