CLINICAL CASE PRESENTATION

64-YEAR-OLD MALE WITH STAGE IV NON-SMALL CELL LUNG CANCER WITH AGGRESSIVE DISEASE*

Clinical Case Presentation By:
Mark A. Socinski, MD
Executive Medical Director
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*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).1

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.

Please see Important Safety Information, including a Boxed Warning for hemorrhage, gastrointestinal perforation, and impaired wound healing, on pages 6-7 and accompanying full Prescribing Information for CYRAMZA.
Dr. Socinski Presents a Challenging Clinical Case of a Patient with Aggressive Disease*†

History of present illness

- The patient is a 64-year-old male who presented with increasing dyspnea as well as low grade fever
- On initial evaluation, a chest X-ray showed a 4-cm left upper lobe mass with mediastinal widening and blunting of the left costophrenic angle
- Pertinent findings related to his physical exam included decreased breath sounds at the left lung base and mild hepatomegaly and trace lower extremity edema
- Chest/abdominal CT confirmed the 4-cm left upper lobe mass without evidence of vessel invasion. There were four hypodense lesions in the liver as well as a 5-cm right adrenal mass consistent with metastases
- A core biopsy as well as several FNAs of the right adrenal mass revealed squamous cell carcinoma
- Brain MRI and bone scan showed no evidence of either brain or bone metastases
- PD-L1 IHC staining was negative (TPS score of <1%)
- The diagnosis was made as stage IV (T2N2M1b) and his ECOG PS was 1

Past Medical History

- Mild COPD and diet controlled diabetes
- Ulcerative colitis inactive for “several years” but he had several flares requiring steroid therapy in the past
- One PPD for 45 years, quitting at age 60

Social History

- Married with three children as well as four grandchildren
- Wife accompanies him to each office visit and often accompanied by his daughter who is a nurse
- Retired only one year ago after 30 years of civil service

Initial Treatment

- Treated with platinum plus a taxane
- Following two cycles of treatment he had no improvement of his symptoms and the concern was progression

Physical Exam/Review of Symptoms at Progression

- He had slight tenderness over his liver on exam
- He was complaining of slight worsening of his dyspnea

Response Assessment/Follow-Up Imaging

- A repeat CT scan after two cycles showed a worsened pleural effusion and progression of the liver metastases

Patient Attitude/Characteristics

- Patient was devastated by the CT showing worsening of his cancer
- He is motivated to attend his grandson’s college graduation, who is graduating from the patient’s alma mater
- He is enthusiastic about starting treatment with the hopes a treatment could shrink his tumor and/or help him live longer

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.
†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).1

COPD= chronic obstructive pulmonary disease; CT=computerized tomography; ECOG=Eastern Cooperative Oncology Group; FNAs= fine needle aspirations; IHC= immunohistochemistry; MRI=magnetic resonance imaging; PD-L1=programmed death-ligand 1; PPD=packs per day; PS=performance status; TPS=tumor proportion score
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.

Treatment Plan

• A variety of treatment options were discussed, and the patient’s history of ulcerative colitis was taken into consideration for the treatment decision
• Considering his complete medical profile, he elected to receive ramucirumab plus docetaxel every 21 days

Why adding CYRAMZA may be appropriate

• Patient presents with aggressive disease†
• ECOG PS 1
• He has aggressive disease and is both determined and focused on exhausting his options
• Patient is hopeful for response and a chance to live longer
• In light of the patient’s poor prognosis, a discussion was had with the patient regarding the risk of side effects as well as potential benefits of treatment

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CYRAMZA Demonstrated Significant Improvements in OS, PFS, and ORR in the REVEL Trial Population When Added to Docetaxel

**ITT POPULATION (N=1253)**

<table>
<thead>
<tr>
<th>OS</th>
<th>Major Outcome Measure (95% CI)*</th>
<th>CYRAMZA + docetaxel</th>
<th>Placebo + docetaxel</th>
<th>10.5 MONTHS†</th>
<th>9.1 MONTHS†</th>
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<tr>
<td></td>
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<td></td>
<td>(9.5, 11.2)</td>
<td>(8.4, 10.0)</td>
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Hazard ratio 0.86 (95% CI: 0.75, 0.98); P=0.024

<table>
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<tr>
<th>PFS</th>
<th>Supportive Outcome Measure (95% CI)‡</th>
<th>CYRAMZA + docetaxel</th>
<th>Placebo + docetaxel</th>
<th>4.5 MONTHS†</th>
<th>3.0 MONTHS†</th>
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<td></td>
<td></td>
<td></td>
<td>(4.2, 5.4)</td>
<td>(2.8, 3.9)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>ORR</th>
<th>Supportive Outcome Measure (95% CI)§</th>
<th>CYRAMZA + docetaxel</th>
<th>Placebo + docetaxel</th>
<th>23%</th>
<th>14%</th>
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</thead>
<tbody>
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<td></td>
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<td>(20, 26)</td>
<td>(11, 17)</td>
</tr>
</tbody>
</table>

P<0.001

CI=confidence interval; ITT=intent to treat; 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.

†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.

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

REVEL Trial Design (N=1253)

The phase III REVEL trial evaluated the efficacy and safety of CYRAMZA plus docetaxel vs placebo plus docetaxel in patients with metastatic NSCLC 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 Eastern Cooperative Oncology Group performance status 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/m² every 21 days.

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.

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REVEL EXPLORATORY ANALYSES

The REVEL trial was not powered for subgroup analyses, nor were any such analyses error-controlled. The primary platinum-refractory population (n=360/N=1253) 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; n=200/N=1253 and n=448/N=1253, respectively) 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.

CONSIDER CYRAMZA PLUS DOCETAXEL FOR PATIENTS WITH AGGRESSIVE DISEASE

With Consistent Results in Patients With Aggressive Disease

Exploratory Subgroup Analysis:

PATIENTS WITH REFRACTORY DISEASE (n=360)

<table>
<thead>
<tr>
<th>Major Outcome Measure (95% CI)</th>
<th>Supportive Outcome Measure (95% CI)</th>
<th>Supportive Outcome Measure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYRAMZA + docetaxel</td>
<td>Placebo + docetaxel</td>
<td>CYRAMZA + docetaxel</td>
</tr>
<tr>
<td>8.3 MONTHS†</td>
<td>6.3 MONTHS†</td>
<td>23% VS 13%</td>
</tr>
<tr>
<td>(6.6, 9.8)</td>
<td>(5.1, 8.0)</td>
<td>(17, 29)</td>
</tr>
<tr>
<td>Unstratified Hazard Ratio 0.86 (95% CI): 0.68, 1.08</td>
<td>Unstratified Hazard Ratio 0.71 (95% CI): 0.57, 0.88</td>
<td></td>
</tr>
</tbody>
</table>

†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).1

‡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.

‡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.
**IMPORTANT SAFETY INFORMATION FOR CYRAMZA**

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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 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 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 antplatelet therapy other than once-daily aspirin or with radiographic evidence of major airway or blood vessel invasion or intratumor caviation 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 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 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 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 Boxed Warnings for hemorrhage, gastrointestinal perforation, and impaired wound healing.
Dr. Mark A. Socinski is a board-certified, fellowship-trained medical oncologist, specializing in all thoracic malignancies, including small cell and non-small cell lung cancers and mesothelioma. He is an internationally recognized expert in the development of novel chemotherapy agents and treatment strategies for advanced non-small cell lung cancer and small-cell lung cancer. His research has focused on incorporating personalized medicine and molecular biomarkers in the treatment of lung cancer. Dr. Socinski received a medical degree from the University of Vermont in Burlington. He completed an internship and residency at Beth Israel Deaconess Medical Center, Harvard Medical School, in Boston, Massachusetts, and fellowships in medical oncology and clinical medicine at the Dana-Farber Cancer Institute in Boston.

He is a member of several professional organizations, including the American College of Physicians, American Society of Clinical Oncology, Cancer and Leukemia Group B, International Association for the Study of Lung Cancer, and the American College of Chest Physicians. He serves as co-Chair of the Thoracic Malignancies Steering Committee for the National Cancer Institute. Dr. Socinski serves on the Respiratory Core Committee of the Cancer and Leukemia Group B (Alliance) and has been instrumental in the development of many cooperative clinical trials. He is also co-Chair of the Winter Lung Cancer Annual Conference, now in its 14th year.