In EGFR mut+ mNSCLC

Find out why your patients with **exon 21 (L858R) substitution** may need additional treatment options[1,2]

EGFR=epidermal growth factor receptor; mNSCLC=metastatic non-small cell lung cancer; mut+=mutation-positive.

INDICATION

CYRAMZA, in combination with erlotinib, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

SELECT IMPORTANT SAFETY INFORMATION

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with NSCLC receiving therapeutic anticoagulation or with evidence of major airway invasion by cancer were excluded from REVEL. In addition, patients with NSCLC with a recent history of gross hemoptysis, those receiving chronic therapy with NSAIDs or other anti-platelet therapy other than once daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor cavitation were excluded from REVEL and RELAY; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

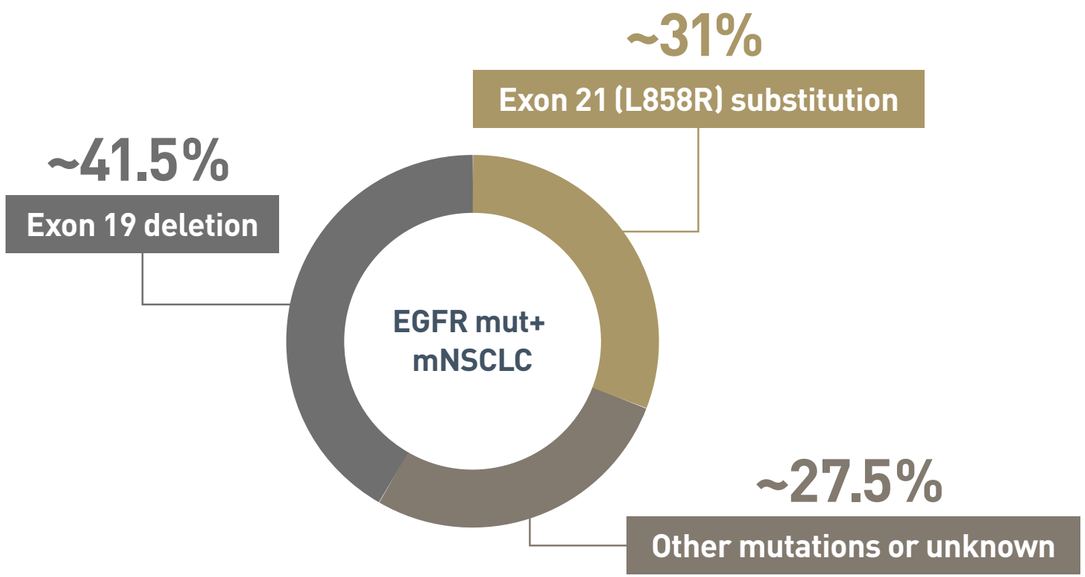
CYRAMZA®
ramucirumab injection
10 mg/mL solution

Please see Important Safety Information on pages 22–24 and full Prescribing Information for CYRAMZA.

Prevalence of EGFR mutations in mNSCLC

- In the United States, ~17% of patients with mNSCLC present with EGFR mutations[3]

Prevalence of EGFR Mutations in the United States[3]



- Increasing evidence suggests patients with the exon 21 mutation may have poorer outcomes than patients with exon 19 mutation[2]
- In patients with EGFR mut+ mNSCLC, the mutation type may impact outcomes[2]
- A different approach may need to be considered for your patients with exon 21 mutation[4]

Do you consider your patient's exon status when initiating treatment?

SELECT IMPORTANT SAFETY INFORMATION

Gastrointestinal Perforations

- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

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The first and only FDA-approved anti-VEGFR/EGFR-TKI combination therapy for EGFR mut+ mNSCLC[5]

Dual-mechanism inhibition

The RELAY trial demonstrated the utility of inhibiting the VEGFR and EGFR signaling pathways together, adding supportive evidence to previous nonclinical and clinical studies exploring this dual inhibition.[5,6]

- CYRAMZA binds directly to the ligand-binding pocket of VEGFR2 to block binding of VEGF-A, VEGF-C, and VEGF-D[5]*
- VEGF-A, VEGF-C, and VEGF-D have been shown to induce angiogenesis in preclinical studies[7,8]

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

TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor; VEGFR2=vascular endothelial growth factor receptor 2.

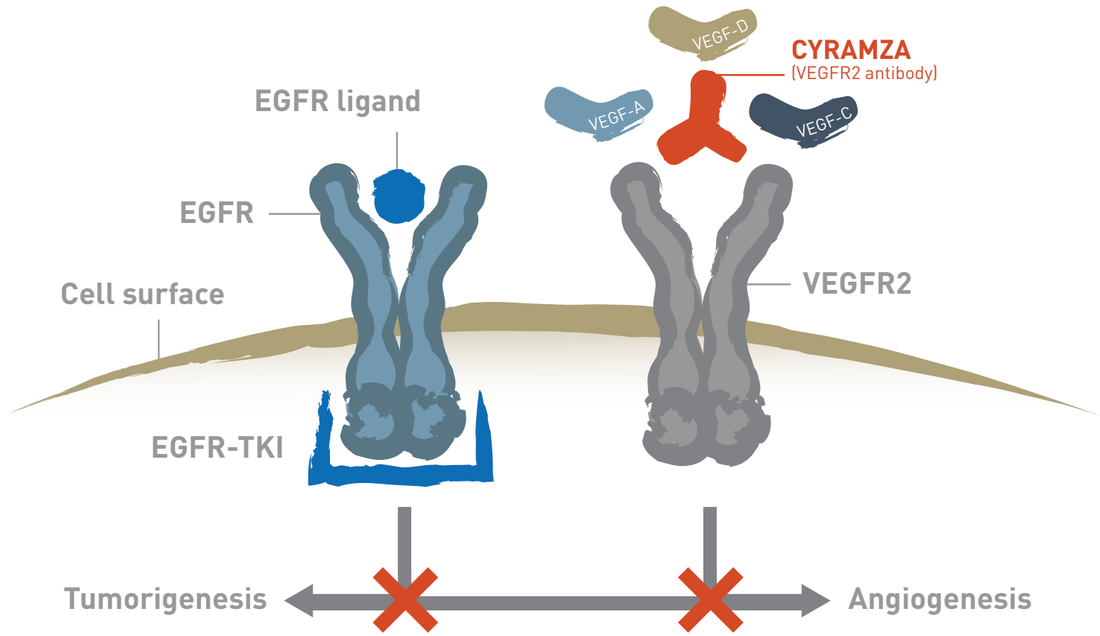
SELECT IMPORTANT SAFETY INFORMATION

Impaired Wound Healing

- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

CYRAMZA and erlotinib, respectively, inhibit VEGFR and EGFR signaling pathways, which are known to play a critical role in tumor growth, metastasis, and angiogenesis[5,9,10]

Dual-mechanism inhibition with CYRAMZA + erlotinib[5,9-13]



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The RELAY trial evaluated the efficacy and safety of CYRAMZA in EGFR mut+ mNSCLC[5,6]

A global, randomized, double-blind, placebo-controlled phase III trial of CYRAMZA + erlotinib as 1st-line therapy[5,6]

RELAY: N=449

CYRAMZA + erlotinib vs placebo + erlotinib

- **mNSCLC**
- **EGFR mut+ exon 21 (L858R) substitution or exon 19 deletion**
- **ECOG PS 0 or 1**
- **No CNS metastases**
- **No known EGFR T790M mutations at baseline**

1:1 RANDOMIZATION*

CYRAMZA 10 mg/kg Q2W via IV + **erlotinib** 150 mg/day orally (n=224)

Placebo Q2W + **erlotinib** 150 mg/day orally (n=225)

TREATMENT UNTIL DISEASE PROGRESSION OR UNACCEPTABLE TOXICITY

Major efficacy outcome measure
PFS
Supportive efficacy outcome measures
OS, ORR, DoR

*Stratification factors: Geographic region (East Asia vs other), gender, EGFR mutation (exon 21 substitution vs exon 19 deletion mutation), and local EGFR testing method (therascreen® and cobas® vs other PCR and sequencing-based methods).
ORR=CR + PR; ORR does not include stable disease.[6]

Prespecified analysis included, but was not limited to, evaluation of PFS outcomes by exon 21 and exon 19 mutations[6]

CNS=central nervous system; CR=complete response; DoR=duration of response; ECOG=Eastern Cooperative Oncology Group; IV=intravenous; ORR=overall response rate; OS=overall survival; PCR=polymerase chain reaction; PFS=progression-free survival; PR=partial response; PS=performance status; Q2W=every 2 weeks.

Please see Important Safety Information on pages 22–24 and full Prescribing Information for CYRAMZA.

Patient demographics and clinical characteristics of patients at baseline (ITT population)[6]

Parameter		CYRAMZA + erlotinib (n=224)	Placebo + erlotinib (n=225)
Age, years	Median (IQR)	65 (57–71)	64 (56–70)
	≥65 years	122 (54%)	111 (49%)
Sex	Female	141 (63%)	142 (63%)
	Male	83 (37%)	83 (37%)
Race†	Asian	172 (77%)	174 (77%)
	White	52 (23%)	48 (21%)
	Other	0	3 (1%)
Smoking status	Ever	64 (29%)	73 (32%)
	Never	134 (60%)	139 (62%)
	Unknown or missing	26 (12%)	13 (6%)
Geographical region‡	East Asia	166 (74%)	170 (76%)
	Other	58 (26%)	55 (24%)
ECOG PS	0	116 (52%)	119 (53%)
	1	108 (48%)	106 (47%)
Pathological diagnosis at study entry	Adenocarcinoma	215 (96%)	218 (97%)
	NSCLC not otherwise specified	9 (4%)	7 (3%)
Disease stage at diagnosis§	Stage IV	195 (87%)	189 (84%)
	Other	29 (13%)	36 (16%)
EGFR mutation type at randomization (eCRF)	Exon 21 (L858R) substitution	99 (44%)	105 (47%)
	Exon 19 deletion	123 (55%)	120 (53%)
	Missing	1 (<1%)	0
	Other	1 (<1%)	0
EGFR testing method	therascreen® or cobas®	96 (43%)	101 (45%)
	Other PCR and sequencing-based methods	127 (57%)	124 (55%)

†Other included American Indian or Alaska Native, black or African-American, or missing; data were missing for 1 patient in the placebo + erlotinib group.
‡East Asia includes South Korea, Hong Kong, Japan, and Taiwan; other includes Canada, France, Germany, Italy, Romania, Spain, Turkey, the United States, and the United Kingdom.
§All patients were required to have stage IV NSCLC at study entry; patients with recurrent metastatic disease were permitted as long as the adjuvant or neoadjuvant therapy was completed ≥12 months prior to development of metastatic disease; previous adjuvant or neoadjuvant therapy was not required; at study entry, all patients (as per inclusion criteria) had metastatic stage IV disease (195 [87%] of 224 in the CYRAMZA + erlotinib group vs 191 [85%] of 225 in the placebo + erlotinib group) or recurrent metastatic stage IV disease (29 [13%] vs 34 [15%]).

eCRF=electronic case report form; IQR=interquartile range; ITT=intent-to-treat.

SELECT IMPORTANT SAFETY INFORMATION

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

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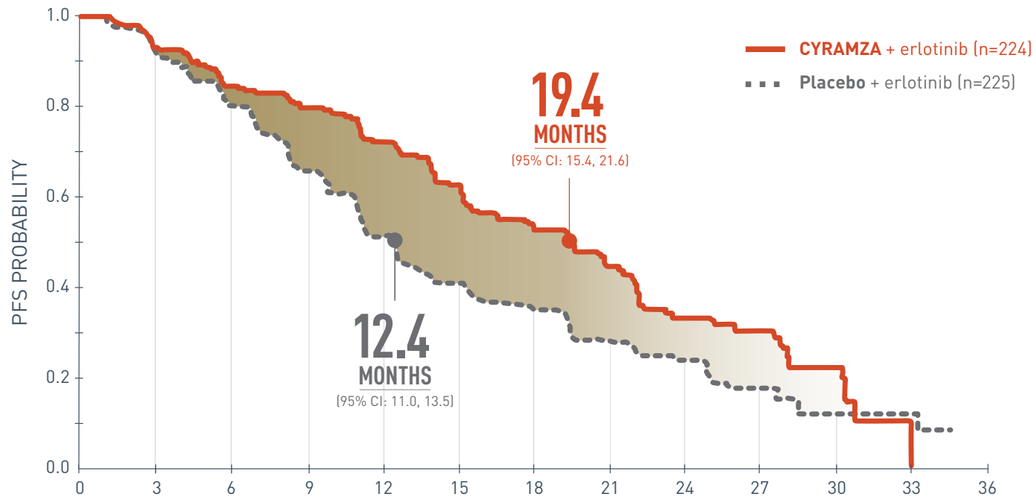
Adding CYRAMZA to erlotinib increased median PFS by 7 months vs placebo + erlotinib[5]

Major Outcome Measure: Median PFS[5]

ITT Population

HR=0.59 (95% CI: 0.46, 0.76); *P*<0.0001



NUMBER AT RISK												
CYRAMZA + erlotinib	224	196	170	154	133	103	69	49	32	20	10	1	0
Placebo + erlotinib	225	196	167	136	99	72	52	37	27	15	4	4	0

- The percentage of events at the time of analysis was 55% (122 patients) and 70% (158 patients) in the CYRAMZA + erlotinib and placebo + erlotinib treatment arms, respectively[5]
- 4 of 122 events in CYRAMZA-treated patients and 1 of 158 events in placebo-treated patients were deaths[5]
- The major efficacy outcome measure was PFS as assessed by the investigator (RECIST v1.1)[5]

Please see Important Safety Information on pages 22–24 and full Prescribing Information for CYRAMZA.

Supportive Outcome Measure: Interim OS[5]

HR=0.83 (95% CI: 0.53, 1.30)

CYRAMZA + erlotinib (n=224) vs **Placebo** + erlotinib (n=225)

- The interim OS data at the time of data cutoff for the primary analysis were immature[5,6]
- At the time of the final analysis of PFS, OS data were not mature as only 26% of planned events for the final analysis had occurred[5]
- A final OS analysis is planned when ≥300 events have occurred[6]

Supportive Outcome Measure ORR: Percentage of Patients[5,6]

76% (95% CI: 71, 82)
CYRAMZA + erlotinib (n=224)

VS

75% (95% CI: 69, 80)
Placebo + erlotinib (n=225)

- ORR was defined as CR + PR. ORR does not include stable disease[6]
- Disease progression and tumor response were assessed by investigators in accordance with RECIST v1.1[6]

ORR was a prespecified secondary efficacy endpoint. ORR was not powered or controlled for type 1 error, and treatment differences observed cannot be regarded as statistically significant.

CI=confidence interval; HR=hazard ratio; RECIST=Response Evaluation Criteria in Solid Tumors.

SELECT IMPORTANT SAFETY INFORMATION

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies, excluding RELAY, in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%. In 221 patients with NSCLC receiving CYRAMZA in combination with erlotinib in the RELAY study, the incidence of new or worsening hypertension was higher (45%), as was the incidence of Grade 3-5 hypertension (24%). Of the patients experiencing new or worsening hypertension in RELAY (N=100 CYRAMZA and erlotinib; N=27 placebo and erlotinib), 13% of those treated with CYRAMZA and erlotinib required initiation of 3 or more antihypertensive medications compared to 4% of patients treated with placebo and erlotinib.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

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Infusion-Related Reactions (IRR)

- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR 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. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1- 9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3- 4 IRR.

Prespecified subgroup analyses of the RELAY major outcome measure: PFS[14]

These analyses were not adjusted for multiplicity or powered to detect the effect of CYRAMZA + erlotinib within subgroups. Therefore, no conclusions of statistical significance can be drawn.

		CYRAMZA + erlotinib	Placebo + erlotinib	Favors CYRAMZA + erlotinib ← 0.2 — 1.0 — 1.6 → Favors placebo + erlotinib
Category	**Subgroup**	**Patients/ Events**	**Patients/ Events**	**HR (95% CI)**
Overall		224 / 122	225 / 158	0.640 (0.505, 0.812)
Gender	Male	83 / 43	83 / 64	0.505 (0.342, 0.747)
	Female	141 / 79	142 / 94	0.731 (0.541, 0.988)
Age	<65	102 / 57	114 / 92	0.534 (0.382, 0.745)
	≥65	122 / 65	111 / 66	0.771 (0.547, 1.088)
Geographical region*	East Asia	166 / 94	170 / 124	0.636 (0.485, 0.833)
	Other	58 / 28	55 / 34	0.605 (0.362, 1.010)
Race	Asian	172 / 97	174 / 127	0.638 (0.489, 0.833)
	Caucasian	52 / 25	48 / 29	0.618 (0.357, 1.070)
ECOG PS at baseline	0	116 / 51	119 / 77	0.584 (0.409, 0.833)
	1	108 / 71	106 / 81	0.671 (0.487, 0.925)
Smoking history	Ever	64 / 32	73 / 55	0.579 (0.373, 0.899)
	Never	134 / 74	139 / 91	0.694 (0.510, 0.946)
	Unknown	26 / 16	13 / 12	0.237 (0.099, 0.565)
Disease stage at diagnosis	Stage IV	195 / 111	189 / 135	0.622 (0.483, 0.801)
	Other	29 / 11	34 / 21	0.735 (0.351, 1.540)
Liver metastases at baseline	Yes	21 / 12	24 / 17	0.480 (0.226, 1.020)
	No	203 / 110	201 / 141	0.652 (0.508, 0.838)
EGFR mutation type	Exon 21 (L858R) substitution	99 / 58	105 / 74	0.618 (0.437, 0.874)
	Exon 19 deletion	123 / 64	120 / 84	0.651 (0.469, 0.903)
EGFR testing method	therascreen®/ cobas®	96 / 46	101 / 74	0.397 (0.271, 0.581)
	Other†	128 / 76	124 / 84	0.873 (0.639, 1.192)

*East Asia includes South Korea, Hong Kong, Japan, and Taiwan, and Other includes Canada, France, Germany, Italy, Romania, Spain, Turkey, the United States, and the United Kingdom.
†Testing method for 1 patient was missing on the CRF. Patient was stratified by other PCR and sequencing-based method in IWRS.
Other trademarks are the property of their respective owners.
CRF=case report form; IWRS=interactive web-response system.

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Median PFS outcomes for patients with exon 21 (L858R) substitution and exon 19 deletion were consistent with the ITT population[6]

Prespecified Subgroup Analysis: Median PFS[6]

Exon 19

Unstratified HR=0.65 (95% CI: 0.47, 0.90)

19.6 MONTHS (95% CI: 15.1, 22.2)
CYRAMZA + erlotinib (n=123)

VS

12.5 MONTHS (95% CI: 11.1, 15.3)
Placebo + erlotinib (n=120)

- The percentage of events at the time of analysis was 52.0% (64 patients) and 70.0% (84 patients) in the CYRAMZA + erlotinib and placebo + erlotinib treatment arms, respectively[6]
- 2 of 64 events in CYRAMZA-treated patients and 0 of 84 events in placebo-treated patients were deaths[15]

The RELAY trial was not adequately powered or error controlled for subgroup analysis. Treatment differences observed in this subgroup cannot be regarded as statistically significant.

SELECT IMPORTANT SAFETY INFORMATION

Worsening of Pre-existing Hepatic Impairment

- 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.
- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatorenal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

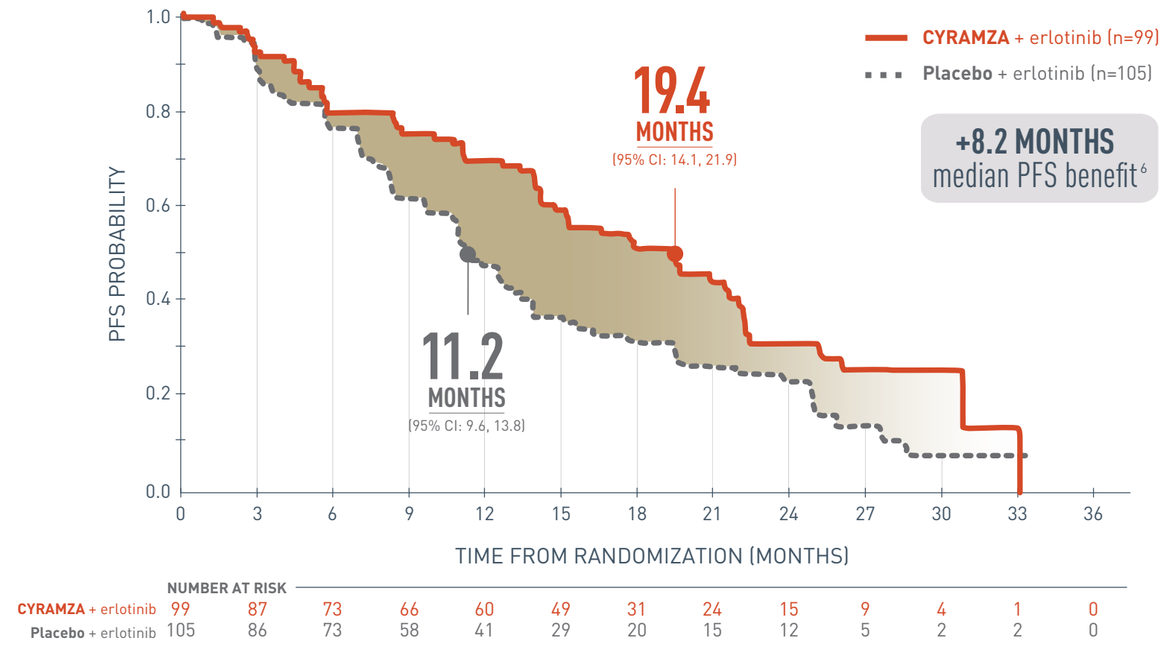
Please see Important Safety Information on pages 22–24 and full Prescribing Information for CYRAMZA.

CYRAMZA + erlotinib demonstrated clinically meaningful benefit in median PFS vs placebo + erlotinib in patients with exon 21 (L858R) substitution[6]

Prespecified Subgroup Analysis: Median PFS[6,15]

Exon 21

Unstratified HR=0.62 (95% CI: 0.44, 0.87)



- The percentage of events at the time of analysis was 58.6% (58 patients) and 70.5% (74 patients) in the CYRAMZA + erlotinib and placebo + erlotinib treatment arms, respectively[15]
- 2 of 58 events in CYRAMZA-treated patients and 1 of 74 events in placebo-treated patients were deaths[15]

The RELAY trial was not adequately powered or error controlled for subgroup analysis. Treatment differences observed in this subgroup cannot be regarded as statistically significant.

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The overall safety profile of CYRAMZA + erlotinib was consistent with that of its individual components[5,6]

Adverse reactions occurring in ≥5% of patients with a ≥2% difference between arms[5]

Adverse Reactions	CYRAMZA + erlotinib (n=221)		Placebo + erlotinib (n=225)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Infections				
Infections*†	81	17	76	7
Vascular				
Hypertension	45	24	12	5
Gastrointestinal				
Diarrhea	70	7	71	1
Stomatitis	42	2	36	1
Gastrointestinal hemorrhage‡	10	1	3	<1
Gingival bleeding	9	0	1	0
Renal and Urinary				
Proteinuria‡	34	3	8	0
Skin and Subcutaneous Tissue				
Alopecia	34	N/A§	20	N/A§
Respiratory, Thoracic, and Mediastinal				
Epistaxis	34	0	12	0
Pulmonary hemorrhage‡‖	7	<1	2	<1
General				
Peripheral edema	23	<1	4	0
Nervous System				
Headache	15	<1	7	0

*Includes all preferred terms that are part of the System Organ Class Infections and Infestations. Most common (≥1%) Grade ≥3 infections and frequencies for CYRAMZA with erlotinib compared to placebo with erlotinib, respectively, include pneumonia (3% versus 0%), cellulitis (1% versus 0%), paronychia (4% versus 3%), skin infection (1% versus 0%), and urinary tract infection (1% versus 0%).
†Includes 3 fatal events in the CYRAMZA arm.
‡Gastrointestinal hemorrhage, proteinuria, and pulmonary hemorrhage are consolidated terms.
§Grade ≥3 does not exist in Common Toxicity Criteria for Adverse Events.
‖Includes 1 fatal event in the CYRAMZA arm.
N/A=not applicable.

- The most common serious adverse reactions in patients who received CYRAMZA with erlotinib were pneumonia (3.2%), cellulitis (1.8%), and pneumothorax (1.8%).
- Treatment discontinuation of all study drugs due to adverse reactions occurred in 13% of CYRAMZA with erlotinib-treated patients, with increased alanine aminotransferase (1.4%) and paronychia (1.4%) being the most common. The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (8.6%) and hyperbilirubinemia (6%).

Please see Important Safety Information on pages 22–24 and full Prescribing Information for CYRAMZA.

Laboratory abnormalities worsening from baseline in ≥20% (all grades) of patients receiving CYRAMZA + erlotinib with a difference between arms of ≥2%[5]

Laboratory Abnormality	CYRAMZA + erlotinib¶		Placebo + erlotinib¶	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
Chemistry				
Alanine aminotransferase increased	74	11	60	13
Aspartate aminotransferase increased	71	6	47	4
Alkaline phosphatase increased	25	<1	16	1
Hypokalemia	24	5	18	2
Hematology				
Anemia	42	5	25	2
Thrombocytopenia	41	3	12	3
Neutropenia	33	7	21	4

¶The denominator used to calculate the incidence varied, based on the number of patients with a baseline, and at least 1 on-study laboratory measurement: CYRAMZA-treated patients (range 215–218 patients) and placebo-treated patients (range 224–225 patients).

ECOG PS

- In the RELAY trial of patients with EGFR mut+ mNSCLC, 92% (207/224) of patients maintained ECOG PS of 0 or 1 while on treatment with CYRAMZA + erlotinib vs 95% (214/225) of patients on placebo + erlotinib[16]

At baseline, approximately 52% of patients in the RELAY trial had an ECOG PS of 0 and approximately 48% of patients had an ECOG PS of 1.[5,6]

Time to deterioration in ECOG PS was a prespecified exploratory analysis. The RELAY trial was not powered to detect statistical differences between treatment groups in regard to time to deterioration in ECOG PS.

CNS metastases

- 0.9% of patients in the CYRAMZA + erlotinib arm (n=2/224) and 3.6% of patients in the placebo + erlotinib arm (n=8/225) developed CNS metastases[17]
  - **This was a prespecified subgroup analysis. Due to the small subset of patients, no conclusion can be made. The RELAY trial was not powered for subgroup analyses, and treatment differences observed cannot be regarded as statistically significant**
  - Patients with CNS metastases were excluded from the RELAY trial[5]

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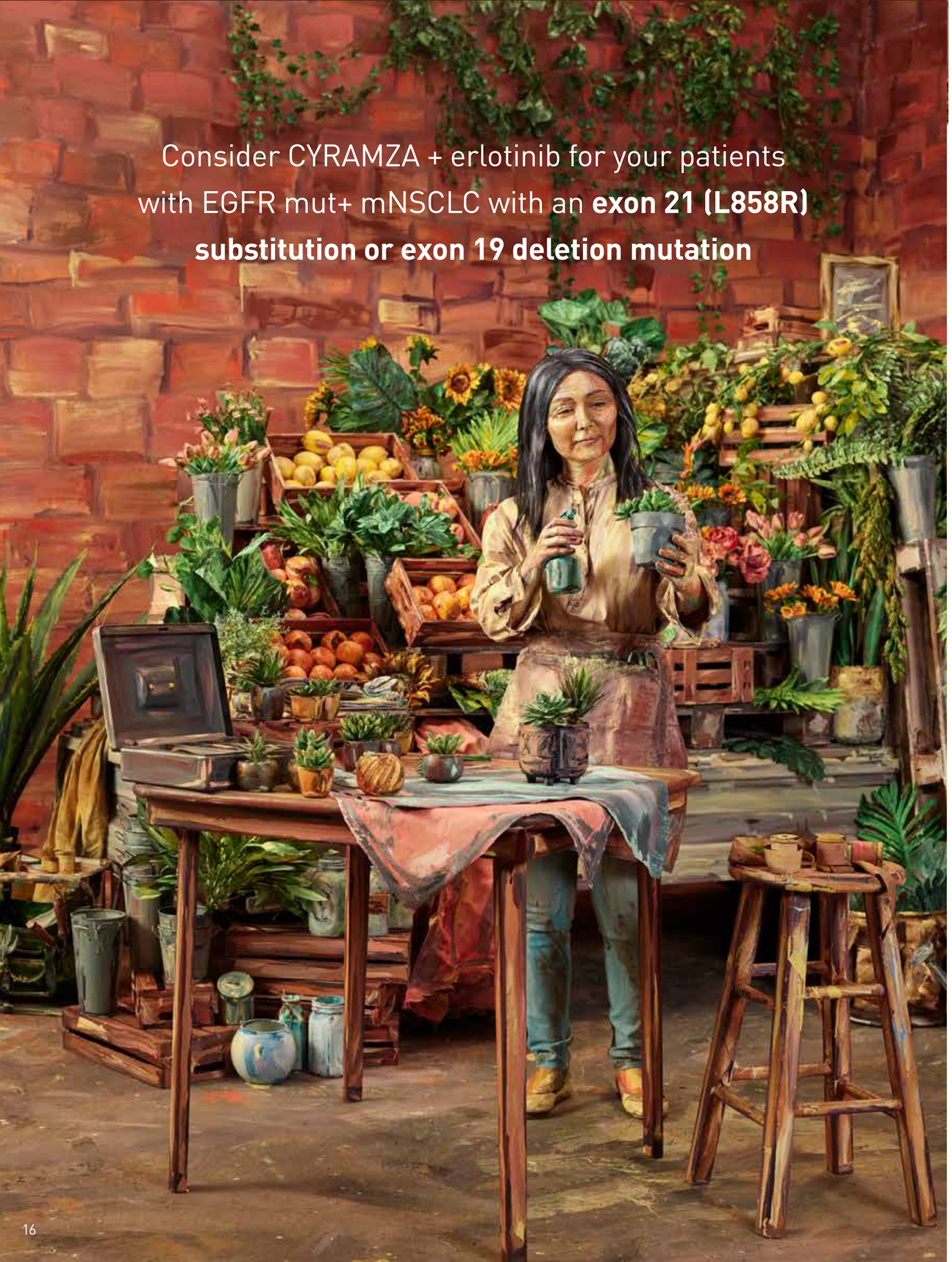

This is a newly diagnosed patient with

EGFR mut+ mNSCLC[5,6]*

- She has an exon 21 substitution
- She had no presence of CNS metastases at diagnosis
- She has an ECOG PS of 1
- She wants to extend her time on an EGFR-TKI–based therapy and delay her disease progression

This patient may be the right candidate for

1L CYRAMZA + erlotinib[5,6]

*Hypothetical patient example.

SELECT IMPORTANT SAFETY INFORMATION

Posterior Reversible Encephalopathy Syndrome (PRES)

- PRES (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported in <0.1% of 2137 patients with various cancers treated with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.
- Permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

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Dosing for the RELAY regimen: An IV infusion of CYRAMZA every 2 weeks in combination with oral once-daily erlotinib[5]

Recommended dose of CYRAMZA for EGFR mut+ mNSCLC[5]

Treatment Regimen	Interval	Dosage	Infusion Time
CYRAMZA	Every 2 weeks	10 mg/kg	60 minutes* If the first infusion of CYRAMZA is tolerated, all subsequent CYRAMZA infusions may be administered over 30 minutes
Erlotinib†	Once daily	150 mg	N/A

*For IV infusion only. Do not administer as an IV push or bolus. Continue CYRAMZA until disease progression or unacceptable toxicity. In the event of a Grade 1 or 2 IRR, reduce infusion rate by 50%.
†Refer to the Prescribing Information for erlotinib for additional dosing information.

CYRAMZA administration[5]

- Prior to each CYRAMZA infusion, premedicate all patients with an IV histamine-1 receptor antagonist (eg, diphenhydramine hydrochloride)
- For patients who have experienced a Grade 1 or 2 IRR, premedicate with a histamine-1 receptor antagonist, dexamethasone (or equivalent), and acetaminophen prior to each CYRAMZA infusion
- Supplied as either 100 mg/10 mL or 500 mg/50 mL (10 mg/mL) solution, single-dose vials

IRR=infusion-related reaction.

Dose modifications for CYRAMZA[5]

ADVERSE REACTION	SEVERITY*	DOSAGE MODIFICATION
Hemorrhage	Grade 3 or 4	• **Permanently discontinue CYRAMZA**
Gastrointestinal perforation	All Grades	• **Permanently discontinue CYRAMZA**
Wound healing complications	All Grades	• **Withhold CYRAMZA** for 28 days prior to elective surgery. Resume CYRAMZA no sooner than 2 weeks after surgery and until adequate wound healing • The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established
Arterial thromboembolic events	All Grades	• **Permanently discontinue CYRAMZA**
Hypertension	Severe hypertension	• **Withhold CYRAMZA** until controlled with medical management
	Severe hypertension that cannot be controlled with antihypertensive therapy	• **Permanently discontinue CYRAMZA**
IRR	Grade 1 or 2 IRR	• **Reduce the infusion rate of CYRAMZA by 50%**
	Grade 3 or 4 IRR	• **Permanently discontinue CYRAMZA**
PRES	All Grades	• **Permanently discontinue CYRAMZA**
Proteinuria	First occurrence of increased urine protein levels greater than or equal to 2 g per 24 hours	• **Withhold CYRAMZA** until urine protein level is less than 2 g per 24 hours • **Resume CYRAMZA at a reduced dose:** — Reduce 10 mg dose to 8 mg
	Reoccurrence of urine protein level greater than 2 g per 24 hours following initial dose reduction	• **Withhold CYRAMZA** until urine protein level is less than 2 g per 24 hours • **Resume CYRAMZA at a reduced dose:** — Reduce 8 mg dose to 6 mg
	Urine protein level greater than 3 g per 24 hours or in the setting of nephrotic syndrome	• **Permanently discontinue CYRAMZA**

*National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 used to identify adverse reactions.
PRES=posterior reversible encephalopathy syndrome.

SELECT IMPORTANT SAFETY INFORMATION

Infusion-Related Reactions (IRR)

- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR 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. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1- 9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3- 4 IRR.

CYRAMZA®
ramucirumab injection
10 mg/mL solution

Please see Important Safety Information on pages 22–24 and full Prescribing Information for CYRAMZA.

About 88% of insured* patients with lung cancer pay $0 per dose of CYRAMZA, with the remaining paying an average of $1,379.21 per dose†

For the most accurate information, encourage patients to talk to their insurance provider for details of their plan.

What your Medicare patients pay for CYRAMZA will depend on what type of Medicare coverage they have. Out-of-pocket costs can vary throughout the year depending on which phase of the Medicare benefit your patients are currently in.

What your patients with insurance through an employer or private individual coverage pay for CYRAMZA will depend on their insurance plan. Each plan has different preferred drug lists and out-of-pocket amounts, and most include an annual deductible. If your patients haven't met their deductible, they will see higher prices and could pay list price until they meet their deductible.

The Lilly Oncology Support Center strives to offer reliable and individualized treatment support for eligible patients prescribed a Lilly Oncology medicine whether they are insured, underinsured, or simply uninsured. With the Lilly Oncology Support Center Savings Card Program, the co-pay may be as little as $25.

For more information about Lilly Oncology Support Center, call 1-866-472-8663, Monday–Friday, 8 AM–10 PM ET, or visit LillyOncologySupportCenter.com.

*Insurance consists of employer or private policy, Medicare Advantage, and Medicare Part B with or without supplemental insurance, and Medicaid.

†Based on information licensed from IQVIA: IQVIA™, Real-World Evidence Claims Data for the period January–December 2019 reflecting estimates of real-world activity. All rights reserved. Accessed on May 15, 2020. IQVIA™ Real-World Evidence Claims Data include all claims of patients with a lung cancer diagnosis.

Please see Important Safety Information on pages 22–24 and full Prescribing Information for CYRAMZA.

Lilly Oncology Support Center: Support and Reimbursement

Find resources and programs to help support your eligible patients during treatment

The Lilly Oncology Support Center is committed to helping qualified patients when they're prescribed a Lilly Oncology product. We focus on financial and coverage issues, offering resources and individualized support for eligible patients, whether they're uninsured, underinsured, or insured. Services include help with benefit verification, prior authorization, paying for medicine, and specialty-pharmacy coordination.

The Lilly Oncology Support Center also can provide support beyond financial assistance for certain products, and it helps patients connect with non-Lilly resources, such as therapeutic-support groups for specific types of cancer.

Savings Card Program

- Supports eligible patients with Savings Cards and coinsurance costs for prescribed Lilly Oncology products*
- No income eligibility requirement
- Provides an annual maximum patient benefit of $25,000

***This offer is invalid for patients whose prescription claims are eligible to be reimbursed, in whole or in part, by any governmental program.**

Insurance Support

- Eligibility determination
- Benefits investigation
- Prior authorization assistance
- Appeals information
- Specialty pharmacy coordination

Resources

- Billing and Coding information
- Payment methodologies and allowables
- Payer policy information
- Pricing information

For more information, visit LillyOncologySupportCenter.com.

For more information about Lilly Oncology Support Center, call 1-866-472-8663, Monday–Friday, 8 AM–10 PM ET, or visit LillyOncologySupportCenter.com.

CYRAMZA®
ramucirumab injection
10 mg/mL solution

IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)

Warnings and Precautions

Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade hemorrhage ranged from 13-55%. Grade 3-5 hemorrhage incidence ranged from 2-5%.
- Patients with NSCLC receiving therapeutic anticoagulation or with evidence of major airway invasion by cancer were excluded from REVEL. In addition, patients with NSCLC with a recent history of gross hemoptysis, those receiving chronic therapy with NSAIDs or other anti-platelet therapy other than once daily aspirin or with radiographic evidence of major blood vessel invasion or intratumor cavitation were excluded from REVEL and RELAY; therefore the risk of pulmonary hemorrhage in these groups of patients is unknown.
- Permanently discontinue CYRAMZA in patients who experience severe (Grade 3 or 4) bleeding.

Gastrointestinal Perforations

- CYRAMZA can increase the risk of gastrointestinal perforation, a potentially fatal event. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade and Grade 3-5 gastrointestinal perforations ranged from <1-2%.
- Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation.

Impaired Wound Healing

- CYRAMZA has the potential to adversely affect wound healing. CYRAMZA has not been studied in patients with serious or non-healing wounds.
- Withhold CYRAMZA for 28 days prior to elective surgery. Do not administer CYRAMZA for at least 2 weeks following a major surgical procedure and until adequate wound healing. The safety of resumption of CYRAMZA after resolution of wound healing complications has not been established.

Arterial Thromboembolic Events (ATEs)

- Serious, sometimes fatal, ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade ATE was 1-3%. Grade 3-5 ATE incidence was <1-2%.
- Permanently discontinue CYRAMZA in patients who experience an ATE.

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. Across five clinical studies, excluding RELAY, in 1916 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-15%. In 221 patients with NSCLC receiving CYRAMZA in combination with erlotinib in the RELAY study, the incidence of new or worsening hypertension was higher (45%), as was the incidence of Grade 3-5 hypertension (24%). Of the patients experiencing new or worsening hypertension in RELAY (N=100 CYRAMZA and erlotinib; N=27 placebo and erlotinib), 13% of those treated with CYRAMZA and erlotinib required initiation of 3 or more antihypertensive medications compared to 4% of patients treated with placebo and erlotinib.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRR)

- IRR, including severe and life-threatening IRR, occurred in CYRAMZA clinical trials. Symptoms of IRR 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. In 2137 patients with various cancers treated with CYRAMZA in which premedication was recommended or required, the incidence of all Grade IRR ranged from <1- 9%. Grade 3-5 IRR incidence was <1%.
- Premedicate prior to each CYRAMZA infusion. Monitor patients during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Reduce the infusion rate by 50% for Grade 1-2 IRR. Permanently discontinue CYRAMZA for Grade 3- 4 IRR.

Worsening of Pre-existing Hepatic Impairment

- 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.
- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatorenal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

Please see Important Safety Information on pages 22–24 and full Prescribing Information for CYRAMZA.

Posterior Reversible Encephalopathy Syndrome (PRES)

- PRES (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported in <0.1% of 2137 patients with various cancers treated with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.
- Permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome

- In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor for proteinuria. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

Thyroid Dysfunction

- In 2137 patients with various cancers treated with CYRAMZA, the incidence of Grade 1-2 hypothyroidism ranged from <1- 3%; there were no reports of Grade 3-5 hypothyroidism. Monitor thyroid function during treatment with CYRAMZA.

Embryo-Fetal Toxicity

- CYRAMZA can cause fetal harm when administered to pregnant women. 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 3 months after the last dose.

Lactation

- Because of the potential risk for serious adverse reactions in breastfed children from ramucirumab, advise women not to breastfeed during treatment with CYRAMZA and for 2 months after the last dose.

Adverse Reactions

REVEL:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with docetaxel at a rate of ≥5% and ≥2% higher than placebo with docetaxel were neutropenia (55% vs 46%), fatigue/asthenia (55% vs 50%), stomatitis/mucosal inflammation (37% vs 19%), epistaxis (19% vs 7%), febrile neutropenia (16% vs 10%), peripheral edema (16% vs 9%), thrombocytopenia (13% vs 5%), lacrimation increased (13% vs 5%), and hypertension (11% vs 5%).
- The most common serious adverse reactions with CYRAMZA with docetaxel were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in CYRAMZA with docetaxel-treated patients versus 37% in patients who received placebo with docetaxel.
- Treatment discontinuation due to adverse reactions occurred more frequently in CYRAMZA with docetaxel-treated patients (9%) than in placebo with docetaxel-treated patients (5%). The most common adverse reactions leading to treatment discontinuation of CYRAMZA were IRR (0.5%) and epistaxis (0.3%).
- For patients with non-squamous histology, the overall incidence of pulmonary hemorrhage was 7% and the incidence of Grade ≥3 pulmonary hemorrhage was 1% for CYRAMZA with docetaxel compared to 6% overall incidence and 1% for Grade ≥3 pulmonary hemorrhage for placebo with 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 with docetaxel compared to 12% overall incidence and 2% for Grade ≥3 pulmonary hemorrhage for placebo with docetaxel.
- Clinically relevant adverse reactions reported in ≥1% and <5% of CYRAMZA with docetaxel-treated patients in REVEL were hyponatremia (4.8%) and proteinuria (3.3%).

CYRAMZA®
ramucirumab injection
10 mg/mL solution

IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab) (cont'd)

RELAY:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with erlotinib at a rate of ≥5% and ≥2% higher than placebo with erlotinib were infections (81% vs 76%), diarrhea (70% vs 71%), hypertension (45% vs 12%), stomatitis (42% vs 36%), alopecia (34% vs 20%), epistaxis (34% vs 12%), proteinuria (34% vs 8%), peripheral edema (23% vs 4%), headache (15% vs 7%), gastrointestinal hemorrhage (10% vs 3%), gingival bleeding (9% vs 1%), and pulmonary hemorrhage (7% vs 2%).
- The most common serious adverse reactions with CYRAMZA with erlotinib were pneumonia (3.2%), cellulitis (1.8%), and pneumothorax (1.8%). Red blood cell transfusions were given to 3.2% of CYRAMZA-treated patients versus 0 patients who received placebo.
- Treatment discontinuation of all study drugs due to adverse reactions occurred in 13% of CYRAMZA with erlotinib-treated patients, with increased alanine aminotransferase (1.4%) and paronychia (1.4%) being the most common. The most common adverse reactions leading to treatment discontinuation of CYRAMZA were proteinuria (8.6%) and hyperbilirubinemia (6%).
- Of the 221 patients who received CYRAMZA with erlotinib, 119 (54%) were 65 and over, while 29 (13%) were 75 and over. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with erlotinib and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 6%).

Please click for full Prescribing Information for CYRAMZA.

RB-L HCP ISI 29MAY2020

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ramucirumab injection
10 mg/mL solution

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CYRAMZA + erlotinib is the first and only FDA-approved 1L combination therapy for patients with EGFR mut+ mNSCLC[5]

INDICATION

CYRAMZA, in combination with erlotinib, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

SELECT IMPORTANT SAFETY INFORMATION

Proteinuria Including Nephrotic Syndrome

- In 2137 patients with various cancers treated with CYRAMZA, the incidence of all Grade proteinuria ranged from 3-34%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.
- Monitor for proteinuria. Withhold CYRAMZA for urine protein levels that are 2 or more grams over 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams over 24 hours or in the setting of nephrotic syndrome.

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