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## CLINICAL CASE PRESENTATION

# 57-YEAR-OLD FEMALE WITH STAGE IV NSCLC WHO IS PROGRESSING ON PLATINUM-BASED CHEMOTHERAPY Patient Rapidly Progressed\* Within 12 Weeks

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Clinical Case Presentation by:

Roy S. Herbst, MD, PhD

Ensign Professor of Medicine  
Professor of Pharmacology  
Chief of Medical Oncology  
Director of the Thoracic Oncology Research Program  
Yale Comprehensive Cancer Center  
Yale School of Medicine  
Smilow Cancer Hospital  
New Haven, Connecticut

**This is a hypothetical patient case based on the author's clinical experience with CYRAMZA in combination with docetaxel for mNSCLC.**

**This clinical case presentation has been sponsored by Eli Lilly and Company.**

\*Rapidly progressing disease is defined as time to progression within 12 weeks after starting initial platinum-based treatment.<sup>1</sup>

NSCLC=non-small cell lung cancer

### 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 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.

### SELECT IMPORTANT SAFETY INFORMATION

#### Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade  $\geq 3$  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.

Please see Important Safety Information on pages 6-7 and click link for [full Prescribing Information](#) for CYRAMZA.

  
**CYRAMZA**<sup>®</sup>  
ramucirumab injection  
10 mg/mL solution

*Lilly*

## Dr. Herbst Presents a Challenging Clinical Case of a Patient on Platinum-based Therapy

### History of Present Illness

- The patient is a 57-year-old female who presented with cough, increasing shortness of breath, and weight loss
- Patient has rapidly progressed\* within 12 weeks
- CT scan of the chest revealed a right upper lobe mass, mediastinal lymph node involvement, bone and liver metastases
- Biopsy of liver metastasis was positive for adenocarcinoma
- Brain MRI was negative for metastasis
- Molecular testing disclosed *KRAS* G12C mutation; WT EGFR and ALK
- PD-L1 expression by immunohistochemistry was positive (TPS=10%)
- Genomic profiling revealed high TMB (19 mut/Mb)
- ECOG PS was 1

### Past Medical History

- Multiple sclerosis
- 30 pack-year smoker; quit 15 years ago
- No history of alcohol or drug use
- No family history of cancer
- No prior history of hypertension or diabetes

### Social History

- Elementary school teacher
- Has 4 children

### Initial Treatment

- The patient received carboplatin and pemetrexed
- Response was transient with progression after 3 cycles of therapy
- Toxicities included mild hypothyroidism, which was treated with thyroid hormone replacement therapy

### Response Assessment/Follow-up Imaging

- Widespread metastatic disease at progression
- CT scan revealed increase in size of primary right upper lobe tumor, new bone and liver metastases
- Increased lymph node involvement
- Brain MRI was still negative for brain metastases

### Patient Attitude/Characteristics

- She is very interested in additional therapy after progression on platinum-based therapy
- Has a strong support system in her family and friends

### Treatment Plan

- CYRAMZA + docetaxel every 21 days



### My Rationale for Considering CYRAMZA as an Option for This Patient:

- ECOG PS 1
- She progressed while on platinum-based therapy after 3 cycles (9 weeks)
- Patient has a strong support system including her family and friends
- Patient had no contraindications that would preclude the use of CYRAMZA + docetaxel
- She is motivated to continue treatment
- CYRAMZA has demonstrated positive OS, ORR, and PFS when added to docetaxel in the REVEL ITT population, with consistent results in patients with rapidly progressing disease\*

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### 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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ALK=anaplastic lymphoma kinase; CT=computerized tomography; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; ITT=intent-to-treat; *KRAS*=Kirsten rat sarcoma; mNSCLC=metastatic non-small cell lung cancer; MRI=magnetic resonance imaging; mut/Mb=mutation/megabase; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; PS=performance status; TMB=tumor mutation burden; TPS=tumor proportion score; WT=wild type.

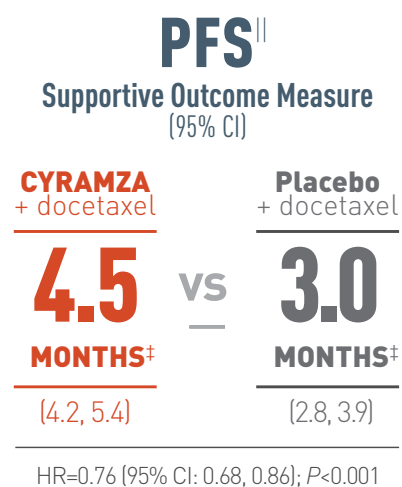
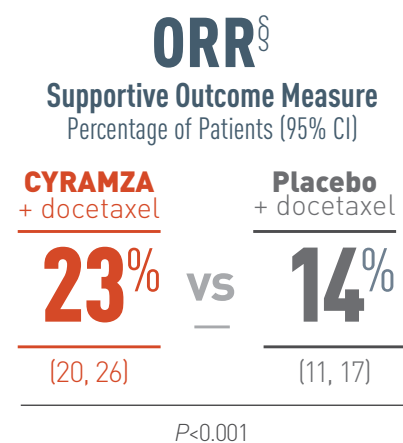
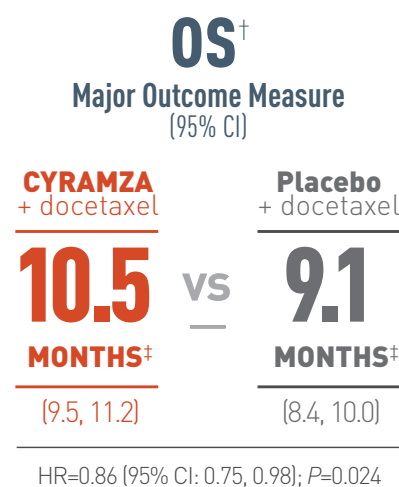
  
**CYRAMZA**<sup>®</sup>  
ramucirumab injection  
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CYRAMZA® (ramucirumab) boosted efficacy results vs docetaxel alone in the REVEL ITT population—with consistent results in patients with rapidly progressing disease\*<sup>1,2</sup>

REVEL Trial: Patients With mNSCLC (n=1253)<sup>2</sup>

CYRAMZA + docetaxel: n=628; placebo + docetaxel: n=625

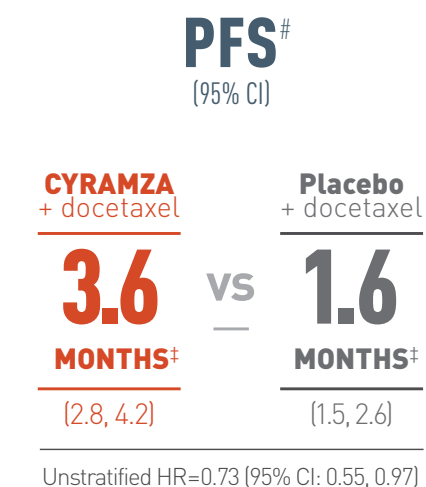
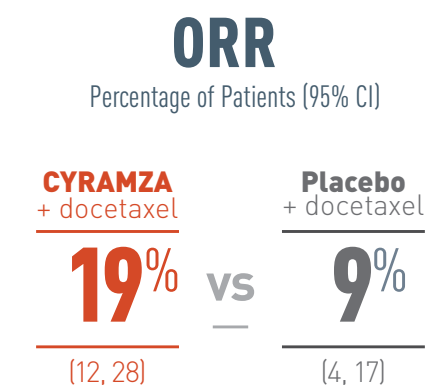
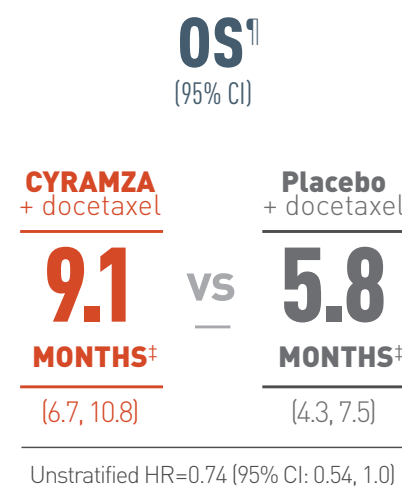
ITT Population



Post Hoc Exploratory Subgroup Analysis: Patients With Rapidly Progressing Disease\* (n=209)<sup>1</sup>

CYRAMZA + docetaxel: n=111; placebo + docetaxel: n=98

Time to Progression ≤12 Weeks



**STUDY DESIGN** The phase III REVEL trial evaluated the efficacy and safety of CYRAMZA plus docetaxel vs placebo plus docetaxel in patients with mNSCLC with disease progression on or after platinum-based chemotherapy. Major efficacy outcome measure was OS. Supportive efficacy outcome measures were PFS and ORR. All patients were required to have ECOG PS 0 or 1. Patients were randomized 1:1 to receive either CYRAMZA 10 mg/kg (n=628) or placebo (n=625), in combination with docetaxel at 75 mg/m<sup>2</sup> every 21 days.<sup>2</sup>

**REVEL EXPLORATORY ANALYSES** The REVEL trial was not adequately powered or error-controlled for subgroup analyses. Treatment differences observed in these subgroups cannot be regarded as statistically significant. The analyses described here were post hoc and exploratory.<sup>1,3,4</sup>

\*Rapidly progressing disease is defined as time to progression within 12 weeks after starting initial platinum-based treatment.<sup>1</sup>

<sup>†</sup>The percentage of deaths at the time of analysis was 68% (428 patients) and 73% (456 patients) in the CYRAMZA + docetaxel and placebo + docetaxel arms, respectively.<sup>2</sup>

<sup>‡</sup>Median.

<sup>§</sup>ORR=complete response rate plus partial response. ORR does not include stable disease. Disease progression and tumor response were assessed by investigators in accordance with RECIST 1.1.<sup>3</sup>

<sup>||</sup>The percentage of events at the time of analysis was 89% (558 patients) and 93% (583 patients) in the CYRAMZA + docetaxel and placebo + docetaxel arms, respectively. 126 of 558 events in CYRAMZA-treated patients and 109 of 583 events in placebo-treated patients were deaths.<sup>2</sup>

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; mNSCLC=metastatic non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors.

<sup>1</sup>The percentage of deaths at the time of analysis in the CYRAMZA + docetaxel arm was 75.7% (84 patients) and 80.6% (79 patients) in the placebo + docetaxel arm.<sup>1,5</sup>

<sup>4</sup>The percentage of events at the time of analysis in the CYRAMZA + docetaxel arm was 91% (101 patients) and 92.9% (91 patients) in the placebo + docetaxel arm.<sup>1,5</sup>

**SELECT IMPORTANT SAFETY INFORMATION**

- The labeling for CYRAMZA contains warnings and precautions for hemorrhage and GI hemorrhage, including severe and sometimes fatal events; gastrointestinal (GI) perforations, a potentially fatal event; impaired wound healing; arterial thromboembolic events (ATEs), including serious and sometimes fatal events; hypertension; infusion-related reactions (IRR), including severe and sometimes fatal events; worsening of pre-existing hepatic impairment; posterior reversible encephalopathy syndrome (PRES), including fatal events; proteinuria including nephrotic syndrome; thyroid dysfunction; and embryo-fetal toxicity. CYRAMZA should be permanently discontinued in patients who experience severe bleeding, a GI perforation, an ATE, uncontrolled hypertension, severe IRR, PRES, or urine protein >3 grams/24 h or nephrotic syndrome.
- In REVEL, the **most common adverse reactions** (all Grades) observed in patients treated with CYRAMZA with docetaxel at a rate of ≥30% and ≥2% higher than placebo with docetaxel were neutropenia (55% vs 46%), fatigue/asthenia (55% vs 50%), and stomatitis/mucosal inflammation (37% vs 19%). 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.





## IMPORTANT SAFETY INFORMATION FOR CYRAMZA® (ramucirumab)

### Warnings and Precautions

#### Hemorrhage

- CYRAMZA increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade  $\geq 3$  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%).

#### 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  $\geq 3$  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  $\geq 5\%$  and  $\geq 2\%$  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  $\geq 3$  pulmonary hemorrhage was 1% for CYRAMZA with docetaxel compared to 6% overall incidence and 1% for Grade  $\geq 3$  pulmonary hemorrhage for placebo with docetaxel. For patients with squamous histology, the overall incidence of pulmonary hemorrhage was 10% and the incidence of Grade  $\geq 3$  pulmonary hemorrhage was 2% for CYRAMZA with docetaxel compared to 12% overall incidence and 2% for Grade  $\geq 3$  pulmonary hemorrhage for placebo with docetaxel.
- Clinically relevant adverse reactions reported in  $\geq 1\%$  and <5% of CYRAMZA with docetaxel-treated patients in REVEL were hyponatremia (4.8%) and proteinuria (3.3%).

##### RELAY:

- The most common adverse reactions (all Grades) observed in patients treated with CYRAMZA with erlotinib at a rate of  $\geq 5\%$  and  $\geq 2\%$  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 see [full Prescribing Information for CYRAMZA](#).

RB-L HCP ISI 29MAY2020

**References:** 1. Reck M, Shepherd F, Pérol M, et al. Effects of second-line ramucirumab after rapid time to progression on first-line therapy: subgroup analysis of REVEL in advanced non-small cell lung cancer. Oral presentation presented at: IASLC 18th World Conference on Lung Cancer; October 15-18, 2017; Yokohama, Japan. 2. CYRAMZA (ramucirumab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2020. 3. 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. 4. Data on File, Lilly USA, LLC, DOF-RB-US-0006. 5. Data on File, Lilly USA, LLC, DOF-RB-US-0007.

  
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## ABOUT THE PRESENTER

# ROY S. HERBST, MD, PHD

Dr. Roy Herbst is the well recognized Ensign Professor of Medicine at Yale School of Medicine, where he also serves as Chief of Medical Oncology, among other notable roles. He has led phase I development of several new-generation targeted and immunogenic agents for NSCLC, including gefitinib, erlotinib, cetuximab, bevacizumab, pembrolizumab, and atezolizumab. Dr. Herbst is responsible for authoring or co-authoring more than 300 publications, which have appeared in prominent journals, such as the *Journal of Clinical Oncology*, *Clinical Cancer Research*, *Nature*, *Lancet*, and the *New England Journal of Medicine*. His work has won him accolades, including the 2015 Herbert Pardes Clinical Research Excellence Award by the Clinical Research Forum, the 2016 Paul A. Bunn, Jr Scientific Award by the International Association for the Study of Lung Cancer (IASLC), and election to the Association of American Physicians (AAP). At Yale, he leads the lung cancer research program and is the principal investigator on the National Cancer Institute (NCI)-funded lung Specialized Programs of Research Excellence (SPORE). He is also a member of the American Association of Cancer Research, where he chairs the Tobacco Task Force, as well as the American Society of Clinical Oncology (ASCO).

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Please see Important Safety Information on pages 6-7 and click link for [full Prescribing Information](#) for CYRAMZA.

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