

FDA Approval Summary: Ramucirumab for Gastric Cancer

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Abstract

The FDA approved ramucirumab (CYRAMZA; Eli Lilly and Company) for previously treated patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma initially as monotherapy (April 21, 2014) and subsequently as combination therapy with paclitaxel (November 5, 2014). In the monotherapy trial, 355 patients in the indicated population were randomly allocated (2:1) to receive ramucirumab or placebo, 8 mg/kg intravenously every 2 weeks. In the combination trial, 665 patients were randomly allocated (1:1) to receive ramucirumab or placebo, 8 mg/kg intravenously every 2 weeks, in combination with paclitaxel, 80 mg/m² on days 1, 8, and 15 of 28-day cycles. Overall survival (OS) was increased in patients who

received ramucirumab in both the monotherapy [HR, 0.78; 95% confidence interval (CI), 0.60–0.998; log rank $P = 0.047$] and combination trials (HR, 0.81; 95% CI, 0.68–0.96; $P = 0.017$). The most common adverse reactions were hypertension and diarrhea in the monotherapy trial and fatigue, neutropenia, diarrhea, and epistaxis in the combination trial. Because of concerns about the robustness of the monotherapy trial results, FDA approved the original application after receiving the results of the combination trial confirming the OS effect. Based on exploratory exposure–response analyses, there is residual uncertainty regarding the optimal dose of ramucirumab. *Clin Cancer Res*; 21(15); 3372–6. ©2015 AACR.

Introduction

Worldwide, 952,000 new cases of stomach cancer were estimated to have occurred in 2012, making it the fifth most common malignancy (1). In the United States, gastric cancer is less frequent (16th most common malignancy). Based on 2007–2011 data, in the United States there were 7.5 new cases of stomach cancer and 3.5 deaths from stomach cancer per 100,000 men and women per year. A total of 22,220 new cases were predicted to occur in 2014 (2).

In the United States, fit patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma receive combination therapy in the first-line setting (e.g., a platinum and fluoropyrimidine combination with or without a third agent, generally a taxane or an anthracycline; ref. 3). In 2010, the FDA

approved trastuzumab for the first-line treatment of HER-2–overexpressing metastatic gastric or GEJ adenocarcinoma based on the results of the ToGA trial, a randomized trial that demonstrated a significant improvement in overall survival (OS) when trastuzumab was combined with cisplatin and 5-fluorouracil or capecitabine (4). However, HER-2 overexpression is observed in only 15% to 22% of patients with gastric cancer (4).

Virtually all patients with advanced gastric cancer will develop progressive disease after first-line therapy. In recent trials, the percentage of patients receiving second-line therapy ranged from 14% to 45% (5). Second-line treatment approaches administered in the community setting include rechallenge with cisplatin and 5-fluorouracil, taxane monotherapy, irinotecan monotherapy, or combination regimens such as FOLFIRI or FOLFOX (3, 6).

Ramucirumab is a fully human IgG1 monoclonal antibody that targets the vascular endothelial growth factor receptor-2 (VEGFR-2), preventing ligand binding and receptor-mediated pathway activation in endothelial cells. Two studies were submitted in support of the approval of ramucirumab for the second-line treatment of gastric and GEJ adenocarcinoma (7, 8). This article summarizes the FDA's review of the trials, the issues that were identified, and the basis for approval.

Clinical Trials

JVBD and JVBE were international, double-blind, placebo-controlled studies. Eligibility was limited to patients 18 years of age or older, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, and histologically confirmed metastatic or unresectable gastric or GEJ adenocarcinoma with documented disease progression on or after systemic first-line treatment. Exclusion criteria in both studies included significant

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gastrointestinal hemorrhage within 3 months, NSAID use, arterial thrombotic events within 6 months, and poorly controlled hypertension.

In JVBD, patients were randomly allocated (2:1) to receive ramucirumab, 8 mg/kg, or placebo intravenously every 2 weeks. Randomization was stratified by weight loss in the prior 3 months, geographic region, and primary tumor location. In JVBE, patients were randomly allocated (1:1) to receive paclitaxel, 80 mg/m² on days 1, 8, and 15 of 28-day cycles, with ramucirumab, 8 mg/kg or placebo intravenously every 2 weeks. Randomization was stratified by geographic region, time to progression on first-line therapy, and disease measurability. In both studies, patients received treatment until disease progression or unacceptable toxicity, and crossover was not allowed.

The primary endpoint was OS in both studies. Key secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and safety. Tumor assessments were performed every 6 weeks until disease progression. As amended, JVBD was designed with 80% power and a two-sided significance level of 0.05 to detect a difference in median OS of 7.25 months versus 5 months following the occurrence of 268 deaths. JVBE was designed with 90% power and a two-sided significance level of 0.05 to detect a difference in median OS of 9.3 months versus 7 months following the occurrence of 510 deaths.

Patient Characteristics

A total of 355 patients (238 patients in the ramucirumab arm and 117 patients in the placebo arm) were randomized in JVBD, and 665 patients (330 patients in the ramucirumab/paclitaxel arm and 335 patients in the placebo/paclitaxel arm) were randomized in JVBE. More Asian patients were enrolled in JVBE (35%) than in JVBD (16%).

In both studies, baseline and disease characteristics were mostly balanced between arms and were similar between studies. Median age was 60 to 61 years; 70% to 71% of patients were male; 77% and 61% patients were white (JVBD and JVBE, respectively), and 74% and 79% had gastric tumors (JVBD and JVBE, respectively).

In JVBD, 81% of patients received platinum/fluoropyrimidine therapy in the first-line setting. As per the eligibility criteria, all patients in JVBE received platinum/fluoropyrimidine therapy in the first-line setting; approximately 25% of patients received a triplet combination regimen.

Efficacy Results

Efficacy results are summarized in Table 1 and Fig. 1. Both studies demonstrated statistically significant improvements in

OS and PFS. Exploratory analyses showed that the effect of ramucirumab was consistent in most subgroups; however, in JVBD, women (*n* = 107) who received ramucirumab had an HR greater than 1.0, favoring the placebo arm [HR, 1.43; 95% confidence interval (CI), 0.85–2.41]. In JVBE, exploratory analyses also showed that the effect of ramucirumab was consistent in most subgroups. Importantly, the HR for OS in women (*n* = 193) in JVBE showed a point estimate of 0.67 (95% CI, 0.48–0.94), favoring the ramucirumab arm.

Exposure–response analyses (population pharmacokinetic model) were conducted by quartile of ramucirumab exposure (*C*_{min}) in study JVBE. Figure 2 shows that in these exploratory analyses, the point estimate for median survival was longer in patients in the highest quartiles of ramucirumab exposure. Additional exploratory analyses using case–control methodology to adjust for ECOG performance status, tumor differentiation, and total number of lesions showed similar findings for patients in the highest two quartiles of exposure.

Safety Results

The primary JVBD safety population included 351 patients who received at least one dose of ramucirumab (*n* = 236) or placebo (*n* = 115). The primary JVBE safety population included 656 patients who received ramucirumab (*n* = 327) or placebo (*n* = 329) in combination with paclitaxel.

In JVBD, the most common adverse reactions (all grades) were hypertension and diarrhea. In general, the incidence of grade 3 to 4 adverse events was comparable between arms. As such, only four adverse events (grades 3–4 in severity) occurred with ≥2% difference in the ramucirumab arm compared with placebo: hypertension (8% vs. 3%), pain (2% vs. none), hyponatremia (3% vs. 1%), and abdominal pain (5% vs. 3%). Hypertension of any severity occurred more frequently in the ramucirumab arm (16% vs. 8%) as did proteinuria as a clinical laboratory finding (8% vs. 3%).

In JVBE, the most common adverse reactions (all grades) were fatigue, neutropenia, diarrhea, and epistaxis. Doses of both ramucirumab and paclitaxel were more frequently delayed, reduced, or omitted in the ramucirumab/paclitaxel arm. Neutropenia was the most common cause for dose modification. Besides neutropenia, other toxicities (all grades) of paclitaxel that occurred more frequently in patients receiving ramucirumab were diarrhea (32% versus 23%) and stomatitis (20% versus 7%). Both hypertension (25% vs. 6%) and hemorrhagic events (42% vs. 18%) were more frequent in the

Table 1. Efficacy of ramucirumab in previously treated patients with gastric-GEJ adenocarcinoma

	JVBD		JVBE	
	Ramucirumab (<i>n</i> = 238)	Placebo (<i>n</i> = 117)	Ramucirumab/PAC (<i>n</i> = 330)	Placebo/PAC (<i>n</i> = 335)
OS				
Number of deaths	179 (75%)	99 (85%)	256 (78%)	260 (78%)
HR ^a (95% CI), <i>P</i> ^b	0.78 (0.60–0.998), <i>P</i> = 0.047		0.81 (0.68–0.96), <i>P</i> = 0.017	
Median survival ^c , mo (95% CI)	5.2 (4.4–5.7)	3.8 (2.8–4.7)	9.6 (8.5–10.8)	7.4 (6.3–8.4)
PFS				
HR ^a (95% CI), <i>P</i> ^b	0.48 (0.38–0.62), <i>P</i> < 0.001		0.64 (0.54; 0.75), <i>P</i> < 0.001	
Median PFS ^c , mo (95% CI)	2.1 (1.5–2.7)	1.3 (1.3–1.4)	4.4 (4.2–5.3)	2.9 (2.8–3.0)

Abbreviation: PAC, paclitaxel.

^aHR estimated using the Cox model.

^bStratified log-rank test.

^cKaplan–Meier estimate.

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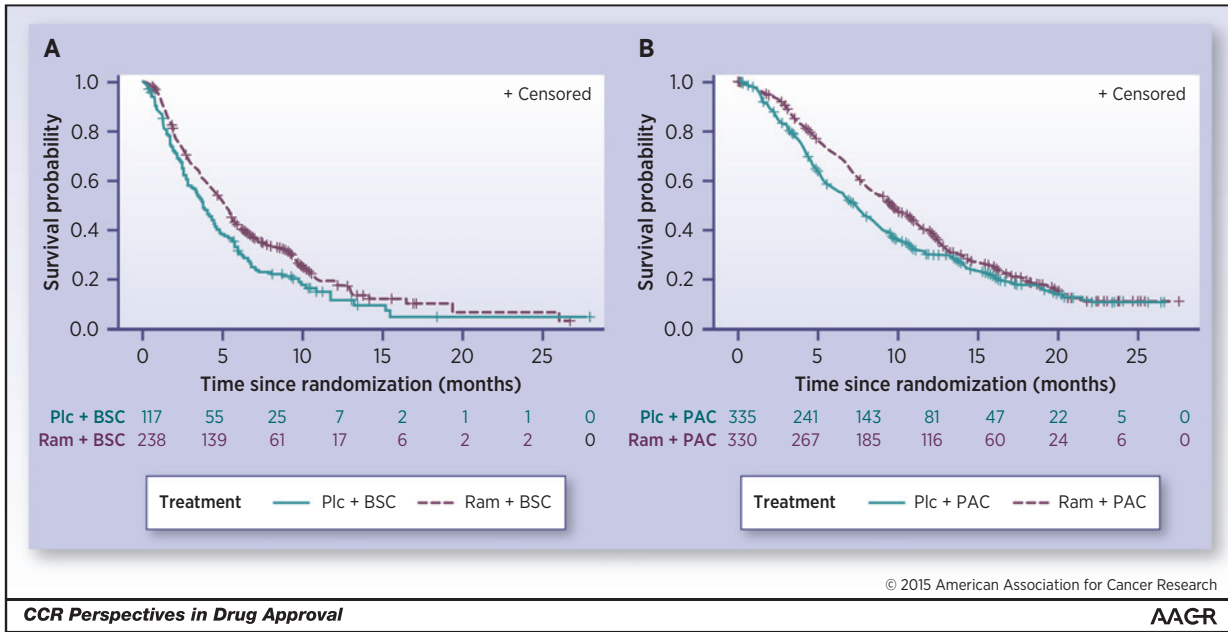


Figure 1. Kaplan-Meier product limit estimates of OS in JVBD (A) and JVBE (B). BSC, best supportive care; PAC, paclitaxel; Plc, placebo; Ram, Ramucirumab.

ramucirumab arm; however, these were mostly grades 1 to 2 in severity. A summary of severe (i.e., grades 3–5) toxicities from JVBE can be found in Table 2.

The risk of severe bleeding in patients who received ramucirumab versus placebo was 3.4% versus 2.6% in JVBD and 4.3% versus 2.4% in JVBE. Other serious adverse reactions (ramucir-

umab vs. placebo) associated with inhibition of the VEGF axis included arterial thromboembolic events (1.7% vs. 0 in JVBD and 1.6% vs. 2.1% in JVBE), gastrointestinal perforations (0.7% vs. 1.2% in JVBD and 1% vs. 0.3% in JVBE), and reversible posterior leukoencephalopathy syndrome (<0.1% across all ramucirumab clinical studies).

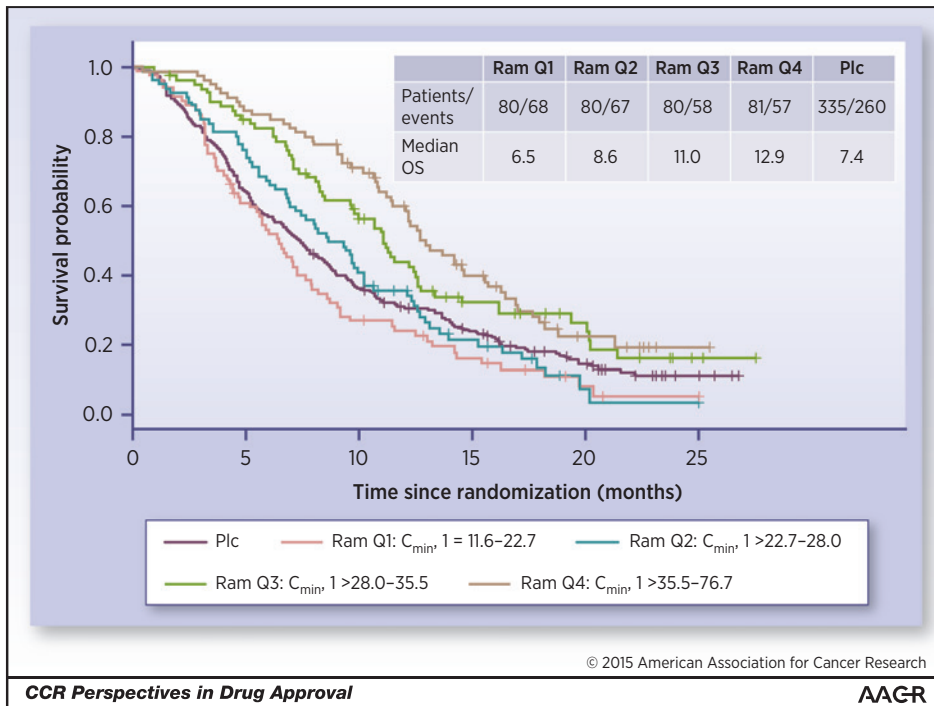


Figure 2. Study JVBE Kaplan-Meier survival curve stratified by C_{min} quartiles. Plc, placebo; Ram, Ramucirumab.

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Table 2. Grade 3 to 5 adverse events in the JVBE study (incidence $\geq 3\%$)

Adverse event	Ramucirumab/PAC (n = 327)	Placebo/PAC (n = 329)
Neutropenia	133 (41%)	62 (19%)
Leukopenia	57 (17%)	22 (7%)
Hypertension	46 (14%)	8 (2%)
Anemia	30 (9%)	34 (10%)
Fatigue/asthenia	39 (12%)	18 (5%)
Abdominal pain	18 (6%)	11 (3%)
Ascites	12 (4%)	13 (4%)
Diarrhea	12 (4%)	5 (2%)
Decreased appetite	10 (3%)	13 (4%)
Vomiting	10 (3%)	12 (4%)
General physical health deterioration	11 (3%)	11 (3%)
Dehydration	9 (3%)	8 (2%)
Febrile neutropenia	10 (3%)	8 (2%)
Peripheral neuropathy	10 (3%)	7 (2%)
Hyponatremia	11 (3%)	4 (1%)
Pulmonary embolism	4 (1%)	10 (3%)

NOTE: Grade 5 events listed in this table were general physical health deterioration (2 in the placebo arm, 1 in ramucirumab arm), dehydration (1 in the ramucirumab arm), febrile neutropenia (1 in the placebo arm), and pulmonary embolism (2 in the placebo arm, 1 in the ramucirumab arm).

Abbreviation: PAC, paclitaxel.

Discussion

In study JVBD, ramucirumab showed a 1.4-month improvement in median OS compared with placebo that was statistically significant but just under the two-sided 0.05 threshold ($P = 0.047$). Of concern, in JVBD, there were potential imbalances in treatment effects by geographic region and sex. Most concerning to FDA was the potential lack of survival improvement in women (HR, 1.43; 95% CI, 0.85–2.41). Therefore, the primary issue considered by FDA during the review of the original Biologics License Application (BLA) was whether the results of this single adequate and well-controlled trial provided the substantial evidence of effectiveness needed to support the approval. The FDA Guidance for Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products states that reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome, and confirmation of the results in a second trial would be practically or ethically impossible (9). Based on the modest effects observed in JVBD (improvement in median OS of 1.4 months with a P value just under 0.05), it could be argued that a second trial of ramucirumab could ethically be conducted, especially to further evaluate the effects of ramucirumab in women.

During the review of the original BLA, however, Lilly submitted the top-line results of JVBE, which confirmed the survival effects of ramucirumab. Data from JVBE submitted in the BLA demonstrated a statistically significant improvement in OS (difference in medians of 2.3 months). Importantly in JVBE, ramucirumab improved survival in women (HR, 0.67; 95% CI, 0.48–0.94). Additionally, in JVBE, a higher number of women were enrolled, and FDA concluded that differences in treatment effects in women represented chance findings.

During the review of the BLA supplement submitted to support the inclusion of the JVBE data in the product label, FDA considered the exposure–response relationship observed in exploratory analyses, suggesting that a higher dose, at least in some patients, might improve the effectiveness of ramucirumab. These exploratory analyses suggested that survival in patients with lower ramucirumab

exposure was shorter than in patients with higher ramucirumab exposure. Ultimately, although the analyses provided data that could support the investigation of higher doses of ramucirumab (if determined to be safe in combination with paclitaxel), they should be interpreted with caution as each subgroup (quartile) was a nonrandomized, underpowered subgroup, and confounding factors were likely present based on patient or disease-related factors. However, based on these exposure–response results, Lilly agreed to conduct a post-marketing study in order to investigate whether a higher dose of ramucirumab could increase PFS compared with the standard dose (both arms in combination with paclitaxel in patients with previously treated gastric cancer). The post-marketing study will have a run-in phase in order to determine whether the higher dose of ramucirumab is reasonably safe to administer to patients because even greater increases in rates of neutropenia and hypertension are possible complications of the higher dose.

Ultimately, this application provided data supporting a favorable risk/benefit profile (i.e., improvement in OS with acceptable toxicity) for ramucirumab, either as monotherapy or in combination with paclitaxel, in patients with previously treated gastric cancer. The improvement in OS observed in JVBD and JVBE came with an increased risk for severe bleeding, arterial thrombotic events (in JVBD), hypertension, and other adverse reactions; however, the absolute risk for severe bleeding and arterial thrombotic events relative to placebo was low ($\leq 2\%$). When administered with paclitaxel in JVBE, ramucirumab increased the risk for toxicities typically associated with chemotherapy, including neutropenia, diarrhea, and stomatitis. Infusion-related reactions (IRR) were labeled as a warning because, prior to institution of premedication recommendations across clinical trials of ramucirumab, IRRs occurred in 6 of 37 (16%) patients, including two severe events. Based on the mechanism of action, the label contains a warning for impaired wound healing. The label also contains a warning (data reviewed from hepatocellular carcinoma trials) to describe the risk of clinical deterioration in patients with Child–Pugh B or C cirrhosis.

Clinicians will need to judge the results of both studies in order to make the determination of which regimen (monotherapy or in combination with paclitaxel) is most appropriate for their patients. In order to approve the applications, FDA considered the totality of the evidence from both studies. Residual uncertainties regarding the optimal dose, the role of ramucirumab with other chemotherapy backbones, and the use of ramucirumab in the first-line setting will need to be addressed in other clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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