CYRAMZA®
ramucirumab injection
10 mg/mL solution

DESPITE RECENT ADVANCEMENTS IN STAGE IV NSCLC,

POST-PLATINUM PATIENTS STILL HAVE A POOR PROGNOSIS, INCLUDING THOSE WITH AGGRESSIVE DISEASE*[1-3]

AGGRESSIVE DISEASE

*** Aggressive disease is defined by those patients who were primary refractory to platinum-based therapy or who experienced limited time on initial platinum-based therapy (≤8 or ≤12 weeks).[3]**

INDICATION

CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

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REVEL: A PIVOTAL PHASE III TRIAL IN POST-PLATINUM, METASTATIC NSCLC IN PATIENTS WITH NONSQUAMOUS OR SQUAMOUS HISTOLOGIES (N=1253)[4]

A large, multinational, randomized, double-blind, placebo-controlled trial in patients with disease progression on or after platinum-based therapy for locally advanced or metastatic disease[4]

REVEL TRIAL DESIGN[4,5]

METASTATIC NSCLC (N=1253)

- Disease progression on or after one platinum-based regimen
- Nonsquamous and squamous histologies
- No major airway or blood vessel invasion by cancer
- No intratumor cavitation
- No gross hemoptysis within 2 months
- No patients whose only prior treatment was a tyrosine kinase (EGFR or ALK) inhibitor
- Treated brain metastases allowed
- ECOG PS 0-1

1:1 Randomization*

CYRAMZA + docetaxel (n=628)

CYRAMZA 10 mg/kg
+
docetaxel† 75 mg/m²

IV every 3 weeks

Placebo + docetaxel (n=625)

Placebo
+
docetaxel† 75 mg/m²

IV every 3 weeks

ECOG=Eastern Cooperative Oncology Group; IV=intravenous; PS=performance status.
*Stratification factors: Geographic region, ECOG PS, prior maintenance therapy, and gender.
†24 patients at East Asian sites received a starting dose of docetaxel at 60 mg/m² every 3 weeks.

- **Major Efficacy Outcome Measure:** Overall survival (OS)
- **Supportive Efficacy Outcome Measures:** Progression-free survival (PFS), objective response rate (ORR)
  — Patients received treatment until disease progression, unacceptable toxicity, withdrawal, or death[6]

SELECT IMPORTANT SAFETY INFORMATION

Hemorrhage

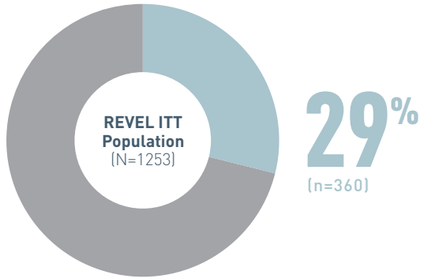
- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

REVEL: EXPLORATORY SUBGROUP ANALYSES OF PATIENTS WITH AGGRESSIVE DISEASE‡[3]

REVEL: AGGRESSIVE DISEASE SUBGROUPS

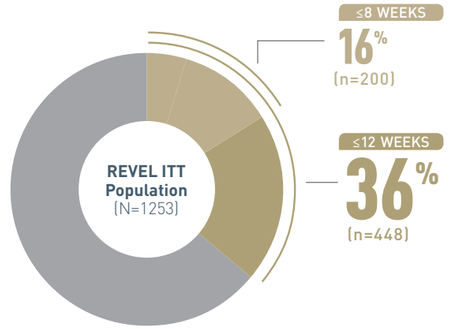
PATIENTS WITH REFRACTORY DISEASE

Patients in the REVEL trial who had a best overall response to platinum-based therapy of progressive disease



PATIENTS WITH LIMITED TIME ON INITIAL PLATINUM-BASED THERAPY

Patients in the REVEL trial with limited time on initial platinum-based therapy (≤8 or ≤12 weeks)



- Similar to the intent-to-treat (ITT) population, the percentage of patients with ECOG PS 1 in the refractory subgroup were balanced between treatment arms[3,4]

‡Aggressive disease is defined by those patients who were primary refractory to platinum-based therapy or who experienced limited time on initial platinum-based therapy (≤8 or ≤12 weeks).[3]

REVEL EXPLORATORY ANALYSES[3,7]

The REVEL trial was not powered for subgroup analyses, nor were any such analyses error-controlled. The primary platinum-refractory population was a pre-specified subgroup in the REVEL trial, however the subgroup of patients with limited time on initial platinum-based therapy (≤8 or ≤12 weeks) was not pre-specified. Each subgroup analysis presented was exploratory. Kaplan-Meier estimates and Cox regression analyses of OS and PFS were performed for all subgroups. The Cochran-Mantel-Haenszel test assessed differences in ORR between treatment groups. Safety analyses were performed on both subsets of patients from the safety population, defined as all patients who had received at least one dose of study drug.

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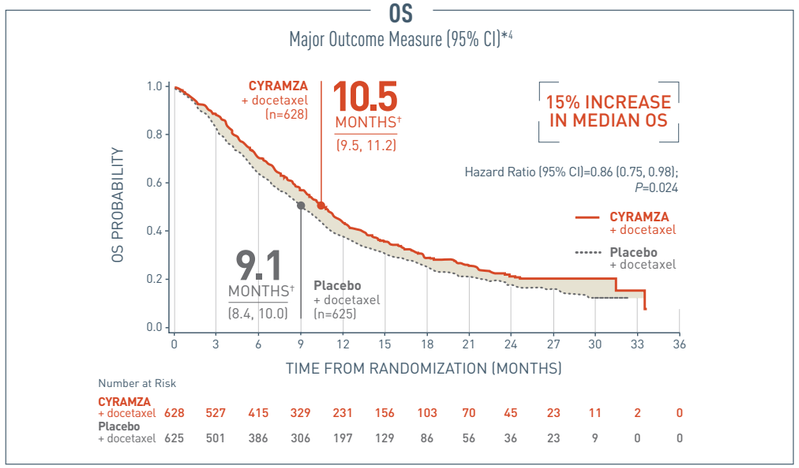
CYRAMZA DEMONSTRATED SIGNIFICANT IMPROVEMENTS IN OS, PFS, AND ORR IN THE REVEL TRIAL POPULATION WHEN ADDED TO DOCETAXEL[4]

ITT POPULATION (N=1253)



Supportive Outcome Measure (95% CI)	CYRAMZA + docetaxel (n=628)	Placebo + docetaxel (n=625)
PFS‡[4]	4.5 months† (4.2, 5.4)	3.0 months† (2.8, 3.9)
	Hazard ratio 0.76 (95% CI: 0.68, 0.86); P<0.001	
ORR§[4]	23% (20, 26)	14% (11,17)
	P<0.001	

CI=confidence interval; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

*The percentage of deaths at the time of analysis was 68% (428 patients) and 73% (456 patients) in the CYRAMZA plus docetaxel and placebo plus docetaxel arms, respectively.[4]

† Median.

‡ The percentage of events at the time of analysis was 89% (558 patients) and 93% (583 patients) in the CYRAMZA plus docetaxel and placebo plus docetaxel arms, respectively.[4]

§ Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[6]
ORR=complete + partial response; does not include stable disease.

SELECT IMPORTANT SAFETY INFORMATION

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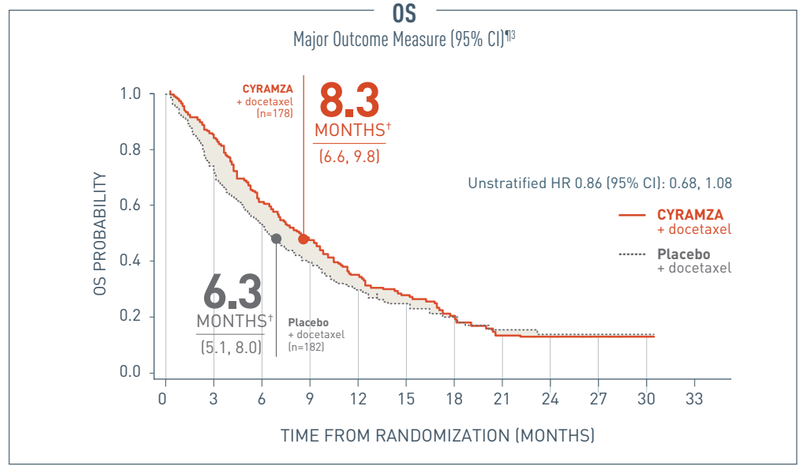
WITH CONSISTENT RESULTS IN PATIENTS WITH AGGRESSIVE DISEASE‖[3]

Exploratory Subgroup Analysis:

PATIENTS WITH REFRACTORY DISEASE (n=360)



Supportive Outcome Measure (95% CI)	CYRAMZA + docetaxel (n=178)	Placebo + docetaxel (n=182)
PFS#[3]	4.0 months† (2.9, 4.4)	2.5 months† (1.6, 2.8)
	Unstratified HR 0.71 (95% CI): 0.57, 0.88	
ORR[3]	23% (17, 29)	13% (8, 18)

The REVEL trial was not adequately powered, nor error-controlled, for subgroup analyses. Treatment differences observed in these subgroups cannot be regarded as statistically significant. The analyses described here were exploratory.[3,7]

‖ Aggressive disease is defined by those patients who were primary refractory to platinum-based therapy or who experienced limited time on initial platinum-based therapy (≤8 or ≤12 weeks).[3]

¶ The percentage of deaths at the time of analysis in the CYRAMZA plus docetaxel arm was 75% (134 patients) and 77% (141 patients) in the placebo plus docetaxel arm.[3]

The percentage of events at the time of analysis in the CYRAMZA plus docetaxel arm was 88% (156 patients) and 92% (168 patients) in the placebo plus docetaxel arm.[3]

SELECT IMPORTANT SAFETY INFORMATION (CONTINUED)

0% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lacrimation increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%). **The most common serious adverse events** with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.

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CYRAMZA DEMONSTRATED SIGNIFICANT IMPROVEMENTS IN OS, PFS, AND ORR IN THE REVEL TRIAL POPULATION WHEN ADDED TO DOCETAXEL[4]

ITT POPULATION (N=1253)

OS

Major Outcome Measure (95% CI)[4]

CYRAMZA + docetaxel		Placebo + docetaxel
10.5 MONTHS* (9.5, 11.2)	VS	**9.1** MONTHS* (8.4, 10.0)

Hazard ratio 0.86 (95% CI: 0.75, 0.98); *P*=0.024

PFS

Supportive Outcome Measure (95% CI)[4]

CYRAMZA + docetaxel		Placebo + docetaxel
4.5 MONTHS* (4.2, 5.4)	VS	**3.0** MONTHS* (2.8, 3.9)

Hazard ratio 0.76 (95% CI: 0.68, 0.86); *P*<0.001

ORR

Supportive Outcome Measure (95% CI)[4]

CYRAMZA + docetaxel		Placebo + docetaxel
23% (20, 26)	VS	**14%** (11, 17)

P<0.001

*Median.

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WITH CONSISTENT RESULTS IN PATIENTS WITH AGGRESSIVE DISEASE†[3]

Exploratory Subgroup Analysis:

PATIENTS WITH LIMITED TIME ON INITIAL PLATINUM-BASED THERAPY

≤8 weeks (n=200)

OS

Major Outcome Measure (95% CI)[3]

CYRAMZA + docetaxel		Placebo + docetaxel
8.6 MONTHS* (6.5, 10.4)	VS	**6.9** MONTHS* (5.0, 9.3)

Unstratified HR 0.83 (95% CI: 0.61, 1.15)

PFS

Supportive Outcome Measure (95% CI)[3]

CYRAMZA + docetaxel		Placebo + docetaxel
3.3 MONTHS* (2.8, 4.2)	VS	**2.5** MONTHS* (1.5, 2.9)

Unstratified HR 0.85 (95% CI: 0.64, 1.14)

ORR

Supportive Outcome Measure (95% CI)[3]

CYRAMZA + docetaxel		Placebo + docetaxel
23% (16, 32)	VS	**11%** (6, 20)

≤12 weeks (n=448)

OS

Major Outcome Measure (95% CI)[3]

CYRAMZA + docetaxel		Placebo + docetaxel
9.2 MONTHS* (8.3, 10.3)	VS	**7.2** MONTHS* (5.9, 9.3)

Unstratified HR 0.85 (95% CI: 0.68, 1.05)

PFS

Supportive Outcome Measure (95% CI)[3]

CYRAMZA + docetaxel		Placebo + docetaxel
4.1 MONTHS* (3.2, 4.4)	VS	**2.8** MONTHS* (1.8, 3.2)

Unstratified HR 0.75 (95% CI: 0.61, 0.91)

ORR

Supportive Outcome Measure (95% CI)[3]

CYRAMZA + docetaxel		Placebo + docetaxel
26% (21, 32)	VS	**12%** (8, 17)

The REVEL trial was not adequately powered, nor error-controlled, for subgroup analyses. Treatment differences observed in these subgroups cannot be regarded as statistically significant. The analyses described here were exploratory.[3,7]

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ADVERSE REACTION PROFILE FOR CYRAMZA IN COMBINATION WITH DOCETAXEL[4]

ADVERSE REACTIONS OCCURRING WITH CYRAMZA PLUS DOCETAXEL AT INCIDENCE RATE ≥5% AND ≥2% HIGHER THAN WITH PLACEBO PLUS DOCETAXEL[4]

ITT POPULATION (N=1253)

Adverse Reactions (MedDRA) System Organ Class	All Grades		Grade 3/4	
	CYRAMZA + docetaxel (n=627)	**Placebo** + docetaxel (n=618)	**CYRAMZA** + docetaxel (n=627)	**Placebo** + docetaxel (n=618)
Blood and Lymphatic System Disorders				
Febrile neutropenia	**16%**	**10%**	**16%**	**10%**
Neutropenia	**55%**	**46%**	**49%**	**40%**
Thrombocytopenia	**13%**	**5%**	**3%**	**<1%**
Gastrointestinal Disorders				
Stomatitis/Mucosal inflammation	**37%**	**19%**	**7%**	**2%**
Eye Disorders				
Lacrimation increased	**13%**	**5%**	**<1%**	**0%**
General Disorders and Administration Site Disorders				
Fatigue/Asthenia	**55%**	**50%**	**14%**	**11%**
Peripheral edema	**16%**	**9%**	**0%**	**<1%**
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	**19%**	**7%**	**<1%**	**<1%**
Vascular Disorders				
Hypertension	**11%**	**5%**	**6%**	**2%**

MedDRA=Medical Dictionary for Regulatory Activities.

- 31% of patients (195 out of 627) in the REVEL trial received CYRAMZA for at least 6 months[4]
  - —Median duration of exposure was 3.5 months (median of 4.5 doses)
- Discontinuation of CYRAMZA/placebo due to ≥1 treatment-emergent adverse event was 1.4% (n=9) in the CYRAMZA plus docetaxel arm vs 1% (n=6) in the placebo plus docetaxel arm. Discontinuation of docetaxel due to ≥1 treatment adverse event was 7.8% (n=49) vs 4.2% (n=26)[8]
  - — Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%)
- The median relative dose intensity was 98.0% for CYRAMZA and 98.7% for placebo. The median relative dose intensity of docetaxel was 93.5% for the CYRAMZA plus docetaxel arm and 96.5% for placebo plus docetaxel arm[9]
- 51% (n=320/628) of patients received ≥1 subsequent therapy post-discontinuation with CYRAMZA plus docetaxel vs 55% (n=343/625) of patients for placebo plus docetaxel[5]

THE INCIDENCE OF ADVERSE EVENTS* OBSERVED IN THE AGGRESSIVE DISEASE† SUBPOPULATIONS WAS CONSISTENT WITH THAT OBSERVED IN THE TOTAL STUDY POPULATION[3]

In the refractory subgroup, discontinuation rates due to TEAE were 5% (n=9) in the CYRAMZA plus docetaxel arm vs 4% (n=7) in the placebo plus docetaxel arm[3]

*Adverse events included treatment-emergent adverse events (TEAEs), grade ≥3 TEAEs, SAE, TEAEs leading to discontinuation, and fatal TEAEs.

†Aggressive disease is defined by those patients who were primary refractory to platinum-based therapy or who experienced limited time on initial platinum-based therapy (≤8 or ≤12 weeks).[3]

SELECT IMPORTANT SAFETY INFORMATION

- The most common serious adverse events observed with CYRAMZA plus docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- In patients ≥65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related reaction (0.5%) and epistaxis (0.3%).
- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel-treated patients in study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

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Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel versus 0.3% for placebo plus docetaxel. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, as an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lacrimation increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).
- The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- In patients ≥65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA were infusion-related reaction (0.5%) and epistaxis (0.3%).
- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel-treated patients in study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and docetaxel.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see accompanying full Prescribing Information for CYRAMZA, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing.

RB-L HCP ISI 17SEP2015

References: 1. Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.4.2017. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed February 10, 2017. To view the most recent and complete version of the guidelines, go online to http://www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc. **2.** Younes RN, Pereira JR, Fares AL, Gross JL. Chemotherapy beyond first-line in stage IV metastatic non-small cell lung cancer. *Rev Assoc Med Bras*. 2011;57(6):686-691. **3.** Reck M, Paz-Ares L, Bidoli P, et al. Exploratory subgroup analysis of patients refractory to first-line chemotherapy from REVEL, a randomized phase III study of docetaxel with ramucirumab or placebo for second-line treatment of stage IV non-small-cell lung cancer. Poster presented at: Annual Meeting of American Society of Clinical Oncology; June 3-7, 2016; Chicago, IL. Abstract 9079. **4.** CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2016. **5.** Supplement to: Garon EB, Ciuleanu T-E, 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(9944):665-673. **6.** Garon EB, Ciuleanu T-E, 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(9944):665-673. **7.** Data on file. Eli Lilly and Company. ONC20170210a. **8.** Data on file. Eli Lilly and Company. ONC20150915a. **9.** Data on file. Eli Lilly and Company. ONC20150915b.

CYRAMZA®
ramucirumab injection
10 mg/mL solution

HELP CONTROL THE DISEASE BY EXTENDING SURVIVAL AFTER PROGRESSION AND DELAYING FURTHER TUMOR GROWTH[4]

SIGNIFICANTLY IMPROVED OS, PFS, AND ORR IN THE REVEL ITT POPULATION, WITH CONSISTENT RESULTS IN PATIENTS WITH AGGRESSIVE DISEASE*[3,4]

ITT POPULATION (N=1253)

OS
Major Outcome Measure (95% CI)[4]

CYRAMZA + docetaxel		Placebo + docetaxel
10.5 MONTHS† (9.5, 11.2)	VS	9.1 MONTHS† (8.4, 10.0)

Hazard ratio 0.86 (95% CI: 0.75, 0.98); *P*=0.024

PFS
Supportive Outcome Measure (95% CI)[4]

CYRAMZA + docetaxel		Placebo + docetaxel
4.5 MONTHS† (4.2, 5.4)	VS	3.0 MONTHS† (2.8, 3.9)

Hazard ratio 0.76 (95% CI: 0.68, 0.86); *P*<0.001

ORR
Supportive Outcome Measure (95% CI)[4]

CYRAMZA + docetaxel		Placebo + docetaxel
23% (20, 26)	VS	14% (11, 17)

P<0.001

CONSIDER CYRAMZA PLUS DOCETAXEL FOR PATIENTS WITH AGGRESSIVE DISEASE

*Aggressive disease is defined by those patients who were primary refractory to platinum-based therapy or who experienced limited time on initial platinum-based therapy (≤8 or ≤12 weeks).[3]
†Median.

SELECT IMPORTANT SAFETY INFORMATION

- The labeling for CYRAMZA contains a **Boxed Warning** for: hemorrhage, including severe and sometimes fatal events; gastrointestinal (GI) perforation, a potentially fatal event; and impaired wound healing. CYRAMZA should be permanently discontinued in patients who experience severe bleeding or a GI perforation. CYRAMZA should be withheld prior to surgery and discontinued if a patient develops wound healing complications. CYRAMZA contains additional **Warnings and Precautions** for arterial thromboembolic events, which are sometimes fatal; hypertension; infusion-related reactions; clinical deterioration in patients with Child-Pugh B or C cirrhosis; reversible posterior leukoencephalopathy syndrome; proteinuria including nephrotic syndrome; thyroid dysfunction; and embryofetal toxicity. **The most commonly reported adverse reactions** (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lacrimation increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%). **The most common serious adverse events** with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 10-11 and accompanying full Prescribing Information for CYRAMZA.

CYRAMZA®
ramucirumab injection
10 mg/mL solution

PP-RB-US-0911 02/2017 PRINTED IN USA

Lilly

TAKE ACTION WITH CYRAMZA

CYRAMZA®
ramucirumab injection
10 mg/mL solution

CYRAMZA HAS **4 POSITIVE PHASE III STUDIES** ACROSS 3 HARD-TO-TREAT TUMORS[1]

ADVANCED GASTRIC OR GEJ ADENOCARCINOMA

- RAINBOW (N=665)
  CYRAMZA + PACLITAXEL
- REGARD (N=355)
  CYRAMZA MONOTHERAPY

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

METASTATIC NON-SMALL CELL LUNG CANCER

- REVEL (N=1253)
  CYRAMZA + DOCETAXEL

CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor or anaplastic lymphoma kinase genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

METASTATIC COLORECTAL CANCER

- RAISE (N=1072)
  CYRAMZA + FOLFIRI

CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 12-15 and accompanying full Prescribing Information for CYRAMZA.

Lilly

MEET DAVID
A patient with mCRC

David is a journalist and, despite his cancer, he continues to work part time as a freelancer. David was recently nominated for a writing award.

DAVID'S PROFILE

- 62 years old
- Male
- Caucasian
- Married, 2 children

DAVID'S MEDICAL HISTORY

- David was diagnosed with a tumor in the distal colon, as well as single liver metastasis
- **His tumor is positive for the *KRAS* exon 2 mutation**
- **He presents 3 months after beginning first-line treatment with mFOLFOX6 + bevacizumab with an additional metastatic mass in his right lung and multiple liver metastases shown by CT scans**
- ECOG PS 1

ECOG=Eastern Cooperative Oncology Group; PS=performance status; *KRAS*=Kirsten rat sarcoma; mFOLFOX6=folinic acid, fluorouracil, and oxaliplatin.

DAVID'S GOALS

David wants to continue to work part time. Having been nominated for a writing award, he wants to be present for the upcoming awards ceremony.

FOR A PATIENT WHO HAS RAPIDLY PROGRESSED, WOULD YOU AGREE MORE OPTIONS ARE NEEDED THAT IMPROVE SURVIVAL?

Hypothetical patient example.

CYRAMZA with FOLFIRI

An antiangiogenic regimen approved for the second-line treatment of patients with mCRC[1]

For complete CYRAMZA clinical data

Please visit
WWW.CYRAMZAHCP.COM

Review the Tabernero (RAISE) publication

Please log in with your credentials at
WWW.THELANCET.COM

CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with mCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

SELECT IMPORTANT SAFETY INFORMATION

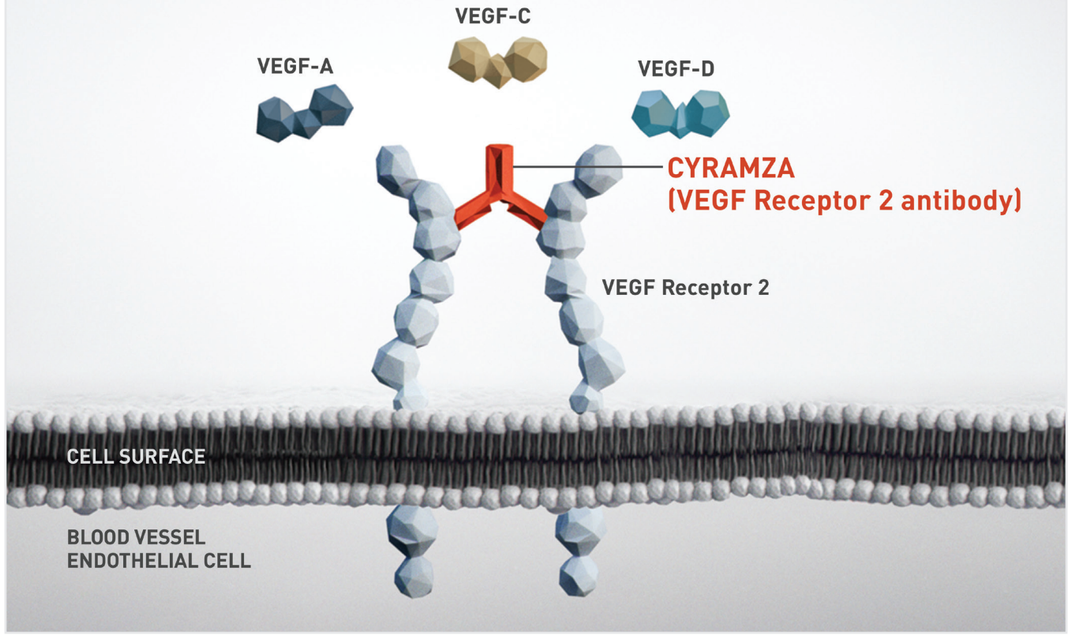
Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 4, which evaluated CYRAMZA plus FOLFIRI in metastatic colorectal cancer, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 12-15 and accompanying full Prescribing Information for CYRAMZA.

CYRAMZA IS A HUMAN, MONOCLONAL ANTIBODY THAT SPECIFICALLY BLOCKS ACTIVATION OF VEGF RECEPTOR 2[1]

CYRAMZA BLOCKS MULTIPLE LIGANDS BY BINDING A SINGLE RECEPTOR[1]



VEGF=vascular endothelial growth factor.

Diagram is not drawn to scale.

As demonstrated in nonclinical studies.
CYRAMZA inhibited angiogenesis in an *in vivo* animal model.

- CYRAMZA binds directly to the ligand-binding pocket of VEGF Receptor 2 to block the binding of VEGF-A, VEGF-C, and VEGF-D[1]

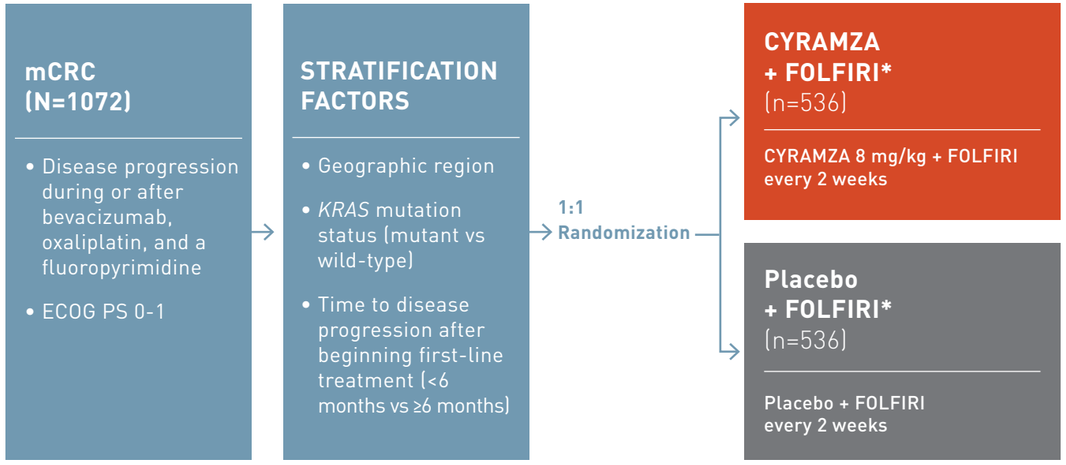
CYRAMZA®
ramucirumab injection
10 mg/mL solution

TAKE ACTION

RAISE: A PIVOTAL PHASE III TRIAL OF SECOND-LINE THERAPY IN PATIENTS WITH mCRC WITH PROGRESSIVE DISEASE (N=1072)[1]

RAISE TRIAL DESIGN[1,2]

A large, multinational, randomized, double-blind, placebo-controlled trial in patients with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine



*Irinotecan 180 mg/m^2 intravenous (IV) infusion over 90 minutes and folinic acid 400 mg/m^2 IV simultaneously over 120 minutes; followed by 5-fluorouracil 400 mg/m^2 IV bolus over 2 to 4 minutes; followed by 5-fluorouracil 2400 mg/m^2 IV by continuous infusion over 46 to 48 hours.

Major Efficacy Outcome Measure: Overall survival (OS)
Supportive Efficacy Outcome Measure: Progression-free survival (PFS)

- Patients received treatment until disease progression or unacceptable toxicity

SELECT IMPORTANT SAFETY INFORMATION

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 12-15 and accompanying full Prescribing Information for CYRAMZA.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS WERE SIMILAR BETWEEN TREATMENT ARMS[1,3-5]

RAISE DEMOGRAPHICS AND BASELINE CHARACTERISTICS[1,3-5]

	CYRAMZA + FOLFIRI (n=536)	Placebo + FOLFIRI (n=536)
Age, median (range)	62 (21-83)	62 (33-87)
Male†	54%	61%
Ethnic origin†		
Caucasian	76%	77%
Asian	21%	19%
ECOG PS		
0	49%	48%
1	50%	51%
Disease stage at initial diagnosis, n (%)		
Stages I-IIIC	24%	24%
Stage IV	76%	76%
KRAS status at study entry, n (%)		
Mutant	50%	49%
Wild-type	50%	51%
<6 months from time to disease progression after beginning first-line treatment‡	23%	24%
Prior therapy		
Prior bevacizumab use ≥3 months	85%	80%
Prior oxaliplatin use ≥3 months	87%	85%
Prior fluoropyrimidine use ≥3 months	93%	90%

Based on intent-to-treat (ITT) population.
†Percentages are based on the total population size (N=1072).
‡Based on case report form (CRF) data if present, or interactive voice response system value if CRF data were missing for the parameter.

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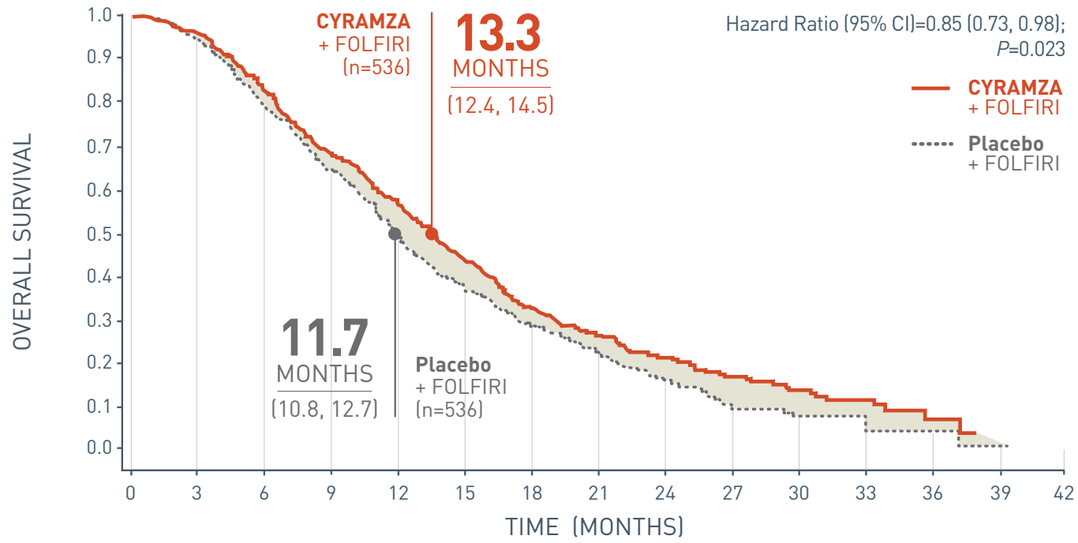
ramucirumab injection
10 mg/mL solution

TAKE ACTION

CYRAMZA PLUS FOLFIRI DEMONSTRATED A STATISTICALLY SIGNIFICANT IMPROVEMENT IN OVERALL SURVIVAL[1]

OVERALL SURVIVAL: MEDIAN - MONTHS (95% CI)[1]

MAJOR OUTCOME MEASURE



Number at Risk

CYRAMZA + FOLFIRI	536	497	421	345	269	195	114	78	53	34	22	12	4	0	0
Placebo + FOLFIRI	536	486	400	329	228	166	108	66	44	22	10	2	2	1	0

- **The treatment effect was consistent across prespecified stratification factors**[1]
- The percentage of deaths at the time of analysis was 69% (372 patients) and 74% (397 patients) in the CYRAMZA plus FOLFIRI and placebo plus FOLFIRI arms, respectively[1]

The phase III RAISE trial evaluated the efficacy and safety of CYRAMZA plus FOLFIRI vs placebo plus FOLFIRI in patients with mCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Major efficacy outcome measure was OS. Supportive efficacy outcome measure was PFS. All patients were required to have ECOG PS 0 or 1. Patients were stratified by geographic region, *KRAS* mutation status, and time to disease progression after the beginning of first-line treatment (<6 months vs ≥6 months). Patients were randomized 1:1 (N=1072) to receive either CYRAMZA 8 mg/kg or placebo, in combination with FOLFIRI every 14 days.

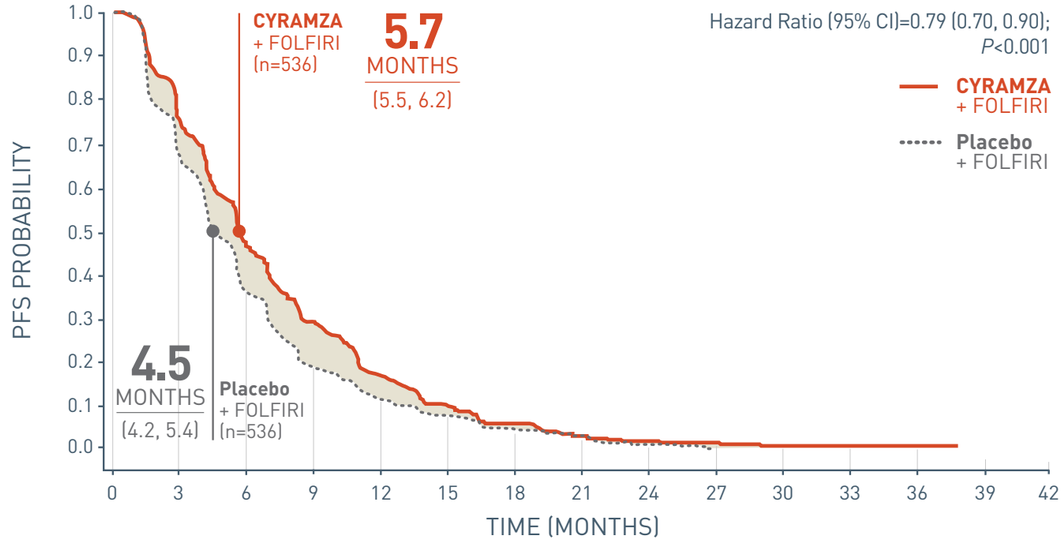
CI=confidence interval.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 12-15 and accompanying full Prescribing Information for CYRAMZA.

CYRAMZA PLUS FOLFIRI DEMONSTRATED A STATISTICALLY SIGNIFICANT DELAY IN DISEASE PROGRESSION[1]

PROGRESSION-FREE SURVIVAL: MEDIAN-MONTHS (95% CI)[1]

SUPPORTIVE OUTCOME MEASURE



Number at Risk

CYRAMZA + FOLFIRI	536	381	234	142	77	38	20	11	6	5	2	1	1	0	0
Placebo + FOLFIRI	536	345	182	92	52	31	17	10	3	1	0	0	0	0	0

- The percentage of events at the time of analysis was 89% (476 patients) and 92% (494 patients) in the CYRAMZA plus FOLFIRI and placebo plus FOLFIRI arms, respectively[1]

SELECT IMPORTANT SAFETY INFORMATION

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

CYRAMZA®
ramucirumab injection
10 mg/mL solution

TAKE ACTION

ADVERSE REACTION PROFILE FOR CYRAMZA IN COMBINATION WITH FOLFIRI[1,6]

ADVERSE REACTIONS OCCURRING AT INCIDENCE RATE ≥5% AND A ≥2% DIFFERENCE BETWEEN ARMS IN PATIENTS RECEIVING CYRAMZA[1,6]

Adverse Reactions (MedDRA) System Organ Class	All Grades		Grade ≥3	
	CYRAMZA + FOLFIRI (n=529)	Placebo + FOLFIRI (n=528)	**CYRAMZA** + FOLFIRI (n=529)	Placebo + FOLFIRI (n=528)
Blood and Lymphatic System Disorders				
Neutropenia	**59%**	46%	**38%**	23%
Thrombocytopenia	**28%**	14%	**3%**	<1%
Gastrointestinal Disorders				
Gastrointestinal hemorrhage events	**12%**	7%	**2%**	1%
Decreased appetite	**37%**	27%	**2%**	2%
Diarrhea	**60%**	51%	**11%**	10%
Stomatitis	**31%**	21%	**4%**	2%
General Disorders and Administration Site Disorders				
Peripheral edema	**20%**	9%	**<1%**	0%
Metabolism and Nutrition Disorders				
Hypoalbuminemia	**6%**	2%	**1%**	0%
Renal and Urinary Disorders				
Proteinuria*	**17%**	5%	**3%**	<1%
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	**33%**	15%	**0%**	0%
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia syndrome	**13%**	5%	**1%**	<1%
Vascular Disorders				
Hypertension	**26%**	9%	**11%**	3%

MedDRA=Medical Dictionary for Regulatory Activities.
*Includes 3 patients with nephrotic syndrome in the CYRAMZA plus FOLFIRI treatment group.

SELECT IMPORTANT SAFETY INFORMATION

- The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
- Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA plus FOLFIRI-treated patients (29%) than in placebo plus FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA plus FOLFIRI as compared to placebo plus FOLFIRI were neutropenia (12.5% versus 5.3%) and thrombocytopenia (4.2% versus 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%) and gastrointestinal perforation (1.7%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus FOLFIRI-treated patients in study 4 consisted of gastrointestinal perforation (1.7% CYRAMZA plus FOLFIRI versus 0.6% for placebo plus FOLFIRI).

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 12-15 and accompanying full Prescribing Information for CYRAMZA.

PatientOne

CONTACT LILLY PATIENTONE FOR INFORMATION ON FINANCIAL ASSISTANCE

The Lilly PatientOne program is committed to helping eligible patients access support programs for their prescribed Lilly Oncology medications. It aims to address both financial and coverage issues for qualified uninsured, underinsured, and insured patients who are prescribed a Lilly Oncology product.

Lilly PatientOne strives to offer resources, ranging from benefits investigations to financial assistance and appeals information, that provide reliable and individualized support for eligible patients.

SERVICES OFFERED BY THIS PROGRAM INCLUDE:

Insurance expertise
- Coding and billing information
- Payment methodologies and allowables
- Payer policy information

Patient financial support
- Information about co-pay assistance foundations
- Lilly PatientOne Co-Pay Program—patients pay not more than $25—to assist eligible patients with co-pay and coinsurance costs for prescribed Lilly Oncology products where available†

†This offer is invalid for patients whose prescription claims are eligible to be reimbursed, in whole or in part, by any governmental program. For more information, including co-pay program terms and conditions, please visit **www.LillyPatientOne.com**.

Reimbursement assistance for eligible Lilly Oncology products for an approved diagnosis
- Eligibility determination
- Benefits investigation
- Prior authorization
- Evaluation of other funding options

Denied claim appeals
- Appeals status if requested
- Denied claims appeals templates, forms, and checklists

For more information, please visit **www.LillyPatientOne.com** or call Lilly PatientOne at **1-866-4PatOne (1-866-472-8663)** Monday–Friday, 9 am–7 pm ET.

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ramucirumab injection
10 mg/mL solution

TAKE ACTION

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage including severe and sometimes fatal hemorrhagic events. In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel in advanced gastric cancer, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. In study 4, which evaluated CYRAMZA plus FOLFIRI in metastatic colorectal cancer, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%), in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), and in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in advanced gastric cancer clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforation was 1.2% for CYRAMZA plus paclitaxel as compared to 0.3% for placebo plus paclitaxel. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel as compared to 0.3% for placebo plus docetaxel. In study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- In study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA. In study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the CYRAMZA plus FOLFIRI-treated patients and 0.9% in the placebo plus FOLFIRI-treated patients.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse events with CYRAMZA in study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.

CYRAMZA®
ramucirumab injection
10 mg/mL solution

TAKE ACTION

- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients vs placebo in study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

Most Common Adverse Reactions—Combination With Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel and ≥2% higher than placebo plus paclitaxel in study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs 0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Most Common Adverse Reactions—Combination With Docetaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lacrimation increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).
- The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- In patients ≥65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA in study 3 were infusion-related reaction (0.5%) and epistaxis (0.3%).
- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel-treated patients in study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Most Common Adverse Reactions—Combination With FOLFIRI

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus FOLFIRI and ≥2% higher than placebo plus FOLFIRI in study 4 were diarrhea (60% vs 51%; 11% vs 10%), neutropenia (59% vs 46%; 38% vs 23%), decreased appetite (37% vs 27%; 2% vs 2%), epistaxis (33% vs 15%; 0% vs 0%), stomatitis (31% vs 21%; 4% vs 2%), thrombocytopenia (28% vs 14%; 3% vs <1%), hypertension (26% vs 9%; 11% vs 3%), peripheral edema (20% vs 9%; <1% vs 0%), proteinuria (17% vs 5%; 3% vs <1%), palmar-plantar erythrodysesthesia syndrome (13% vs 5%; 1% vs <1%), gastrointestinal hemorrhage events (12% vs 7%; 2% vs 1%), hypoalbuminemia (6% vs 2%; 1% vs 0%). Twenty percent of patients treated with CYRAMZA plus FOLFIRI received granulocyte colony-stimulating factors.
- The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
- Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA plus FOLFIRI-treated patients (29%) than in placebo plus FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA plus FOLFIRI as compared to placebo plus FOLFIRI were neutropenia (12.5% versus 5.3%) and thrombocytopenia (4.2% versus 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%) and gastrointestinal perforation (1.7%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus FOLFIRI-treated patients in study 4 consisted of gastrointestinal perforation (1.7% CYRAMZA plus FOLFIRI versus 0.6% for placebo plus FOLFIRI).
- Thyroid-stimulating hormone (TSH) was evaluated in 224 patients (115 CYRAMZA plus FOLFIRI-treated patients and 109 placebo plus FOLFIRI-treated patients) with normal baseline TSH levels. Patients received periodic TSH assessments until 30 days after the last dose of study treatment. Increased TSH was observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and paclitaxel, between ramucirumab and docetaxel, or between ramucirumab and irinotecan or its active metabolite, SN-38.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and pediatric development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see accompanying full Prescribing Information for CYRAMZA, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing.

RB-P HCP ISI 17SEP2015

CYRAMZA®
ramucirumab injection
10 mg/mL solution

TAKE ACTION

FOR YOUR mCRC PATIENTS WHO HAVE PROGRESSED, CONSIDER A

SWITCH TO CYRAMZA + FOLFIRI

CYRAMZA®
ramucirumab injection
10 mg/mL solution

TAKE ACTION

CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with mCRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

LEARN MORE AT
WWW.CYRAMZAHCP.COM

SELECT IMPORTANT SAFETY INFORMATION

The labeling for CYRAMZA contains a Boxed Warning for: hemorrhage, including severe and sometimes fatal events; gastrointestinal (GI) perforation, a potentially fatal event; and impaired wound healing. CYRAMZA should be permanently discontinued in patients who experience severe bleeding or a GI perforation. CYRAMZA should be withheld prior to surgery and discontinued if a patient develops wound healing complications. CYRAMZA contains additional Warnings and Precautions for arterial thromboembolic events, hypertension, infusion-related reactions, clinical deterioration in patients with Child-Pugh B or C cirrhosis, reversible posterior leukoencephalopathy syndrome, proteinuria including nephrotic syndrome, thyroid dysfunction, and embryofetal toxicity. The most common adverse reactions (all grades) observed in CYRAMZA plus FOLFIRI-treated patients at a rate of ≥30% and ≥2% higher than placebo plus FOLFIRI were diarrhea, neutropenia, decreased appetite, epistaxis, and stomatitis. The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%); 20% of patients treated with CYRAMZA plus FOLFIRI received granulocyte colony-stimulating factors.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 12-15 and accompanying full Prescribing Information for CYRAMZA.

References: 1. CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2015. **2.** Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol.* 2015;16(5):499-508. **3.** Data on file, Eli Lilly and Company. ONC20150418a. **4.** Data on file, Eli Lilly and Company. ONC20150629a. **5.** Data on file, Eli Lilly and Company. ONC20150624a. **6.** Data on file, Eli Lilly and Company. ONC20150419a.

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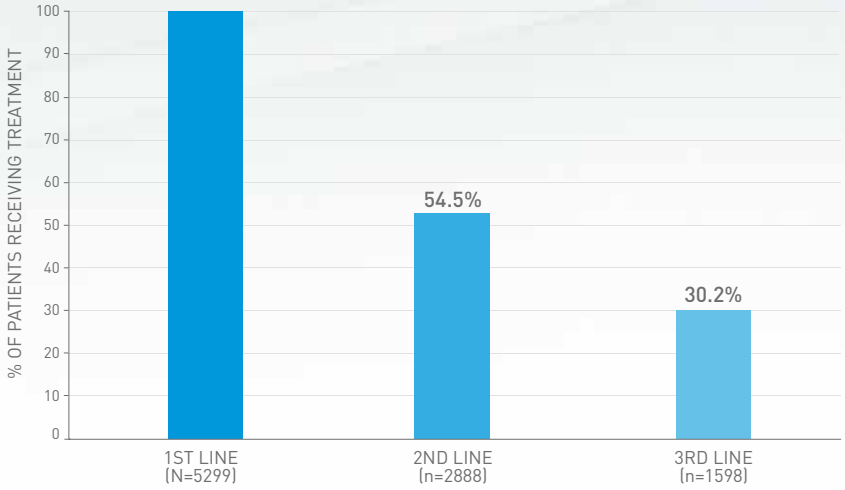
Lilly

DO YOU CONSIDER SUBSEQUENT THERAPY WHEN STARTING FIRST-LINE GASTRIC OR GEJ TREATMENT?

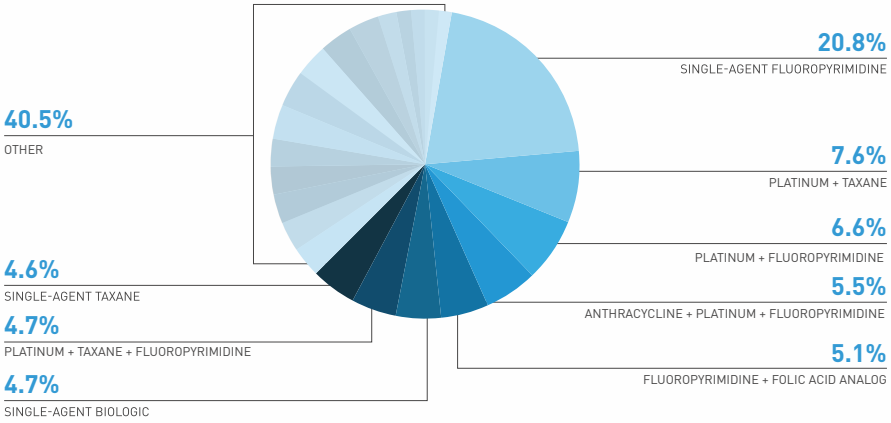
OVER HALF OF PATIENTS WITH ADVANCED GASTRIC OR GEJ ADENOCARCINOMA RECEIVE SUBSEQUENT THERAPY[1]

ADVANCED GASTRIC AND GEJ ADENOCARCINOMA TREATMENT PATTERNS: ADMINISTRATIVE DATA, 2004-2012*[1]



THE SECOND-LINE GASTRIC AND GEJ ADENOCARCINOMA TREATMENT LANDSCAPE HAS BEEN HIGHLY FRAGMENTED[1,2]

SECOND-LINE TREATMENT REGIMENS (N=2831): ADMINISTRATIVE DATA, 2004-2012*[1,2]



- 351 unique drug combinations were used in the second-line setting based on a retrospective claims analysis of 2831 patients with gastric or GEJ adenocarcinoma

THERE IS A NEED FOR SECOND-LINE TREATMENT OPTIONS WITH HIGH-LEVEL EVIDENCE FOR DEMONSTRATED IMPROVEMENT

*Patients age 18 or older with a new diagnosis of gastric cancer (ICD-9-CM 151.0–151.9) between January 1, 2004 and March 31, 2012 (administrative database) were eligible for inclusion. The first occurrence of the eligible ICD-9 code was defined as the "index diagnosis." Patients were ineligible if they had any evidence of cancer within 6 months before the index diagnosis or if they had any evidence of gastrointestinal stromal tumor (ICD-9-CM 238.1) at any time. Continuous medical benefits for 6 months before the index diagnosis were required for eligibility of patients in the administrative dataset.

GEJ=gastroesophageal junction; ICD=International Classification of Diseases.

IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (RAMUCIRUMAB)

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

VEGF=vascular endothelial growth factor.

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroid anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforations was also increased in patients who received CYRAMZA plus paclitaxel (1.2%) as compared to patients who received placebo plus paclitaxel (0.3%). Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse events with CYRAMZA in study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

Most Common Adverse Reactions—Combination With Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel and ≥2% higher than placebo plus paclitaxel in study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs 0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab (CYRAMZA) and paclitaxel.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see accompanying full Prescribing Information for CYRAMZA, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing.

RB-G HCP ISI 17SEP2015

References: 1. Hess LM, Michael D, Mytelka DS, et al. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. *Gastric Cancer.* March 20, 2015 (Epub ahead of print) DOI 10.1007/s10120-015-0486-z. **2.** Data on file, Eli Lilly and Company. ONC20160310a. **3.** CYRAMZA (ramucirumab) (package insert). Indianapolis, IN: Eli Lilly and Company; 2015. **4.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.1.2016. © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed April 20, 2016. To view the most recent and complete version of the guidelines, go online to http://www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc. **5.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Esophageal and Esophagogastric Junction Cancers V.3.2015. © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed March 2, 2016. To view the most recent and complete version of the guidelines, go online to http://www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.

CYRAMZA™ ramucirumab injection | 10 mg/mL solution

RAMUCIRUMAB + PACLITAXEL

THE FIRST AND ONLY FDA-APPROVED combination regimen included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with a CATEGORY 1 recommendation

for the treatment of locally advanced or metastatic gastric or GEJ adenocarcinoma in the second-line setting[3-5]

CYRAMZA® (ramucirumab) as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

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CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

A PREFERRED OPTION[4,5]

CATEGORY 1 NCCN Guidelines® Recommendations:

Locally Advanced or Metastatic Gastric Adenocarcinoma*[4]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

Locally Advanced or Metastatic Esophagogastric Junction Adenocarcinoma†[5]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

CATEGORY 1: Based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate.

*NCCN Guidelines for Gastric Cancer V.1.2016 recommend single-agent ramucirumab (CYRAMZA) and ramucirumab (CYRAMZA) in combination with paclitaxel as preferred second-line treatment options for locally advanced or metastatic gastric adenocarcinoma.

†NCCN Guidelines for Esophageal and Esophagogastric Junction (EGJ) Cancers V.3.2015 recommend single-agent ramucirumab (CYRAMZA) and ramucirumab (CYRAMZA) in combination with paclitaxel as preferred second-line treatment options for locally advanced or metastatic EGJ adenocarcinoma.

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation,and impaired wound healing on the inside spread and accompanying full Prescribing Information for CYRAMZA.

Lilly

RAMUCIRUMAB + PACLITAXEL

THE FIRST AND ONLY FDA-APPROVED combination regimen included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with a CATEGORY 1 recommendation

for the treatment of locally advanced or metastatic gastric or GEJ adenocarcinoma in the second-line setting[1-3]

CYRAMZA® (ramucirumab) as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

LEARN MORE AT
WWW.CYRAMZAHCP.COM

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

A PREFERRED OPTION[2,3]

CATEGORY 1 NCCN Guidelines® Recommendations:

Locally Advanced or Metastatic Gastric Adenocarcinoma*[2]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

Locally Advanced or Metastatic Esophagogastric Junction Adenocarcinoma†[3]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

CATEGORY 1: Based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate.

*NCCN Guidelines for Gastric Cancer V.3.2015 recommend single-agent ramucirumab (CYRAMZA) and ramucirumab (CYRAMZA) in combination with paclitaxel as preferred second-line treatment options for locally advanced or metastatic gastric adenocarcinoma.

†NCCN Guidelines for Esophageal and Esophagogastric Junction (EGJ) Cancers V.3.2015 recommend single-agent ramucirumab (CYRAMZA) and ramucirumab (CYRAMZA) in combination with paclitaxel as preferred second-line treatment options for locally advanced or metastatic EGJ adenocarcinoma.

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Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

VEGF=vascular endothelial growth factor.

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing on the inside spread and full Prescribing Information for CYRAMZA.

Lilly

IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (RAMUCIRUMAB)

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

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Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroid anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforations was also increased in patients who received CYRAMZA plus paclitaxel (1.2%) as compared to patients who received placebo plus paclitaxel (0.3%). Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).
- The most common serious adverse events with CYRAMZA in study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

Most Common Adverse Reactions—Combination With Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel and ≥2% higher than placebo plus paclitaxel in study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs 0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab (CYRAMZA) and paclitaxel.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see accompanying full Prescribing Information for CYRAMZA, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing.

RB-G HCP ISI 17SEP2015

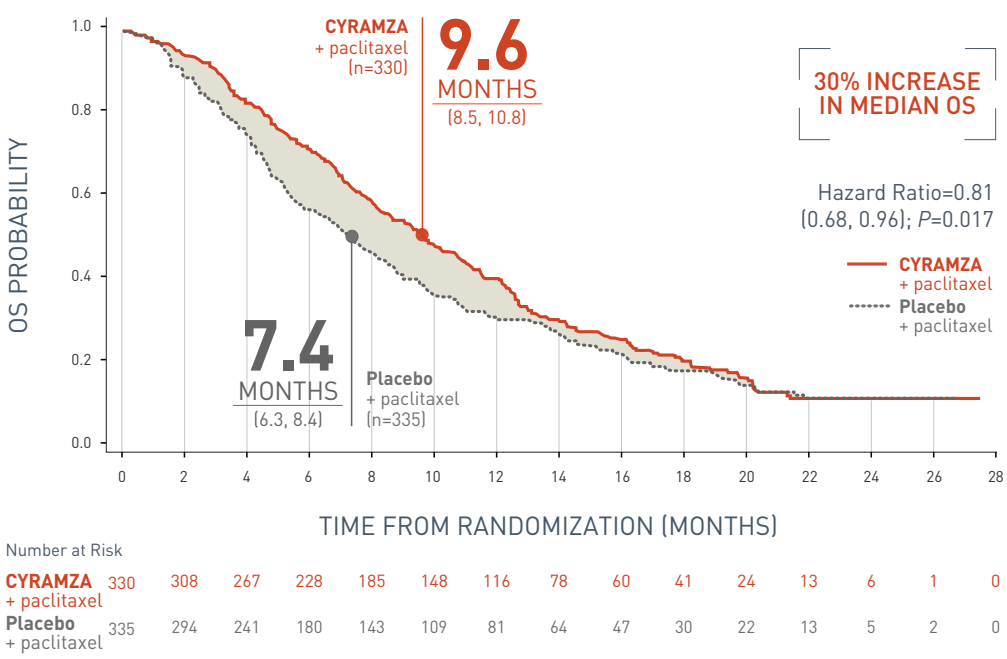
References: 1. CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2015. **2.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.3.2015. © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed February 11, 2016. To view the most recent and complete version of the guidelines, go online to http://www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc. **3.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Esophageal and Esophagogastric Junction Cancers V.3.2015. © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed February 11, 2016. To view the most recent and complete version of the guidelines, go online to http://www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc. **4.** Data on file, Eli Lilly and Company. ONC09302014b.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

CYRAMZA PLUS PACLITAXEL SIGNIFICANTLY EXTENDED OVERALL SURVIVAL[1]

RAINBOW OS: MEDIAN - MONTHS (95% CI)*[1]



Number at Risk

CYRAMZA + paclitaxel	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
Placebo + paclitaxel	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

MAJOR OUTCOME MEASURE

30% INCREASE IN MEDIAN OS

Hazard Ratio=0.81
(0.68, 0.96); *P*=0.017

CYRAMZA + paclitaxel
Placebo + paclitaxel

The phase III RAINBOW trial evaluated the efficacy and safety of CYRAMZA plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were progression-free survival and objective response rate. All patients were Eastern Cooperative Oncology Group performance status 0 or 1. Prior to enrollment, 97% of patients had progressed during treatment or within 4 months after the last dose of first-line chemotherapy for metastatic disease. Twenty-five percent of patients had received anthracycline in combination with platinum/fluoropyrimidine therapy, while 75% did not. Patients were randomized 1:1 to CYRAMZA 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of each 28-day cycle. Patients in both arms received paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.[1,4]

CI=confidence interval; OS=overall survival.
*Intent-to-treat (ITT) population.
The percentage of deaths at the time of analysis was 78% (256 patients) and 78% (260 patients) in the CYRAMZA plus paclitaxel and placebo plus paclitaxel arms, respectively.[1]

For more about CYRAMZA, visit
www.CYRAMZAHCP.com

- Full combination and monotherapy clinical data
- Professional resources and downloads
- PatientOne financial assistance information

SELECT IMPORTANT SAFETY INFORMATION

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroid anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing on the inside spread and full Prescribing Information for CYRAMZA.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

CYRAMZA® (ramucirumab) HAS **4 POSITIVE PHASE III STUDIES**[1]

ADVANCED GASTRIC OR GEJ ADENOCARCINOMA

- RAINBOW (N=665)
  CYRAMZA + PACLITAXEL
- REGARD (N=355)
  CYRAMZA MONOTHERAPY

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

METASTATIC NON-SMALL CELL LUNG CANCER

- REVEL (N=1253)
  CYRAMZA + DOCETAXEL

CYRAMZA, in combination with docetaxel, is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA.

METASTATIC COLORECTAL CANCER

- RAISE (N=1072)
  CYRAMZA + FOLFIRI

CYRAMZA, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

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VEFG=vascular endothelial growth factor.

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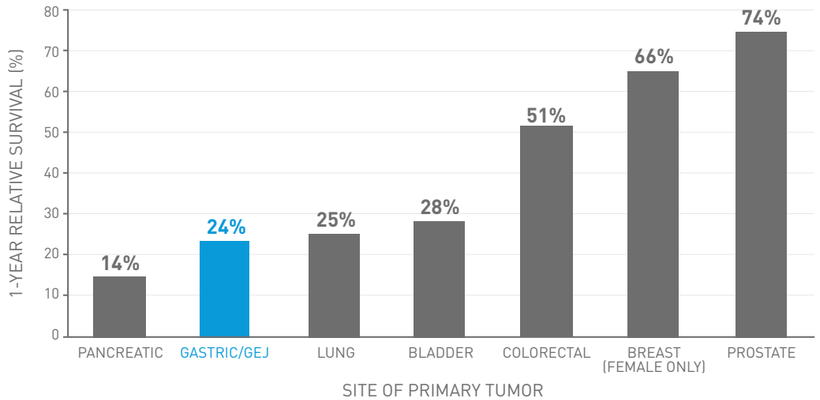
Lilly

ADVANCED GASTRIC AND GEJ ADENOCARCINOMA: DISMAL DISEASES WITH TREATMENT CHALLENGES[2]

ONE-YEAR RELATIVE SURVIVAL IS LOW, ESPECIALLY WHEN COMPARED WITH OTHER SOLID TUMORS[3]

AGE-ADJUSTED SURVIVAL RATE FOR PATIENTS DIAGNOSED AT ADVANCED STAGE, 2000-2012 SEER

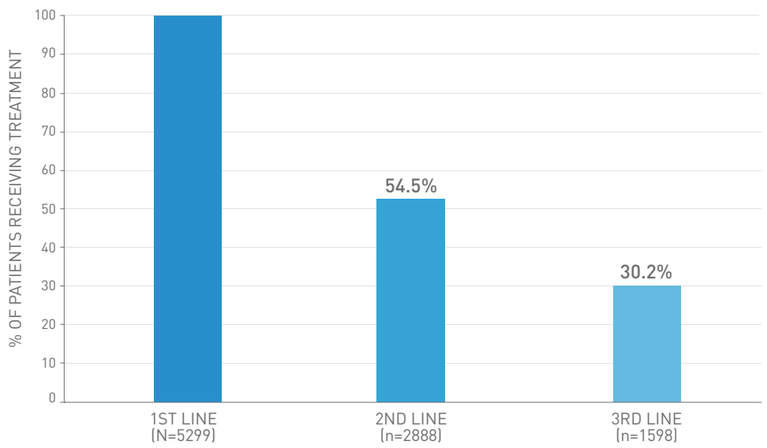


SEER=Surveillance, Epidemiology, and End Results.

Tumor types were selected to provide a spectrum of survival rates across solid tumors by which to compare 1-year survival in gastric cancer, with pancreatic historically holding the lowest survival and prostate one of the highest.

OVER HALF OF PATIENTS WITH ADVANCED GASTRIC OR GEJ ADENOCARCINOMA RECEIVE SUBSEQUENT THERAPY[4]

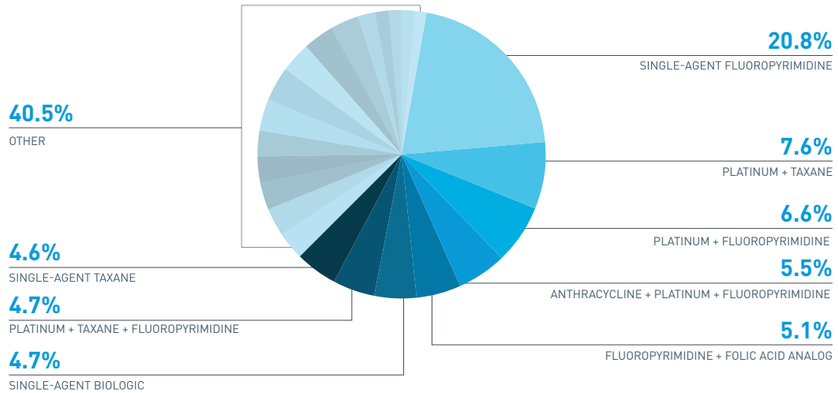
ADVANCED GASTRIC AND GEJ ADENOCARCINOMA TREATMENT PATTERNS: ADMINISTRATIVE DATA, 2004-2012*



DO YOU CONSIDER SUBSEQUENT THERAPY WHEN STARTING FIRST-LINE TREATMENT?

THE SECOND-LINE GASTRIC AND GEJ ADENOCARCINOMA TREATMENT LANDSCAPE HAS BEEN HIGHLY FRAGMENTED[4,5]

SECOND-LINE TREATMENT REGIMENS (N=2831): ADMINISTRATIVE DATA, 2004-2012*



- **351 unique drug combinations were used in the second-line setting based on a retrospective claims analysis of 2831 patients with gastric/GEJ adenocarcinoma[4,5]**

THERE IS A NEED FOR SECOND-LINE TREATMENT OPTIONS WITH HIGH-LEVEL EVIDENCE FOR DEMONSTRATED IMPROVEMENT

*Patients age 18 or older with a new diagnosis of gastric cancer (ICD-9-CM 151.0–151.9) between January 1, 2004 and March 31, 2012 (administrative database) were eligible for inclusion. The first occurrence of the eligible ICD-9 code was defined as the ¨index diagnosis.¨ Patients were ineligible if they had any evidence of cancer within 6 months before the index diagnosis or if they had any evidence of gastrointestinal stromal tumor (ICD-9-CM 238.1) at any time. Continuous medical benefits for 6 months before the index diagnosis were required for eligibility of patients in the administrative dataset.

ICD=International Classification of Diseases.

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 20-23 and accompanying full Prescribing Information for CYRAMZA.

RAMUCIRUMAB + PACLITAXEL

THE FIRST AND ONLY FDA-APPROVED combination regimen included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with a CATEGORY 1 recommendation

for the treatment of locally advanced or metastatic gastric or GEJ adenocarcinoma in the second-line setting[1,6,7]

A PREFERRED OPTION[6,7]

CATEGORY 1 NCCN Guidelines® Recommendations:

Locally Advanced or Metastatic Gastric Adenocarcinoma*[6]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

Locally Advanced or Metastatic Esophagogastric Junction Adenocarcinoma†[7]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

CATEGORY 1: Based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate.

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INDICATION

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with **advanced or metastatic gastric** or **GEJ adenocarcinoma** with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 20-23 and accompanying full Prescribing Information for CYRAMZA.

CYRAMZA IS A HUMAN, MONOCLONAL ANTIBODY THAT SPECIFICALLY BLOCKS ACTIVATION OF VEGF RECEPTOR 2[1]

CYRAMZA BLOCKS MULTIPLE LIGANDS BY BINDING A SINGLE RECEPTOR[1]

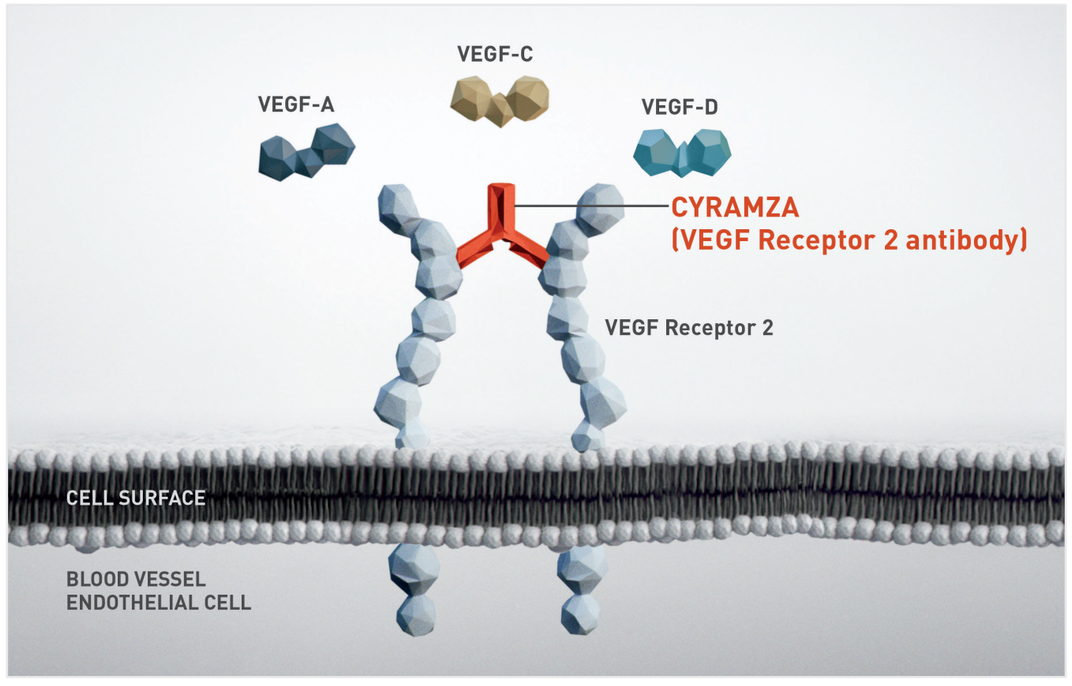

Diagram is not drawn to scale.

As demonstrated in nonclinical studies.
CYRAMZA inhibited angiogenesis in an *in vivo* animal model.

- CYRAMZA binds directly to the ligand-binding pocket of VEGF Receptor 2 to block the binding of VEGF-A, VEGF-C, and VEGF-D[1]

SELECT IMPORTANT SAFETY INFORMATION

Hemorrhage

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CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

CYRAMZA: TWO FDA-APPROVED TREATMENT REGIMENS FOR SECOND-LINE ADVANCED GASTRIC AND GEJ ADENOCARCINOMA[1]

CYRAMZA IS APPROVED AS MONOTHERAPY OR IN COMBINATION WITH PACLITAXEL[1]

LOCALLY ADVANCED OR METASTATIC GASTRIC OR GEJ ADENOCARCINOMA

REGARD MONOTHERAPY (N=355)		RAINBOW COMBINATION THERAPY (N=665)	
CYRAMZA + BSC (n=238)	**Placebo + BSC** (n=117)	**CYRAMZA + paclitaxel** (n=330)	**Placebo + paclitaxel** (n=335)
OVERALL SURVIVAL	MAJOR EFFICACY OUTCOME MEASURE	**OVERALL SURVIVAL**	
PFS	SUPPORTIVE EFFICACY OUTCOME MEASURES	**PFS, ORR**	

BSC=best supportive care; PFS=progression-free survival; ORR=objective response rate.

- In both trials, patients received treatment until disease progression or unacceptable toxicity[8,9]

INDICATION

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with **advanced or metastatic gastric** or **GEJ adenocarcinoma** with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

SELECT IMPORTANT SAFETY INFORMATION

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 20-23 and accompanying full Prescribing Information for CYRAMZA.

RAINBOW: THE PIVOTAL PHASE III TRIAL FOR CYRAMZA IN COMBINATION WITH PACLITAXEL (N=665)[1,8,10]

RAINBOW TRIAL DESIGN[1,8,10]

A large, multicenter, randomized, double-blind trial of locally advanced or metastatic gastric or GEJ adenocarcinoma patients previously treated with fluoropyrimidine- and platinum-containing chemotherapy*

LOCALLY ADVANCED OR METASTATIC GASTRIC/GEJ ADENOCARCINOMA (N=665)

- Progression during treatment or within 4 months after last dose of first-line fluoropyrimidine- and platinum-containing regimen
- ECOG PS 0-1

1:1 Randomization†

CYRAMZA + paclitaxel (n=330)
CYRAMZA 8 mg/kg days 1, 15
+ paclitaxel 80 mg/m^2
days 1, 8, 15
28-day cycle

Placebo + paclitaxel (n=335)
Placebo days 1, 15
+ paclitaxel 80 mg/m^2
days 1, 8, 15
28-day cycle

ECOG=Eastern Cooperative Oncology Group; PS=performance status.

*75% of patients randomized in the study received prior platinum/fluoropyrimidine combination therapy without anthracycline; 25% received platinum/fluoropyrimidine combination therapy with anthracycline.
†Stratification factors were geographic region, time to progression on first-line therapy (<6 months vs ≥6 months), and disease measurability (measurable vs nonmeasurable disease).

Major Efficacy Outcome Measure: Overall survival (OS)
Supportive Efficacy Outcome Measures: PFS, ORR

- Patients received treatment until disease progression or unacceptable toxicity[8]
  - If one study agent (either CYRAMZA/placebo or paclitaxel) was discontinued as a result of toxicity, then treatment with the other study agent was allowed to continue[10]

SELECT IMPORTANT SAFETY INFORMATION

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%) and in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

RAINBOW: DEMOGRAPHIC AND BASELINE CHARACTERISTICS WERE SIMILAR BETWEEN TREATMENT ARMS[1,8]

RAINBOW: DEMOGRAPHIC AND BASELINE CHARACTERISTICS[8,11]

	CYRAMZA + paclitaxel (n=330)	**Placebo** + paclitaxel (n=335)
Age, median (range)	**61 (25-83)**	**61 (24-84)**
Male	**69%**	**73%**
Ethnic origin*		
Caucasian	**63%**	**59%**
Asian	**33%**	**36%**
Black or other	**4%**	**4%**
Previous line of chemotherapy		
First-line	**100%**	**100%**
Adjuvant	**9%**	**10%**
ECOG PS		
0	**35%**	**43%**
1	**65%**	**57%**
Measurable disease	**81%**	**81%**
Location of primary tumor		
Gastric	**80%**	**79%**
GEJ	**20%**	**21%**

*By self-report.

SELECT IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

RAINBOW: TREATMENT ADMINISTERED PRIOR TO ENROLLMENT INCLUDED A NUMBER OF DIFFERENT REGIMENS[12]

RAINBOW: PRIOR CHEMOTHERAPY REGIMENS ACROSS TREATMENT ARMS[12]

Prior first-line treatment, n (%)		
CF	31	(9.4)
DCF	1	(0.3)
ECF	22	(6.7)
ECX	19	(5.8)
EOF	1	(0.3)
EOX	31	(9.4)
FLOX	3	(0.9)
FLP	11	(3.3)
FOLFOX4	16	(4.8)
FOLFOX6	8	(2.4)
FP	16	(4.8)
S1	18	(5.5)
S1/Cisplatin	50	(15.2)
XELOX	37	(11.2)
XP	36	(10.9)
Other	78	(23.6)

Prior adjuvant treatment, n (%)		
CF	3	(0.9)
ECF	2	(0.6)
ECX	1	(0.3)
FOLFIRI	2	(0.6)
FOLFOX4	1	(0.3)
FP	2	(0.6)
S1	8	(2.4)
S1/Cisplatin	2	(0.6)
XELOX	1	(0.3)
XP	1	(0.3)
Other	11	(3.3)

Note that patients may have received more than one chemotherapy regimen.

- 39 patients received trastuzumab as part of an anticancer treatment regimen prior to the study (20 patients in the CYRAMZA plus paclitaxel arm vs 19 patients in the placebo plus paclitaxel arm)[13]

SELECT IMPORTANT SAFETY INFORMATION

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforations was also increased in patients who received CYRAMZA plus paclitaxel (1.2%) as compared to patients who received placebo plus paclitaxel (0.3%). Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

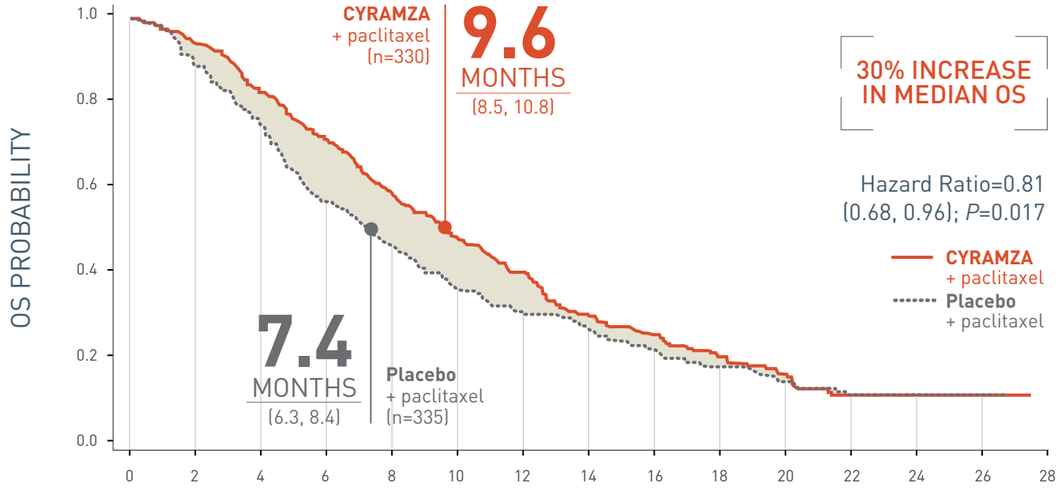
CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

CYRAMZA PLUS PACLITAXEL SIGNIFICANTLY EXTENDED OVERALL SURVIVAL[1]

RAINBOW OVERALL SURVIVAL: MEDIAN – MONTHS (95% CI)*[1]

MAJOR OUTCOME MEASURE



Number at Risk

CYRAMZA + paclitaxel	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
Placebo + paclitaxel	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

*Intent-to-treat (ITT) population.

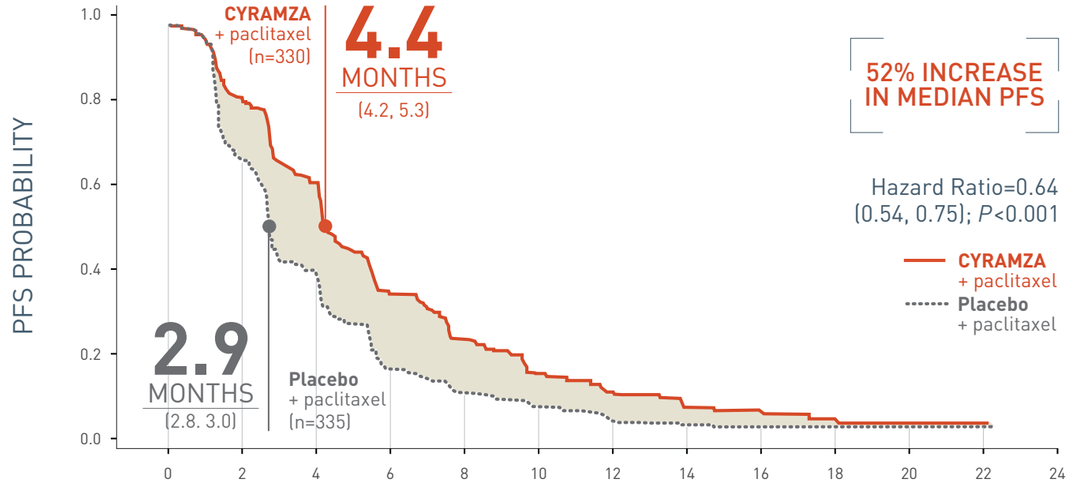
- The percentage of deaths at the time of analysis was 78% (256 patients) and 78% (260 patients) in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively[1]

The phase III RAINBOW trial evaluated the efficacy and safety of CYRAMZA plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were ECOG PS 0 or 1. Prior to enrollment, 97% of patients had progressed during treatment or within 4 months after the last dose of first-line chemotherapy for metastatic disease. Twenty-five percent of patients had received anthracycline in combination with platinum/fluoropyrimidine therapy, while 75% did not. Patients were randomized 1:1 to CYRAMZA 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of each 28-day cycle. Patients in both arms received paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.[1,14]

CYRAMZA PLUS PACLITAXEL SIGNIFICANTLY DELAYED DISEASE PROGRESSION[1]

RAINBOW PROGRESSION-FREE SURVIVAL: MEDIAN – MONTHS (95% CI)*[1,8]

SUPPORTIVE OUTCOME MEASURE



Number at Risk

CYRAMZA + paclitaxel	330	259	188	104	70	43	28	15	11	7	3	1	-
Placebo + paclitaxel	335	214	124	50	34	21	12	8	5	3	3	3	-

*ITT population.

- The percentage of events at the time of analysis was 85% (279 patients) and 88% (296 patients) in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively[1]

SELECT IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

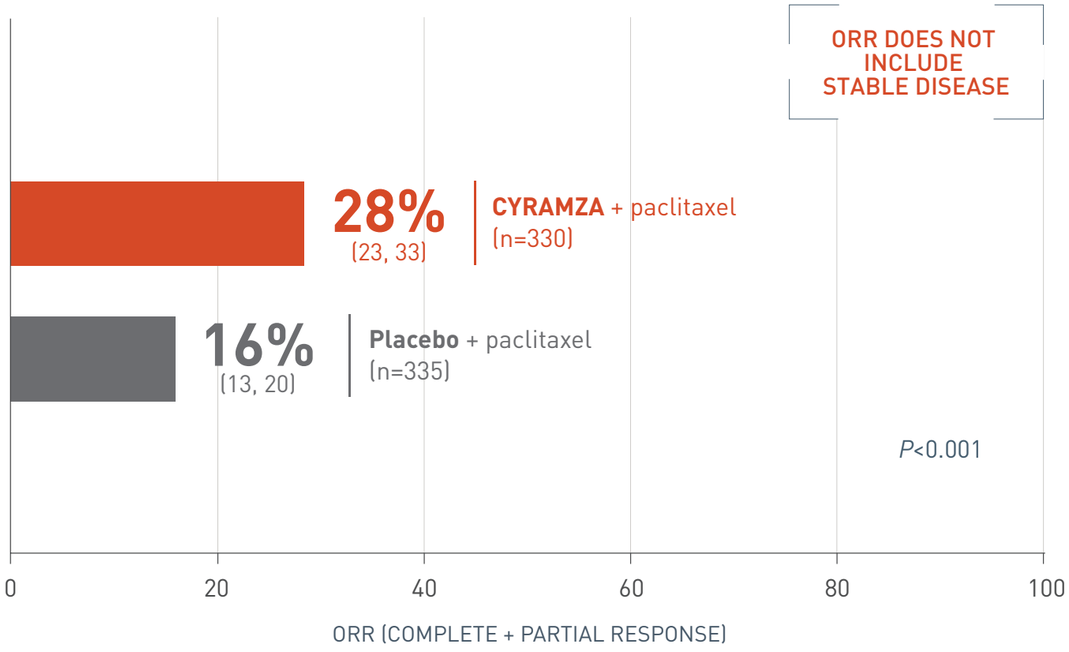
TAKE ACTION

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 20-23 and accompanying full Prescribing Information for CYRAMZA.

SIGNIFICANTLY MORE PATIENTS RESPONDED TO CYRAMZA COMBINED WITH PACLITAXEL THAN TO PACLITAXEL[8]

RAINBOW OBJECTIVE RESPONSE RATE: PERCENT OF PATIENTS (95% CI)*[1]

SUPPORTIVE OUTCOME MEASURE



*ITT population. ORR was defined as complete plus partial response. Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[8]

The phase III RAINBOW trial evaluated the efficacy and safety of CYRAMZA plus paclitaxel vs placebo plus paclitaxel in patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- and platinum-containing chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were ECOG PS 0 or 1. Prior to enrollment, 97% of patients had progressed during treatment or within 4 months after the last dose of first-line chemotherapy for metastatic disease. Twenty-five percent of patients had received anthracycline in combination with platinum/fluoropyrimidine therapy, while 75% did not. Patients were randomized 1:1 to CYRAMZA 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of each 28-day cycle. Patients in both arms received paclitaxel 80 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.[1,14]

ADVERSE REACTION PROFILE FOR CYRAMZA MONOTHERAPY[1]

REGARD: ADVERSE REACTIONS OCCURRING WITH CYRAMZA AT INCIDENCE RATE ≥5% AND ≥2% HIGHER THAN PLACEBO[1]

	All Grades		Grade 3/4	
Adverse Reactions	**CYRAMZA** 8 mg/kg (n=236)	Placebo (n=115)	**CYRAMZA** 8 mg/kg (n=236)	Placebo (n=115)
Hypertension	**16%**	8%	**8%**	3%
Diarrhea	**14%**	9%	**1%**	2%
Headache	**9%**	3%	**0%**	0%
Hyponatremia	**6%**	2%	**3%**	1%

- 14% of patients in the REGARD trial received CYRAMZA for at least 6 months[1]
  - The median duration of exposure was 8 weeks

SELECT IMPORTANT SAFETY INFORMATION

- The most common serious adverse events with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo. Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients in the REGARD trial were: neutropenia (4.7% CYRAMZA vs 0.9% placebo), epistaxis (4.7% CYRAMZA vs 0.9% placebo), rash (4.2% CYRAMZA vs 1.7% placebo), intestinal obstruction (2.1% CYRAMZA vs 0% placebo), and ATEs (1.7% CYRAMZA vs 0% placebo). Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions (IRRs). In the REGARD trial, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in the REGARD trial was 0.8% and the rate of IRRs was 0.4%.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 20-23 and accompanying full Prescribing Information for CYRAMZA.

ADVERSE REACTION PROFILE FOR CYRAMZA IN COMBINATION WITH PACLITAXEL[1,15]

RAINBOW: ADVERSE REACTIONS OCCURRING AT INCIDENCE RATE ≥5% AND A ≥2% DIFFERENCE BETWEEN ARMS IN PATIENTS RECEIVING CYRAMZA IN COMBINATION WITH PACLITAXEL[1]

	All Grades		Grade 3/4	
Adverse Reactions	CYRAMZA + paclitaxel (n=327)	Placebo + paclitaxel (n=329)	CYRAMZA + paclitaxel (n=327)	Placebo + paclitaxel (n=329)
Fatigue/Asthenia	57%	44%	12%	6%
Neutropenia	54%	31%	41%	19%
Diarrhea	32%	23%	4%	2%
Epistaxis	31%	7%	0%	0%
Hypertension	25%	6%	15%	3%
Peripheral edema	25%	14%	2%	1%
Stomatitis	20%	7%	1%	1%
Proteinuria	17%	6%	1%	0%
Thrombocytopenia	13%	6%	2%	2%
Hypoalbuminemia	11%	5%	1%	1%
Gastrointestinal hemorrhage events	10%	6%	4%	2%

- The incidence of febrile neutropenia was 2.4% and 1.2% in the CYRAMZA plus paclitaxel and placebo plus paclitaxel treatment arms, respectively[1,15]
- 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors vs 8.5% of patients treated with paclitaxel[1,16]
- In the RAINBOW trial, 28% of patients in the CYRAMZA plus paclitaxel treatment arm received CYRAMZA for at least 6 months[1]
  - In the CYRAMZA plus paclitaxel treatment arm, the median duration of exposure to CYRAMZA was 18 weeks and to paclitaxel was 17.7 weeks. In the placebo plus paclitaxel treatment arm, the median duration of exposure was 12 weeks for each[1,17]

SELECT IMPORTANT SAFETY INFORMATION

- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 20-23 and accompanying full Prescribing Information for CYRAMZA.

ADDITIONAL ADVERSE REACTIONS TO CONSIDER FOR CYRAMZA AS AN ANTIANGIOGENIC THERAPY OBSERVED IN THE REGARD AND RAINBOW TRIALS[1]

REGARD AND RAINBOW: ADDITIONAL ADVERSE REACTIONS[1,18,19]

	REGARD		RAINBOW	
Adverse Reactions	CYRAMZA (n=236)	Placebo (n=115)	CYRAMZA + paclitaxel (n=327)	Placebo + paclitaxel (n=329)
Grades 3/4 events				
Severe hypertension	8%	3%	15%	3%
Severe bleeding	3.4%	2.6%	4.3%	2.4%
All grades				
Proteinuria	8%*	3%*	17%	6%
Arterial thromboembolic events	1.7%	0%	1.8%	1.5%
Gastrointestinal perforations	0.8%	0.9%	1.2%	0.3%
Infusion-related reactions	0.4%	1.7%	5.8%	3.6%

*Lab assessment.

SELECT IMPORTANT SAFETY INFORMATION

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

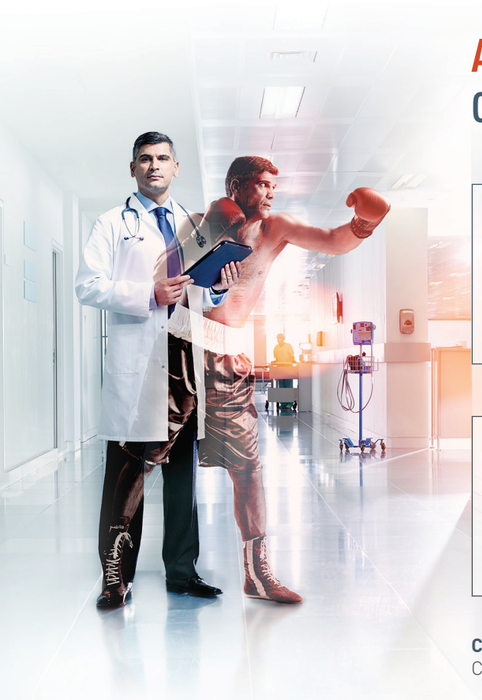
CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

RAMUCIRUMAB + PACLITAXEL

THE FIRST AND ONLY FDA-APPROVED combination regimen included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with a CATEGORY 1 recommendation

for the treatment of locally advanced or metastatic gastric or GEJ adenocarcinoma in the second-line setting[1,6,7]



A PREFERRED OPTION[6,7]

CATEGORY 1 NCCN Guidelines® Recommendations:

Locally Advanced or Metastatic Gastric Adenocarcinoma*[6]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

Locally Advanced or Metastatic Esophagogastric Junction Adenocarcinoma†[7]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

CATEGORY 1: Based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate.

*NCCN Guidelines for Gastric Cancer V.3.2015 recommend single-agent ramucirumab (CYRAMZA) and ramucirumab (CYRAMZA) in combination with paclitaxel as preferred second-line treatment options for locally advanced or metastatic gastric adenocarcinoma.

†NCCN Guidelines for Esophageal and Esophagogastric Junction (EGJ) Cancers V.3.2015 recommend single-agent ramucirumab (CYRAMZA) and ramucirumab (CYRAMZA) in combination with paclitaxel as preferred second-line treatment options for locally advanced or metastatic EGJ adenocarcinoma.

INDICATION

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with **advanced or metastatic gastric** or **GEJ adenocarcinoma** with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 20-23 and accompanying full Prescribing Information for complete safety information for CYRAMZA.

CYRAMZA + PACLITAXEL: EFFICACY OVERVIEW[1]

MEDIAN OS

Major Outcome Measure (95% CI)

CYRAMZA + paclitaxel (n=330): **9.6** MONTHS (8.5, 10.8)

VS

Placebo + paclitaxel (n=335): **7.4** MONTHS (6.3, 8.4)

Hazard ratio=0.81 [0.68, 0.96]; *P*=0.017

MEDIAN PFS

Supportive Outcome Measure (95% CI)

CYRAMZA + paclitaxel (n=330): **4.4** MONTHS (4.2, 5.3)

VS

Placebo + paclitaxel (n=335): **2.9** MONTHS (2.8, 3.0)

Hazard ratio=0.64 (0.54, 0.75); *P*<0.001

ORR

Supportive Outcome Measure (95% CI)

CYRAMZA + paclitaxel (n=330): **28%** (23, 33)

VS

Placebo + paclitaxel (n=335): **16%** (13, 20)

P<0.001

SELECT IMPORTANT SAFETY INFORMATION

The labeling for CYRAMZA contains **Boxed Warnings for:** hemorrhage, including severe and sometimes fatal events; gastrointestinal (GI) perforation, a potentially fatal event; and impaired wound healing. CYRAMZA should be permanently discontinued in patients who experience severe bleeding or a GI perforation. CYRAMZA should be withheld prior to surgery and discontinued if a patient develops wound healing complications. CYRAMZA contains **additional Warnings and Precautions** for arterial thromboembolic events, hypertension, infusion-related reactions, clinical deterioration in patients with Child-Pugh B or C cirrhosis, reversible posterior leukoencephalopathy syndrome, proteinuria including nephrotic syndrome, thyroid dysfunction, and embryofetal toxicity. In study 2, **the most common adverse reactions** observed in patients treated with CYRAMZA plus paclitaxel at a rate of ≥30% and ≥2% higher than placebo plus paclitaxel were fatigue (57% vs 44%), neutropenia (54% vs 31%), diarrhea (32% vs 23%), and epistaxis (31% vs 7%). **The most common serious adverse events** with CYRAMZA in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

PatientOne

CONTACT LILLY PATIENTONE FOR INFORMATION ON PATIENT ASSISTANCE PROGRAMS

The Lilly PatientOne program is committed to helping eligible patients access support programs for their prescribed Lilly Oncology medications. It aims to address both financial and coverage issues for qualified uninsured, underinsured, and insured patients who are prescribed a Lilly Oncology product.

Lilly PatientOne strives to offer resources, ranging from benefits investigations to financial assistance and appeals information, that provide reliable and individualized support for eligible patients.

SERVICES OFFERED BY THIS PROGRAM INCLUDE:

Insurance expertise
- Coding and billing information
- Payment methodologies and allowables
- Payer policy information

Patient Assistance Program*
- Drug replacement for eligible patients

*Product provided free of charge to eligible patients currently through the Lilly PatientOne Patient Assistance Program will be provided by the Lilly Cares Foundation, an independent non-profit 501(c)(3) organization that helps eligible patients obtain certain products listed in this application free of charge and PatientOne will collect information on behalf of the Lilly Cares Foundation for that purpose. All determinations of eligibility will be made by the Lilly Cares Foundation.

Patient financial assistance
- Information about co-pay assistance foundations
- Lilly PatientOne Co-Pay Program—patients pay no more than $25—to assist eligible patients with co-pay and coinsurance costs for prescribed Lilly Oncology products where available†

†This offer is invalid for patients whose prescription claims are eligible to be reimbursed, in whole or in part, by any governmental program. For more information, including co-pay program terms and conditions, please visit **www.LillyPatientOne.com**.

Reimbursement assistance for eligible Lilly Oncology products for an approved diagnosis
- Eligibility determination
- Benefits investigation
- Prior authorization
- Evaluation of other funding options

Denied claim appeals
- Appeals status if requested
- Denied claims appeals templates, forms, and checklists

For more information, please visit **www.LillyPatientOne.com** or call Lilly PatientOne at **1-866-4PatOne (1-866-472-8663)** Monday–Friday, 9 am–7 pm ET.

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 20-23 and accompanying full Prescribing Information for CYRAMZA.

REFERENCES

1. CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2015.
2. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev.* 2010 Mar 17;(3):CD004064.
3. National Cancer Institute. Surveillance, Epidemiology, and End Results Web site. http://seer.cancer.gov. Accessed March 7, 2016.
4. Hess LM, Michael D, Mytelka DS, et al. Chemotherapy treatment patterns, costs, and outcomes of patients with gastric cancer in the United States: a retrospective analysis of electronic medical record (EMR) and administrative claims data. *Gastric Cancer*. March 20, 2015 [Epub ahead of print] DOI 10.1007/s10120-015-0486-z.
5. Data on file, Eli Lilly and Company. ONC20160310a.
6. Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.3.2015. © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed February 1, 2016. To view the most recent and complete version of the guidelines, go online to http://www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.
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8. Wilke H, Muro K, Van Cutsem E, et al; for the RAINBOW Study Group. 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.
9. Fuchs CS, Tomasek J, Yong CJ, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014;383:31-39.
10. Supplement to: Wilke H, Muro K, Van Cutsem E, et al; for the RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastrooesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15(11):1224-1235.
11. Data on file, Eli Lilly and Company. ONC20141014a.
12. Data on file, Eli Lilly and Company. ONC09302014g
13. Data on file, Eli Lilly and Company. ONC09302014f.
14. Data on file, Eli Lilly and Company. ONC09302014b.
15. Data on file, Eli Lilly and Company. ONC09302014c.
16. Data on file, Eli Lilly and Company. ONC09302014d.
17. Data on file, Eli Lilly and Company. ONC20141014b.
18. Data on file, Eli Lilly and Company. ONC20140729a.
19. Data on file, Eli Lilly and Company. ONC09302014e.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

IMPORTANT SAFETY INFORMATION FOR CYRAMZA

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORATION, AND IMPAIRED WOUND HEALING

Hemorrhage: CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Gastrointestinal Perforation: CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications.

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage including severe and sometimes fatal hemorrhagic events. In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel in advanced gastric cancer, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. In study 3, which evaluated CYRAMZA plus docetaxel in metastatic non-small cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic anticoagulation or chronic therapy with NSAIDs or other antiplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from study 3; therefore, the risk of pulmonary hemorrhage in these groups of patients is unknown. In study 4, which evaluated CYRAMZA plus FOLFIRI in metastatic colorectal cancer, the incidence of severe bleeding was 2.5% for CYRAMZA plus FOLFIRI and 1.7% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia occurred in clinical trials including 1.7% of 236 patients who received CYRAMZA as a single agent for gastric cancer in study 1. Permanently discontinue CYRAMZA in patients who experience a severe ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA as a single agent (8%) as compared to placebo (3%), in patients receiving CYRAMZA plus paclitaxel (15%) as compared to placebo plus paclitaxel (3%), and in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (11%) as compared to placebo plus FOLFIRI (3%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every 2 weeks or more frequently as indicated during treatment. Temporarily suspend CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRRs)

- Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, IRRs occurred in 6 out of 37 patients (16%), including 2 severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue CYRAMZA for grade 3 or 4 IRRs.

Gastrointestinal Perforations

- CYRAMZA is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received CYRAMZA as a single agent in advanced gastric cancer clinical trials experienced gastrointestinal perforation. In study 2, the incidence of gastrointestinal perforation was 1.2% for CYRAMZA plus paclitaxel as compared to 0.3% for placebo plus paclitaxel. In study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel as compared to 0.3% for placebo plus docetaxel. In study 4, the incidence of gastrointestinal perforation was 1.7% for CYRAMZA plus FOLFIRI and 0.6% for placebo plus FOLFIRI. Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. CYRAMZA has not been studied in patients with serious or nonhealing wounds. CYRAMZA, an antiangiogenic therapy, has the potential to adversely affect wound healing. Discontinue CYRAMZA therapy in patients with impaired wound healing. Withhold CYRAMZA prior to surgery. Resume CYRAMZA following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed.

Clinical Deterioration in Child-Pugh B or C Cirrhosis

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- RPLS has been reported at a rate of <0.1% in clinical studies with CYRAMZA. Confirm the diagnosis of RPLS with MRI and discontinue CYRAMZA in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- In study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio for the development of worsening of proteinuria during CYRAMZA therapy. Withhold CYRAMZA for urine protein levels that are ≥2 g over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to <2 g over 24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- Monitor thyroid function during treatment with CYRAMZA. In study 4, the incidence of hypothyroidism reported as an adverse event was 2.6% in the CYRAMZA plus FOLFIRI-treated patients and 0.9% in the placebo plus FOLFIRI-treated patients.

Embryofetal Toxicity

- Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Most Common Adverse Reactions—Single Agent

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA and ≥2% higher than placebo in study 1 were hypertension (16% vs 8%; 8% vs 3%), diarrhea (14% vs 9%; 1% vs 2%), headache (9% vs 3%; 0% vs 0%), and hyponatremia (6% vs 2%; 3% vs 1%).

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

- The most common serious adverse events with CYRAMZA in study 1 were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients vs 8.7% of patients who received placebo.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA-treated patients vs placebo in study 1 were: neutropenia (4.7% vs 0.9%), epistaxis (4.7% vs 0.9%), rash (4.2% vs 1.7%), intestinal obstruction (2.1% vs 0%), and arterial thromboembolic events (1.7% vs 0%).
- Across clinical trials of CYRAMZA administered as a single agent, clinically relevant adverse reactions (including grade ≥3) reported in CYRAMZA-treated patients included proteinuria, gastrointestinal perforation, and infusion-related reactions. In study 1, according to laboratory assessment, 8% of CYRAMZA-treated patients developed proteinuria vs 3% of placebo-treated patients. Two patients discontinued CYRAMZA due to proteinuria. The rate of gastrointestinal perforation in study 1 was 0.8% and the rate of infusion-related reactions was 0.4%.

Most Common Adverse Reactions—Combination With Paclitaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus paclitaxel and ≥2% higher than placebo plus paclitaxel in study 2 were fatigue/asthenia (57% vs 44%; 12% vs 6%), neutropenia (54% vs 31%; 41% vs 19%), diarrhea (32% vs 23%; 4% vs 2%), epistaxis (31% vs 7%; 0% vs 0%), hypertension (25% vs 6%; 15% vs 3%), peripheral edema (25% vs 14%; 2% vs 1%), stomatitis (20% vs 7%; 1% vs 1%), proteinuria (17% vs 6%; 1% vs 0%), thrombocytopenia (13% vs 6%; 2% vs 2%), hypoalbuminemia (11% vs 5%; 1% vs 1%), and gastrointestinal hemorrhage events (10% vs 6%; 4% vs 2%).
- The most common serious adverse events with CYRAMZA plus paclitaxel in study 2 were neutropenia (3.7%) and febrile neutropenia (2.4%); 19% of patients treated with CYRAMZA plus paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA plus paclitaxel combination in 2% or more patients in study 2 were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of the CYRAMZA plus paclitaxel-treated patients in study 2 were sepsis (3.1% for CYRAMZA plus paclitaxel vs 1.8% for placebo plus paclitaxel) and gastrointestinal perforations (1.2% for CYRAMZA plus paclitaxel vs 0.3% for placebo plus paclitaxel).

Most Common Adverse Reactions—Combination With Docetaxel

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus docetaxel and ≥2% higher than placebo plus docetaxel in study 3 were neutropenia (55% vs 46%; 49% vs 40%), fatigue/asthenia (55% vs 50%; 14% vs 11%), stomatitis/mucosal inflammation (37% vs 19%; 7% vs 2%), epistaxis (19% vs 7%; <1% vs <1%), febrile neutropenia (16% vs 10%; 16% vs 10%), peripheral edema (16% vs 9%; 0% vs <1%), thrombocytopenia (13% vs 5%; 3% vs <1%), lacrimation increased (13% vs 5%; <1% vs 0%), and hypertension (11% vs 5%; 6% vs 2%).
- The most common serious adverse events with CYRAMZA plus docetaxel in study 3 were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA plus docetaxel-treated patients versus 37% in patients who received placebo plus docetaxel.
- In patients ≥65 years of age, there were 18 (8%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients <65 years of age, there were 13 (3%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 26 (6%) deaths for placebo plus docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA plus docetaxel-treated patients (9%) than in placebo plus docetaxel-treated patients (5%). The most common adverse events leading to treatment discontinuation of CYRAMZA in study 3 were infusion-related reaction (0.5%) and epistaxis (0.3%).
- For patients with nonsquamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA plus docetaxel compared to 6% overall incidence and 1% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of grade ≥3 pulmonary hemorrhage was 2% for CYRAMZA plus docetaxel compared to 12% overall incidence and 2% for grade ≥3 pulmonary hemorrhage for placebo plus docetaxel.

- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus docetaxel-treated patients in study 3 were hyponatremia (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (3.3% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

Most Common Adverse Reactions—Combination With FOLFIRI

- The most commonly reported adverse reactions (all grades; grade 3/4) occurring in ≥5% of patients receiving CYRAMZA plus FOLFIRI and ≥2% higher than placebo plus FOLFIRI in study 4 were diarrhea (60% vs 51%; 11% vs 10%), neutropenia (59% vs 46%; 38% vs 23%), decreased appetite (37% vs 27%; 2% vs 2%), epistaxis (33% vs 15%; 0% vs 0%), stomatitis (31% vs 21%; 4% vs 2%), thrombocytopenia (28% vs 14%; 3% vs <1%), hypertension (26% vs 9%; 11% vs 3%), peripheral edema (20% vs 9%; <1% vs 0%), proteinuria (17% vs 5%; 3% vs <1%), palmar-plantar erythrodysesthesia syndrome (13% vs 5%; 1% vs <1%), gastrointestinal hemorrhage events (12% vs 7%; 2% vs 1%), hypoalbuminemia (6% vs 2%; 1% vs 0%). Twenty percent of patients treated with CYRAMZA plus FOLFIRI received granulocyte colony-stimulating factors.
- The most common serious adverse events with CYRAMZA plus FOLFIRI were diarrhea (3.6%), intestinal obstruction (3.0%), and febrile neutropenia (2.8%).
- Treatment discontinuation of any study drug due to adverse reactions occurred more frequently in CYRAMZA plus FOLFIRI-treated patients (29%) than in placebo plus FOLFIRI-treated patients (13%). The most common adverse reactions leading to discontinuation of any component of CYRAMZA plus FOLFIRI as compared to placebo plus FOLFIRI were neutropenia (12.5% versus 5.3%) and thrombocytopenia (4.2% versus 0.8%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (1.5%) and gastrointestinal perforation (1.7%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA plus FOLFIRI-treated patients in study 4 consisted of gastrointestinal perforation (1.7% CYRAMZA plus FOLFIRI versus 0.6% for placebo plus FOLFIRI).
- Thyroid-stimulating hormone (TSH) was evaluated in 224 patients (115 CYRAMZA plus FOLFIRI-treated patients and 109 placebo plus FOLFIRI-treated patients) with normal baseline TSH levels. Patients received periodic TSH assessments until 30 days after the last dose of study treatment. Increased TSH was observed in 53 (46%) patients treated with CYRAMZA plus FOLFIRI compared with 4 (4%) patients treated with placebo plus FOLFIRI.

Drug Interactions

- No pharmacokinetic interactions were observed between ramucirumab and paclitaxel, between ramucirumab and docetaxel, or between ramucirumab and irinotecan or its active metabolite, SN-38.

Use in Specific Populations

- Pregnancy: Based on its mechanism of action, CYRAMZA can cause fetal harm. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. There are no available data on CYRAMZA use in pregnant women to inform any drug-associated risks. No animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and pediatric development, and to use effective contraception during CYRAMZA therapy and for at least 3 months following the last dose of CYRAMZA.
- Lactation: Because of the potential risk for serious adverse reactions in nursing infants from ramucirumab, advise women that breastfeeding is not recommended during treatment with CYRAMZA.
- Females of Reproductive Potential: Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

Please see accompanying full Prescribing Information for CYRAMZA, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing.

RB-P HCP ISI 17SEP2015

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

RAMUCIRUMAB + PACLITAXEL

THE FIRST AND ONLY FDA-APPROVED combination regimen included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) with a CATEGORY 1 recommendation

for the treatment of locally advanced or metastatic gastric or GEJ adenocarcinoma in the second-line setting[1,6,7]

A PREFERRED OPTION[6,7]

CATEGORY 1 NCCN Guidelines® Recommendations:

Locally Advanced or Metastatic Gastric Adenocarcinoma*[6]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

Locally Advanced or Metastatic Esophagogastric Junction Adenocarcinoma†[7]

- ✓ Single-agent ramucirumab
- ✓ Ramucirumab with paclitaxel

CATEGORY 1: Based upon high-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate.

*NCCN Guidelines for Gastric Cancer V.3.2015 recommend single-agent ramucirumab (CYRAMZA) and ramucirumab (CYRAMZA) in combination with paclitaxel as preferred second-line treatment options for locally advanced or metastatic gastric adenocarcinoma.

†NCCN Guidelines for Esophageal and Esophagogastric Junction (EGJ) Cancers V.3.2015 recommend single-agent ramucirumab (CYRAMZA) and ramucirumab (CYRAMZA) in combination with paclitaxel as preferred second-line treatment options for locally advanced or metastatic EGJ adenocarcinoma.

INDICATION

CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with **advanced or metastatic gastric** or **GEJ adenocarcinoma** with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.[1]

SELECT IMPORTANT SAFETY INFORMATION

Arterial Thromboembolic Events (ATEs)

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. In study 1, which evaluated CYRAMZA as a single agent in advanced gastric cancer, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In study 2, which evaluated CYRAMZA plus paclitaxel, the incidence of severe bleeding was 4.3% for CYRAMZA plus paclitaxel and 2.4% for placebo plus paclitaxel. Patients with gastric cancer receiving nonsteroid anti-inflammatory drugs (NSAIDs) were excluded from enrollment in studies 1 and 2; therefore, the risk of gastric hemorrhage in CYRAMZA-treated patients with gastric tumors receiving NSAIDs is unknown. Permanently discontinue CYRAMZA in patients who experience severe bleeding.

Please see Important Safety Information, including Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing on pages 20-23 and accompanying and full Prescribing Information for CYRAMZA.

CYRAMZA™
ramucirumab injection
10 mg/mL solution

TAKE ACTION

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