Ramucirumab (Cyramza)
National Drug Monograph
March 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Ramucirumab is a fully human monoclonal antibody (IgG1) directed against vascular endothelial growth factor (VEGF) receptor. By binding to VEGFR2, it inhibits ligand-stimulated activation of the VEGF receptor, ligand-induced proliferation and migration of human endothelial cells. VEGFR2 inhibition results in reduced tumor vascularity and growth.
Indication(s) Under Review	Advanced gastric or gastro-esophageal junction (GEJ) adenocarcinoma, as a single agent or in combination with paclitaxel after prior fluoropyrimidine- or platinum-containing chemotherapy. Metastatic non-small cell lung cancer (NSCLC), in combination with docetaxel after progression on or after platinum-based chemotherapy.
Dosage Form(s) Under Review	100 mg/10 mL (10 mg per mL) solution, single-dose vial 500 mg/50 mL (10 mg per mL) solution, single-dose vial
REMS	□ REMS ■ No REMS *See Other Considerations for additional REMS information*
Pregnancy Rating	Category C

Executive Summary

Efficacy

- **Gastric/GEJ adenocarcinoma.** Improved overall survival (OS) was demonstrated in a multinational, randomized (2:1), double-blind, multicenter study that enrolled 355 patients with previously treated advanced or metastatic, gastric or GEJ adenocarcinoma.[1] Median overall survival (OS) was statistically significantly improved for patients randomized to receive ramucirumab compared to placebo (5.2 mos vs. 3.8 mos) [HR 0.776; p =0.047]. Median progression-free survival (PFS) was longer in the ramucirumab arm compared to the placebo arm (2.1 mos vs. 1.3 mos) [HR 0.483; p<0.0001].
- **Gastric/GEJ adenocarcinoma.** The phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic GEJ and gastric adenocarcinoma enrolled 655 patients.[2] The OS hazard ratio (HR) was 0.807 (p=0.017) with a median OS of 9.6 mos for ramucirumab + paclitaxel vs. 7.4 mos for placebo + paclitaxel. The HR for PFS was 0.635 (p<0.0001) with a median PFS of 4.4 mos for ramucirumab + paclitaxel and 2.9 mos for placebo + paclitaxel.
- **NSCLC**. In the double-blind, randomized phase III trial of ramucirumab plus docetaxel vs. placebo plus docetaxel for second-line treatment of stage IV NSCLC after disease progression on platinum-based therapy, 1,253 patients were enrolled.[3] The median OS was 10.5 mos for patients in the ramucirumab + docetaxel group vs. 9.1 mos for the placebo + docetaxel group (HR 0.86; p=0.023). The median PFS was 4.5 mos for the ramucirumab group compared with 3 mos for the control group (HR 0.76; p<0.0001).

Safety[4]	• **Gastric/GEJ adenocarcinoma.** Most common adverse reactions (all grades) observed in ramucirumab-treated patients (monotherapy) at a rate ≥10% and ≥2% higher than placebo were hypertension and diarrhea. • **Gastric/GEJ adenocarcinoma.** Most common adverse reactions (all grades) observed in ramucirumab plus paclitaxel at a rate of ≥30% and ≥2% higher than placebo plus paclitaxel were fatigue, neutropenia, diarrhea, and epistaxis. • **NSCLC.** Most common adverse reactions (all grades) observed in patients treated with ramucirumab plus docetaxel at a rate of ≥30% and ≥2% higher than placebo placebo plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. • Black Box Warning: Ramucirumab is known to increase the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Ramucirumab should be discontinued in patients who experience severe bleeding.
Other Considerations	

Outcome in clinically significant area	GI/GEJ mono: OS 5.2 vs. 3.8 mos GI/GEJ combo: OS 9.6 vs. 7.4 mos Lung: OS 10.5 vs. 9.1 mos
Effect Size	GI/GEJ mono: HR 0.776 (0.603-0.998); p=0.047 GI/GEJ combo: HR 0.807 (0.678-0.962); p=0.017 Lung: HR 0.86 (0.75-0.98); p= 0.023
Potential Harms	GI/GEJ mono: (Gr 3 or higher) HTN 8%, abd pain 6%, bleeding/hemorrhage 3%, thromboembolism 2% GI/GEJ combo: (Gr 3 or higher) neutropenia 41%, leukopenia 18%, HTN 14%, fatigue 12% Lung: (Gr 3 or higher) fatigue 14%, neutropenia 49%, febrile neutropenia 16%, leukopenia 14%, HTN 6%
Net Clinical Benefit	GI/GEJ mono: Minimal – Low benefit, low risk of harm GI/GEJ combo: Minimal – Low benefit, low risk of harm Lung: Minimal – Low benefit, low risk of harm

Potential Impact	• Ramucirumab as second line therapy for gastric and GEJ is a category 1 recommendation from the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of gastric cancer.[5] The survival benefit was found to be short for both ramucirumab monotherapy and in combination with paclitaxel at 1.4 and 2.2 months, respectively. The addition of paclitaxel to ramucirumab may offer an additional benefit in survival for patients. • Ramucirumab in combination with docetaxel as second line therapy for metastatic NSCLC is a category 2B recommendation from the NCCN guidelines.[6] The duration of survival benefit for lung cancer was small at 1.4 months.

Background

Purpose for review

The purposes of this monograph are (1) evaluate the available evidence of efficacy, safety, tolerability, cost and other pharmaceutical issues that are relevant to ramucirumab as a possible addition to VA National formulary. In addition to (2) define ramucirumab's role in therapy and to (3) identify monitoring parameters for use within the VA.

Gastric/GEJ adenocarcinoma- Gastric cancer is the fourth most common malignant disease and second leading cause of cancer mortality worldwide.[7] The American Cancer Society estimates in 2014 there will be 22,220 new cases of gastric cancer and 10,990 deaths in the United States alone.[8] Locally advanced unresectable and metastatic gastric and gastroesophageal cancers are not curable conditions, and the five-year survival rates are among the worst reported for any malignancy. Most patients present with advanced staged disease and can expect a median survival of about 8 months after palliative procedures, and a median

survival of about 5 months for advanced disease without an operation.[9] The 5-year survival rate of patients with advanced gastric cancer is approximately 3.1%. After first-line treatment with standard cytotoxic chemotherapy, patients may expect a median survival ranging from 8-10 months.[1] Adenocarcinomas of the esophagogastric junction (GEJ) are defined as tumors that cross the most proximal extent of the gastric folds regardless of where the bulk of the tumor lies, and the incidence of this malignancy continues to rise.

Goals of therapy for gastric or GEJ include palliation of symptoms and prolongation of survival. In randomized trials, a platinum-containing or fluoropyrimidine-containing regimen have emerged as standard regimens for first-line treatment.[5] There is no standard approach for second-line therapy for this malignancy; therefore, new targeted systemic drugs have been a large area of development to improve patient outcomes. Quality of life and minimization of side effects are important considerations in determining the therapeutic approach for second-line treatments.

A randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care (BSC) alone, found salvage line chemotherapy (SLC) for pretreated gastric cancer patients is tolerated and significantly improves OS when added to BSC.[10] In this study, patients with one or two prior chemotherapy regimens involving both fluoropyrimidines and platinum agents, and with Eastern Cooperative Oncology Group performance status 0 or 1 received SLC (docetaxel 60 mg/m^2 every 3 weeks or irinotecan 150 mg/m^2 every 2 weeks) plus BSC or BSC alone. The median OS was 5.3 months among 133 patients in SLC arm vs. 3.8 months among 69 patients in the BSC arm (p=0.007). When comparing docetaxel to irinotecan as SLC options, no difference in the median OS was detected (p=0.116).

NSCLC- Lung cancer is the leading cause of cancer-related mortality in the US, and it is estimated 224,000 new cases will be diagnosed and 159,000 deaths will occur in 2014.[7] Patients with advanced NSCLC who have a good functional status, platinum-based first-line chemotherapy has been shown to improve quality of life, improves survival and reduces disease-related symptoms.[6] The platinum-doublet combinations have provided 1-year survival rates between 30-40%. Inevitably patients with advanced/metastatic disease experience disease progression, generally within a median of 3-6 months of initiating chemotherapy.[11] The reported response rates to second-line systemic therapy have generally been less than 10%. Patients likely to receive second-line therapy include those with good performance status and tolerated previous therapy without significant toxicities.

Other therapeutic options

GI/GEJ adenocarcinoma: For patients who retain an adequate performance status, there is no standard approach for second-line therapy after failure of the first-line regimen. Active cytotoxic chemotherapy agents not used in the first-line regimen are reasonable, either in combination or as serial single agents.[5]

Metastatic Lung: Three agents are approved by the U.S. FDA in the second-line setting: two cytotoxic chemotherapy agents, docetaxel and pemetrexed, and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib.[11]

Formulary alternatives for GI/GEJ adenocarcinoma	**Other Considerations** (For example efficacy, dosing regimen, safety concerns, storage limitations, etc.)
Docetaxel 60 mg/m^2 IV every three weeks	- Statistically significant prolongation of median survival (5.2 mos vs. 3.6 mos)

	compared to placebo[12] - Common adverse effects (grade ≥3): neuropathy, alopecia, N/V, edema, anemia, neutropenia, asthenia
Paclitaxel 80 mg/m^2 IV on days 1, 8, and 15, every 4 weeks	- Median OS was 9.5 mos; median PFS was 3.6 mos; response rate was 20.9%[13] - Common adverse effects (grade ≥3): neutropenia (28.7%), anemia (21.3%), anorexia (7.4%)
Irinotecan 150 mg/m^2 IV every two weeks	- Median OS was 8.4 mos; median PFS was 2.3 mos; response rate was 13.6%[13] - Common adverse effects (grade ≥3): neutropenia (39.1%), anemia (30%), anorexia (17.3%)
Formulary alternatives for metastatic NSCLC	**Other Considerations** **(For example efficacy, dosing regimen, safety concerns, storage limitations, etc.)**
Docetaxel 75 mg/m^2 IV every three weeks	- Median OS was 7.5 months; 1-year survival was 37%[14] - Common adverse effects (grade ≥3): neutropenia (67%), febrile neutropenia (1.8%), anemia (2.9%)
Pemetrexed 500 mg/m^2 IV every three weeks	- Median OS was 8.3 mos; median PFS was 2.9 mos; 1-year survival time was 29.7%[15] - Common adverse effects (grade ≥3): neutropenia (5.3%), anemia (4.2%), fatigue (5.3%)
Erlotinib 150 mg PO daily	- Median OS was 6.7 mos; median PFS was 2.2 mos[16] - Common adverse effects (grade ≥3): rash (9%), anorexia (9%), fatigue (19%)

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline using the search terms <ramucirumab> and <Cyramza>. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Advanced Gastric or GEJ Adenocarcinoma

- The FDA approval of ramucirumab as a single agent for the treatment of patients with advanced or metastatic, gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy was based on the multinational, randomized (2:1), double-blind, multicenter study (REGARD) that enrolled 355 patients.[17] Patients enrolled in REGARD trial were randomized to receive either ramucirumab (8 mg/kg) plus best supportive care (BSC) or placebo plus BSC every two weeks.[1] The median overall survival was 5.2 months in the ramucirumab plus BSC arm and 3.8 months in the placebo plus BSC arm [HR 0.776 (95% CI: 0.603-0.998), p =0.047]. Median progression-free

survival was longer in the ramucirumab arm compared to the placebo arm (2.1 months vs. 1.3 months) [HR 0.483 (95% CI: 0.376-0.620), p <0.0001]. Quality of life (QoL) was assessed at baseline and after 6, 12, and 18 weeks of treatment with the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30, version 3.0). Of patients who provided 6 week data, a larger proportion of those in the ramucirumab group reported stable or improved global quality of life than those in the placebo group (34% vs. 11%); however, this difference was not significant (p=0.23).

- Ramucirumab was also granted FDA approval in combination with paclitaxel for advanced gastric/GEJ adenocarincoma based on the multinational, randomized, double-blind, phase III (RAINBOW) study that randomized patients 1:1. A survival benefit for ramucirumab in combination with paclitaxel was demonstrated by comparing weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle) plus ramucirumab (8 mg/kg IV every two weeks) or placebo in 665 patients with metastatic gastric or EGJ adenocarcinoma who had disease progression on or within four months after first-line platinum and fluoropyrimidine-based combination therapy.[2] This study found median overall survival was significantly better with ramucirumab (9.6 vs. 7.4 months) [HR 0.807, 95% CI 0.678-0.962; p=0.017] as well as progression-free survival (4.4 vs. 2.9 months) [HR 0.635, 95% CI 0.536-0.752; p<0.0001] and objective response rate (28% vs. 16%; p<0.001).

Metastatic NSCLC

- The FDA approval of ramucirumab in combination with docetaxel for the treatment of metastatic non-small cell lung cancer (NSCLC) after progression on or after platinum-based chemotherapy was based on the multinational, double-blind, randomized phase 3 trial (REVEAL) that enrolled 1,253 patients.[17] Patients were eligible if they had squamous or non-squamous histology who had progressed during or after a first-line platinum-based chemotherapy regimen. Patients were randomized to receive docetaxel 75 mg/m^2 and either ramucirumab (10 mg/kg) or placebo on day 1 of a 21-day cycle until disease progression, unacceptable toxicity, withdrawal, or death. Ramucirumab plus docetaxel demonstrated a survival advantage as a second-line treatment of patients with stage IV NSCLC. Median overall survival was 10.5 months for those allocated to ramucirumab plus docetaxel and 9.1 months for patients who received placebo plus docetaxel (HF 0.86, 95% CI 0.75-0.98; p=0.023). Median progression-free survival was 4.5 months for the ramucirumab group compared with 3 months for the control group (HR 0.76, 95% CI 0.68-0.86; p<0.0001).

Potential Off-Label Use

- This section is not intended to promote any off-label use. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).
- Current areas of investigation per www.clinicaltrials.gov include: Irinotecan, levofolinate & 5-fluorouracil (FOLFIRI) plus ramucirumab for colorectal carcinoma (completed-has results); ramucirumab and paclitaxel in participants with solid tumors (active, not recruiting-has results); paclitaxel with or without ramucirumab for metastatic gastric adenocarcinoma (active, not recruiting-has results); ramucirumab in participants with liver cancer who have not previously been treated with chemotherapy (completed-has results); ramucirumab in participants with breast cancer (completed-has results); study of ramucirumab in colorectal cancer (completed-has results); ramucirumab in participants with metastatic renal cell carcinoma (completed-has results); ramucirumab in ovarian cancer (active, not recruiting-has results)
- The RAISE trial is a phase III study evaluating ramucirumab plus FOLFIRI to placebo plus FOLFIRI in the second-line setting of metastatic colorectal cancer after progressive disease with bevacizumab, oxaliplatin and a fluoropyrimidine as first-line therapy. In September 2014, the company indicated that the primary endpoint of the trial, OS, was met. They are planning to present their data and initiate regulatory submissions early in 2015.

Safety[4,18]
(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• Ramucirumab is known to increase the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Ramucirumab should be permanently discontinued in patients who experience severe bleeding.
Contraindications	• None
Warnings/Precautions	• Increased risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Incidence of severe bleeding was 3.4% for ramucirumab monotherapy vs. 2.6% for placebo, and ramucirumab + paclitaxel was 4.3% vs. 2.4% for placebo + paclitaxel. Patients receiving antiplatelet therapy, including aspirin (max dose of 325 mg/day was permitted), non-steroid anti-inflammatory drugs (NSAIDs), clopidogrel and similar agents were excluded from the studies; therefore, the risk of gastric hemorrhage in ramucirumab-treated patients with gastric tumors is unknown. The incidence of severe bleeding was 2.4% for ramucirumab + docetaxel and 2.3% for placebo + docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDS or other antiplatelet therapy were excluded. • Serious, sometimes fatal, arterial thromboembolic events (ATEs) occurred in clinical trials and it was reported that 1.7% of 236 patients who received ramucirumab as a single agent for gastric cancer. • An increased risk of severe hypertension occurred with ramucirumab as a single agent (8%) vs. placebo (3%), and in patients receiving ramucirumab + paclitaxel (15%) vs. placebo + paclitaxel (3%), and for patients receiving ramucirumab + docetaxel (6%) as compared to placebo + docetaxel (2%). Hypertension should be controlled prior to initiating ramucirumab and blood pressure monitored at least every 2 weeks or as clinically indicated during therapy. If significant hypertension is not controllable with antihypertensive therapy or if hypertensive crisis occurs, permanently discontinue ramucirumab. • Increased risk of infusion-related reactions (IRRs) without premedication (occurred in 6 out of 37 patients (16%), including 2 severe events). Monitor patients during the infusion for signs and symptoms of IRRs. • Ramucirumab as monotherapy can increase the risk of gastrointestinal (GI) perforation (0.7%), which was also increased when patients received ramucirumab with paclitaxel (1.2%) and with docetaxel (1%). Permanently discontinue ramucirumab in patients who experience a GI perforation. • Ramucirumab has the potential to adversely affect wound healing and should be held prior to surgery, and resumed based on clinical judgment. Ramucirumab has not been studied in patients with serious or non-healing wounds. • Risk for higher clinical deterioration in patients with Child-Pugh B or C cirrhosis. Use ramucirumab only if potential benefits of treatment outweigh the risks of clinical deterioration. • Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported with a rate <0.1% in clinical studies. Discontinue ramucirumab in patients who develop RPLS.

Safety Considerations[4]

- **Gastric/GEJ Adenocarcinoma.** In the REGARD trial, the most common adverse reactions (all grades) observed in ramucirumab treated patients at a rate ≥10% and ≥2% higher than placebo were hypertension and diarrhea. The most common serious adverse events were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of patients who received ramucirumab vs. 8.7% of patients who

received placebo.

- **Gastric/GEJ Adenocarcinoma.** In the RAINBOW trial, the most common adverse reactions (all grades) observed in ramucirumab + paclitaxel group at a rate ≥30% and ≥2% higher than placebo + paclitaxel were fatigue, neutropenia, diarrhea, and epistaxis. The most common serious adverse events with ramucirumab + paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients required granulocyte colony-stimulating factors.
- **NSCLC.** In the REVEL trial, the most common adverse reactions (all grades) observed in the ramucirumab + docetaxel group at a rate ≥30% and ≥2% higher than placebo + docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. Treatment discontinuation due to adverse reactions occurred more frequently in ramucirumab + docetaxel-treated patients (9%) than in the control group (5%). The most common serious adverse events with ramucirumab + docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). Use of granulocyte colony-stimulating factors was 42% in ramucirumab + docetaxel-treated patients vs. 37% in the control group. Among those age ≥ 65 years, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for ramucirumab + docetaxel vs. 9 (4%) deaths for those in the placebo + docetaxel arm. Comparatively, those age < 65 years noted 13 (3%) deaths in the treatment arm vs. 26 (6%) in the placebo arm.

Adverse Reactions[4,18]

Common adverse reactions (monotherapy)	Cardiovascular: Hypertension (16%; grades 3/4: 8%) Gastrointestinal: Diarrhea (14%) Hematologic & oncologic: Decreased red blood cells (requiring transfusion; 11%), neutropenia (5%), anemia (4%), hemorrhage Central nervous system: Headache (9%) Endocrine & metabolic: Hyponatremia (6%) Genitourinary: Proteinuria (8%) Immunologic: Antibody development (6%; neutralizing: 1%) Miscellaneous: Infusion related reaction (≤16%)
Death/Serious adverse reactions	Severe hypertension, impaired wound healing, bowel obstruction, GI perforation, anemia, arterial thromboembolism, hemorrhage, infusion reaction, posterior reversible encephalopathy syndrome
Discontinuations due to adverse reactions	Ramucirumab monotherapy group 11% vs. 6% in the placebo group[1]

Drug Interactions[4,18]

Drug-Drug Interactions

- Ramucirumab is not expected to have an effect on CYP enzymes or be metabolized by CYP enzymes and therefore unlikely to have clinically relevant drug-drug interactions.

Drug-food Interactions

- Belimumab: Monoclonal antibodies may enhance the adverse/toxic effect of belimumab. Risk X: Avoid combination
- Bisphosphonate Derivatives: Systemic angiogenesis inhibitors may enhance the adverse/toxic effect of bisphosphonate derivatives; specifically, the risk for osteonecrosis of the jaw may be increased. Risk C: Monitor therapy

Drug-Lab Interactions

- None reported

Risk Evaluation

As of December, 2014

	Comments
Sentinel event advisories	• None Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials (LASA)	• *Ramucirumab*: ranibizumab, rituximab, regorafenib, raxibacumab • *Cyramza*: Cimzia, Cinryze, Cymbalta Sources: Based on clinical judgement and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank and ISMP Confused Drug Name List)

Other Considerations

- Monitoring Parameters (monotherapy)[18]: Blood pressure (every 2 weeks; more frequently if indicated); liver function tests; urine protein; signs/symptoms of infusion-related reactions (during infusion); signs/symptoms of arterial thromboembolic events, gastrointestinal perforation, wound healing impairment, and reversible posterior leukoencephalopathy syndrome.

Gastric/GEJ Adenocarcinoma

- In the REGARD trial quality of life (QoL) was assessed at baseline and after 6, 12, and 18 weeks of treatment with the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30, version 3.0).[1] Of patients who provided 6 week data, a larger proportion of those in the ramucirumab group reported stable or improved global quality of life than those in the placebo group (34% vs. 11%); however, this difference was not significant (p=0.23).
- In the RAINBOW trial, there were 15 QoL parameters and 14 had HRs <1, indicating similar or longer time to deterioration (TtD) in QoL for ramucirumab + paclitaxel. For all QoL parameters, the proportion of patients reporting improved or stable scores were numerically greater for ramucirumab + paclitaxel.[19]
- Ramucirumab as second line therapy for gastric and GEJ is a category 1 recommendation from the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of gastric cancer.[5]

NSCLC

- Ramucirumab in combination with docetaxel as second line therapy for metastatic NSCLC is a category 2B recommendation from the NCCN guidelines.[6]
- Quality of life data was provided in the REVEL trial at a 30-day follow up.[3] The global QoL analysis showed that time to deterioration did not differ between treatment groups (HR 1.0, p=0.99).
- Metastatic NSCLC patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.[4]
- The survival benefit of ramucirumab in patients ≥ 65 years of age is unclear. A post-hoc exploratory subgroup analysis of patients ≥ 65 years compared to patients < 65 years suggests that there is no difference in median overall survival. As this finding is not consistent with other phase 3 ramucirumab trials, the REVEL authors suggest addressing this issue on a case-by-case basis of risk vs. benefit assessment.

Outcome in clinically significant area	GI/GEJ mono: OS 5.2 vs. 3.8 mos GI/GEJ combo: OS 9.6 vs. 7.4 mos Lung: OS 10.5 vs. 9.1 mos
Effect Size	GI/GEJ mono: HR 0.776 (0.603-0.998); p=0.047 GI/GEJ combo: HR 0.807 (0.678-0.962); p=0.017 Lung: HR 0.86 (0.75-0.98); p= 0.023
Potential Harms	GI/GEJ mono: (Gr 3 or higher) HTN 8%, abd pain 6%, bleeding/hemorrhage 3%, thromboembolism 2% GI/GEJ combo: (Gr 3 or higher) neutropenia 41%, leukopenia 18%, HTN 14%, fatigue 12% Lung: (Gr 3 or higher) fatigue 14%, neutropenia 49%, febrile neutropenia 16%, leukopenia 14%, HTN 6%
Net Clinical Benefit	GI/GEJ mono: Minimal – Low benefit, low risk of harm GI/GEJ combo: Minimal – Low benefit, low risk of harm Lung: Minimal – Low benefit, low risk of harm

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration[4,18]

- Do not administer ramucirumab as an intravenous push or bolus.
- Gastric Cancer
  - Either as a single agent or in combination with weekly paclitaxel is 8 mg/kg every 2 weeks administered as an intravenous infusion over 60 minutes. Continue until disease progression or unacceptable toxicity.
- Non-Small Cell Lung Cancer
  - Administer at 10 mg/kg intravenously over approximately 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue ramucirumab until disease progression or unacceptable toxicity.
- When given in combination, administer ramucirumab prior to administration of paclitaxel or docetaxel.
- Premedication:
  - Prior to each ramucirumab infusion, pre-medicate all patients with intravenous histamine H_1 antagonist.
  - For patients who have experienced a Grade 1 or 2 infusion reaction, also pre-medicate with dexamethasone (or equivalent) and acetaminophen prior to each ramucirumab infusion.
- Dosing: Adjustment for Toxicity
  - Infusion-related reaction:
    - Grade 1 or 2: Reduce infusion rate by 50%
    - Grade 3 or 4: Permanently discontinue
  - Hypertension:
    - Severe hypertension: Interrupt infusion until controlled with medical management
    - Severe hypertension, uncontrollable with antihypertensive therapy: Permanently discontinue
  - Proteinuria:
    - Urine protein ≥2 g/24 hours: Withhold treatment; when urine protein returns to <2 g/24 hours, reinitiate at a reduced dose (refer to table 1)
    - Recurrent urine protein ≥2 g/24 hours: Withhold treatment; when urine protein returns to <2 g/24 hours, reinitiate at a reduced dose (refer to table 1)
    - Urine protein >3 g/24 hours: Discontinue permanently

    Table 1: Ramucirumab Dose Reductions for Proteinuria

Initial Ramucirumab Dose	First Dose Reduction to:	Second Dose Reduction to:
8 mg/kg	6 mg/kg	5 mg/kg
10 mg/kg	8 mg/kg	6 mg/kg

  - Nephrotic syndrome: Discontinue permanently
  - Arterial thrombotic events: Discontinue permanently
  - Bleeding, grade 3 or 4: Discontinue permanently
  - Gastrointestinal perforation: Discontinue permanently
  - Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue permanently for confirmed diagnosis
  - Wound healing complications: Withhold treatment prior to surgery; do not reinitiate until the surgical wound is fully healed
- Refer to package insert for full dosing and administration information

Special Populations (Adults)

- **Gastric/GEJ Adenocarcinoma.** In the REGARD trial, survival benefit associated with ramucirumab was similar between Asian patients and those from America, Europe, and Australia, although relatively few Asian patients were enrolled (8% in the ramucirumab treatment group).[1] In the RAINBOW trial, OS in the ramucirumab plus paclitaxel group compared with placebo plus paclitaxel was increased, but not significantly for Asian patients compared to non-Asians (12.1 mos vs. 8.5 mos).[2]
- **NSCLC.** Although not powered for subgroup analysis, the REVEL trial revealed a longer survival on ramucirumab-docetaxel than placebo-docetaxel for patients with non-squamous disease (11.1 mos vs. 9.7 mos; HR 0.83) and responders to first-line platinum treatment (11.2 mos vs. 10.3 mos; HR 0.84).[3]

- In the REVEL trial, an increased incidence of neutropenia and febrile neutropenia was found in east Asia (South Korea or Taiwan), which led to a docetaxel dosage change in this region (27% of the patients received docetaxel 60 mg/m^2).[3] The lowered dose decreased the incidence of febrile neutropenia and the rate of neutropenia was much the same as in non-Asian patients.
- All three trials (REGARD, RAINBOW, REVEL) excluded patients with ECOG performance status of 2 or greater, uncontrolled hypertension, major surgery within 28 days, or patients receiving chronic anti-platelet therapy other than once daily aspirin.[1-3] REGARD and REVEL trials also excluded patients with bilirubin ≥1.5 mg/dL, and the RAINBOW trial excluded patients with bilirubin >1.5 times the upper limit of normal.

	Comments
Elderly	• In the REGARD and RAINBOW trials, 36% were ≥65 years old, while 7% were ≥75 years old.[1,2] • In the REVEL trial 36% were ≥65 years old and 7% were ≥75 years old.[3] • No differences were observed for safety/efficacy between younger and older patients, although a post-hoc exploratory subgroup analysis by age suggest that REVEL trial participants ≥ 65 years did not attain a survival benefit compared to younger counterparts. The hazard ratio for overall survival in patients less than 65 years of age was 0.74 (95% CI: 0.62, 0.87) and in patients ≥ 65 years was 1.10 (95% CI: 0.89, 1.36).
Pregnancy[4]	• Animal reproductions studies have not been conducted. • Ramucirumab inhibits angiogenesis, which is of critical importance to human fetal development. Based on the mechanism of action, ramucirumab may cause fetal harm if administered during pregnancy. Women of reproductive potential should avoid becoming pregnant during and for at least 3 months after the last ramucirumab dose. Ramucirumab may impair fertility in women.
Lactation[4]	• Excretion in breast milk unknown/not recommended.
Renal Impairment[4]	• No dose adjustment recommended based upon population PK data.
Hepatic Impairment[4]	• No dose adjustment is recommended for patients with mild hepatic dysfunction (total bilirubin >1.0-1.5 times upper limit of normal [ULN] and any AST) or moderate hepatic impairment (total bilirubin >1.5-3.0 times ULN and any AST). New onset or worsening encephalopathy, ascites, or hepatorenal syndrome have been reported in patients with Child-Pugh class B or C cirrhosis receiving ramucirumab. Use ramucirumab in patients with Child-Pugh class B or C impairment only if the potential benefits outweigh the potential risks.
Pharmacogenetics/genomics[4]	• No data identified

Projected Place in Therapy

Advanced Gastric or GEJ Adenocarcinoma

- Gastric cancer is the fourth most common malignancy in the world and second leading cause of cancer mortality.[5] Systemic chemotherapy is the standard first-line treatment for advanced gastric adenocarcinoma, and the median time of survival ranges from 8 to 10 months on average.[1] There is no standard approach for second-line therapy after failure of the first-line regimen for patients with advanced or metastatic gastric or EGJ adenocarcinomas. It is therefore important to consider the patient's quality of life and tolerability when choosing the next therapeutic approach.
- Ramucirumab received U. S. Food and Drug Administration approval for use as a single agent or in combination with paclitaxel for the treatment of patients with advanced or metastatic, gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy.[17]

- Ramucirumab as second line therapy for gastric and GEJ patients who have disease progression on or after prior treatment with fluoropyrimidine or platinum-containing chemotherapy is a category 1 recommendation from the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of gastric cancer.[5]
- The FDA approval for advanced or metastatic, gastric or gastroesophageal junction (GEJ) adenocarcinoma was based on the demonstration of improved overall survival (OS) in a multinational, randomized (2:1), double-blind, multicenter study (REGARD) enrolling 355 patients with previously treated advanced or metastatic, gastric or GEJ adenocarcinoma.[1] Patients enrolled were randomized to receive either ramucirumab plus best supportive care (BSC) or placebo plus BSC. The median overall survival was 5.2 months in the ramucirumab arm and 3.8 months in the placebo arm [HR 0.776 (95% CI: 0.603-0.998), p =0.047]. The median progression-free survival was found to be longer in the ramucirumab arm compared to the placebo arm (2.1 vs. 1.3 months) [HR 0.483 (95% CI: 0.376-0.620), p <0.0001].
- In the phase III, placebo-control, double-blind RAINBOW trial, ramucirumab plus paclitaxel significantly increased overall survival compared with placebo plus paclitaxel in patients with advanced gastric or gastro-esophageal junction adenocarcinoma that had progressed after first-line chemotherapy.[2] This study found median overall survival was significantly better with ramucirumab (9.6 vs. 7.4 months) [HR 0.807 (95% CI: 0.678-0.962) p=0.017] as well as progression-free survival (4.4 versus 2.9 months) [HR 0.635 (95% CI: 0.536-0.752) p<0.0001] and objective response rate (28% vs. 16%).
- In comparison to other treatment alternatives in the 2nd line setting for gastric and GEJ patients, docetaxel 60 mg/m^2 every 3 weeks demonstrated a statistically significant prolongation of median survival compared to placebo (5.2 vs. 3.6 months), paclitaxel 80 mg/m^2 on days 1, 8 and 15 in a 4-week cycle demonstrated a median OS of 9.5 months and PFS of 3.6 months, and irinotecan 150 mg/m^2 every 2 weeks demonstrated a median OS of 8.4 months and median PFS of 2.3 months.[12,13]
- In regards to safety, ramucirumab was evaluated as a single agent for the treatment of locally advanced or metastatic gastric or GEJ adenocarcinoma, with an ECOG performance status of less than or equal to 1 in the REGARD study. Ramucirumab was found to be well tolerated with similar rates for most adverse events between the ramucirumab and placebo groups. Most common adverse effects (all grades) include hypertension and diarrhea. The grade 3-4 adverse reactions reported at a higher incidence in the ramucirumab arm (greater than or equal to 2% difference between arms) included hypertension and hyponatremia. Ramucirumab was not associated with increased rates of vomiting, fatigue, decreased appetite, or anemia compared to placebo. Other important risks described in labeling include hemorrhage, arterial thrombotic events, infusion-related reactions, gastrointestinal perforation, impaired wound healing, clinical deterioration in patients with cirrhosis, and reversible posterior leukoencephalopathy. The most frequent non-hematological adverse effects when ramucirumab was combined with paclitaxel were fatigue, diarrhea, and abdominal pain.[2] Neutropenia was one of the most frequently reported hematological toxicities, and had a similar incidence to that reported in other trials of the same paclitaxel dose and schedule. Although severe neutropenia was more frequently reported for ramucirumab plus paclitaxel, the incidence of febrile neutropenia was low and similar in the groups.

<u>Metastatic NSCLC</u>

- Lung cancer is the leading cause of death from cancer in the world with NSCLC being responsible for the majority of these cases.[6] Although 30-40% of patients respond to initial first-line therapy (platinum-based chemotherapy is the standard of care), patients inevitably have disease progression on or after treatment. Three agents have been approved as second-line therapies for NSCLC: docetaxel, erlotinib, and pemetrexed.[11] The clinical outcomes in the second-line setting are poor with objective response rates of <10%, median PFS of <4 months and median OS ranging from 7-9 months.
- Ramucirumab received U. S. Food and Drug Administration approval for use in combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy.[17] Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.
- In the phase III randomized, double-blind study conducted in patients with NSCLC for locally advanced or metastatic disease (REVEL) patients received either ramucirumab 10 mg/kg intravenously plus docetaxel 75 mg/m^2 intravenously every 3 weeks or placebo plus docetaxel 75 mg/m^2 intravenously every 3 weeks.[3] Due to an increased rate of neutropenia and febrile neutropenia in patients enrolled in East Asian sites, the study was amended and 24 patients at East Asian sites received a starting dose of docetaxel at 60 mg/m^2 every 3 weeks. Overall survival and progression-free survival were statistically significantly improved in patients randomized to receive ramucirumab plus docetaxel compared to the control group. Median overall survival was 10.5

months for those allocated to ramucirumab plus docetaxel and 9.1 months for patients who received placebo plus docetaxel (HF 0.086, 95% CI 0.75-0.98; p=0.023). Median progression-free survival was 4.5 months for the ramucirumab group compared with 3 months for the control group (HR 0.76, 95% CI 0.68-0.86; p<0.0001).

- In comparison to other treatment alternatives in the 2nd line setting for metastatic NSCLC, docetaxel led to improved overall survival compared with best supportive care (median OS was 7.5 months; 1-year survival was 37%) and erlotinib led to improved survival compared with placebo (median OS was 6.7 months; median PFS was 2.2 months).[14,16] Pemetrexed also improved OS and is approved for non-squamous NSCLC (median OS was 8.3 months; median PFS was 2.9 months; 1-year survival time was 29.7%).[15]
- No differences were observed for safety/efficacy between younger and older patients, although a post-hoc exploratory subgroup analysis by age suggest that REVEL trial participants ≥ 65 years did not attain a survival benefit compared to younger counterparts. The hazard ratio for overall survival in patients less than 65 years of age was 0.74 (95% CI: 0.62, 0.87) and in patients ≥ 65 years was 1.10 (95% CI: 0.89, 1.36).
- In regards to safety, the most common adverse reactions (all types) observed with ramucirumab plus docetaxel-treated patients at a rate ≥30% and ≥2% higher than the control group were neutropenia, fatigue/asthenia and stomatitis/mucosal inflammation.[3] Treatment discontinuation due to adverse reactions occurred more frequently in ramucirumab treated patients (9%) compared with the control group (5%). The most common adverse events leading to treatment discontinuation were infusion-related reaction (0.5%), and epistaxis (0.3%). Within the lung cancer trial, more patients in the age ≥ 65 year-population died during or soon after ramucirumab + docetaxel therapy compared to those receiving placebo + docetaxel (8 vs. 4%) and their younger counterparts receiving active therapy (8 vs. 3%).

References

1. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomized, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383:31-39.
2. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15(11):1224-1235.
3. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014; 384: 665–73.
4. Cyramza [package insert]. Eli Lilly and Company. Indianapolis, IN; December 2014. http://pi.lilly.com/us/cyramza-pi.pdf. Accessed December 20, 2014.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer, 2014. Available at: http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer, 2014. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
7. American Cancer Society: Cancer Facts and Figures 2014. Atlanta, Ga: American Cancer Society, 2014. http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf. Accessed December 1, 2014.
8. Dicken BJ, Bigam DL, Cass C, et al. Gastric adenocarcinoma review and considerations for future directions. *Ann Surg.* 2005;24(1):27-39.
9. Yang D, Hendifar A, Lenz C, et al. Survival of metastatic gastric cancer: significance of age, sex and race/ethnicity. *J Gastrointest Oncol.* 2011;2(2):77-84.
10. Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *The Oncologist*. 2008;13(1):28-36.
11. Kang JH, Lee SI, Lim DH, et al. Salvage Chemotherapy for Pretreated Gastric Cancer: A Randomized Phase III Trial Comparing Chemotherapy Plus Best Supportive Care With Best Supportive Care Alone. *J Clin Oncol.* 2012; 30:1513-1518.
12. Cook N, Marshall A, Blazeby JM, et al. COUGAR-02: a randomized phase III study of docetaxel versus active symptom control in patients with relapsed esophago-gastric adenocarcinoma (abstract). *J Clin Oncol* 2013 (suppl; abstr 4023). http://meetinglibrary.asco.org/content/112834-132
13. Hironaka S, Ueda S, Yasui H, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol.* 2013;31(35):4438.
14. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18:2095-2103.
15. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol.* 2004;22:1589-1597.
16. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353:123-132
17. Ramucirumab. Drugs@FDA. Food and Drug Administration Web site. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm394260.htm. Accessed November 1, 2014.
18. Lexicomp Online® , Ramucirumab: Drug information, Hudson, Ohio: Lexi-Comp, Inc. 2014.
19. Al-Batran SE, Van Cutsem E, Cheul Oh S, et al. RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel patients with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma: Quality-of-life (QoL) results. *J Clin Oncol*. 2014.32:5s (suppl; abstr 4058).
20. Garassino MC, Martelli O, Broggini M for the TAILOR Trialists. Erlotinib versus Docetaxel as Second-line Treatment of Patients with advanced non-small-cell lung cancer and wild-type EGFR tumors (TAILOR): a randomized controlled trial. *Lancet Oncol.* 2013; 14: 981-988.

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Appendix 1: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.

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