Cyramza (Ramucirumab) Approved for the Treatment of Advanced Gastric Cancer and Metastatic Non–Small-Cell Lung Cancer

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Gastric cancer and lung cancer impose a substantial burden on patients. In light of the high mortality rate and quality-of-life issues associated with these 2 types of cancer, there is a marked need for additional therapeutic options to improve outcomes for patients with gastric or lung cancer.

Gastric Cancer

The prevalence of gastric cancer has been on the decline in the United States in the past 80 years.[1] Gastric cancer is most common in older people aged >65 years, affecting 6 in 10 people in this age-group. It is estimated that 24,590 new cases of gastric cancer will be diagnosed in the United States in 2015.[1]

The gastroesophageal junction (GEJ) is the area just beneath the diaphragm, where the esophagus joins the stomach. GEJ adenocarcinoma (or stomach cancer) is a cancer that affects this region of the gastric tract.[2]

As with other types of cancer, early detection and advances in treatment have improved the outlook for patients with gastric cancer. However, most gastric cancers are diagnosed at advanced stages rather than at early stages, resulting in a low survival rate.[3] Overall, the 5-year relative survival rate of all patients with gastric cancer in the United States is approximately 29%.[3]

The total US expenditures for stomach cancer were estimated to be $1.8 billion in 2010.[4]

Lung Cancer

Lung cancer is the second most common cancer in men and in women in the United States, with an estimated 221,200 new cases projected for 2015.[5] Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases of lung cancer.[6] Overall, lung cancer claims more lives than any other type of cancer—more than that of colon, breast, and prostate cancers combined—accounting for approximately 27% of all cancer deaths in the United States.[5]

Although the 5-year survival rate for localized lung cancer is 54%, only 15% of lung cancers are diagnosed at this stage.[7] For all lung cancer cases diagnosed between 2003 and 2009, the 1-year relative survival rate was 43%, and the 5-year relative survival rate was 17%.[7] Lung cancer is the third costliest cancer in the United States, after breast cancer and colorectal cancer, with a total estimated annual cost of $10.3 billion.[8]

The Vascular Endothelial Growth Factor Pathway

Angiogenesis, the formation of new capillaries and blood vessels, is a process involved in tumor growth.[9] Vascular endothelial growth factor (VEGF) is a primary mediator of angiogenesis in normal physiology and in certain diseases.[9] VEGF and VEGF receptor-2–mediated signaling and angiogenesis may play a key role in the pathogenesis of gastric cancer and lung cancer.[10-12] The blockade of VEGF receptor-2 signaling inhibits angiogenesis (ie, blood supply) to tumors.[12] A number of small molecule inhibitors and antibody-based agents that target the VEGF pathway have been studied across various cancer types.[9] In clinical studies, targeting the VEGF receptor-2 pathway has shown promise as a second-line treatment for patients with gastric or lung cancer.[10-12]

Ramucirumab Receives Several FDA Approvals in 2014

A New Option for Advanced Stomach Cancer

On April 21, 2014, ramucirumab (Cyramza; Eli Lilly), a human VEGF receptor-2 antagonist, was approved by the US Food and Drug Administration (FDA) as a single agent for the treatment of patients with advanced stomach cancer or GEJ adenocarcinoma that has progressed with or after fluoropyrimidine- or platinum-containing chemotherapy.[13] Ramucirumab is a recombinant human immunoglobulin G1 monoclonal antibody, also referred to as an angiogenesis inhibitor (ie, blocking the blood supply to tumors).[13]

The FDA granted ramucirumab a priority review based on its potential to provide a significant improvement in safety or effectiveness in the treatment of advanced gastric cancer or GEJ adenocarcinoma. The FDA also designated ramucirumab as an orphan drug because it is approved for a rare disease.[13]

According to Richard Pazdur, MD, Director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, "Although the rates of stomach cancer in the United States

have decreased over the past 40 years, patients require new treatment options, particularly when they no longer respond to other therapies. Ramucirumab is a new treatment option that has demonstrated an ability to extend patients' lives and slow tumor growth."[13]

Expanded indication. On November 5, 2014, the FDA expanded the initial indication of ramucirumab to be used alone or with paclitaxel for the treatment of patients with advanced stomach cancer that has progressed with or after previous fluoropyrimidine- or platinum-containing chemotherapy.[14]

A New Option for Non–Small-Cell Lung Cancer

On December 12, 2014, the FDA approved ramucirumab to be used in combination with docetaxel for the treatment of patients with metastatic NSCLC that has progressed with or after platinum-based chemotherapy.[15] In patients with lung cancer and the *EGFR* or *ALK* genetic mutations, ramucirumab should only be used after their disease has progressed while using FDA-approved therapies for these mutations.[16]

Dr Pazdur commented, "Today's approval is the third indication that Cyramza has received in 2014."[15] He further stated, "The commitment to study Cyramza in a variety of malignancies provides important treatment options to patients."[15]

Mechanism of Action

Ramucirumab is a VEGF receptor-2 antagonist that specifically binds VEGF receptor-2 and blocks the binding of VEGF receptor ligands, VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand-stimulated activation of VEGF receptor-2, thereby inhibiting ligand-induced proliferation and migration of human endothelial cells.[16]

Table 1 The REGARD Trial: Ramucirumab versus Placebo in Gastric Cancer

Efficacy measure	Ramucirumab + best supportive therapy (N = 238)	Placebo + best supportive therapy (N = 117)
Overall survival		
Deaths, N (%)	179 (75)	99 (85)
Median, mo	5.2 (95% CI, 4.4-5.7)	3.8 (95% CI, 2.8-4.7)
Hazard ratio	0.78 (95% CI, 0.60-0.998)	
Stratified log-rank *P* value	.047	
Progression-free survival		
Events, N (%)	199 (84)	108 (92)
Median, mo	2.1 (95% CI, 1.5-2.7)	1.3 (95% CI, 1.3-1.4)
Hazard ratio	0.48 (95% CI, 0.38-0.62)	
Stratified log-rank *P* value	<.001	

CI indicates confidence interval.
Source: Cyramza (ramucirumab) injection prescribing information; December 2014.

Dosing and Administration

Ramucirumab is administered as an intravenous (IV) infusion only. It should not be administered as an IV push or bolus.[16]

For patients with advanced gastric cancer, the recommended dose of ramucirumab, either as a single agent or in combination with weekly paclitaxel, is 8 mg/kg every 2 weeks.[16]

For patients with metastatic NSCLC, the recommended dose of ramucirumab is 10 mg/kg, administered intravenously on day 1 of a 21-day cycle, before the infusion of docetaxel.[16]

Ramucirumab is available as an injection in single-dose vials in a 100-mg/10-mL (10 mg per mL) solution and in a 500-mg/50-mL (10 mg per mL) solution.[16]

Clinical Studies

The REGARD Trial: Gastric Cancer

The REGARD trial was a multinational, randomized, double-blind study that evaluated the efficacy of ramucirumab plus best supportive care compared with placebo plus best supportive care and randomized (in a 2:1 ratio) 355 patients with locally advanced or metastatic gastric cancer, including GEJ adenocarcinoma.[10,16] The patients (median age, 60 years) received either an IV infusion of ramucirumab 8 mg/kg or placebo every 2 weeks. The primary efficacy end point was overall survival (OS), and the supportive outcome measure was progression-free survival (PFS).[10,16]

The efficacy results from the REGARD trial are shown in **Table 1**. Patients randomized to receive ramucirumab had significant improvements in OS and PFS compared with patients randomized to placebo.[10,16] The median OS was 5.2 months in the ramucirumab group compared with 3.8 months in the placebo group.[10,16] Moreover, treatment with ramucirumab was associated with a 52% reduction in the risk for disease progression or death from any cause compared with placebo.[10]

According to the REGARD study investigators, ramucirumab is the first biologic agent given as a monotherapy to demonstrate survival benefits in patients with advanced gastric cancer or GEJ adenocarcinoma that had progressed after first-line chemotherapy.[10] The investigators stated that these findings reinforce the importance of targeting the VEGF receptor-2 pathway when treating patients with advanced gastric cancer.[10]

The RAINBOW Trial: Gastric Cancer

The RAINBOW trial, a multinational, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel, included 665 patients (randomized in a 1:1 ratio) with locally advanced or metastatic gastric cancer (including GEJ adenocarcinoma) who received platinum-containing and fluoropyrimidine-containing chemotherapy.[11,16] The patients (median age, 61 years) were randomized to receive either ramucirumab 8 mg/kg or placebo as an IV infusion on days 1, 8, and 15 of each 28-day cycle. The primary efficacy outcome measure was OS, and the supportive outcome measures were PFS and objective response rate.[11,16]

As shown in **Table 2**, treatment with ramucirumab plus paclitaxel showed a significantly longer OS compared with placebo plus paclitaxel (9.6 months vs 7.4 months, respectively).[11,16] Moreover, ramucirumab plus paclitaxel demonstrated significant improvements in PFS and objective response rate compared with placebo plus paclitaxel.[11,16]

The RAINBOW study's investigators suggested that ramucirumab plus paclitaxel could be considered a standard second-line treatment option for patients with advanced gastric cancer.[11]

Table 2 The RAINBOW Trial: Ramucirumab plus Paclitaxel versus Placebo plus Paclitaxel in Gastric Cancer

Efficacy measure	Ramucirumab + paclitaxel (N = 330)	Placebo + paclitaxel (N = 335)
Overall survival		
Deaths, N (%)	256 (78)	260 (78)
Median, mo	9.6 (95% CI, 8.5-10.8)	7.4 (95% CI, 6.3-8.4)
Hazard ratio	0.81 (95% CI, 0.68-0.96)	
Stratified log-rank *P* value	.017	
Progression-free survival		
Events, N (%)	279 (85)	296 (88)
Median, mo	4.4 (95% CI, 4.2-5.3)	2.9 (95% CI, 2.8-3.0)
Hazard ratio	0.64 (95% CI, 0.54-0.75)	
Stratified log-rank *P* value	<.001	
Objective response rate (complete response plus partial response)		
Rate, %	28 (95% CI, 23-33)	16 (95% CI, 13-20)
Stratified CMH *P* value	<.001	

CI indicates confidence interval; CMH, Cochran-Mantel-Haenszel.
Source: Cyramza (ramucirumab) injection prescribing information; December 2014.

The REVEL Trial: Non–Small-Cell Lung Cancer

The REVEL trial was a multinational, randomized, double-blind study in patients with NSCLC that had progressed while receiving or after receiving 1 platinum-based therapy regimen for locally advanced or metastatic NSCLC.[12,16] Patients (median age, 62 years) received either ramucirumab 10 mg/m^2 intravenously plus docetaxel 75 mg/m^2 intravenously every 21 days or placebo plus docetaxel 75 mg/m^2 intravenously every 21 days. The primary end point was OS, and the supportive outcome measures were PFS and objective response rate.[12,16]

Efficacy results from the REVEL trial are shown in **Table 3**. Patients in the ramucirumab plus docetaxel group had statistically significant improvements in OS and PFS compared with patients in the placebo plus docetaxel group. Moreover, the objective response rate (complete response or partial response) for patients receiving ramucirumab plus docetaxel was 23% (95% confidence interval, 20-26) compared with 14% (95% confidence interval, 11-17) for patients receiving placebo plus docetaxel (*P* <.001).[16]

Table 3 The REVEL Trial: Ramucirumab plus Docetaxel versus Placebo plus Docetaxel in Non–Small-Cell Lung Cancer

Efficacy measure	Ramucirumab + docetaxel (N = 628)	Placebo + docetaxel (N = 625)
Overall survival		
Deaths, N (%)	428 (68)	456 (73)
Median, mo	10.5 (95% CI, 9.5-11.2)	9.1 (95% CI, 8.4-10.0)
Hazard ratio	0.86 (95% CI, 0.75-0.98)	
Stratified log-rank *P* value	.024	
Progression-free survival		
Events, N (%)	558 (89)	583 (93)
Median, mo	4.5 (95% CI, 4.2-5.4)	3.0 (95% CI, 2.8-3.9)
Hazard ratio	0.76 (95% CI, 0.68-0.86)	
Stratified log-rank *P* value	<.001	

CI indicates confidence interval.
Source: Cyramza (ramucirumab) injection prescribing information; December 2014.

Safety

The most common adverse reactions observed in patients treated with single-agent ramucirumab at a rate of ≥10% and ≥2% higher than placebo were hypertension (16%) and diarrhea (14%).[16]

In patients treated with ramucirumab plus paclitaxel, the most common adverse reactions observed at a rate of ≥30% and ≥2% higher than placebo plus paclitaxel were fatigue/asthenia (57%), neutropenia (54%), diarrhea (32%), and epistaxis (31%).[16]

In patients receiving ramucirumab plus docetaxel, the most common adverse reactions observed at a rate of ≥30% and ≥2% higher than placebo plus docetaxel

were neutropenia (55%), fatigue/asthenia (55%), and stomatitis/mucosal inflammation (37%).[16]

No pharmacokinetic interactions were observed between ramucirumab and paclitaxel or between ramucirumab and docetaxel.[16]

There are no contraindications associated with ramucirumab.[16]

Warnings and Precautions

Boxed warning. Ramucirumab was approved with a boxed warning about the increased risk for hemorrhage, including severe and sometimes fatal hemorrhagic events. Ramucirumab should be discontinued in patients who have severe bleeding.[16]

Arterial thromboembolic events. Serious, sometimes fatal, arterial thromboembolic events occurred in clinical trials. Ramucirumab should be permanently discontinued in patients who experience a severe arterial thromboembolic event.[16]

Hypertension. An increased incidence of severe hypertension occurred in patients receiving ramucirumab as a single agent and in patients receiving ramucirumab combined with paclitaxel and combined with docetaxel. Hypertension should be controlled before initiating treatment with ramucirumab. Blood pressure should be monitored every 2 weeks or more frequently as indicated during treatment.[16]

Infusion-related reactions. Patients should be monitored for the signs and symptoms of infusion-related reactions during the infusion of ramucirumab.[16]

Gastrointestinal perforation. As an antiangiogenic therapy, ramucirumab can increase the risk for gastrointestinal perforation, which can be fatal. Ramucirumab should be permanently discontinued in patients with a gastrointestinal perforation.[16]

Impaired wound healing. Ramucirumab has not been studied in patients with serious or nonhealing wounds. As an antiangiogenic therapy, ramucirumab has the potential to adversely affect wound healing. Ramucirumab should be withheld before surgery and resumed after surgery based on adequate wound healing. If wound-healing complications develop during treatment, ramucirumab should be discontinued until the wound is fully healed.[16]

Clinical deterioration of cirrhosis. New-onset or worsening encephalopathy, ascites, or hepatorenal syndrome can occur in patients with Child-Pugh class B or C cirrhosis. Ramucirumab should be only used in patients with Child-Pugh class B or C cirrhosis if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.[16]

Reversible posterior leukoencephalopathy syndrome. This syndrome has been reported in clinical studies with ramucirumab. If the diagnosis of reversible leukoencephalopathy is confirmed with magnetic resonance imaging, ramucirumab should be discontinued.[16]

Use in Specific Populations

Pregnancy. Based on its mechanism of action, ramucirumab may cause fetal harm. If ramucirumab is used during pregnancy, or if the patient becomes pregnant while taking the drug, assess the potential hazard to the fetus.[16]

Nursing mothers. It is not known whether ramucirumab is excreted in human milk. Whether the patient should discontinue nursing or discontinue the drug is dependent on the importance of the drug to the mother.[16]

Pediatric use. The safety and effectiveness of ramucirumab in pediatric patients have not been established.[16]

Geriatric use. Among patients receiving ramucirumab in the 2 gastric cancer clinical trials, no overall differences in safety or efficacy were observed between patients aged ≥65 years and younger patients.[16]

Renal impairment. No dose adjustment is recommended for patients with renal impairment.[16]

Hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment.[16]

Reproductive potential. Ramucirumab may impair fertility. Females of reproductive potential should be advised to avoid getting pregnant while receiving ramucirumab and for at least 3 months after the last dose.[16]

Conclusion

In 2014, ramucirumab received FDA approval for 3 indications—as a single agent or in combination with paclitaxel for advanced gastric cancer, and in combination with docetaxel for metastatic NSCLC. These FDA approvals mark the availability of an additional second-line treatment option for 2 types of advanced cancer.

In patients with advanced stomach cancer or GEJ adenocarcinoma, ramucirumab as a single agent and in combination with paclitaxel demonstrated significant improvements in OS and PFS compared with placebo, and compared with placebo in combination with paclitaxel, based on findings from the REGARD and the RAINBOW clinical trials.

In patients with metastatic NSCLC, ramucirumab plus docetaxel showed significant improvements in OS and PFS compared with placebo plus docetaxel, as was demonstrated in the REVEL study. ■

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