The ION Solutions Precision Medicine Center is your gateway to a single, centralized library of precision medicine testing recommendations and resources. Access all of the testing recommendations created by our physician- and pharmacist-based advisory panel as well as resources curated by ION Solutions and our precision medicine partners to help you make informed decisions for your patients.

View testing recommendations by tumor categories:
- Breast Cancer
- NSCLC
- Colorectal
- Genitourinary
- Lymphoma
- Rare Disease

As precision medicine continues to evolve, ION will continue to provide the tools your practice needs.
Precision Medicine Center

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- Lymphoma
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As precision medicine continues to evolve, ION will continue to provide the tools your practice needs.
When Dr. Harsha Vyas, who practices in Dublin, Ga., faced a potential practice-closing issue in 2017, he quickly became a passionate advocate for community oncology. His efforts paid off, and the Department of Veterans Affairs stopped a reimbursement clawback. This is a prime example of when oncology practices speak, policy can change. Learn more about Dr. Vyas’ efforts on page 12.

Biosimilars have the potential to reduce cost and expand access to lifesaving drugs in the U.S. Given that a number of biologics will lose patent protection over the next several years, there could be significant opportunities for biosimilar manufacturers to bring cost-saving alternatives to patients. Starting on page 14 we examine the unique aspects of biosimilars, Medicare payment for biosimilars, legislative and regulatory considerations and more.

ION Solutions is committed to community oncology. As healthcare delivery transforms, we remain a steadfast partner to support community oncology practices with GPO procurement services, technologies, advocacy resources and expertise to help you improve your clinical and operational management.

Thank you for your partnership,
Brian Ansay
President, ION Solutions
# 2019 Meeting Schedule

<table>
<thead>
<tr>
<th>Meeting Date</th>
<th>Meeting Name</th>
<th>Location</th>
<th>Venue</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 16-17</td>
<td>Smart ID User Conference</td>
<td>Charlotte, NC</td>
<td>Westin Charlotte</td>
</tr>
<tr>
<td>May 17-18</td>
<td>National Healthcare Practitioners</td>
<td>Charlotte, NC</td>
<td>Westin Charlotte</td>
</tr>
<tr>
<td>September 5-7</td>
<td>Precision Oncology</td>
<td>Austin, TX</td>
<td>Fairmont Austin</td>
</tr>
<tr>
<td>November 1-2</td>
<td>ION National</td>
<td>Phoenix, AZ</td>
<td>Sheraton Wild Horse</td>
</tr>
</tbody>
</table>

*Meeting Dates Subject to Change*

Registration will be available approximately 60 days prior to each event. To register, visit www.iononline.com.
INDICATION AND IMPORTANT SAFETY INFORMATION

ALUNBRIG® (brigatinib) is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. See accelerated approval information above.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)/Pneumonitis: Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG. In Trial AL TA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90–180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of ALUNBRIG; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%. Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

ALK+, anaplastic lymphoma kinase-positive; NSCLC, non-small cell lung cancer.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
For patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib

Think One Step Ahead With ALUNBRIG® (brigatinib)

Robust Overall Efficacy

<table>
<thead>
<tr>
<th>ALTA Efficacy Results</th>
<th>IRC Assessment*</th>
<th>Investigator Assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90 mg once daily (n=112)</td>
<td>90→180 mg once daily (n=110)</td>
</tr>
<tr>
<td>Overall Response Rate, (95% CI)</td>
<td>48% (39-58)</td>
<td>53% (43-62)</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>4 (3.6)</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>50 (45)</td>
<td>53 (48)</td>
</tr>
<tr>
<td>Duration of Response, Median in Months (95% CI)</td>
<td>13.8 (7.4-NE)</td>
<td>13.8 (9.3-NE)</td>
</tr>
</tbody>
</table>

*180 mg once daily with a 7-day lead-in at 90 mg once daily.

CI: confidence interval; NE: not estimable.

ALTA Study Design: The safety and efficacy of ALUNBRIG were evaluated in a global, two-arm, open-label, multicenter trial. The trial consisted of 222 adult patients with locally advanced or metastatic ALK+ NSCLC who had progressed on crizotinib. Patients were randomized to receive the recommended dosing regimen of 180 mg of ALUNBRIG orally once daily with a 7-day lead-in at 90 mg once daily (n=110, 18 with measurable brain metastases), or 90 mg of ALUNBRIG orally once daily (n=112, 26 with measurable brain metastases). The major efficacy outcome measure was confirmed objective response rate (cORR) according to Response Evaluation Criteria In Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included Investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hypertension: In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

Bradycardia: Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

Visual Disturbance: In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group. Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

Creatine Phosphokinase (CPK) Elevation: In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90→180 mg group. The incidence of Grade 3–4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 43% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Hyperglycemia: In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

Embryo–Fetal Toxicity: Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.
b 180 mg once daily with a 7-day lead-in at 90 mg once daily.

CYP3A Inhibitors: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If coadministration of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG.

CYP3A Inducers: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, increase the dose of ALUNBRIG.

CYP3A Substrates: Coadministration of ALUNBRIG with sensitive CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates.

**IMPORTANT SAFETY INFORMATION (continued) ADVERSE REACTIONS**

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

The most common adverse reactions (≥25%) in the 90 mg group were nausea (33%), fatigue (29%), headache (28%), and dyspnea (27%) and in the 90→180 mg group were nausea (40%), diarrhea (38%), fatigue (36%), cough (34%), and headache (27%).

**DRUG INTERACTIONS**

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** ALUNBRIG can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.

**Lactation:** There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG.

**Females and Males of Reproductive Potential:**

**Contraception:** Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG.

**Infertility:** ALUNBRIG may cause reduced fertility in males.

**Pediatric Use:** The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

**Geriatric Use:** Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

**Hepatic or Renal Impairment:** No dose adjustment is recommended for patients with mild or moderate hepatic impairment or mild or moderate renal impairment. Reduce the dose of ALUNBRIG for patients with severe hepatic impairment or severe renal impairment.

Visit ALUNBRIG.com to learn more.

**Meaningful CNS Efficacy**

<table>
<thead>
<tr>
<th>Intracranial Objective Response in Patients With Measurable Brain Metastases* in ALTA</th>
<th>IRC Assessment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 mg once daily (n=26)</td>
<td>90→180 mg once daily* (n=18)</td>
</tr>
<tr>
<td>Intracranial Overall Response Rate, (95% CI)</td>
<td>42% (23–63)</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>Duration of Intracranial Response</td>
<td></td>
</tr>
<tr>
<td>Intracranial Response ≥6 Months</td>
<td>64% (7/11)</td>
</tr>
<tr>
<td>Intracranial Response ≥12 Months</td>
<td>36% (4/11)</td>
</tr>
</tbody>
</table>

*Median duration of follow-up was 8 months (range: 0.1–20.1). *180 mg once daily with a 7-day lead-in at 90 mg once daily. *≥10 mm in longest diameter (at baseline).

**ALUNBRIG is an ALK inhibitor with a one-tablet, once-daily recommended dosage regimen that can be taken with or without food.*

*The recommended dosage regimen is 90 mg orally once daily for the first 7 days. If tolerated during the first 7 days, increase dose to 180 mg orally once daily.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Intestinal Lung Disease (ILD)/Pneumonitis
- Hypertension
- Bradycardia
- Visual Disturbance
- Creative Phosphokinase (CPK) Elevation
- Pancreatic Enzymes Elevation
- Hyperglycemia

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates observed in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who received at least 1 dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg once daily continuously (90 mg group) or 90 mg once daily for 7 days followed by 180 mg once daily (90 → 180 mg group).

The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90 → 180 mg group. A total of 150 (69%) patients were exposed to ALUNBRIG for greater than or equal to 6 months and 42 (19%) patients were exposed for greater than or equal to 1 year.

The study population characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (58%), White (67%), Asian (31%), Stage IV disease (98%), NSCLC adenocarcinoma histology (97%), never or former smoker (85%), ECOG Performance Status (PS) 0 or 1 (83%), and brain metastases at baseline (69%).

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90 → 180 mg group. The most common serious adverse reactions were pneumonia (15.5% overall, 3.7% in the 90 mg group, and 3.7% in the 90 in the 90 → 180 mg group and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 1.8% in the 90 → 180 mg group).

The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90 → 180 mg group) and pneumonia (1.8% in the 90 → 180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (3.7% in the 90 mg group and 20% in the 90 → 180 mg group). The most common adverse reaction that led to dose reduction was increased creatine phosphokinase for both regimens (1.6% in the 90 mg group and 4.5% in the 90 → 180 mg group).

Table 3 and Table 4 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

### Table 3: Adverse Reactions in ≥10% of Patients (Alunbrig) (Trials A-027/ALTA)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>90 mg once daily</th>
<th>90 → 180 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>0.9</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>0.9</td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>15</td>
<td>1.8</td>
</tr>
<tr>
<td>Respiratory, Thoracic And Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea†</td>
<td>27</td>
<td>2.8</td>
</tr>
<tr>
<td>Fatigue‡</td>
<td>3.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Headache¶</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Skin Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>15</td>
<td>1.8</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>5.5</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>10</td>
<td>1.8</td>
</tr>
<tr>
<td>Myalgia†</td>
<td>9.2</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism And Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>22</td>
<td>0.9</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Disturbance‡</td>
<td>7.3</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.6</td>
<td>2.8†</td>
</tr>
</tbody>
</table>

* † ‡ • Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
† Includes abdominal distension, abdominal pain, and epigastric discomfort
‡ Includes nausea, vomiting, surgery, and antiemetic medication
§ Includes headache and sinus headache
¶ Includes peripheral sensory neuropathy and paresthesia
* Includes autonomic dysreflexia, orthostatic hypotension, syncope, and vasovagal reactions
Table 4: Laboratory Abnormalities in ≥20% (All Grades*) of Patients by Regimen in ALTA (N=219)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>90 mg once daily</th>
<th>90 → 180 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>38</td>
<td>3.7</td>
</tr>
<tr>
<td>Hyperglycemia†</td>
<td>38</td>
<td>3.7</td>
</tr>
<tr>
<td>Increased creatine phosphokinase</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>21</td>
<td>4.6</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>27</td>
<td>3.7</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td>Decreased phosphorus</td>
<td>15</td>
<td>1.8</td>
</tr>
<tr>
<td>Prolonged activated partial thromboplastin time</td>
<td>22</td>
<td>1.6</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>23</td>
<td>0.9</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>19</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* Per CTCAEv3 version 4.0
† Elevated blood insulin was also observed in both regimens

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ALUNBRIG

Strong or Moderate CYP3A Inhibitors

Co-administration of ALUNBRIG with a strong or moderate CYP3A inhibitor increased brigatinib plasma concentrations, which may increase the incidence of adverse reactions. Avoid co-administration of ALUNBRIG with strong or moderate CYP3A inhibitors. If co-administration of strong or moderate CYP3A inhibitors cannot be avoided, modify dose as recommended.

Strong or Moderate CYP3A Inducers

Co-administration of ALUNBRIG with a strong or moderate CYP3A inducer decreased brigatinib plasma concentrations, which may decrease the efficacy of ALUNBRIG. Avoid co-administration of ALUNBRIG with strong or moderate CYP3A inducers. If co-administration of moderate CYP3A inducers cannot be avoided, modify dose as recommended.

7.2 Effect of ALUNBRIG on Other Drugs

CYP3A Substrates

Brigatinib may decrease the concentrations of sensitive CYP3A substrates. Co-administration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats resulted in skeletal (incomplete ossification) and visceral alterations (anophthalmia, forelimb hyperflexion, small and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding through a defect in the abdominal wall)) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

8.2 Lactation

Risk Summary

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG.

Contraception

ALUNBRIG can cause fetal harm.

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Counsel patients to use a non-hormonal method of contraception since ALUNBRIG can render some hormonal contraceptives ineffective.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males.

8.4 Pediatric Use

The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). Reduce the dose of ALUNBRIG for patients with severe hepatic impairment (Child-Pugh C).

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance (CrCl) 30 to 89 mL/min by Cockcroft-Gault). Reduce the dose of ALUNBRIG for patients with severe renal impairment (CrCl 15 to 29 mL/min).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the symptoms and risks of serious pulmonary adverse reactions such as ILD/ pneumonitis. Advise patients to immediately report any new or worsening respiratory symptoms.

Hypertension

Advise patients of risks of hypertension and to promptly report signs or symptoms of hypertension.

Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of heart and blood pressure medications.

Visual Disturbance

Advise patients to inform their healthcare provider of any new or worsening vision symptoms.

Cytotoxic Phosphokinase (CKP) Elevation

Inform patients of the signs and symptoms of cytotoxic phosphokinase (CKP) elevation and the need for monitoring during treatment. Advise patients to inform their healthcare provider of any new or worsening symptoms of unexplained muscle pain, tenderness, or weakness.

Pancreatic Enzymes Elevation

Inform patients of the signs and symptoms of pancreatitis and the need to monitor for amylase and lipase elevations during treatment.

Hyperglycemia

Inform patients of the risks of new or worsening hyperglycemia and the need to periodically monitor plasma glucose levels. Advise patients with diabetes mellitus or glucose intolerance that antihyperglycemic medications may need to be adjusted during treatment with ALUNBRIG.

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity

Advise females and males of reproductive potential that ALUNBRIG can cause fetal harm.

- Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Lactation

Advise females not to breastfeed during treatment with ALUNBRIG and for at least 1 week following the final dose.

Infertility

Advise males of reproductive potential of the potential for reduced fertility from ALUNBRIG.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit or grapefruit juice while taking ALUNBRIG.

Storage and Administration

Instruct patients to start with 90 mg of ALUNBRIG once daily for the first 7 days and if tolerated, increase the dose to 180 mg once daily. Advise patients to take ALUNBRIG with or without food.

Missed Dose

Advise patients that if a dose of ALUNBRIG is missed or if the patient vomits after taking a dose of ALUNBRIG, not to take an extra dose, but to take the next dose at the regular time.

Please see full Prescribing Information for ALUNBRIG at ALUNBRIG.com.

Manufactured for: Takeda Pharmaceutical Company Limited

40 Landsdowne Street, Cambridge, MA 02139-4234

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03/19 MAT-USD-BRG-19-00029
Community practices provide healthcare to America’s eligible Veterans when the U.S. Department of Veterans Affairs (VA) cannot deliver the care they need. Veterans living in rural areas and facing a cancer diagnosis often are authorized to receive care at oncology practices in their local communities.

This was the case for many years for Dr. Harsha Vyas, Hematologist/Oncologist, who practices at Cancer Center of Middle Georgia in Dublin, Ga., 135 miles south of Atlanta. Since 20?? Dr. Vyas has provided care to Veterans without an agreement, contract, registration or negotiated rates as an out-of-network private physician practice. The local VA pre-authorized Veterans to seek care, providing Dr. Vyas and other community oncology practices assurance that the services were approved.

“And it was working,” Dr. Vyas says. “It worked fine for many, many years.” Until it stopped working.

In 2017, the VA engaged a third-party contractor to recoup what they deemed to be overpayment of claims dating as far back as 2013. Practices began to receive letters demanding repayment. The contractor said the VA had been overpaying community oncology clinics because the loaded rates were incorrect. Practices were given a short
time to pay what they owed or risk being turned over to the Treasury Offset Program, which collects delinquent debts owed to federal agencies and states. This led to a serious, sudden disruption for Veterans accessing cancer care and the potential for permanent financial damage to practices. According to Dr. Vyas, the contractor’s actions were “practice closing.”

With the help of AmerisourceBergen’s Government Affairs team and Specialty Physician Services Senior Vice President and President Barry Fortner, Ph.D., Dr. Vyas began meeting with members of Congress and the VA to provide context on the issue and ask for their help to stop the contractor from recouping dollars from non-contracted providers. Six months of arduous meetings, follow-up emails, awareness building and education ensued. Dr. Vyas even joined with other rural practices to develop a backup plan in case there was a need to litigate. But, there was no need. The audit and its findings were cancelled.

“If these takebacks had been allowed to occur, it would have caused any number of oncology providers in Georgia, and nationally, to close our doors due to the sheer volume of dollars at stake. The net result would have been an even more severe access to care issue, not only for our Veterans, but for our entire community,” Dr. Vyas says.

A Needed View from the Trenches

When appealing to his representatives, Dr. Vyas found that his audience was most receptive when he gave them a view from the trenches. They needed to understand the issue from his perspective.

“I think if physicians take the initiative, take their time, and I know it’s not easy but if they do it, they will see some change because we have an out-sized voice in the community just because of what we do. We are healers. We treat people, and we’re generally respected. So, go and meet your congressman and tell him about the issues that have an out-sized impact compared to anything else. I urge all my fellow physicians to take some time and do their own advocacy on issues passionate to them before it’s too late,” Dr. Vyas says.

Patients Are Advocates, Too

While the view from the trenches was important, Dr. Vyas believes the voice of the patient—the constituents—was the most impactful. Some of Dr. Vyas’ Veteran patients wrote letters to their congressmen. A few even spoke to U.S. Rep. Rick Allen (R-GA) when he visited the practice.

“I think the most significant piece of information was in all my communications I basically did mention about how the rural Veteran is the most disadvantaged Veteran. Just because he’s far, far away from a metro area and the fact that he’s seeking care locally is because he has a lack of resources. He’s choosing to live here and you just can’t say, ‘Hey yeah, that’s fine. Go to the Atlanta VA 126 miles from here and get your care.’ He’s not going to go,” says Dr. Vyas.

Because of this issue Dr. Vyas’ passion for advocacy grew and he championed the opening of the first rural Georgia Community Oncology Alliance (COA) Patient Advocacy Network (CPAN) in his cancer center. The chapter opened in November 2018 and had its first chapter meeting in early 2019.

“Advocacy works,” says Dr. Vyas, “I saw it with my own eyes and efforts in 2018, and I’m glad I did it and would do it again for issues close to my heart simply because if doctors don’t speak up for themselves on important practice closing issues, we will continue to see the lopsided consolidation of healthcare in metro areas and in larger hospitals.”

Tricia Musslewhite is manager, marketing and communications, at AmerisourceBergen.

“Never doubt that a small group of thoughtful committed citizens can change the world; indeed, it’s the only thing that ever has.”

-MARGARET MEAD
Biosimilars have a lot of potential to reduce cost and expand access to lifesaving drugs in the U.S. This is particularly the case for patients dealing with cancer; anemia; inflammatory bowel disease; autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, psoriasis and Crohn’s; and other inflammatory diseases, which are effectively treated with biologics, including biosimilars. Given that a number of biologics will lose patent protection over the next several years, there could be significant opportunities for biosimilar manufacturers to bring cost-saving alternatives to patients. This article reviews the unique aspects to biosimilars; Medicare payment for biosimilars in different settings; legislative and regulatory considerations; and payer, provider and patient views of biosimilars.

Background

With the recent Food and Drug Administration (FDA) approval of Pfizer’s TRAZIMERA™ (trastuzumab-qyyp), a biosimilar for HERCEPTIN® (trastuzumab), the total number of biosimilars rises to 18, with others soon to follow. As of July 1, 2018, there were 68 biosimilars for 31 different reference products in various stages of development. This could mean a huge decrease to direct spending on biologic drugs, estimated at a whopping $54 billion from 2017 to 2026. Given the Administration’s ongoing focus to reduce drug prices, biosimilars could alter the healthcare landscape, including oncology and hematology. It’s important for the oncology and hematology community to be knowledgeable about biosimilars and, even more essential, understand the role biosimilars might play in cancer treatment.

Unique Aspects to Biosimilars

Understanding Biosimilars

The Biologics Price Competition and Innovation Act (BPCIA) of 2009, included as part of the Affordable Care Act (ACA), defines a biosimilar or biosimilarity as:

A biological product that is highly similar to the reference biologic notwithstanding minor differences in clinically inactive components; and

...There are no clinically meaningful differences between the biological product and the reference biologic in terms of the safety, purity, and potency of the product

This new law created an abbreviated pathway for follow-on biologics; these products are known as biosimilars and interchangeables. The idea behind this law is to enable more competition, and increase lower-cost options for patients, once exclusivity has lapsed on the reference drug. While biosimilars are highly similar to the reference product, they are not generics, since they are not chemically identical to reference products. “Naming” is another way that these biologic products are unlike brand and generic small-molecule drugs, as biosimilars and reference biologics do not share the same nonproprietary name. Rather, a 4-letter, FDA-designated suffix follows the core name of a biosimilar to improve the detection of safety signals over time and to minimize inadvertent substitution. In March 2019, the FDA issued a draft guidance on the naming of biosimilars and interchangeable biosimilars. The FDA will receive comments on the draft guidance over the next 60 days with the intent of issuing a final version of the guidance at a later date.
Extrapolation and Interchangeability

Unlike reference products, biosimilars do not have to prove safety and efficacy for every single indication. Rather, the FDA considers the extrapolation of a biosimilar for use in an indication not directly studied against the reference product. As a result, manufacturers may not have to develop as many clinical studies for biosimilars as would be required for the reference product, saving time and resources. For a biosimilar to have an “interchangeable” designation, the manufacturer must provide additional information to demonstrate that the biosimilar is expected to produce the same clinical result as the reference product in any given patient. To date, the FDA has not approved any biosimilar to be interchangeable to its reference product.

Payment for Biosimilars

Several legislative and regulatory efforts have paved the way for biosimilars to succeed in the U.S. market. The ACA established payment for biosimilars under Medicare Part B to be average sales price (ASP) plus 6 percent of the reference product’s ASP (4.3% after sequestration). The Centers for Medicare & Medicaid Services (CMS) recently made a policy change to level the playing field between biosimilars and reference products. In 2017, CMS announced it would be assigning unique Healthcare Common Procedure Coding System (HCPCS) codes (“J-codes”) to each biosimilar, beginning on or after Jan 1, 2018.

Payment for biosimilars is a dynamic, changing marketplace. In 2019, CMS finalized its proposal to pay non-pass-through biosimilars acquired under the 340B program at the biosimilar’s ASP minus 22.5 percent of the (presumably lower) biosimilar’s ASP, instead of the biosimilar’s ASP minus 22.5 percent of the (presumably higher) reference product’s ASP. Hospitals not participating in the 340B program receive ASP plus 6 percent of the reference product (4.3% after sequestration). Also new for this year, the definition of generic drugs was changed for the purposes of the non-Low-Income Subsidy (non-LIS) catastrophic and LIS cost-sharing to include biosimilar therapies. Finally, this year, biosimilar manufacturers will begin covering 70 percent of patients’ donut-hole expenses. (See table 1 summarizing these changes below.)

Table 1. Medicare Payment for Biosimilars

<table>
<thead>
<tr>
<th>Setting</th>
<th>Medicare Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>Bundled into hospital payment for Medicare Severity Diagnosis-Related Group (MS-DRG)</td>
</tr>
<tr>
<td>Office</td>
<td>Average sales price (ASP) plus 6% of the reference product’s ASP (4.3% after sequestration)</td>
</tr>
<tr>
<td>Outpatient Hospital After Pass-Through Status</td>
<td>340B Hospital: ASP – 22.5% of biosimilar’s ASP (−23.7% after seq)* Non-340B Hospital: ASP + 6% of reference product’s ASP (4.3% after seq)</td>
</tr>
<tr>
<td>Part D</td>
<td>As of 2019, biosimilars are treated as a brand for non-low-income subsidy (LIS) patients, so the manufacturer coverage gap discount applies. For LIS, biosimilars count as a generic product so beneficiaries are responsible for the lower copay</td>
</tr>
</tbody>
</table>

Key: seq – sequestration.

*In flux because of current lawsuit by AHA et al.

Pricing and discounting will depend on the number of biosimilars on the market. As an example, the table below shows the NEULASTA™ (pegfilgrastim) price increasing without competition until just prior to the time a biosimilar, FULPHILA™ (pegfilgrastim-jmdb), came into market at the end of 2018. After that, the prices of both NEULASTA and FULPHILA decreased. The recent launch of another biosimilar, UDENYCA™ (pegfilgrastim-cbqv), is priced just slightly above that of FULPHILA and brings healthy competition to this market, resulting in lower cost and greater access for patients.
Legislative and Regulatory Considerations

There is much promise for biosimilars and support by Congress, regulators and payers, but there are also hurdles that are evidenced by the fact that only seven biosimilars are currently available in the U.S. market. One of the biggest hurdles is the patent exclusivity issue, which needs legislation to change. During recent Senate hearings on reducing drug prices, panel members noted that brand manufacturers have sued biosimilar manufacturers to delay onset of products that would compete against the original products. A Senate bill was introduced in early March that would require drug manufacturers to publicly disclose all patents as a way to facilitate biosimilars and introduce competition into the market. While it may be difficult for this legislation to gain traction due to the financial interest of the innovator manufacturer to protect their market, it is hopeful that the settlements in some of the cases will soon set a precedent to spur other biosimilars on to successful launch.

At the state level with laws in 45 states and Puerto Rico that declare that a biosimilar must have interchangeability for pharmacists to make a switch without having to go back to the prescriber to check. While interchangeability would seem to have advantages for all stakeholders, only one manufacturer has publicly announced plans to submit an application for interchangeability. Boehringer Ingelheim (BI) has publicly announced plans to seek interchangeability designation for its adalimumab biosimilar, CYLTEZOTM (adalimumab-adbm), approved to treat multiple chronic inflammatory diseases. Manufacturers may be waiting for the FDA to finalize their 2017 draft guidance document on how to demonstrate interchangeability.

Payer, Provider and Patient Views

Payers, providers and patients are becoming more receptive to biosimilar communications as the number of biosimilars on the market increases. Payers have a few things to consider for coverage and payment of biosimilars above and beyond clinical evaluation. This includes whether or not the biosimilar covers the full range of indications, how difficult it may be to transfer patients already on a biosimilar product and the reliability of the manufacturer to continually supply these products. Coverage of biosimilars seems to be pretty good with an informal Xcenda survey of payer policies showing that about half of scenarios had reference products in an advantageous position (either preferred or first line) and half of payers that had biosimilars in advantageous positions.

Prescriber comfort is growing because of providers’ knowledge about biosimilar regulations, interchangeability, safety and cost. However, willingness to prescribe a biosimilar may vary by prescriber specialty and specialists who heavily use biosimilars (eg, oncologists and hematologists) may be more comfortable than others in prescribing. As indicated by recent survey data, healthcare professionals and providers are showing a desire for more education on the subject and want to share information about biosimilars with colleagues and patients. Prescribers want to learn more, potentially and at least partially, as an effect of the FDA’s outreach campaign launched in 2018. Additionally, education in the format of peer-review literature or other materials that come from professional organizations, such as American Society of Clinical Oncology (ASCO) and Pharmaceutical and Research Manufacturers of America (PhRMA) are viewed most favorably by providers.

While patients will still likely need education, the knowledge gained by providers will help patients to also become more familiar and comfortable about using biosimilars. Biosimilars have significant advantages for patients given these products are reimbursed under the specialty tier. This is where biosimilars have an advantage over a reference product, with a 20-30 percent discount in price which can result in much lower co-insurance payments per month. The access to more options for treatments as a result of more biosimilars on the market is also a huge benefit to patients.
It’s important for the oncology and hematology community to be knowledgeable about biosimilars and, even more essential, understand the role biosimilars might play in cancer treatment.

Conclusion

While the EU has had a head start in launching biosimilars compared to the U.S., the healthcare environment is favorable for the biosimilar market to accelerate quickly in the U.S. Congressional and Administrative support have resulted in recent policy changes that allow the same opportunity for usage of biosimilars as reference products. The FDA released its Biosimilars Action Plan23 last summer, showing the agency’s commitment to ensuring competition in the biosimilar market that can and should be leveraged to reduce drug prices. Similarly, the American Patients First: The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs proposal released in May 2018 by the Department of Health and Human Services also supports competition by promoting the use of biosimilars, and notes the FDA’s plans to release new policies on the adoption of biosimilars, as well as plans to educate clinicians, patients and payers about biosimilar and interchangeable products, and increase their awareness. Given this support, it won’t be surprising for payers, providers and patients to gain confidence in biosimilars and for their utilization to increase substantially.


18. Ibid.


Jenna Kappel is Associate Director, Health Policy, Xcenda.
CYRAMZA boosted efficacy results vs docetaxel alone in the REVEL ITT population—with consistent results in patients with rapidly progressing disease*1

Exploratory Subgroup Analysis: Patients With Rapidly Progressing Disease* (n=209)

<table>
<thead>
<tr>
<th>Major Outcome Measure</th>
<th>CYRAMZA + docetaxel</th>
<th>Placebo + docetaxel</th>
</tr>
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<tbody>
<tr>
<td>OS†</td>
<td>10.5 months‡</td>
<td>9.1 months‡</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(9.5, 11.2)</td>
<td>(8.4, 10.0)</td>
</tr>
<tr>
<td>HR=0.74 (95% CI: 0.54, 1.00) P=0.024</td>
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<tr>
<th>Supportive Outcome Measure</th>
</tr>
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<tbody>
<tr>
<td>ORR‡</td>
</tr>
<tr>
<td>CYRAMZA + docetaxel</td>
</tr>
<tr>
<td>23% (20, 26)</td>
</tr>
<tr>
<td>Placebo + docetaxel</td>
</tr>
<tr>
<td>14% (11, 17)</td>
</tr>
<tr>
<td>P=0.001</td>
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<table>
<thead>
<tr>
<th>Supportive Outcome Measure</th>
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<tbody>
<tr>
<td>PFS†</td>
</tr>
<tr>
<td>CYRAMZA + docetaxel</td>
</tr>
<tr>
<td>4.5 months‡</td>
</tr>
<tr>
<td>(4.2, 5.4)</td>
</tr>
<tr>
<td>Placebo + docetaxel</td>
</tr>
<tr>
<td>3.0 months‡</td>
</tr>
<tr>
<td>(2.8, 3.9)</td>
</tr>
<tr>
<td>HR=0.74 (95% CI: 0.68, 0.84) P=0.001</td>
</tr>
</tbody>
</table>

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/m2 every 21 days.3

REVEL EXPLORATORY ANALYSIS The REVEL trial was not adequately powered, nor error-controlled, for subgroup analysis. Treatment differences observed in this subgroup cannot be regarded as statistically significant. The analysis described here was post hoc and exploratory.2

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.

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, the incidence of severe bleeding was 3.4% for CYRAMZA and 2.6% for placebo. In Study 2, 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, the incidence of severe bleeding was 2.4% for CYRAMZA plus docetaxel and 2.3% for placebo plus docetaxel. Patients with NSCLC receiving therapeutic angiogenesis or chronic therapy with NSAIDs or other antithrombotic 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, 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**

Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardioembolic stroke, coronary artery, 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 pacitaxel (15%) as compared to placebo plus paclitaxel (2%), in patients receiving CYRAMZA plus docetaxel (6%) as compared to placebo plus docetaxel (2%), and in patients receiving CYRAMZA plus FOLFIRI (1%) as compared to placebo plus FOLFIRI (5%). Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two 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 if patients experience a hypertensive crisis or hypertensive encephalopathy.

**Infusion-Related Reactions**

Prior to the institution of premedication recommendations across clinical trials of CYRAMZA, infusion-related reactions (IRRs) occurred in 6 out of 37 patients (16%), including two severe events. The majority of IRRs across trials occurred during or following a first or second CYRAMZA infusion. Symptoms of IRRs included rigor/tremor, back pain/spasm, chest pain/lack of tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasms, 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 2, the incidence of gastrointestinal perforation was 0.9% for CYRAMZA plus docetaxel and 0.3% for placebo plus docetaxel. In Study 3, the incidence of gastrointestinal perforation was 1% for CYRAMZA plus docetaxel and 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. Discontinue CYRAMZA therapy in patients with impaired wound healing. 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, embryonic 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.

**CONTRAINDICATIONS**

None.

**ADVERSE REACTIONS**

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**CYRAMZA Administered in Combination with Docetaxel**

Study 3 was a multinational, randomized, double-blind study conducted in patients with NSCLC with disease progression on or after one platinum-based therapy for locally advanced or metastatic disease. Patients received either CYRAMZA 10 mg/kg intravenously plus docetaxel 75 mg/m² intravenously every 3 weeks or placebo plus docetaxel 75 mg/m² intravenously every 3 weeks. Due to an increased incidence of neutropenia and febrile neutropenia in patients enrolled in East Asian sites, Study 3 was amended and 24 patients (11 CYRAMZA plus docetaxel, 13 placebo plus docetaxel) at East Asian sites started a starting dose of docetaxel at 60 mg/m² every 3 weeks. Study 3 excluded patients with an ECOG PS of 2 or greater, bilirubin greater than the upper limit of normal (ULN), uncontrolled hypertension, major surgery within 28 days, radiographic evidence of major airway or blood vessel invasion by cancer, radiographic evidence of intra-tumor cavitation, or gross hemolysis within the preceding 2 months, and patients receiving therapeutic angioplastation or stented anti-platelet therapy other than once daily aspirin. The study also excluded patients whose only prior treatment for advanced NSCLC was a tyrosine kinase (epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) inhibitor. The data described below reflect exposure to CYRAMZA plus docetaxel in 627 patients in Study 3. Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 84% were White and 12% were Asian; 33% had ECOG PS 0; 74% had non-squamous histology and 25% had squamous histology. Patients received a median of 4.5 doses of CYRAMZA; the median duration of exposure was 3.5 months, and 18% (31 of 627) patients received CYRAMZA for at least six months. In Study 3, the most common adverse reactions (all grades) observed in CYRAMZA plus docetaxel-treated patients at a rate of >35% and ≥2% higher than placebo plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. 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%). The incidence of 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 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. The most common serious adverse events 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, 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, 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. Table 4 provides the frequency and severity of adverse reactions in Study 3.

**Table 4: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 3**

<table>
<thead>
<tr>
<th>Adverse Reactions (MedRA)</th>
<th>System Organ Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYRAMZA plus docetaxel</td>
<td>Placebo plus docetaxel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All Grades (Frequency %)</th>
<th>Grade 3-4 (Frequency %)</th>
<th>All Grades (Frequency %)</th>
<th>Grade 3-4 (Frequency %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>16.0</td>
<td>16.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>55.0</td>
<td>49.0</td>
<td>46.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13.0</td>
<td>5.0</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>
Clinically relevant adverse drug reactions reported in ≥1% and <5% of the CYRAMZA plus docetaxel–treated patients in Study 3 were hypotension (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (0.5% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

**Immunogenicity**
As with all therapeutic proteins, there is the potential for immunogenicity. In 23 clinical trials, 86/2930 (3.0%) of CYRAMZA–treated patients tested positive for treatment-emergent anti–ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti–ramucirumab antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

**DRUG INTERACTIONS**
No pharmacokinetic (PK) interactions were observed between ramucirumab and docetaxel.

**USE IN SPECIFIC POPULATIONS**

### Pregnancy

**Risk Summary**
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 in pregnant women to inform any drug-related risks. No studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. The background risk of major birth defects and miscarriage for the indicated populations is unknown. A U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. Advise pregnant women of the potential risk to a fetus.

**Animal Data**
No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryofetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR2 signaling was associated with development and maintenance of endothelial and placental vascular function, successful blastocyst implantation, maternal and fetal-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with developmental anomalies including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels.

**Lactation**
Risk Summary
There is no information on the presence of ramucirumab in human milk, the effects on the breast-fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts.

**Contraception**
Based on its mechanism of action, CYRAMZA can cause fetal harm. Advise females of reproductive potential to use effective contraception while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

### Geriatric Use
Of the 563 CYRAMZA–treated patients in two randomized gastric cancer clinical studies, 36% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Of the 1253 patients in Study 3, 405 (36%) were 65 and over and 64 (7%) were 75 and over. Of the 627 patients who received CYRAMZA plus docetaxel in Study 3, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of Study 3, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years or older was 1.10 (95% CI: 0.89, 1.36).

### Renal Impairment
No dose adjustment is recommended for patients with renal impairment based on population pharmacokinetic analysis.

### Hepatic Impairment
No dose adjustment is recommended for patients with mild (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase [AST] <ULN), or moderate (total bilirubin >1.0-1.5 times ULN and any AST) hepatic impairment based on population pharmacokinetic analysis. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

### DOSAGE AND ADMINISTRATION
Do not administer CYRAMZA as an intravenous push or bolus.

#### Recommended Dose and Schedule
The recommended dose of CYRAMZA is 10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue CYRAMZA until disease progression or unacceptable toxicity.

**Premedication**
Prior to each CYRAMZA infusion, premedicate all patients with an intravenous histamine H₂ antagonist (e.g., diphenhydramine hydrochloride). For patients who have experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion.

#### Dose Modifications

**Infusion-Related Reactions (IRR)**
- Reduce the infusion rate of CYRAMZA by 50% for Grade 1 or 2 IRRs.
- Permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

**Hypertension**
- Interrupt CYRAMZA for severe hypertension until controlled with medical management.
- Permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy.

**Proteinuria**
- Interrupt CYRAMZA for urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose of 8 mg/kg every 3 weeks once the urine protein level returns to <2 g/24 hours. If the protein level ≥2 g/24 hours reoccurs, interrupt CYRAMZA and reduce the dose to 6 mg/kg every 3 weeks once the urine protein level returns to <2 g/24 hours.
- Permanently discontinue CYRAMZA for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome.

### Wound Healing Complications
- Interrupt CYRAMZA prior to scheduled surgery until the wound is fully healed.

**Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding**
- Permanently discontinue CYRAMZA.

For toxicities related to docetaxel, refer to the current respective prescribing information.

### PATIENT COUNSELING INFORMATION

**Hemorrhage:**
Advise patients that CYRAMZA can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.

**Arterial Thromboembolic events:**
Advise patients of an increased risk of an arterial thromboembolic event.

**Hypertension:**
- Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.

**Gastrointestinal perforations:**
- Advise patients to notify their health care provider for severe diarrhea, vomiting, or severe abdominal pain.

**Impaired wound healing:**
Advise patients that CYRAMZA has the potential to impair wound healing, instruct patients not to undergo surgery without first discussing this potential risk with their health care provider.

**Pregnancy and fetal harm:**
- Advise females of reproductive potential of the potential risk for maintaining pregnancy, risk to the fetus, and risk to postnatal 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:**
- Advise patients not to breastfeed during CYRAMZA treatment.

**Infertility:**
- Advise females of reproductive potential regarding potential infertility effects of CYRAMZA.

Additional information can be found at www.CYRAMZAhcp.com.

**Lilly**
Eli Lilly and Company, Indianapolis, IN 46285, USA
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**References:**
- RL-HCP BS 27MAR2017
- PP-RL-US-0984
Treatment Options in Non-Small Cell Lung Cancer

Ralph Boccia, M.D., Chair of ION’s Medical Advisory Panel, recently talked with Florida Cancer Specialists’ David Wenk, M.D., about the role of chemotherapy—especially Cyramza® (ramucirumab)—as 2nd line therapy in non-small cell lung cancer (NSCLC).

RALPH BOCCIA: How does 1st line treatment of patients with PDL high (>50%) and low PDL impact later lines of therapy?

DAVID WENK: From multiple studies that have been conducted over the last few years, I think we’ve seen that the use of pembrolizumab in the frontline setting has had significant benefits, specifically in patients with high PDL1—greater than 50 percent. Initially the approval of the chemotherapy came out of these studies.

More recently, however, we’ve seen additional data on combination therapy for all patients with PDL1 status. So, for me personally, this led me to altering how I treat some patients a bit in the sense that I used to treat everyone with single agent pembrolizumab in the front-line setting; however, I now look at some of the data out there in terms of therapy and hazard ratios, and if I’m seeing someone with a very good performance status who maybe has a larger burden of disease, I tend to go with triplet therapy rather than the single agent in that setting.

RB: Can you talk about appropriate treatment options for 2nd line NSCLC and some experiences you’ve had in practice?

DW: Today the 2nd line setting has become a lot more complicated than it used to be due to the available choices and the different agents that are used more in the frontline setting. Given recent approvals and recent pembrolizumab data, for a typical non-small cell lung cancer patient, assuming they’re a candidate for immunotherapy, and with adenocarcinoma and in the squamous cell population, I am likely to utilize frontline immunotherapy in both histologies. After utilizing immunotherapy up front, we currently don’t have data that would look at using different immunotherapies in subsequent lines of treatment. So, in the 2nd line setting, I tend to go to a traditional regimen, including the consideration of a taxane, in this case docetaxel, in combination with Cyramza®.

Also, in a patient population that has not received a taxane in the frontline setting, I would consider using paclitaxel instead of docetaxel, particularly with someone who maybe is not as fit. Perhaps I would then consider adjusting to weekly paclitaxel with Cyramza rather than the every-three-week docetaxel which unfortunately can be tough to tolerate in some patients whose performance status may have declined after frontline therapy.

RB: So in instances where you have used an IO product in 1st line, whether it’s pembrolizumab or pemetrexed for injection, is Cyramza typically your next course of action for 2nd line?

DW: Regardless of how the patient is progressing on therapy—meaning if they are a rapid progressor or if they’ve gone through four cycles of combination therapy and then have gone on to maintenance therapy with pembrolizumab or pemetrexed—I still would end up utilizing Cyramza if they are a candidate for a taxane. Ultimately, after maybe four cycles, I might consider dropping off the taxane and continuing on single agent Cyramza.

RB: Patients with disease progression on or after platinum-based therapy seem to have an unmet need for options that can extend survival. Can you talk about your experience with Cyramza, and the role you see it playing in this 2nd line NSCLC treatment?

DW: When investigators looked at the subset of patients in the REVEL trial who were identified as rapid progressors, it was seen that these patients were progressing while on platinum-based therapy, or shortly thereafter.
Unfortunately, those patients typically do very poorly long term and there are very limited treatment options for them.

Looking at the data in this rapid progressing population, we see that, in my opinion, the combination of docetaxel and Cyramza is very impressive, in terms of the response rate as well as overall progression free survival.

Specifically looking at the response rate, these are patients where you need to get rapid control of the disease. If you aren’t able to do that, you’re probably going to end up losing these patients and really looking at palliative care only. So this is a setting where the combination of Cyramza and docetaxel is definitely useful in helping to get control of the disease. With Cyramza and docetaxel we’ve seen response rates approaching 20 percent versus what we may see at less than 10 percent with standard therapy.

RB: What characteristics are you looking for in patients when trying to determine if Cyramza may be the best treatment option?

DW: I find Cyramza is actually a very well-tolerated drug, so I don’t really find many patients who are not good candidates for therapy. I find it’s a drug that can be easily administered with minimal complications and patients can actually stay on therapy long term. So to me anyone who has progressed on frontline therapy who has not seen a taxane would be a good candidate, especially in the rapid progressors where there are really no other options. But even in those who are not in the rapid progressor category, where we are looking at a population where otherwise we’d be treating with agents such as gemcitabine and navelbine, really going back in time almost in how we used to treat lung cancer—these patients can benefit as well. I really think it’s an appropriate 2nd line therapy on almost all patients.

RB: What are the most common adverse reactions that you are aware of?

DW: We see a lot of cytopenia but that has more to do with the effects of docetaxel than Cyramza. One thing that I have been seeing more of recently in the combination therapy is mucosal inflammation. But whether it’s mucositis or stomatitis, it can be managed. The same can be said for occurrences of colitis.

Outside of that the cytopenia’s are fairly easy to manage. Fatigue is real, but that can almost be attributed in any regimen. All of what I’ve seen can be pretty well managed. I’ve had patients on Cyramza for quite a long amount of time—upwards of a year or more—and most of them really have minimal to no tolerability issues.

RB: Is there literature or trial data available for your peers to seek out as reference?

DW: If you’re looking at lung cancer, specifically for Cyramza in the 2nd line setting, I always recommend referring back to the REVEL trial and then looking specifically at the sub-analysis in those rapid progressors. This gives a unique perspective on how a drug can be very valuable in that hard-to-treat population, so I would refer back to that clinical study that, in my mind, gives a lot of credence to using Cyramza in the 2nd line setting.

I think it’s important to note that lung cancer has changed dramatically in the last several years, and thankfully we have many new therapies and targeted agents now. Immunotherapy is held in high regard, as it should be, but it’s important to remember that it doesn’t work for everyone. We cannot forget that there is still a role for chemotherapy in this disease. With immunotherapy you either respond or you don’t, and when you don’t respond, and a patient’s quality of life declines rapidly and their condition worsens, using chemotherapy in the 2nd line setting is very appropriate and can lead to better outcomes.

That is my key takeaway in all of this: don’t forget about the role of chemotherapy in lung cancer.

Dr. Wenk received his undergraduate degree from the University of Virginia and his medical degree with high honors from Ross University School of Medicine. He then completed his internal medicine residency training at the University of South Florida, where he was Chief Resident during his third year. Dr. Wenk then completed his fellowship in hematology and oncology at the H. Lee Moffitt Cancer and Research Institute. While at Moffitt, Dr. Wenk served as a Clinical Faculty Member in the Department of Medicine as well as the Department of Blood and Marrow Transplantation. Dr. Wenk holds ABIM board certifications in Internal Medicine, Medical Oncology and Hematology. Dr. Wenk treats all hematologic and oncologic malignancies as well as benign hematologic disorders.
CYRAMZA boosted efficacy results vs docetaxel alone in the REVEL ITT population—
with consistent results in patients with rapidly progressing disease*1

Exploratory Subgroup Analysis: Patients With Rapidly Progressing Disease* (n=209)

<table>
<thead>
<tr>
<th>Major Outcome Measure</th>
<th>Placebo + docetaxel</th>
<th>CYRAMZA + docetaxel</th>
<th>Unstratified HR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS†</td>
<td>5.8 months</td>
<td>9.1 months‡</td>
<td>0.74</td>
<td>(0.54, 1.00)</td>
</tr>
</tbody>
</table>

PFS§

<table>
<thead>
<tr>
<th>Supportive Outcome Measure</th>
<th>Placebo + docetaxel</th>
<th>CYRAMZA + docetaxel</th>
<th>Unstratified HR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR1</td>
<td>14%</td>
<td>23%</td>
<td>0.73</td>
<td>(0.55, 0.97)</td>
</tr>
</tbody>
</table>

Time-to-progression ≤12 weeks

REVEL EXPLORATORY ANALYSIS The REVEL trial was not adequately powered, nor error-controlled, for subgroup analysis. Treatment differences observed in this subgroup cannot be regarded as statistically significant. The analysis described here was post hoc and exploratory.2

REVEL ITT Population (n=1253)

<table>
<thead>
<tr>
<th>Major Outcome Measure</th>
<th>Placebo + docetaxel</th>
<th>CYRAMZA + docetaxel</th>
<th>Unstratified HR</th>
<th>(95% CI)</th>
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<td>0.73</td>
<td>(0.55, 0.97)</td>
</tr>
</tbody>
</table>

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/m² every 21 days.3

* Rapidly progressing disease is defined by time-to-progression within 9 or 12 weeks after starting initial platinum-based treatment. The percentage of deaths at the time of analysis in the CYRAMZA plus docetaxel arm was 73.7% (84 patients) and 80.6% (79 patients) in the placebo plus docetaxel arm. Median.

†The percentage of deaths at the time of analysis in the CYRAMZA plus docetaxel arm was 73.7% (84 patients) and 80.6% (79 patients) in the placebo plus docetaxel arm.

‡The percentage of events at the time of analysis was 85% (518 patients) in the placebo plus docetaxel arm, respectively.

§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.

CRAMZA, 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.

INDICATION

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**

**Hypertension**

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA plus docetaxel compared to placebo plus docetaxel (2% vs 0.3%). Monitor blood pressure every 2 weeks. Discontinue CYRAMZA in patients who experience severe ATEs.

**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 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 and risk to newborn and infant development, and to use effective contraception during treatment with CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

**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 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 (59% vs 46%; 49% vs 46%), fatigue/asthenia (55% vs 50%; 14% vs 11%), thrombocytopenia (13% vs 5%; 3% vs <1%), hypertension (11% vs 5%; 6% vs 2%).

**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.

**Visit CYRAMZAhcp.com to find out more**

**References:**

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been reported with 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 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

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

Embolitic Toxicity

Based on its mechanism of action, CYRAMZA can cause fatal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryonic 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.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

CYRAMZA Administered in Combination with Docetaxel

Study 3 was a multinational, randomized, double-blind study conducted in patients with NSCLC with disease progression or on or after one platinum-based therapy for locally advanced or metastatic disease. Patients received either CYRAMZA 10 mg/kg intravenously plus docetaxel 75 mg/m2 intravenously every 3 weeks or placebo plus docetaxel 75 mg/m2 intravenously every 3 weeks. Asymptomatic neutropenia occurred in 38% of patients treated with CYRAMZA plus docetaxel versus 26% of patients treated with placebo plus docetaxel. Due to an increased incidence of neutropenia and febrile neutropenia in patients enrolled in East Asian sites, Study 3 was amended and 24 patients (11 CYRAMZA plus docetaxel, 13 placebo plus docetaxel) at East Asian sites started a starting dose of docetaxel at 60 mg/m2 every 3 weeks. Study 3 excluded patients with an ECOG PS of 2 or greater, bilirubin greater than the upper limit of normal (ULN), uncontrolled hypertension, major surgery within 28 days, radiographic evidence of major airway or blood vessel invasion by cancer, radiographic evidence of intra-tumor cavitation, or gross hemolysis within the preceding 2 months, and patients receiving therapeutic anticoagulation or anti-platelet therapy other than once daily aspirin. The study also excluded patients whose only prior treatment for advanced NSCLC was a tyrosine kinase (epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) inhibitor. The data described below reflect exposure to CYRAMZA plus docetaxel in 627 patients in Study 3. Demographics and baseline characteristics were similar between treatment arms. Median age was 62 years; 67% of patients were men; 84% were White and 12% were Asian; 33% had ECOG PS 0; 74% had no squamous histology and 25% had squamous histology. Patients received a median of 4.5 doses of CYRAMZA; the median duration of exposure was 3.5 months, and 18% (31 of 627) patients received CYRAMZA for at least six months. In Study 3, the most common adverse reactions (all grades) observed in CYRAMZA plus docetaxel-treated patients at a rate of >35% and >2% higher than placebo plus docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation. 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%). Patients with no-squamous 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. The most common serious adverse events 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, there were 18 (6%) deaths on treatment or within 30 days of discontinuation for CYRAMZA plus docetaxel and 9 (4%) deaths for placebo plus docetaxel. In patients aged 65-75 years, 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. Table 4 provides the frequency and severity of adverse reactions in Study 3.

Table 4: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 3

<table>
<thead>
<tr>
<th>Adverse Reactions (MedDRA)</th>
<th>CYRAMZA plus docetaxel (N=267)</th>
<th>Placebo plus docetaxel (N=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (Frequency %)</td>
<td>Grade 3-4 (Frequency %)</td>
<td>All Grades (Frequency %)</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>13</td>
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</tbody>
</table>
### Table 4: Adverse Reactions Occurring at Incidence Rate ≥5% and a ≥2% Difference Between Arms in Patients Receiving CYRAMZA in Study 3 (Contd.)

<table>
<thead>
<tr>
<th>Adverse Reactions (MedDRA) System Organ Class</th>
<th>CYRAMZA plus docetaxel (N=627)</th>
<th>Placebo plus docetaxel (N=618)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis/Mucosal inflammation</td>
<td>37/12 (5.9%)</td>
<td>7/12 (2.1%)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laceration increased</td>
<td>13/6 (2.1%)</td>
<td>&lt;1/6 (0.2%)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/Athetia</td>
<td>55/7 (8.8%)</td>
<td>14/7 (4.2%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>16/9 (2.5%)</td>
<td>0/9 (&lt;1%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>19/6 (&lt;1%)</td>
<td>7/6 (&lt;1%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11/6 (1.7%)</td>
<td>6/5 (&lt;1%)</td>
</tr>
</tbody>
</table>

**Gastrointestinal Effects:**
- Clinically relevant adverse drug reactions reported in ≥1% and <5% of the CYRAMZA plus docetaxel-treated patients in Study 3 were hypotension (4.8% CYRAMZA plus docetaxel versus 2.4% for placebo plus docetaxel) and proteinuria (0.5% CYRAMZA plus docetaxel versus 0.8% placebo plus docetaxel).

**Immunogenicity:**
- As with all therapeutic proteins, there is the potential for immunogenicity. In 23 clinical trials, 862/2890 (3.0%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

**Genitourinary:**
- The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

### Drug Interactions
No pharmacokinetic (PK) interactions were observed between ramucirumab and docetaxel.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy
- Risk Summary
  - 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 in pregnant women to inform any drug-associated risks. Animal studies have been conducted to evaluate the effect of ramucirumab on reproduction and fetal development. The background risk of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.
- Animal Studies
  - No animal studies have been specifically conducted to evaluate the effect of ramucirumab on reproduction and fetal development. In mice, loss of the VEGFR2 gene resulted in embryofetal death and these fetuses lacked organized blood vessels and blood islands in the yolk sac. In other models, VEGFR signaling was associated with development and maintenance of endometrial and placental vascular function, successful blastocyst implantation, maternal and fetal-placental vascular differentiation, and development during early pregnancy in rodents and non-human primates. Disruption of VEGF signaling has also been associated with development anomalies including poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels.

#### Lactation
- Risk Summary
  - There is no information on the presence of ramucirumab in human milk, the effects on the breast-fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts.

#### Females and Males of Reproductive Potential

##### Contraception
- Females
  - Based on its mechanism of action, CYRAMZA can cause fetal harm. Advise females of reproductive potential to use effective contraception while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA.
- Infertility
  - Females
    - Advise females of reproductive potential that based on animal data CYRAMZA may impair fertility.

#### Pediatric Use
- The safety and effectiveness of CYRAMZA in pediatric patients have not been established. In animal studies, effects on epithelial growth plates were identified. In cynomolgus monkeys, anatomical pathology revealed adverse effects on the epithelial growth plate (thickening and osteochondropathy) at all doses tested (5-50 mg/kg). Ramucirumab exposure at the lowest weekly dose tested in the cynomolgus monkey was 0.2 times the exposure in humans at the recommended dose of ramucirumab as a single agent.

#### Geriatric Use
- Of the 563 CYRAMZA-treated patients in two randomized gastric cancer clinical studies, 36% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed among these subjects and younger subjects. Of the 1253 patients in Study 3, 45% (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA plus docetaxel in Study 3, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of Study 3, the hazard ratio for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years or older was 1.10 (95% CI: 0.89, 1.36).

### Renal Impairment
No dose adjustment is recommended for patients with renal impairment based on population pharmacokinetic analysis.

### Hepatic Impairment
No dose adjustment is recommended for patients with mild (total bilirubin within upper limit of normal [ULN]) and asymptotic aminotransferase [AST] = ULN, or total bilirubin >1.0-1.5 times ULN and any AST) or moderate (total bilirubin >1.5-3.0 times ULN and any AST) hepatic impairment based on population pharmacokinetic analysis. Clinical deterioration was reported in patients with Child-Pugh B or C cirrhosis who received single-agent CYRAMZA.

### DOSAGE AND ADMINISTRATION
Do not administer CYRAMZA as an intravenous push or bolus.

#### Recommended Dose and Schedule
The recommended dose of CYRAMZA is 10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. Continue CYRAMZA until disease progression or unacceptable toxicity.

**Premedication**
- Prior to each CYRAMZA infusion, premedicate all patients with an intravenous histamine H₂ antagonist (e.g., diphenhydramine hydrochloride). For patients who have experienced a Grade 1 or 2 infusion reaction, also premedicate with dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion.

#### Dose Modifications

- **Infusion-Related Reactions (IRR)**
  - Reduce the infusion rate of CYRAMZA by 50% for Grade 1 or 2 IRRs.
  - Permanently discontinue CYRAMZA for Grade 3 or 4 IRRs.

- **Hypertension**
  - Interrupt CYRAMZA for severe hypertension until controlled with medical management.
  - Permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy.

- **Proteinuria**
  - Interrupt CYRAMZA for urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose of 8 mg/kg every 3 weeks once the urine protein level returns to <2 g/24 hours. If the protein level ≥2 g/24 hours reoccurs, interrupt CYRAMZA and reduce the dose to 6 mg/kg every 3 weeks once the urine protein level returns to <2 g/24 hours.
  - Permanently discontinue CYRAMZA for urine protein level ≥3 g/24 hours or in the setting of nephrotic syndrome.

#### Wound Healing Complications
- **Hypertension**
  - Interrupt CYRAMZA prior to scheduled surgery until the wound is fully healed.

#### Arterial Thromboembolic Events
- **Hypertension**
  - Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.

#### Gastrointestinal Perforations
- **Hypertension**
  - Advise patients to notify their health care provider for bleeding or symptoms of bleeding including lightheadedness.

### Patient Counseling Information

- **Hemorrhage**
  - Advise patients that CYRAMZA can cause severe bleeding. Advise patients to contact their health care provider for bleeding or symptoms of bleeding including lightheadedness.

- **Arterial Thromboembolic Events**
  - Advise patients of an increased risk of an arterial thromboembolic event.

- **Hypertension**
  - Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.

- **Gastrointestinal Perforations**
  - Advise patients to notify their health care provider for severe diarrhea, vomiting, or severe abdominal pain.

- **Impaired wound healing**
  - Advise patients that CYRAMZA has the potential to impair wound healing. Instruct patients not to undergo surgery without first discussing this potential risk with their health care provider.

- **Postoperative bleeding**
  - Advise patients that CYRAMZA has the potential to impair wound healing. Instruct patients not to undergo surgery without first discussing this potential risk with their health care provider.

- **Renal Impairment**
  - Advise patients of renal impairment potential regarding potential infertility effects of CYRAMZA.

Additional information can be found at www.CYRAMZAhcp.com.
Advanced Analytics are Vital to an In-Office Dispensing Program’s Success

In an article published to Oncology Live’s website in November 2018, Barry Fortner, Ph.D., Senior Vice President and President of Specialty Physician Services at AmerisourceBergen wrote, “Medically integrated dispensing programs have emerged as crucial assets for community oncology practices as they work to stay viable in an ultracompetitive market.”

ION Solutions’ Specialty Oncology Network (SON) pharmacy and dispensing program was developed to help community oncology practices capture additional revenue from filling oral oncology prescriptions. An in-office dispensing program also helps to provide a seamless treatment experience for the patient, as well as continued education on the importance of medication adherence and compliance.

The advanced analytics available through the SON make it easy for practices to measure performance and optimize patient care. One tool, Smart Rx Analyzer, provides a dynamic view of a practice’s dispenses so staff can quickly detect patterns and take steps to improve clinical operations and efficiencies.

With the ability to export dispensing data—and easy to interpret graphs and visuals—practices can determine high and low capture rates by prescriber and drug, evaluate margin changes with adjustable capture rate percentages and modify practice workflow to improve capture rates.

Data is refreshed daily, resulting in analytics that help practices quickly adapt to dispensing trends. A one-click DIR (direct and indirect remuneration) fee calculator applies estimated DIR fees to margins, making it easier to manage the bottom line. In addition, practices can manage their compliance to contracts and benchmark their dispensing metrics against other practices in the SON.

Smart Rx Analyzer uses a practice’s dispensary’s processing system’s data supplemented with acquisition costs from Oncology Supply drug purchases. The practice’s dispense data is combined with a list of oncology drugs from a third-party data intelligence source to calculate in-office capture rate.

Practices interested in learning more about how in-office dispensing and Smart Rx Analyzer can maximize their practice’s revenue and enhance patient care should contact SON@iononline.com.

Best Practices for Effective Genomic Testing in Community Oncology

Oncology Times recently published an article on best practices for introducing genomic testing into community oncology practices. ION member, Lucio Gordan, M.D., of Florida Cancer Specialists is featured in the article, which focuses on what community oncologists need to properly implement testing into practice.

Also highlighted in the article is the work of ION’s Precision Medicine Advisory Panel and the Precision Medicine Center available on iononline.com.
This is more than just lip-service.

As the pioneers of performance-based contracting, we have always been focused on the future of community oncology. That long-standing commitment remains as the healthcare landscape evolves due to changing regulations and industry standards.

Care for you, so that you can care for patients.

As patient needs evolve, so do the tools and resources you depend upon to meet those needs. We do our part by investing in technology, research and other resources to help you elevate the quality of patient care.

Your success is our success.

Our purpose is to ensure your viability as an independent practice and to help you grow. That can’t be fulfilled if we are not providing the results and resources that you need-and that forges lasting partnerships.